Catalytic Enantioselective Conjugate Addition of Dialkylzinc Compounds to Chalcones

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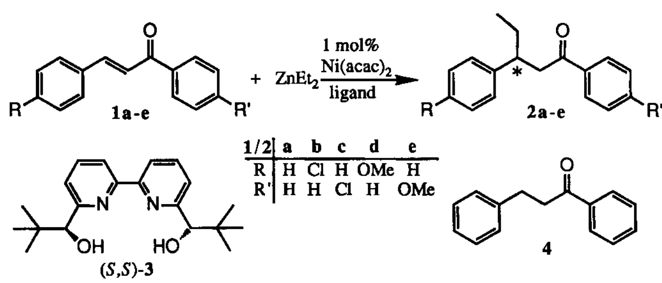
Conjugate addition of diethylzinc to enones is catalyzed by a complex derived from $Ni(acac)_2$ and C_2-symmetric 2,2′-bipyridine **3** or chiral pyridines **5**−**12**. The products are obtained with optical purities up to 89% ee. A strong positive nonlinear relationship between the enantiomeric excess of the ligand and the ee of the product has been observed. The factors which govern catalyst activity and enantioselectivity have been investigated.

Carbon−carbon bond formation by conjugate addition of organometallic reagents to α,β-unsaturated enones is an efficient and reliable method for the synthesis of β-substituted carbonyl compounds. In particular, organocopper reagents have successfully been applied to regio-, chemo- and stereoselective alkylations[1]. *Enantioselective* conjugate additions of organometallics were first described by Kretschmer[2a] and Seebach[2b,c] using sparteine or 1,4-(dialkylamino)-2,3-dimethoxybutane, respectively, as chiral coordinating ligands. Leyendecker[2d] employed *N*-alkylprolinol, and recently Alexakis[2e] used chiral phosphorus derivatives to induce asymmetry during the conjugate addition. Other efforts have focused on the development of organo(hetero)cuprates carrying optically active nontransferable ligands[3]. In some cases, enantioselectivities up to 97% were achieved. In general, these methods require stoichiometric or often excess amounts of chiral reagents. Despite the increasing importance of *catalytic* enantioselective transformations, reports on *chiral catalysts* for conjugate addition reactions are still rare[4]. Lippard et al. reported that copper(I) complexes with bidentate *N,N*-dialkyl-substituted aminotropone imines catalyze the 1,4-addition of *n*-butylmagnesium chloride to cyclohexenone[5]. The corresponding product was obtained with up to 74% ee. However, the scope of this reaction is rather limited, and other reactants gave products with very low enantiomeric excess. Jansen and Feringa described the conjugate addition of Grignard reagents to enones catalyzed by chiral zinc(II) complexes derived from diamines and amino alcohols[6]. With this system, optical yields up to 33% ee were achieved. Based on some earlier work by Luche et al.[7], Soai and co-workers developed an enantioselective modification of the nickel-catalyzed alkyl transfer from diorganozincs to enones[8]. A complex prepared in situ from nickel acetylacetonate [$Ni(acac)_2$] and *N,N*-dialkylnorephedrine afforded the products with moderate to good enantioselectivity. The degree of asymmetric induction could then be substantially raised by the addition of achiral ligands such as 2,2′-bipyridine or 1,10-phenanthroline[8a].

Our interest in this area derived from our previous work on the enantioselective alkylation of aldehydes catalyzed by optically active bipyridines and pyridine derivatives[9,10]. We found that nickel complexes of C_2-symmetric bipyridine **3**[11] catalyzed the conjugate addition of diethylzinc to chalcones and afforded addition products with high enantiomeric excess[12]. In this paper, we describe further details of our investigations and report the use of substituted pyridines for this enantioselective alkylation.

Variation of the Catalyst Composition

A nickel complex derived from $Ni(acac)_2$ and bipyridine (*S,S*)-**3** catalyzed the conjugate addition of diethylzinc to chalcone **1a**. The (*R*) enantiomer of **2a** with an enantiomeric excess of up to 72% was obtained as the major product[12]. The optical yield of **2a** was determined by HPLC using a chiral stationary phase (Daicel, Chiralcel OD). Measurements of the optical rotation and comparison with known data gave the absolute configuration of **2a**[13,14].



The chemical yields of this alkylation were generally in the range of 70 to 85% with the exception of reactions with very high ligand concentrations (for example Table 1, entries 1 and 9). In these cases, stirring of the reaction mixture became almost impossible due to precipitation of reactants. The optical purity of **2a** was strongly dependent on the ligand concentration and nickel-to-ligand ratio (Table 1). High optical yields were only obtained by using 1 mol-% of $Ni(acac)_2$ and 20 or 30 mol-% of ligand **3**. Decreasing the amount of **3** to 10 or 5 mol-% lowered the enantiomeric excess of **2a** to 54 and 20%, respectively. At constant nickel-to-ligand ratio, enantioselectivity was increased by raising the amount of $Ni(acac)_2$ (Table 1, entries 4/5, 6/7). Without the nickel salt, but in the presence of 5 mol-% of **3**, only traces of **2a** (<5%) were formed (18 h, −30°C). The use of $Co(acac)_2$ instead of $Ni(acac)_2$ resulted in low conversion of **1a**, and only a 10% yield of **2a** was obtained. Racemic **2a** was synthesized in 73% yield by nickel catalysis *in the absence* of a chiral ligand. In this reaction, small amounts of **4** were detected by ^1H-NMR spectroscopy of crude samples. Under standard reaction conditions (acetonitrile, −30°C, 18 h, 20 mol-% of ligand), the formation of **4** was never observed. However, we also established that the presence of small amounts of possibly undetected **4** did not interfere with the HPLC analysis of the optical purity of **2a**.

Table 1. Effect of nickel and ligand concentration on the enantiomeric excess of **2a**[a]

Entry	Ligand, (mol-%)	$Ni(acac)_2$ (mol-%)	**2a** Yield (%)	ee (%)
1	**3**, 30	1	55	72
2	**3**, 20	1	75	72
3	**3**, 10	1	82	54
4	**3**, 5	1	74	20
5	**3**, 10	2	66	48
6	**3**, 6	2	73	18
7	**3**, 15	5	58	58
8	**3**, 5	5	69	18
9	**5**[b], 30	1	62	86
10	**5**[b], 20	1	79	82
11	**5**[b], 10	1	81	53

[a] In acetonitrile, −30°C, 18 h. — [b] Ligand **5** with 92% ee was used.

Table 2 shows the effect of solvent on the enantiomeric excess of **2a**. In order to obtain high optical yields, the use of acetonitrile or propionitrile was essential. Toluene, DMF, or THF solutions gave **2a** with lower ee's.

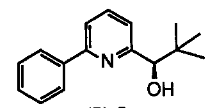
Table 2. Effect of solvent on the enantiomeric excess of **2a**[a]

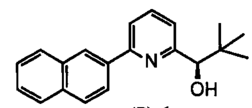
Entry	Solvent[b]	**2a** Yield (%)	ee (%)
1	acetonitrile	58	58
2	toluene	68	26
3	DMF	58	4
4	THF	77	8

[a] For 5 mol-% of $Ni(acac)_2$ and 15 mol-% of (*S*,*S*)-**3**, −30°C, 15−18 h. — [b] Addition of $ZnEt_2$ in hexane.

Variation of the Ligand Structure

In an attempt to further improve the enantioselectivity, we turned our attention to the ligand structure[11]. Addition product (*S*)-**2a** was formed as the major product when (*R*)-configurated pyridines were used. In screening experiments we found that aryl-substituted pyridines **5** and **6** gave **2a** with even higher enantiomeric excess (82 and 86% ee, respectively) than obtained with C_2-symmetric bipyridine **3** (Table 3). The same optical yield was observed when chiral ligand (*R*)-**7** was employed (82% ee of **2a**). In this compound, the methoxy substituent should be capable of further chelation to the organometallic reagents.


(*R*)-**5**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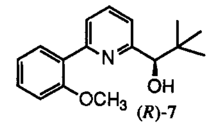
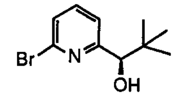
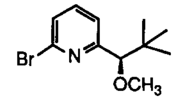
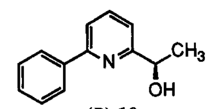
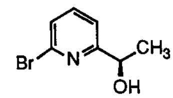
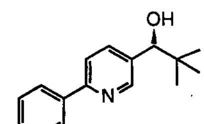

(*R*)-**7**


(*R*)-**8**


(*R*)-**9**


(*R*)-**10**


(*R*)-**11**


(*R*)-**12**

The steric bulk of the *tert*-butyl group was found to be essential for high enantioselectivity. Essentially racemic **2a** (2% ee) was obtained by using (*R*)-**10** or (*R*)-**11**, in which the substituent at the chiral center was changed from *tert*-butyl to methyl. Methyl ether (*R*)-**9** and 2,5-disubstituted pyridine (*R*)-**12** gave an almost racemic product (Table 3), indicating the necessities of direct metal binding at the oxygen atom and of internal chelation with the pyridine nitrogen atom.

Table 3. Effect of ligand structure on the enantiomeric excess of **2a**[a]

Entry	Ligand, ee (%)	Ni^{II}/ligand ratio[b]	**2a** Yield (%)	ee (%)
1	**3**, >98	1:20	75	72
2	**5**, 92	1:19	79	82
3	**6**, 90	1:22	84	86
4	**7**, 96	1:20	64	82
5	**8**[c], 92	1:20	75	60
6	**9**[c], ca. 92	1:20	>70	0
7	**10**, 70	1:22	72	2
8	**11**, 68	1:22	79	2
9	**12**, 86	1:20	64	2

[a] In acetonitrile, −30°C, ca. 18 h. — [b] Use of 1 mol-% of $Ni(acac)_2$. — [c] Contained small amounts of the corresponding chloride; see ref.[11].

Variation of the Reaction Conditions

Due to its ease of accessibility, we decided to use pyridine **5** for further studies. With respect to the required ligand concentration for high asymmetric induction in the conjugate addition, **5** showed the same behavior as bipyridine **3**. By increasing the amount of **5** (with 92% ee) from 10 to 20 mol-%, the enantiomeric excess of **2a** was raised from 53 to 82%. By using 30 mol-% of **5**, **2a** was obtained with 86% ee (Table 1, entries 9−11).

The highest asymmetric induction in the formation of **2a** using **5** (with 90% ee) and a nickel-to-ligand ratio of 1:20 was observed when a substoichiometric amount of diethylzinc was used. Addition of only 0.3 equivalents of the zinc reagent (1 M in hexane) to **1a** gave **2a** with an enantiomeric excess of 89%. This slightly enhanced enantioselectivity could either be explained by the lower concentration of diethylzinc or by the reduced relative amount of hexane in the solvent mixture with propionitrile. At a later stage (vide infra), we demonstrated that the asymmetric induction in the formation of **2a** showed only little dependence on the reactant concentrations. However, since the reaction was highly sensitive to solvent variations, the observed increase in ee was most likely due to the small change of the solvent system.

In order to gain more insight into the reaction details, the dependence of the optical purity of **2a** on reaction time and conversion of **1a** was studied (Table 4).

Table 4. Effect of reaction time on the enantiomeric excess of **2a**[a]

Entry	Reaction time [h]	ee of **5** (%)	Conversion of **1a** (%)[b]	ee of **2a** (%)
1	0.25	89	nd[c]	88
2	0.5	89	39	88
3	0.75	89	50	87
4	1	89	56	87
5	2	89	80	83
6	4	89	90	81
7	7	89	>95	80
8	9	89	>98	80
9	0.25	19	nd[c]	87
10	0.75	19	20	78
11	1.5	19	nd[c]	69
12	3	19	nd[c]	60
13	18	19	>98	51

[a] In propionitrile, −30°C. — [b] Determined by ^{1}H-NMR measurements of crude samples. — [c] nd: not determined.

At various time intervals, aliquots of the reaction mixture were withdrawn, and the usual workup was followed by ^{1}H-NMR measurements of the crude mixture to determine the conversion of **1a**. **2a** was isolated by column chromatography, and its optical purity was determined by HPLC analysis. Table 4 shows that the enantiomeric excess of **2a** *decreased* with time. Whereas the product isolated after 15 min had an enantiomeric excess of 88%, it had only 80% ee after 7 h. Thus, at higher conversion of **1a**, product **2a** with a lower optical purity was obtained. In these studies, pyridine **5** had an enantiomeric excess of 89%. The decrease of product ee with time became even more pronounced when ligands with lower optical purity were used (vide infra).

Variation of the Substrates and Reagents; Modification of the Catalyst

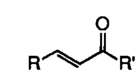
Substituted chalcones **1b**−**e** were alkylated in yields up to 78% by using the standard reaction conditions described above (ligand **5**; nickel-to-ligand ratio of 1:20). Methoxy and chloro substituents at both aromatic rings were tolerated, and enantioselectivities in the range of 72 to 90% were achieved (Table 5). The optical purities of the products were determined by HPLC using a chiral stationary phase. To ensure the correct assignment of the HPLC signals, racemic products were analogously synthesized by nickel catalysis and analyzed by the same method.

Table 5. Enantioselective alkylation of various substrates using pyridine **5**[a]

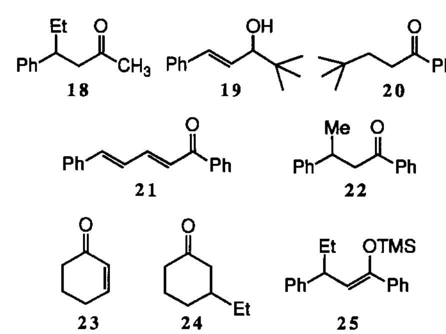
Entry	Substrate	Product	Yield (%)	ee (%)
1	**1a**	**2a**	79	82
2	**1b**	**2b**	78	90
3	**1c**	**2c**	71	72
4	**1d**	**2d**	75	80
5	**1e**	**2e**	61	86
6	**1e**[b]	**2e**	68	74
7	**13**[b,c]	**18**	76	2
8	**23**	**24**	ca. 35[d]	0

[a] Use of 1 mol-% of $Ni(acac)_2$ and 20 mol-% of **5** in acetonitrile, −30°C, ca. 18 h. — [b] Use of 10 mol-% of bipyridine **3**. — [c] Use of 2 mol-% of $Ni(acac)_2$ for 46 h. — [d] Slightly impure.

Benzalacetone (**13**) gave the conjugate addition product **18** in 76% chemical yield, but measurement of the optical rotation showed it to be essentially racemic. Increasing the steric requirements at the carbonyl carbon atom resulted in the reduction of the oxo group, and alcohol **19** was obtained from the corresponding ketone **14**. Attempted nickel-catalyzed alkylation of **15** gave only reduced product **20** in low yield, and the expected product of conjugate addition was not obtained. Other aromatic enones and unsaturated esters such as 4-nitrochalcone (**16**), ethyl cinnamate (**17**), or cinnamylidenacetophenone (**21**) gave either unidentified product mixtures or else no conjugate addition occurred. In the absence of a chiral ligand, 2-cyclohexenone (**23**) was alkylated to give *rac*-**24** in 76% yield. Chiral modification of the nickel salt with (*S*)-**5** led to a decrease of the chemical yield, and **24** was formed nonenantioselectively.



	13	14	15	16	17
R	Ph	Ph	*t*-Bu	*p*-NO_2Ph	Ph
R'	Me	*t*-Bu	Ph	Ph	OEt



We briefly examined the nickel-catalyzed conjugate addition of organoaluminum and Grignard reagents to **1a**. Mole et al. had described the nickel-catalyzed methylation of **1a** using trimethylaluminum in hydrocarbon solvents to give **22** in 70% yield[15]. In an attempt to apply our modified catalyst to an enantioselective methylation (Ni^{II}:**5** = 1:20), only racemic **22** was obtained in low yield[16]. Diethylaluminum chloride in toluene in the presence of $Ni(acac)_2$ did not add to **1a**. When ethylmagnesium bromide (in THF) was added to a toluene solution of 1 mol-% of $Ni(acac)_2$ and 20 mol-% of (*S*)-**5**, rapid alkylation of **1a** occurred even at −78°C, and **2a** was isolated in 53% yield[17]. When (*S*)-

5 was deprotonated by *n*-butyllithium before the addition of the nickel salt, slightly less **2a** (43%) was obtained. In both cases, **2a** was found to be racemic.

The presence of nickel(II) salts was essential for an effective catalysis. In the absence of Ni^{II}, stirring of a mixture of **1a**, $ZnEt_2$ and 20 mol-% of (*S*)-**5** at room temperature for 4 days gave **2a** in only 49% yield with an enantiomeric excess of 14%. In general, $Ni(acac)_2$ was used for all of the reactions, and the Ni^{II}-to-ligand ratio was 1:20. The use of nickel acetate instead of $Ni(acac)_2$ gave almost identical results (65% yield, 83% ee for **2a**). The suspension of nickel salt and ligand in acetonitrile was heated to ca. 80°C for 1 h, before an acetonitrile solution of the substrate was added at room temperature followed by diethylzinc at −35°C. The enantiomeric excess of the product was found to be slightly lower without this pretreatment. Copper(II) acetate and copper(I) bromide (as $CuBr \cdot SMe_2$) did not effect ethyl transfer from diethylzinc to **1a** in acetonitrile at −30°C. Activation was observed by the addition of an excess of trimethylsilyl chloride (TMSCl)[18]. In the presence of 10 mol-% of copper(II) acetate[19] or $Ni(acac)_2$, addition of 3 equivalents of TMSCl led to rapid alkylation of **1a** by $ZnEt_2$, and the corresponding trimethylsilyl enol ether **25** was obtained as the major product. Trimethylsilyl chloride itself did not catalyze the ethyl transfer. The combination of 1 mol-% of $Ni(acac)_2$, 20 mol-% of (*S*)-**5** and 300 mol-% of TMSCl afforded a mixture of **1a** and **25**. Desilylation of **25** using tetrabutylammonium fluoride in THF gave **1a** which was found to be optically inactive.

Structure and reactivity of organometallic reagents are severely influenced by the presence of metal salts[20]. Addition of 3 equivalents of lithium bromide to the modified nickel catalyst almost inhibited the alkylation of **1a**, and only a 14% yield of racemic **2a** was isolated. Soai et al. had described an improvement of enantioselectivity upon addition of 2,2′-bipyridine or 1,10-phenanthroline to a chiral nickel catalyst[8a]. No major change in the optical purity of **2a** was observed when 7 mol-% of 2,2′-bipyridine were added to a catalytic system consisting of 7 mol-% of $Ni(acac)_2$ and 17 mol-% of (*S*)-**5**. **2a** was obtained in 74% chemical yield having an enantiomeric excess of 78%.

Asymmetric Amplification

Whereas the enantiomeric excess of bipyridine (*R*,*R*)-**3** was >98%, the optical purities of pyridines **5**−**12** were only in the range of 90 to 96% ee. Further enrichment of the major enantiomers of **5** and **6** was achieved by separation of the diastereomers of the camphanic acid esters followed by hydrolysis under basic conditions. In order to determine the relationship between the enantiomeric excess of the ligand and the ee of the product, scalemic[21] **5** with defined lower optical purity was employed in the nickel-catalyzed conjugate addition of diethylzinc to chalcone **1a**[22]. These ligand samples were prepared by mixing (*S*)-**5** with racemic **5**. The enantiomeric excess of each sample of **5** was then analyzed by HPLC using a chiral stationary phase[11]. A strong *positive nonlinear relationship* between the ee of pyridine **5** and the ee of **2a** was found (Figure 1).

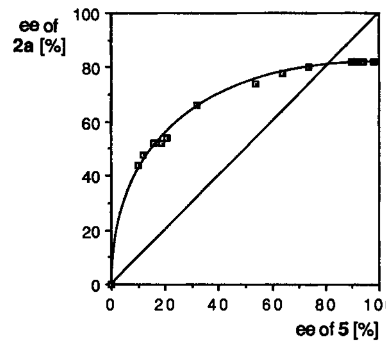


Figure 1. Relationship between the enantiomeric excess of **2a** and the ee of **5**

The use of **5** with 10% enantiomeric excess resulted in the formation of **2a** with an ee of 44%. Thus, the product ee was 4.4 times higher than the optical purity of the chiral ligand. Such strong asymmetric amplification was only observed when using **5** with low optical purity. With increasing ee this phenomenon became less distinct (Table 6). Thus, **5** with an ee of 12% gave **2a** with 48% ee (amplification factor: 4.0) whereas when **5** had 32% ee, **2a** was obtained with only 66% optical purity (amplification factor: 2.1).

Table 6. Effect of optical purity of **5** on the enantiomeric excess of **2a**[a]

Entry	ee of **5** (%)	ee of **2a** (%)	Amplification factor[b]	Yield of **2a** (%)
1	10	44	4.4	61
2	12	48	4.0	74
3	16	52	3.3	73
4[c]	19	52	2.7	66
5[c]	21	54	2.6	67
6	32	66	2.1	77
7	54	74	1.4	81
8	64	78	1.2	77
9	74	80	1.1	77
10[c]	90	82	0.9	70
11	92	82	0.9	77
12[c]	94	82	0.9	68
13	98	82	0.8	75

[a] In acetonitrile (unless indicated otherwise), −30°C, 18 h, 1 mol-% of $Ni(acac)_2$ and 20 mol-% of **5**. − [b] Defined as quotient of ee of **2a** over ee of **5**. − [c] In propionitrile.

The use of **5** with ee's ⩾90% did not lead to further enhancement of the enantioselectivity in the formation of **2a** (Table 6, entries 11−14). In these cases, the enantiomeric excess of 82% for **2a** remained unchanged, regardless if the ligand had 90, 92, 94, or 98% ee.

Next, we examined the influence of the metal-to-ligand ratio on the asymmetric amplification (Table 7). Therefore, the concentration of **5** having a low optical purity was varied, while the amount of $Ni(acac)_2$ was kept constant. A combination of 1 mol-% of $Ni(acac)_2$ and 10, 20, or 30 mol-% of **5** with 10% ee was used as catalyst. Increasing the amount of ligand raised the enantiomeric excess of **2a** from 30 to 44% ee. At this level, the ee remained constant (Table 7, entries 1−3).

Table 7. Effect of catalyst concentration on the enantiomeric excess of **2a**[a]

Entry	$Ni(acac)_2$ (mol-%)	**5** (mol-%), ee (%)	**2a** Yield (%)	ee (%)
1	1	10, 10	85	30
2	1	20, 10	61	44
3	1	30, 10	61	44
4	1	10, 16	76	36
5	2	20, 16	69	52
6	3	30, 16	77	62
7	4	40, 16	69	64

[a] In acetonitrile, $-30\,^{\circ}C$, ca. 18 h.

Figure 2 shows the dependence of the asymmetric amplification on the overall catalyst concentration with a *constant* $Ni(acac)_2$-to-ligand ratio of 1:10. As before, the enantiomeric excess of **2a** was raised by increasing the amount of catalyst (Table 7, entries 4–7). The use of 1 mol-% of nickel salt and 10 mol-% of **5** (with 16% ee) resulted in the formation of **2a** with 36% ee. If 3 mol-% of $Ni(acac)_2$ and 30 mol-% of **5** (with 16% ee) were used, **2a** was obtained with 62% ee. A further increase of catalyst concentration resulted in only a slight additional enhancement of asymmetric induction.

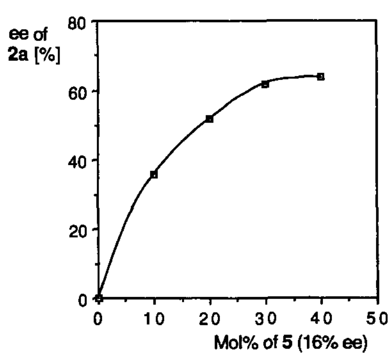


Figure 2. Influence of the catalyst concentration on the enantiomeric excess of **2a** [Ni^{II}: **5** = 1:10; ee(**5**) = 16%]

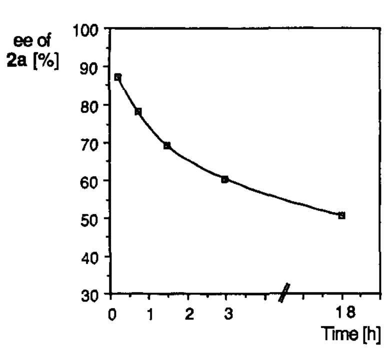


Figure 3. Dependence of the enantiomeric excess of **2a** on reaction time (**5** with an ee of 19%)

The asymmetric amplification was strongly dependent on reaction time and conversion of **1a** (Table 4, entries 9–13 and Figure 3). The use of **5** with an enantiomeric excess of 19% gave **2a** with 87% ee after 15 min. The optical purity of **2a** decreased to 78% after 45 min (20% conversion of **1a**), and it was even further reduced to 51% after 18 h (complete conversion of **1a**).

Even after complete conversion of **1a**, the catalytic system remained active. Thus, when additional zinc reagent and chalcone **1a** were added after 18 h, further formation of **2a** was observed. Before this second addition of reactants, the enantiomeric excess of **2a** was 49%. A sample taken 45 min after the second addition gave a product with a substantially lower ee. When the second cycle was complete (36 h of reaction time), the ee of **2a** had dropped to 36%, indicating that now mainly a racemic product had been formed.

Next, the influence of the substrate concentration on the asymmetric amplification was studied. In order to minimize the change of chalcone concentration, additional **1a** was successively added to the reaction mixture during the catalysis. The use of 20 mol-% of pyridine **5** with 21% ee gave **2a** with an enantiomeric excess of 67% after 1.5 h. This result demonstrated the minor influence of the change of chalcone concentration on the optical purity of the product. In an attempt to keep the amount of zinc reagent constant, an excess of diethylzinc (1 M in hexane) was continuously added. Under these conditions, a slightly lower ee than expected was observed (60% ee for **2a** after 1.5 h using **5** with an optical purity of 18%). In this case, the decrease of ee is believed to be predominantly due to the change of the solvent system and the increased amount of hexane in the reaction mixture. Thus again, the substrate concentration had only a minor effect on the asymmetric induction in the formation of **2a**.

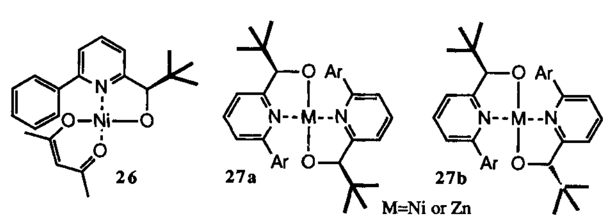
Discussion

Control of enantioselectivity in conjugate addition reactions to α,β-unsaturated carbonyl compounds is of particular value for the synthesis of optically active compounds. Despite considerable efforts and detailed mechanistic investigations[23–25a], high asymmetric induction is still mainly based on empirical changes of ligand structures and reaction variables. In particular, studies on *catalytic* enantioselective transformations suffer from the fact that mechanistic details are still unclear.

In the beginning, our efforts focused on the use of C_2-symmetric bipyridine (*S,S*)-**3** in the nickel-catalyzed conjugate addition of organozinc reagents to chalcone **1a**. Studies of the reaction variables quickly showed that 1 mol-% of a nickel salt such as $Ni(acac)_2$ or nickel acetate was sufficient to catalyze the ethyl transfer from diethylzinc. In the presence of the chiral ligand, the alkylated product was obtained with an enantiomeric excess of up to 72%. In order to obtain a product with high optical purity, an appropriate amount of ligand was required, and the optimized nickel-to-ligand ratio of 1:20 was used for further studies. The dependence of the asymmetric induction seems to indicate an equilibrium between ligand-bound and uncomplexed catalytically active nickel species. The former would produce enantiomerically enriched product, whereas the latter would lead to the formation of racemic β-alkylated ketone in a competitive pathway. The use of aceto- or propionitrile was found to be essential for catalyst activity and high asymmetric induction. Increasing amounts of hydrocarbons such as hexane or toluene reduced the enantiomeric excess of the product. This result is in contrast to the solvent effect observed in the asymmetric alkylation of aldehydes with dialkylzinc catalyzed by bipyridine (*S,S*)-**3**[9]. In this catalysis, the presence of coordinating solvents is deleterious. The strong solvent dependence in the conjugate addition reaction seems to indicate the necessity to further stabilize catalytically active (and chirality transferring) metal species by coordinated solvent molecules[26].

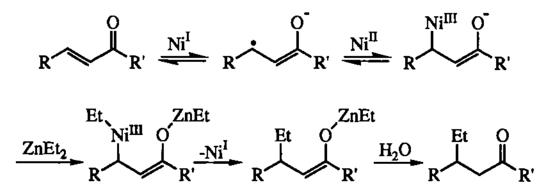
A major part of our studies dealt with the use of optically active pyridines as chiral ligands for the nickel catalysis. C_2 symmetry, which has often been advantageous for enantioselective catalysis[27], was not essential for high asymmetric induction. Screening experiments showed that aryl-substituted pyridines effected the transfer of chirality in the conjugate addition reaction equally well. Comparison of the effects of ligand substructures revealed that at least three structural features are crucial for high enantioselectivity in the formation of the alkylated product: (i) the presence of the *tert*-butyl group, (ii) the presence of the free hydroxy group, and (iii) chiral substitution in the 2-position of the pyridine ring. These observations are in accord with the ones made in the enantioselective alkylation of aldehydes[9b,10]. In the latter case, covalently bound organozinc complexes are responsible for the asymmetric induction. One of these complexes was isolated, and its crystal structure was determined by X-ray diffraction analysis[9b]. In analogy, metal complexes of type **26** or **27** are believed to be important intermediates. However, attempts to synthesize these chiral complexes have not yet been successful[28].

Chalcone **1a** was used as substrate for most of the studies described here in order to make comparisons with the literature results and due to the ease of ee determination of the corresponding addition product **2a** by HPLC analysis using a chiral stationary phase. After optimization of the reaction conditions, **2a** was obtained with a maximum ee of 89% by using chiral pyridine (*R*)-**5**. Substituted chalcones were alkylated equally well, and the enantiomeric excess was in the range of 72 to 90%. However, changing the substitution pattern of the enone had a major effect on reactivity, optical yield, and formation of undesired byproducts. Whereas ethyl cinnamate was not alkylated at all, benzalacetone gave only racemic product. Enones carrying *tert*-butyl groups led to the formation of reduction products. Either the double bond or the oxo group was reduced giving rise to the corresponding saturated ketone or allylic alcohol, respectively.



Although the mechanism of the enantioselective nickel-catalyzed conjugate addition is currently not known, an electron transfer involving changes in the oxidation state from Ni^{II} to Ni^{I} and Ni^{0} could be proposed. In this scenario, the organozinc reagent is used to reduce $Ni(acac)_2$ to a catalytically active nickel(I) species[29]. Electron transfer from Ni^{I} to the substrate generates a ketyl radical which reacts with the resulting nickel(II) species. Transmetallation followed by reductive elimination gives the zinc enolate and regenerates the catalytically active nickel(I) species (Scheme 1).

Scheme 1



According to this mechanism, the asymmetric induction could be dictated by an enantioselective formation of the nickel(III) intermediate followed by a stereoselective reductive elimination. A related reaction, the nickel-catalyzed conjugate addition of alkenylzirconium reagents to enones, was investigated by Schwartz et al. using chemical and electrochemical methods[25a]. In this process, diisobutylaluminum hydride (Dibal) was used to reduce $Ni(acac)_2$ to give "a family of nickel species" of which Ni^{I} was most likely to be responsible for an efficient catalysis by electron transfer. In this respect, the mechanism of the nickel-catalyzed conjugate addition of organometallic reagents to enones is similar to the one proposed by House for the reaction of organocuprates[24]. Inspection of the reduction potentials of the carbonyl compounds used in the nickel catalysis and their correlation with the ability to add the organozinc reagent did not reveal an obvious relationship between the E_{red} values and the tendency to form reduced or alkylated product. Whereas **1a** and **13** with reduction potentials of -1.41 V and -1.63 V, respectively[24,30], were readily alkylated, compounds **14** and **15** having similar E_{red} values (-1.70 V and -1.69 V, respectively) gave only reduction products. Ester **17** ($E_{red} = -1.81$ V) did not react at all. The lack of correlation between the E_{red} values and the ability to serve as Michael acceptor for the zinc reagent might be explained by the fact that steric interactions between the enone and the nucleophile[30], as well as changes of the reduction potential by complexation of a reduced nickel species with the double bond of the enone[31] are not considered[32].

The proposed electron-transfer mechanism in the nickel-catalyzed conjugate addition might also explain the dependence of the enantiomeric excess of the product on reaction time. The change of oxidation state from Ni^{II} to Ni^{I}, and finally to Ni^{0}, generates a number of reactive nickel species of which some are highly enantioselective. After a certain time, most of these selective catalysts are transformed into species which are still catalytically active, but which produce racemic material. As a result, the overall optical purity of the product will decrease with time. The change of concentration of starting materials during the reaction has only a minor influence on the enantiomeric excess. Keeping the concentrations of reactants at a constant level did not substantially change the ee of the product[33]. Even after complete conversion of starting materials, the catalyst remains active. The conjugate addition of diethylzinc to newly added chalcone is still catalyzed, but now mainly racemic product is formed.

Several attempts were made to use other metal salts or nucleophilic reagents. However, the combination of nickel(II) and diorganozinc was the only one which led to a highly enantioselectively catalyzed conjugate addition. Although trimethylaluminum and ethylmagnesium bromide did add to the enone, only racemic product was obtained. Copper salts did not catalyze the conjugate addition of diethylzinc to chalcone unless a large excess of trimethylsilyl chloride was added[18]. This acceleration by TMSCl was also observed in the nickel-catalysis[34] in which the expected trimethylsilyl enol ether **25** was isolated as the major product. However, desilylation of **25** afforded only racemic **1a**. The presence of lithium bromide substantially retarded the catalysis, and only small amounts of racemic product were formed.

Finally, in a major part of our work, we investigated the relationship between the enantiomeric excess of the ligand and the optical yield in the conjugate addition. A strong asymmetric amplification was observed when ligands of low optical purity were used. Thus, product **2a** was obtained with an ee of 44% when ligand **5** had only 10% ee. With increasing optical purity of the ligand, this phenomenon became less distinct. With **5** having ee's $\geqslant 90\%$ no further enhancement of the asymmetric induction in the formation of the product was observed. In these cases, the maximum enantiomeric excess of **2a** was 82%. The dependence of the overall catalyst concentration and the metal-to-ligand ratio on the asymmetric amplification was studied. Thus, in order to obtain the highest asymmetric induction in the formation of **2a** using ligands of low optical purity, it was essential to use at least 20 mol-% of ligand. Only a slight additional improvement of enantioselection was observed when the ligand concentration was raised even further.

Nonlinear relationships between the enantiomeric excess of chiral auxiliaries and products were described for asymmetric oxidations and aldol reactions by Kagan and Agami et al.[35]. Intensive investigations were carried out by Oguni[36], Noyori[37], and Bolm[9b] on the asymmetric amplification in the enantioselective alkylation of aldehydes catalyzed by β-amino alcohols and pyridine derivatives. Studies directed towards the use of chiral titanium compounds revealed positive nonlinear effects in ene reactions[38] and trimethylsilylcyanations[39,40]. In general, these phenomena have been interpreted in terms of differences in the chemical behavior of diastereomeric *dinuclear* complexes containing *two identical* metals.

In contrast, efficient catalysis of the conjugate addition described here requires positive interactions between nickel and organozinc reagents. Two alternatives should be considered if the asymmetric amplification in the present system is also to be explained by the difference in chemical properties of diastereomeric complexes: (i) The reaction of diethylzinc with scalemic[21] pyridine **5** could give two diastereomeric dinuclear zinc complexes, of which the less stable one with homochiral ligands would preferentially react further to give a chiral catalytically active nickel species. A dinuclear zinc chelate complex of this type, in which the optically active pyridines are covalently bound to zinc atoms has been described and characterized by X-ray diffraction analysis[9b]. However, this explanation is based on the proposed mechanism for the amino alcohol catalyzed enantioselective alkylation of aldehydes, in which hydrocarbon solvents are essential for efficient asymmetric induction. Coordinating solvents such as aceto- or propionitrile which are required for the nickel catalysis are deleterious for the alkylation of aldehydes. Presumably due to the reduced formation of dinuclear zinc complexes in these solvents, enantioselectivity is significantly lowered. (ii) Alternatively, enantiomerically enriched pyridines could form diastereomeric *mononuclear* metal complexes of type **27a** and **27b** with either zinc or nickel atoms[28]. Predominant reaction of diethylzinc with the less stable optically active nickel complex **27a** would lead to the formation of a homochiral catalytically active species. The minor enantiomer of the ligand is trapped in the more stable *meso* complex **27b**, and it thereby becomes less accessible to catalyst formation[41–43].

Although in recent years major progress in the area of enantioselective catalysis has been achieved, rational catalyst design is still far from being attained. The presented study provides further insight into the important factors which govern activity and stereoselectivity of asymmetric metal-catalyzed conjugate addition reactions.

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Experimental

^{1}H and ^{13}C NMR: Varian Gemini 300, Varian VXR 400; multiplicities determined with the APT pulse sequence; solvent $CDCl_3$, unless noted otherwise; chemical shifts in values relative to TMS ($\delta = 0$) for protons or $CDCl_3$ ($\delta = 77$) for carbon atoms. – Melting points: Kofler melting point apparatus (corrected values) and Büchi 530 (uncorrected values). – IR: Perkin-Elmer 781. – MS: VG 70–250. Optical rotations: Perkin-Elmer 141 (RT: room temp.). – Elemental analyses: Leco CHN-900. – HPLC: Kontron Instruments (pump: Kontron 420, detector: Kontron 432); column: Chiralcel OD (Daicel), 25 cm × 0.46 cm i.d. – All reactions were carried out in flame-dried glassware under argon by using anhydrous solvents; products were isolated by CC or flash chromatography on SiO_2 (Chemische Fabrik Uetikon, size: C 560, 35–70 micron) or Al_2O_3 (Fluka, type 507C neutral, activity I, 100–125 mesh) and detected by UV or revealed by coloration with phosphomolybdic acid (PMA). – The following compounds were commercially available and were used without further purification: 1,3-diphenylpropenone (**1a**; Aldrich), 3-(4-chlorophenyl)-1-phenyl-2-propen-1-one (**1b**; Lancaster), 1-(4-chlorophenyl)-3-phenyl-2-propen-1-one (**1c**;

Lancaster), 3-(4-methoxyphenyl)-1-phenyl-2-propen-1-one (**1d**; Lancaster), 1-(4-methoxyphenyl)-3-phenyl-2-propen-1-one (**1e**; Aldrich), 1-phenyl-1-buten-3-one (**13**; Fluka), 3-(4-nitrophenyl)-1-phenyl-2-propen-1-one (**16**; Aldrich), cinnamylideneacetophenone (**21**; Lancaster), 2-cyclohexenone (**23**; Fluka), nickel(II) acetylacetonate (anhydr.; Merck-Schuchardt), diethylzinc (1 M in hexane; Fluka), (*R*,*R*)-2,3-butanediol (Fluka).

Preparation of Compounds: Optically active bipyridine **3**[11], pyridines **5**–**12**[11], and 4,4-dimethyl-1-phenyl-1-penten-3-one (**14**)[44] were prepared according to published procedures.

(R)-1,3-Diphenyl-1-pentanone [(*R*)-**2a**][14]. – *Representative Procedure:* In a flame-dried flask 2.6 mg (0.01 mmol) of $Ni(acac)_2$ and 48 mg (0.2 mmol) of (*S*,*S*)-6,6'-bis(1-hydroxy-2,2-dimethylpropyl)-2,2'-bipyridine [(*S*,*S*)-**3**] in 2 ml of dry acetonitrile were stirred at ca. 80°C (oil bath temp.) under argon for 1 h. The suspension was cooled to room temp., and a solution of 208 mg (1 mmol) of 1,3-diphenylpropenone (**1a**) in 2 ml of dry acetonitrile was added. The mixture was cooled to −35°C, and 1.5 ml of a 1 M solution of diethylzinc in hexane (1.50 mmol) was added dropwise. No color change was observed. Stirring was continued at −30°C for 18 h (color changed to light brown). The reaction was quenched with 10 ml of 1 M hydrochloric acid, and the mixture was extracted three times with 20 ml of dichloromethane. The combined organic layers were washed with 20 ml of brine and dried with sodium sulfate. Evaporation of the solvent gave a crude product (270 mg) that was analyzed by ^{1}H-NMR spectroscopy to determine the conversion of **1a**. CC [SiO_2, petroleum ether/ethyl acetate (100:1)] yielded 189 mg (79%) of (*R*)-**2a** as a colorless oil; TLC: R_f = 0.55 [SiO_2, petroleum ether/ethyl acetate (5:1)] compared to R_f = 0.46 for **1a**. – ^{1}H NMR: δ = 0.80 (t, *J* = 7.4 Hz, 3H, CH_3), 1.56–1.69 (m, 1H, CH_2CH_3), 1.75–1.83 (m, 1H, CH_2CH_3), 3.21–3.31 (m, 3H, $CHCH_2$), 7.14–7.31 (m, 5H, aromatic H), 7.40–7.45 (m, 2H, aromatic H), 7.50–7.56 (m, 1H, aromatic H), 7.80–8.00 (m, 2H, aromatic H). – $[\alpha]_D^{RT}$ = −7.6 (*c* = 3.96, EtOH) {ref.[14] $[\alpha]_D^{23}$ = +10.5 (*c* = 2.5, EtOH) for (*S*)-**2a**}. – Ratio of enantiomers (*R*)-**2a**:(*S*)-**2a** = 91:9 (determined by HPLC); HPLC: Daicel (Chiralcel OD), flow 1 ml/min, UV detector (254 nm), 0.2% 2-propanol in hexane; retention times: (*S*)-**2a**: 17.1 min (*k'* = 4.7); (*R*)-**2a** 20.8 min (*k'* = 5.9). *rac*-**2a** gave two base-line-separated signals for (*S*)-**2a** and (*R*)-**2a** with equal peak areas.

In the absence of the ligand at 0°C the formation of ca. 5% of 1,3-diphenylpropane (**4**) was revealed by ^{1}H- and ^{13}C-NMR spectroscopy[45] and MS. **2a** and **4** were separated by CC; TLC: R_f = 0.52 [SiO_2, petroleum ether/ethyl acetate (5:1)].

(S)-1,3-Diphenyl-1-pentanone [(*S*)-**2a**]: According to the representative procedure using 104 mg (0.5 mmol) of 1,3-diphenylpropenone (**1a**), 1.3 mg (0.005 mmol) of $Ni(acac)_2$, 0.75 ml (1 M in hexane, 0.75 mmol) of diethylzinc, and 24 mg (0.1 mmol) of (*R*)-2,2-dimethyl-1-(6-phenylpyridin-2-yl)propanol [(*R*)-**5**] [(*R*):(*S*) = 96:4] in 2 ml of propionitrile. Yield 83 mg (70%) of (*R*)-**2a** as a colorless oil. – $[\alpha_D^{RT}$ = +9.0 (*c* = 2.2, EtOH) {ref.[14] $[\alpha]_D^{23}$ = +10.5 (*c* = 2.5, EtOH) for (*S*)-**2a**}. – Ratio of enantiomers (*R*)-**2a**:(*S*)-**2a** = 9:91 (determined by HPLC).

3-(4-Chlorophenyl)-1-phenyl-1-pentanone (**2b**): According to the representative procedure using 243 mg (1 mmol) of 3-(4-chlorophenyl)-1-phenylpropen-1-one (**1b**), 2.6 mg (0.01 mmol) of $Ni(acac)_2$, 1.5 ml (1 M in hexane, 1.5 mmol) of diethylzinc, and 48 mg (0.2 mmol) of (*S*)-**5** [(*S*):(*R*) = 96:4] in 7 ml of acetonitrile; 280 mg of crude product; TLC: R_f = 0.43 [SiO_2, petroleum ether/ethyl acetate (5:1)]; CC: 10 g of SiO_2, petroleum ether/ethyl acetate (100:1). Yield 213 mg (78%) of **2b** as a colorless oil. – IR (film): $\tilde{\nu}$ = 2970 cm^{-1}, 1690, 1492, 1450, 1015, 752, 690. – ^{1}H NMR: δ = 0.80 (t, *J* = 7.3 Hz, 1H, CH_3), 1.54–1.71 (m, 1H, CH_2CH_3), 1.74–1.82 (m, 1H, CH_2CH_3), 3.19–3.24 (m, 3H, CH_2CH), 7.13–7.18 (m, 2H, aromatic H), 7.21–7.27 (m, 2H, aromatic H), 7.38–7.46 (m, 2H, aromatic H), 7.50–7.57 (m, 1H, aromatic H), 7.86–7.91 (m, 2H, aromatic H). – ^{13}C NMR: δ = 11.7 (CH_3), 29.0 (CH_2), 42.2 (CH), 45.2 (CH_2), 128.2 (CH), 128.7 (CH), 128.7 (CH), 129.2 (CH), 132.0 (C), 133.2 (CH), 137.3 (C), 143.4 (C), 199.2 (C). – MS (EI, 70 eV): *m/z* (%) = 272 (4) [M^+], 245 (11), 243 (34), 154 (20), 152 (63), 153 (12), 125 (21), 120 (18), 105 (100), 77 (56); (CI; NH_3): *m/z* (%) = 273 (27) [M^+ + 1]. – $[\alpha]_{436}^{RT}$ = −14.5 (*c* = 3.14, EtOH). – Ratio of enantiomers A:B = 5.4:94.6 (determined by HPLC).

$C_{17}H_{17}ClO$ (272.8) Calcd. C 74.86 H 6.28
Found C 74.82 H 6.45

HPLC: Daicel (Chiralcel OD), flow 1 ml/min, UV detector (254 nm), 0.2% 2-propanol in hexane (aged solvent mixture); retention times: enantiomer A: 32.5 min (*k'* = 9.8); enantiomer B: 33.7 min (*k'* = 10.3). The signals for the enantiomers of *rac*-**2b** had equal peak areas, but were not base-line-separated. For unknown reasons, aged solvent mixtures gave longer retention times and a better peak separation. The absolute configuration of **2b** was not determined.

1-(4-Chlorophenyl)-3-phenyl-1-pentanone (**2c**): According to the representative procedure using 243 mg (1 mmol) of 1-(4-chlorophenyl)-3-phenylpropen-1-one (**1c**), 2.6 mg (0.01 mmol) of $Ni(acac)_2$, 1.5 ml (1 M in hexane, 1.5 mmol) of diethylzinc, and 48 mg (0.2 mmol) of (*S*)-**5** [(*S*):(*R*) = 96:4] in 7 ml of acetonitrile; 280 mg of crude product; TLC: R_f = 0.56 [SiO_2, petroleum ether/ethyl acetate (5:1)]; CC: 20 g of SiO_2, petroleum ether/ethyl acetate (100:1). Yield 194 mg (71%) of **2c** as a colorless oil. – IR (film): $\tilde{\nu}$ = 2960 cm^{-1}, 1685, 1589, 1089, 1009, 696. – ^{1}H NMR: δ = 0.81 (t, *J* = 7.3 Hz, 3H, CH_3), 1.60–1.83 (m, 2H, CH_2CH_3), 3.16–3.28 (m, 3H, CH_2CH), 7.16–7.32 (m, 5H, aromatic H), 7.38–7.42 (m, 2H, aromatic H), 7.82–7.86 (m, 2H, aromatic H). – ^{13}C NMR: δ = 11.8 (CH_3), 29.0 (CH_2), 42.9 (CH), 45.4 (CH_2), 126.5 (CH), 127.8 (CH), 128.6 (CH), 129.0 (CH), 129.6 (CH), 135.7 (C), 139.5 (C), 144.6 (C), 198.4 (C). – MS (EI, 70 eV): *m/z* (%) = 272 (3) [M^+], 245 (15), 243 (46), 141 (22), 139 (69), 118 (100), 111 (26), 91 (39); (CI, NH_3): *m/z* (%) = 273 (30) [M^+ + 1]. – $[\alpha]_{436}^{RT}$ = −5.7 (*c* = 4.55, EtOH). – Ratio of enantiomers A:B = 14.3:85.7 (determined by HPLC).

$C_{17}H_{17}ClO$ (272.8) Calcd. C 74.86 H 6.28
Found C 74.87 H 6.45

HPLC: Daicel (Chiralcel OD), flow 1 ml/min, UV detector (254 nm), 0.2% 2-propanol in hexane; retention times: enantiomer A: 24.3 min (*k'* = 7.1); enantiomer B: 28.2 min (*k'* = 8.4). *rac*-**2c** gave two base-line-separated signals with equal peak areas. The absolute configuration was not determined.

3-(4-Methoxyphenyl)-1-phenyl-1-pentanone (**2d**): According to the representative procedure using 238 mg (1 mmol) of 3-(4-methoxyphenyl)-1-phenylpropen-1-one (**1d**), 2.6 mg (0.01 mmol) of $Ni(acac)_2$, 1.5 ml (1 M in hexane, 1.5 mmol) of diethylzinc, and 48 mg (0.2 mmol) of (*S*)-**5** [(*S*):(*R*) = 96:4] in 4 ml of acetonitrile; 280 mg of a crude yellow oil; TLC: R_f = 0.38 [SiO_2, petroleum ether/ethyl acetate (5:1)]; CC: 9 g of SiO_2, petroleum ether/ethyl acetate (100:1). Yield 200 mg (75%) of **2d** as a white solid. – IR (film): $\tilde{\nu}$ = 2960 cm^{-1}, 1685, 1610, 1511, 1448, 1247, 1175, 1033, 688. – ^{1}H NMR: δ = 0.80 (t, *J* = 7.3 Hz, 1H, CH_3), 1.55–1.65 (m, 1H, CH_2CH_3), 1.73–1.81 (m, 1H, CH_2CH_3), 3.16–3.25 (m, 3H, CH_2CH), 3.78 (s, 3H, CH_3), 6.84 (d, *J* = 8.4 Hz, 2H, aromatic H), 7.15 (d, *J* = 8.5 Hz, 2H, aromatic H), 7.41–7.46 (m, 2H, aromatic H), 7.52–7.56 (m, 1H, aromatic H), 7.91 (d, *J* = 7.2 Hz, 2H, aromatic H). – ^{13}C NMR: δ = 11.8 (CH_3), 29.1 (CH_2), 42.1 (CH), 45.7 (CH_2), 55.0 (CH_3), 113.8 (CH), 128.2 (CH), 128.6 (CH), 133.0 (CH), 136.8 (C), 137.4 (C), 158.2 (C), 199.7 (C). – MS (EI, 70 eV): *m/z* (%) = 268 (22) [M^+], 149 (67), 148 (21), 121 (22), 105 (100), 77 (40). – $[\alpha]_D^{RT}$ = –15.3 (*c* = 2.99, EtOH). – Ratio of enantiomers A:B = 89.6:10.4 (determined by HPLC).

$C_{18}H_{20}O_2$ (268.4) Calcd. C 80.56 H 7.51
Found C 80.41 H 7.66

HPLC: Daicel (Chiralcel OD), flow 1 ml/min, UV detector (254 nm), 0.5% 2-propanol in hexane; retention times: enantiomer A: 13.3 min (k' = 3.4); enantiomer B: 14.9 min (k'= 4.0). *rac*-**2d** gave two base-line-separated signals with equal peak areas. The absolute configuration was not determined.

(R)-1-(4-Methoxyphenyl)-3-phenyl-1-pentanone [(*R*)-**2e**][8a]. a) *Use of (S)-2,2-Dimethyl-1-(6-phenylenpyridin-2-yl)propanol* [(*S*)-**5**]: According to the representative procedure using 238 mg (1 mmol) of 1-(4-methoxyphenyl)-3-phenylpropen-1-one (**1e**), 2.6 mg (0.01 mmol) of Ni(acac)$_2$, 1.5 ml (1 M in hexane, 1.5 mmol) of diethylzinc, 48 mg (0.2 mmol) of (*S*)-**5** [(*S*):(*R*) = 96:4] in 6 ml of acetonitrile; 300 mg of crude product; TLC: R_f = 0.32 [SiO$_2$, petroleum ether/ethyl acetate (5:1)]; CC: 9 g of SiO$_2$, petroleum ether/ethyl acetate (70:1). Yield 164 mg (61%) of **2e** as a white solid. – ^{1}H NMR: δ = 0.80 (t, *J* = 7.4 Hz, 1H, CH$_3$), 1.58–1.68 (m, 1H, C*H*$_2$-CH$_3$), 1.74–1.79 (m, 1H, C*H*$_2$CH$_3$), 3.18–3.25 (m, 3H, CHCH$_2$), 3.85 (s, 3H, OCH$_3$), 6.89–6.92 (m, 2H, aromatic H), 7.18–7.31 (m, 5H, aromatic H), 7.89 (d, *J* = 8.9 Hz, 2H, aromatic H). – $[\alpha]_{365}^{RT}$ = –90.7 (*c* = 2.19, EtOH). – Ratio of enantiomers (*S*)-**2e**:(*R*)-**2e** = 7.3:92.7 (determined by HPLC, assignment of the absolute configuration based on elution order[8a]; HPLC: Daicel (Chiralcel OD), flow 1 ml/min, UV detector (254 nm), 1.5% 2-propanol in hexane; retention times: (*S*)-**2e**: 12.7 min (k' = 3.2); (*R*)-**2e**: 14.4 min (k' = 3.8). *rac*-**2e** gave two base-line-separated signals with equal peak areas.

b) *Use of (S,S)-6,6'-Bis-(1-hydroxy-2,2-dimethylpropyl)-2,2'-bipyridine* [(*S,S*)-**3**]: According to the representative procedure using 238 mg (1 mmol) of 1-(4-methoxyphenyl)-3-phenylpropen-1-one (**1e**), 2.6 mg (0.01 mmol) of Ni(acac)$_2$, 1.5 ml (1 M in hexane, 1.5 mmol) of diethylzinc, and 33 mg (0.1 mmol) of (*S,S*)-**3** in 6 ml of acetonitrile; 256 mg of crude product; CC: 8 g of SiO$_2$, petroleum ether/ethyl acetate (70:1). Yield 182 mg (68%) of **2e**. – $[\alpha]_{365}^{RT}$ = –71.5 (*c* = 3.03, EtOH). – Ratio of enantiomers (*S*)-**2e**:(*R*)-**2e** = 12.8:87.2 (determined by HPLC, assignment of the absolute configuration based on elution order [8a]).

4-Phenyl-2-hexanone (**18**)[14]: According to the representative procedure using 146 mg (1 mmol) of benzalacetone (**13**), 5.1 mg (0.02 mmol) of Ni(acac)$_2$, 1.5 ml (1 M in hexane, 1.5 mmol) of diethylzinc, and 33 mg (0.1 mmol) of (*S,S*)-**3** in 4 ml of acetonitrile for 46 h; 190 mg of crude product; CC: 6 g of SiO$_2$, petroleum ether/ethyl acetate (25:1). Yield 134 mg (76%) of **18**. – $[\alpha]_D^{RT}$ = –0.5 (*c* = 4.35, EtOH) {ref.[14] $[\alpha]_D^{22}$ = +30 (*c* = 2.3, EtOH) for (*S*)-**18**}. – ^{1}H NMR: δ = 0.78 (t, *J* = 7.3 Hz, 3H, CH$_3$), 1.51–1.73 (m, 2H, CH$_2$), 2.00 (s, 3H, CH$_3$), 2.71 (d, *J* = 7.1 Hz, 2H), 2.97–3.07 (m, 1H, CH), 7.14–7.31 (m, 5H, aromatic H). – ^{13}C NMR: δ = 11.9 (CH$_3$), 29.3 (CH$_2$), 30.5 (CH), 42.9 (CH$_3$), 50.5 (CH$_2$), 126.3 (CH), 127.5 (CH), 128.4 (CH), 144.2 (C), 207.9 (C).

rac-4,4-Dimethyl-1-phenyl-1-penten-3-ol (**19**)[46]: According to the representative procedure using 376 mg (2 mmol) of 4,4-dimethyl-1-phenyl-1-penten-3-one (**14**), 5.1 mg (0.02 mmol) of Ni(acac)$_2$, and 3 ml (1 M in hexane, 3 mmol) of diethylzinc in 8 ml of acetonitrile at 0°C for 8 h, followed by 14 h at room temp.; 380 mg of a crude yellowish oil; TLC: **19**: R_f = 0.33; **14**: R_f = 0.49 [SiO$_2$, petroleum ether/ethyl acetate (5:1)]; CC: 10 g of SiO$_2$, petroleum ether/ethyl acetate (100:1, then 10:1). Yield 151 mg (66%) of **19** as a colorless oil. – ^{1}H NMR: δ = 0.97 (s, 9H, CH$_3$), 1.59 (s, 1H, OH), 3.93 (d, *J* = 7.2 Hz, 1H), 6.30 (dd, *J* = 15.9, 7.2 Hz, 1H, CH), 6.58 (d, *J* = 15.9 Hz, 1H, CH), 7.26–7.41 (m, 5H, aromatic H). – ^{13}C NMR: δ = 25.7 (CH$_3$), 35.2 (C), 80.8 (CH), 126.4 (CH), 127.4 (CH), 128.5 (CH), 129.5 (CH), 131.7 (CH), 136.8 (C). – MS (EI, 70 eV): *m/z* (%) = 190 (4) [M^+], 157 (13), 133 (100), 115 (17), 57 (19).

4,4-Dimethyl-1-phenyl-1-pentanone (**20**)[47]. – a) *Without Ligand:* According to the representative procedure using 93 mg (0.5 mmol) of 4,4-dimethyl-1-phenyl-2-penten-1-one (**15**), 1.3 mg (0.005 mmol) of Ni(acac)$_2$, and 0.75 ml (1 M in hexane, 0.75 mmol) of diethylzinc in 2 ml of acetonitrile at 0°C for 3 h, followed by 22 h at room temp.; 110 mg of crude product; TLC: **20**: R_f = 0.68; **15**: R_f = 0.53 [SiO$_2$, petroleum ether/ethyl acetate, (5:1)]; CC: 5 g of SiO$_2$, petroleum ether/ethyl acetate (100:1). Yield 37 mg of **20** (chemical purity ca. 90%, rest unknown) as a colorless oil. – ^{1}H NMR: δ = 0.97 (s, 9H, CH$_3$), 1.56–1.68 (m, 2H, CH$_2$), 2.92–2.97 (m, 2H, CH$_2$), 7.45–7.57 (m, 3H, aromatic H), 7.96–7.99 (m, 2H, aromatic H). – ^{13}C NMR: δ = 29.0 (CH$_3$), 34.1 (CH$_2$), 38.0 (CH$_2$), 30.0 (C), 128.2 (CH), 128.7 (CH), 133.0 (CH), 137.3 (C), 201.5 (C). – MS (EI, 70 eV): *m/z* (%) = 190 (5) [M^+], 133 (18), 105 (100), 77 (33); (CI, NH$_3$): *m/z* (%) = 191 (100) [M^+ + 1].

b) *With Ligand:* According to the representative procedure using 94 mg (0.5 mmol) of 4,4-dimethyl-1-phenyl-2-penten-1-one (**15**), 13 mg (0.05 mmol) of Ni(acac)$_2$, 0.75 ml (1 M in hexane, 0.75 mmol) of diethylzinc, and 24 mg (0.1 mmol) of (*S*)-**5** [(*S*):(*R*) = 94:4] in 2 ml of acetonitrile at room temp. for 40 h; 100 mg of crude product. – ^{1}H NMR: Mixture of **15** and **20**.

1,3-Diphenyl-1-butanone (**22**)[48]: According to the representative procedure using 208 mg (1 mmol) of 1,3-diphenylpropenone (**1a**), 2.6 mg (0.01 mmol) of Ni(acac)$_2$, 0.75 ml (2 M in hexane, 1.5 mmol) of trimethylaluminum, and 48 mg (0.2 mmol) of (*S*)-**5** [(*S*):(*R*) = 96:4] in 4 ml of acetonitrile; 240 mg of a crude yellow oil; TLC: R_f = 0.44 [SiO$_2$, petroleum ether/ethyl acetate (5:1)]; CC: 8 g of SiO$_2$, petroleum ether/ethyl acetate (100:1). Yield 28 mg (13%) of **22** as a white solid. – ^{1}H NMR: δ = 1.33 (d, *J* = 7.0 Hz, 3H, CH$_3$), 3.17 (dd, *J* = 16.5, 8.3 Hz, 1H, C*H*$_2$CH), 3.29 (dd, *J* = 16.5, 5.7 Hz, 1H, C*H*$_2$CH), 3.47–3.54 (m, 1H, C*H*CH$_3$), 7.15–7.24 (m, 1H, aromatic H), 7.25–7.32 (m, 4H, aromatic H), 7.40–7.45 (m, 2H, aromatic H), 7.50–7.55 (m, 1H, aromatic H), 7.90–7.93 (m, 2H, aromatic H). – ^{13}C NMR: δ = 21.8, 35.4, 47.0, 126.2, 126.8, 128.0, 128.5, 137.2, 146.5, 199.0. – $[\alpha]_{546}^{RT}$ = +1.2 (*c* = 1.37, CCl$_4$) {ref.[48] $[\alpha]_{546}^{25}$ = +18.9 (*c* = 2.6, CCl$_4$) for (*S*)-**22**}. – Ratio of enantiomers: (*R*)-**22**:(*S*)-**22** = 1:1 (determined by HPLC); HPLC: Daicel (Chiralcel OD), flow 1 ml/min, UV detector (254 nm), 0.2% 2-propanol in hexane; retention times: enantiomer A: 19.9 min (k' = 5.6), enantiomer B: 22.5 min (k' = 6.5). *rac*-**22** gave two base-line-separated signals with equal peak areas.

3-Ethylcyclohexanone (**24**)[49a]. – a) *Without Ligand:* According to the representative procedure using 336 mg (3.5 mmol) of 2-cyclohexenone (**23**), 45 mg (0.18 mmol) of Ni(acac)$_2$, and 5 ml (1 M in hexane, 5 mmol) of diethylzinc in 12 ml of acetonitrile at –10°C for 4 h; 570 mg of crude product; CC: 20 g of SiO$_2$, petroleum ether/ethyl acetate (10:1). Yield 335 mg (76%) of **24** as a colorless oil. – ^{13}C NMR: δ = 10.8, 25.0, 29.0, 30.6, 40.5, 41.2, 47.6, 212.4. – ee analysis by ^{13}C-NMR measurements of the ketal derived from (*R,R*)-(–)-2,3-butanediol[49] (data given for a mixture of diastereomers): δ = 11.17/11.21, 16.89/17.00, 17.06/17.07, 22.89/23.27, 29.55/29.62, 31.29/31.32, 36.09/36.62, 37.12/37.14, 42.61/43.57, 77.66, 78.01/78.08, 108.61/108.63.

b) *With Ligand:* According to the representative procedure using 192 mg (2 mmol) of 2-cyclohexenone (**23**), 2.6 mg (0.01 mmol) of

$Ni(acac)_2$, 3 ml (1 M in hexane, 3 mmol) of diethylzinc, and 47 mg (0.2 mmol) of (*S*)-**5** [(*S*):(*R*) = 96:4] in 4 ml of acetonitrile; 390 mg of crude product; CC: 20 g of SiO_2, petroleum ether/ethyl acetate (10:1). Yield 87 mg of **24** [ca. 35%, contained traces of (*S*)-**5**]. ee analysis by ^{13}C-NMR measurements of the ketal derived from (*R,R*)-(−)-2,3-butanediol[49]: Ratio of diastereomers ca. 1:1.

1,3-Diphenyl-1-trimethylsilyloxy-1-pentene (**25**): According to the representative procedure using 208 mg (1 mmol) of 1,3-diphenylpropenone (**1a**), 2.6 mg (0.01 mmol) of $Ni(acac)_2$, 1.5 ml (1 M in hexane, 1.5 mmol) of diethylzinc, 325 mg (2.99 mmol) of trimethylsilyl chloride, and 49 mg (0.2 mmol) of (*S*)-**5** [(*S*):(*R*) = 96:4], in 4 ml of acetonitrile; workup modification: quenching with satd. aqueous $NaHCO_3$ instead of hydrochloric acid; 335 mg of a crude yellowish oil; TLC: R_f = 0.66 [SiO_2, petroleum ether/ethyl acetate (5:1)]; CC: 10 g of SiO_2, petroleum ether/ethyl acetate (250:1, then 100:1). Yield 230 mg (ca. 74%, contained traces of **1a**) of **25** as a colorless oil. – ^{1}H NMR: δ = 0.08 [s, 9H, $Si(CH_3)_3$], 0.90 (t, *J* = 7.4 Hz, 3H, CH_3), 1.70–1.77 (m, 2H, CH_2), 3.66–3.74 (m, 1H, $CHCH_2$), 5.39 (d, *J* = 9.9 Hz, 1H, CH), 7.15–7.32 (m, 8H, aromatic H), 7.47 (dd, *J* = 8.0, 1.5 Hz, 2H, aromatic H). – ^{13}C NMR: δ = 0.4 [$Si(CH_3)_3$], 12.0 (CH_3), 30.5 (CH_2), 43.7 (CH), 115.2 (CH), 126.0 (CH), 127.7 (CH), 128.2 (CH), 128.5 (CH), 139.6 (C), 146.0 (C), 149.4 (C). – MS (EI, 70 eV): *m/z* (%) = 282 (24), 281 (100), 73 (46); (CI, NH_3): *m/z* (%) = 311 (100) [M^+ + 1]. – ee analysis after desilylation of **25** using Bu_4NF in THF. Ratio of enantiomers 1:1 (HPLC analysis of **1a**).

$C_{20}H_{26}OSi$ (310.5)	Calcd.	C 77.36	H 8.44
	Found	C 77.08	H 8.65

Asymmetric Amplification: The optical purity of (*R*)-**5** was adjusted by mixing appropriate amounts of (*R*)-**5** and *rac*-**5** to give 24 mg (0.1 mmol) of scalemic ligand. **5** was dissolved in 1 ml of acetonitrile (or propionitrile; see text and Table 5), and 20 μl of the resulting solution was withdrawn. From this sample the solvent was removed, and the optical purity of the ligand was determined by HPLC[11]. $Ni(acac)_2$ (1.3 mg, 0.005 mmol) was added to the remaining solution of **5**, and the representative procedure was followed by using 104 mg (0.5 mmol) of 1,3-diphenylpropenone (**1a**) and 0.75 ml (1 M in hexane, 0.75 mmol) of diethylzinc in 2 ml of aceto- or propionitrile. The conversion of **1a** was determined by ^{1}H-NMR measurements of the crude mixture. After purification of the product by CC, the optical purity of **2a** was determined by HPLC. Yields and ee values are given in Table 6.

Time Dependence of the ee Values: The optical purity of **5** was adjusted and determined by HPLC[11] as described above. The representative procedure was applied, and at various time intervals aliquots of the solution were withdrawn. After workup, the conversion of **1a** was determined by ^{1}H-NMR measurements of the crude mixture. Purification of the product by CC was followed by determination of the optical purity of **2a** by HPLC. Units of time and ee values are given in Table 4.

CAS Registry Numbers

1a: 94-41-7 / **1b**: 956-04-7 / **1c**: 956-02-5 / **1d**: 959-33-1 / **1e**: 959-23-9 / (*R*)-**2a**: 115730-45-5 / (*S*)-**2a**: 16460-86-9 / **2b**: 138982-96-4 / **2c**: 138982-97-5 / **2d**: 138982-98-6 / (*R*)-**2e**: 123559-91-1 / (*S*)-**2e**: 123559-92-2 / **3**: 131726-65-3 / **4**: 1081-75-0 / (*R*)-**5**: 138982-99-7 / (*S*)-**5**: 136859-86-4 / **6**: 138983-01-4 / **7**: 138983-02-5 / **8**: 127912-58-7 / **9**: 127049-49-4 / **10**: 138983-03-6 / **11**: 138983-04-7 / **12**: 138983-05-8 / **13**: 122-57-6 / **14**: 538-44-3 / **15**: 20157-18-0 / **16**: 1222-98-6 / **17**: 103-36-6 / **18**: 68522-85-0 / **19**: 106353-34-8 / **20**: 37608-93-8 / **21**: 614-57-3 / (*S*)-**22**: 20698-95-7 / (*R*)-**22**: 20698-96-8 / **23**: 930-68-7 / **24**: 64847-85-4 / **25**: 138983-00-3 / $Ni(acac)_2$: 3264-82-2 / diethylzinc: 557-20-0

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