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ASYMMETRIC AMPLIFICATION IN NICKEL-CATALYZED CONJUGATE ADDITION TO CHALCONE

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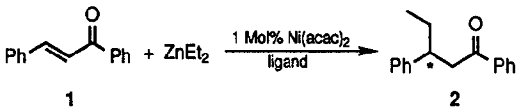
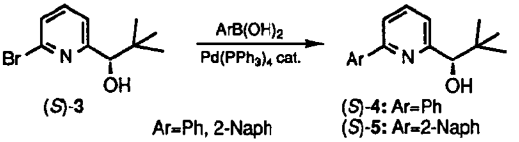
Abstract: Nickel complexes with optically active pyridine ligands catalyze the conjugate addition of diethyl zinc to chalcone. This *catalytic* alkylation gives products with *ee*'s of up to 86%. Strong asymmetric amplification has been observed using ligands of low optical purity.

Recently we investigated the use of a chiral bipyridine/nickel complex as catalyst for the enantioselective conjugate addition of diethyl zinc to chalcone [Eq. (a)].[1,2] Product **2** was obtained in good yield with an enantiomeric excess of up to 72%. We now report an improved enantioselectivity in this reaction using optically active pyridine derivatives. We also show the nonlinear relationship between the *ee* of the ligand and the *ee* of the product constituting a case of strong asymmetric amplification.



(a)

Pyridines (*S*)-**4** and (*S*)-**5** were prepared in good yield by palladium catalyzed cross coupling of (*S*)-**3**[3] with the corresponding aryl boronic acids [Eq. (b)]. The enantiomeric excess remained unchanged, as determined by HPLC on a stationary chiral phase[4] and by ^1H NMR spectroscopy of the diastereomeric camphanic ester derivatives. The optical purity of scalemic[5] **4** or **5** was enriched by separation of the diastereomers of the camphanic esters by column chromatography followed by hydrolysis under basic conditions (K_2CO_3, MeOH).[6]

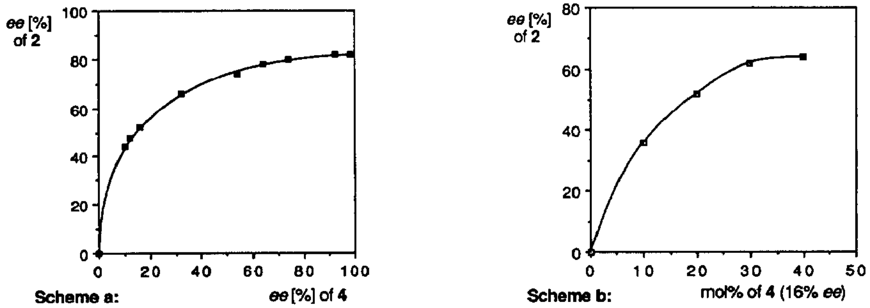


(b)

The combination of 1 mol% of Ni(acac)$_2$ (acac= acetyl acetonate) and 20 mol% of pyridine (*S*)-**4** or (*S*)-**5** in acetonitrile gave an active species which catalyzed the enantioselective addition of diethyl zinc to chalcone **1** [Eq. (a)]. The addition product **2** was obtained in high yield and with an enantiomeric excess of up to 86% (Table).[6] Using (*S*)-**4** or (*S*)-**5**, the (*R*)-enantiomer of **2** was the major product; the optical purity was determined by HPLC on a chiral stationary phase.[4]

In order to study the dependence of the enantioselectivity of the product on the optical purity of the ligands, scalemic mixtures of **4** and **5** were used. A strong ***nonlinear relationship*** between the *ee* of **4** or **5** and the *ee* of the product was found (Table, Scheme). Use of **4** with an enantomeric excess of 10% [(*S*)-**4**:(*R*)-**4**=55:45] led to the formation of **2** with 44% *ee*. Such strong asymmetric amplification was only observed when using **4** of low optical purity. With increasing *ee* of the ligand, this phenomenon became less distinct

(Scheme, Table). Using **4** with an *ee* of 12%, asymmetric amplification led to **2** with a 48% *ee* (amplification factor[7]: 4.0). When **4** had an *ee* of 32%, the amplification factor dropped to 2.1 and **2** was produced with a 66% *ee* . Use of **4** with 54% *ee* gave a 74% *ee* for **2** (amplification factor of 1.4). No further enhancement of the asymmetric induction in the formation of **2** was observed for **4** or **5** having *ee*'s ≥92%. Thus, pyridine **4** with an *ee* of 92%, as well as 98%, gave an enantiomeric excess of 82% [(*R*)-**2**:(*S*)-**2**=91:9] (Table, entries 9 and 10). An enantiomeric excess of 86% [(*R*)-**2**:(*S*)-**2**=93:7] was obtained using (*S*)-**5** with 90% or 98% *ee*.



Scheme a:

Scheme b:

Schemes: a) Correlation between the *ee* of product **2** and the *ee* of ligand **4**. b) Influence of the catalyst concentration on the *ee* of **2** [Eq. (a)] (Ni(acac)$_2$: **4** = 1:10, *ee* of **4**: 16%).

The enantiomeric excess of the product also depends on the metal/ligand ratio and increases with the amount of ligand. Raising the ligand concentration from 10 to 20 mol% of **4** (92%*ee*) at a constant Ni(acac)$_2$ concentration of 1 mol% resulted in a strong increase in *ee* (from 53% to 82% *ee* for **2** [Table: entries 13 and 9]). With 30 mol% of **4**, the product was formed with 86% *ee* (Table: entry 14). In order to determine the influence of the metal/ligand ratio on the asymmetric amplification, the concentration of scalemic **4** of low enantiomeric excess was varied. A combination of 1 mol% of Ni(acac)$_2$ and 10, 20, or 30 mol% of **4** of 10% *ee*

Table: Asymmetric nickel-catalyzed conjugate addition of diethyl zinc to chalcone **1**.

No.	Ni(acac)$_2$ [mol%]	**4** [mol%]	*Ee* of **4** [%][a]	*Ee* of **2** [%][a]	Amplification factor[b]	Yield [%]
1	1	0				73
2	1	20	10	44	4.4	61
3	1	20	12	48	4.0	74
4	1	20	16	52	3.3	73
5	1	20	32	66	2.1	77
6	1	20	54	74	1.4	81
7	1	20	64	78	1.2	77
8	1	20	74	80	1.1	77
9	1	20	92	82	0.9	77
10	1	20	98	82	0.8	75
11	1	10	10	30	3.0	85
12	1	30	10	44	4.4	61
13	1	10	92	53	0.6	81
14	1	30	92	86	0.9	62
15	1	10	16	36	2.3	76
16	2	20	16	52	3.3	69
17	3	30	16	62	3.9	77
18	4	40	16	64	4.0	69

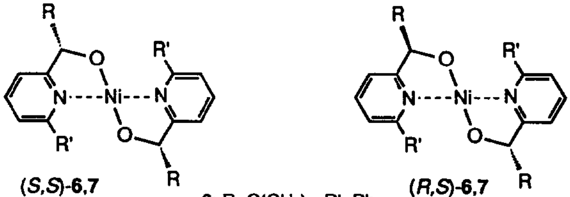
[a] Determined by HPLC.[4] [b] Defined as quotient of *ee* of **2** over *ee* of **4**.

was used as catalyst. At a nickel/ligand ratio of 1:10, the *ee* of the product was three times higher than the *ee* of the ligand (amplification factor: 3.0; Table: entry 11). At higher ratios [1:20 (entry 2) or 1:30 (entry 12)], the amplification factor increases to 4.4.

The dependence of the asymmetric amplification on the overall catalyst concentration with a constant ratio of Ni(acac)$_2$ and ligand **4** was next examined. Scheme b shows the nonlinear relationship between the *ee* of the product as a function of the catalyst concentration. The asymmetric amplification is stronger at higher catalyst concentration. If 1 mol% of Ni(acac)$_2$ and 10 mol% of **4** (16% *ee*) were used, **2** was obtained with an *ee* of 36% (amplification factor: 2.3). Use of 3 mol% of Ni(acac)$_2$ and 30 mol% of **4** (16% *ee*) gave an enantiomeric excess of 62% for **2** (amplification factor of 3.9) A further increase to 4 mol% of Ni(acac)$_2$ and 40 mol% of **4** (16% *ee*) resulted in only a slight additional improvement of the enantioselection (to 64% *ee* of **2**, amplification factor: 4.0).

A nonlinear relationship between the enantiomeric excess of chiral auxiliaries and products was described for an asymmetric oxidation and an aldol reaction by *Kagan* and *Agami* et al.[8] The asymmetric amplification in the enantioselective alkylation of aldehydes catalyzed by β-amino alcohols was intensively investigated by *Oguni* and *Noyori*.[9,10] Positive nonlinear effects were also found in titanium catalyzed asymmetric reaction.[11-13] All of these phenomena have been interpreted in terms of differential chemical behaviour of diastereomeric *dinuclear* metal complexes containing two *identical* metals.

In contrast, the nickel catalysis described here requires the interaction of two *different* metal species. The asymmetric amplification can thus be explained by the difference in chemical properties of diastereomeric complexes in which the optically active pyridines are bounded to either nickel or zinc atoms. With enantiomerically enriched **4** two diastereomeric *mononuclear* nickel complexes **6** and **7** are possible [for (*S*)-**4** as the major enantiomer: (*S*,*S*)-**6** and (*R*,*S*)-**6**].[14,15] Predominate reaction of diethyl zinc with the less stable optically active complex (*S*,*S*)-**6** would lead to the formation of a homochiral catalytical active species. The more stable ***meso*** complex (*R*,*S*)-**6** is less reactive, and traps the minor ligand enantiomer, making it inaccessible for catalyst formation.[16]



(*S*,*S*)-**6**,**7**

(*R*,*S*)-**6**,**7**

6: R=C(CH$_3$)$_3$, R'=Ph
7: R=Ph, R'=H

Alternatively, the reaction of diethyl zinc with scalemic **4** could give diastereomeric *dinuclear* zinc chelate complexes.[17] The less stable complex with homochiral ligands would preferentially react further to give a chiral catalytically active nickel species.

Further investigations of bis-chelate metal complexes[18] will lead to a deeper understanding of the enantioselective catalysis and the asymmetric amplification observed with these complexes.

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3. C. Bolm, M. Zehnder, D. Bur, *Angew. Chem. 102* (1990) 206 - 208; *Angew. Chem. Int. Ed. Engl. 29* (1990) 205 - 207.

4. CHIRALCEL OD (Daicel), flow rate: 1.0 ml/min, UV detector (254 nm); retention time for **2** (0.2% 2-propanol in hexane): (*S*)-enantiomer: 18.5 min, (*R*)-enantiomer 22.3 min; retention time for **4** (1.5% 2-propanol in hexane): (*R*)-enantiomer: 16.6 min, (*S*)-enantiomer 19.5 min.

5. The term "scalemic" has been introduced for the description of an unequal mixture of enantiomers. C. H. Heathcock,B. L. Finkelstein, E. T. Jarvi, P. A. Radel, C. R. Hadley, *J. Org. Chem. 53* (1988) 1922 - 1942.

6. Ee_{max} for **4** and **5**: 98%. Mol% of $Ni(acac)_2$ and **4**/**5** is based on the amount of **1**. For the general reaction conditions see ref. 1a.

7. Amplification factor: defined as the quotient of $ee_{product}$ over ee_{ligand}.

8. C. Puchot, O. Samuel, E. Duñach, S. Zhao, C. Agami, H. B. Kagan, *J. Am. Chem. Soc. 108* (1986) 2353 - 2357.

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14. For the structurally related nickel complex **7**, *Tissier* found a major stability difference between the optically active complex (*S*,*S*)-**7** and *meso*-complex (*R*,*S*)-**7**. Upon mixing equimolar amounts of both enantiomers of **7** [(*S*,*S*)-**7** and (*R*,*R*)-**7**] exclusive formation of optically inactive (*R*,*S*)-**7** was observed. The *cis-trans* arrangement for optically active **7** discussed by *Tissier* would lead to a severe steric interaction of the phenyl groups at C(6) in **4**. C. Tissier, *Bull. Soc. Chim. Fr. 1961*, 2308 - 2312.

15. Diastereomeric interactions of coordinate molecules on nickel ions allow the determination of optical purities by NMR spectroscopy. M. L. Pasquier, W. Marty, *Angew. Chem. 97* (1985) 328 - 329; *Angew. Chem. Int. Ed. Engl. 24* (1985) 315 - 316.

16. Attempts to synthesize **6** have not yet been unsuccessful.

17. This explanation is based on the mechanism for the amino alcohol catalyzed enantioselective alkylation of aldehydes in hexane or toluene proposed by *Noyori* et al..[10] The use of acetonitrile, which is essential in the nickel catalysis results in low chemical and optical yields in this reaction.[3] (I thank Prof. Dr. *A. Pfaltz* for a stimulating discussion on the mechanism.)

18. a) C. Bolm, K. Weickhardt, M. Zehnder, T. Ranff, *Chem. Ber. 124* (1991) 1173 - 1180; b) C. Bolm, K. Weickhardt, M. Zehnder, D. Glasmacher, *Helv. Chim. Acta* in press.