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Asymmetric conjugate addition of diethylzinc to chalcone catalyzed by nickel complexes containing derivatives of (1*R*,2*S*,3*R*)-3-mercaptocamphan-2-ol

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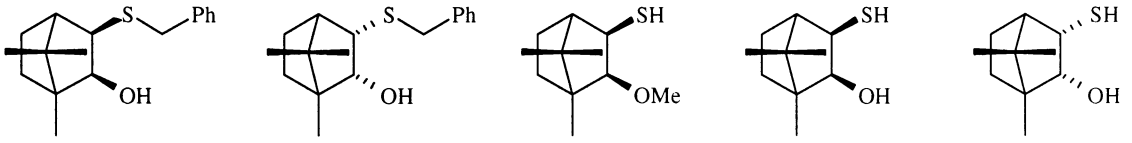
Abstract

In the presence of Ni complexes and chiral ligand **1b**, the asymmetric conjugate addition of diethylzinc to chalcone in acetonitrile at −30°C proceeded in 86% e.e. The factors influencing the enantioselectivity of the reaction were studied.

1. Introduction

The enantioselective conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds has been an important method for asymmetric carbon–carbon bond formation. Recently, nickel[1], copper[2] and cobalt[3] catalysts containing various chiral ligands such as amino alcohols, phosphites, phosphorus amidites and phosphines have been developed for this reaction. However, chiral ligands containing a mercapto group are relatively rare. We have reported that the derivatives of MerCO [(1*R*,2*S*,3*R*)-3-mercaptocamphan-2-ol] (Fig. 1) could serve as efficient auxiliaries in asymmetric synthesis.[4] More recently, we found MerCO derivatives could also act as chiral ligands in the asymmetric borane reduction of ketone.[5] Herein, we



1a **1b** **1c** **1d** **1e**

Figure 1.

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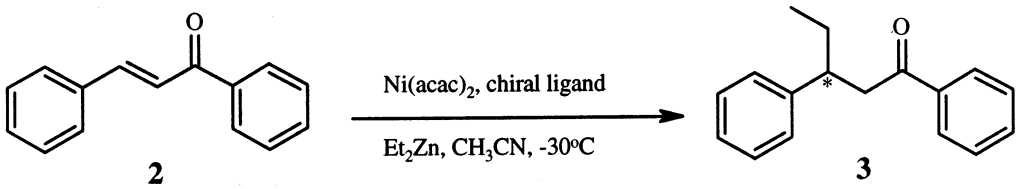
report the catalytic conjugate addition of diethylzinc to chalcone **2** using the Ni complexes of MerCO derivatives as catalysts to produce adduct **3** in high yield with good enantioselectivity (Scheme 1).



Scheme 1.

2. Results and discussion

Table 1 summarizes the results of using 2 mol% of $Ni(acac)_2$ and 9 mol% of various chiral derivatives of MerCO to catalyze the conjugate addition. Of the five chiral ligands used, compound **1b** affords the best enantioselectivity (60% e.e.) in *S* configuration.

Table 1
Asymmetric conjugate addition of Et_2Zn to chalcone using MerCO's derivatives[a]

Entry[a]	$Ni(acac)_2$ (mol%)[b]	**1** (mol%)[b]	**2** conversion (%)	**3** yield (%)[c]	**3** (e.e.%)[d]
1	2	**1a** (9)	100	99	20 (*R*)
2	2	**1b** (9)	100	94	60 (*S*)
3	2	**1c** (9)	83	58	22 (*S*)
4	2	**1d** (9)	100	86	12 (*S*)
5	2	**1e** (9)	77	52	2 (*S*)

[a] All reactions were performed with 2.4 equiv. Et_2Zn in acetonitrile for 12 h at −30°C.
[b] The mol% was calculated based on chalcone used in the reaction.
[c] All yields were calculated based on conversion ratio.
[d] The e.e. values were determined by HPLC with Daicel chiral OD column, 0.3% IPA/hexane as eluent, flow rate 0.7 ml/min, and 254 nm. The retention time of the *S*-form was 17.1 min and the retention time of the *R*-form was 20.8 min.

To further improve the enantioselectivity of the title reaction, we have examined the factors such as reaction temperature, ratio of nickel complexes, chiral ligand **1b** and chalcone used for this addition process. The best enantioselectivity (86%) was found at −30°C with 2 mol% of $Ni(acac)_2$ and 50 mol% of chiral ligand **1b** against chalcone. The experimental results are summarized in Table 2.

The temperature study indicates that lower temperatures gave better enantioselectivity, which implies this reaction is very likely a kinetically controlled process. We found that 60% e.e. was obtained at −30°C and it dropped to 36% e.e. when the temperature was increased to 30°C (entries 1 and 2). However, the reaction rate was too low if the reaction temperature dropped further to −40°C (the conversion of **2** is less than 5%).

Table 2
Variable effects of asymmetric conjugate addition of Et_2Zn to chalcone[a]

Entry[a]	$Ni(acac)_2$ (mol%)[b]	**1b** (mol%)[b]	Temp. (°C)	**2** conversion (%)	**3** yield (%)[d]	e.e.%[e]
1	2.0	9	30	100	58	36
2	2.0	9	−30	100	94	60
3	1.0	20	−30	74	91	72
4[c]	1.0	20	−30	49	71	70
5	2.0	20	−30	71	97	80
6[c]	2.0	20	−30	59	68	70
7	2.0	50	−30	69	98	86
8	–	20	−30	5	–	–
9	3.5	20	−30	100	92	68
10	7.0	20	−30	100	86	68
11	2.0	16	−30	100	79	72
12	7.0	16	−30	100	79	60

[a] The chalcone was added before the addition of 2.4 equiv. Et_2Zn.
[b] The mol% was calculated based on chalcone used in the reaction.
[c] $Ni(acac)_2$ and **1b** were refluxed for 60 min in CH_3CN, then 2.4 equiv. Et_2Zn was added at the indicated temperature, followed by addition of chalcone.
[d] All yields were calculated based on conversion ratio.
[e] The e.e. value was determined by HPLC with Daicel chiral OD column, 0.3% IPA/hexane as eluent, flow rate 0.7 ml/min. The retention time of the *S*-form was 17.1 min and the retention time of the *R*-form was 20.8 min.

On the other hand, the addition sequence of the reactants is also important for the conversion ratio as well as the enantioselectivity of the conjugate addition. A better sequence is to premix chalcone with $Ni(acac)_2$ and the chiral ligand so that it produces a chiral intermediate as a nickel complex. If the diethylzinc is added to the reaction system of the nickel complex before the addition of chalcone, a lot of the nickel(II) cation of the nickel complex would be reduced by diethylzinc. Therefore, there is not enough nickel(II) chelated chalcone chiral complex for the asymmetric addition process, thus both the conversion ratio and enantioselectivity are lower. We believe that the chiral complex of chalcone, $Ni(acac)_2$ and chiral ligand not only provide an asymmetric environment to produce the chiral adduct, but also play an important role in accelerating the reaction rate. The absence of such a chiral complex would lead to much lower chemical yields (entries 4 and 6). Besides, if we increased the amounts of $Ni(acac)_2$, it would make it easier for the chalcone to be attacked by the nucleophile, but the enantioselectivity was decreased because some nickel and chalcone complexes did not contain the chiral ligand during the diethylzinc addition process (entries 3, 5, 9, 10 and 11, 12). The enantioselectivity of the reaction was favored by using a greater amount of chiral ligand. We found that when the amount of chiral ligand was raised from 9 to 20%, then to 50% molar ratio, the enantioselectivity was increased from 60, 80, to 86%, respectively (entries 2, 5 and 7).

In summary, this paper has uncovered a series of sulfur-containing chiral ligands for the nickel complex catalyzed asymmetric conjugate addition of diethylzinc to chalcone. Through the manipulation of the reaction conditions, we were able to achieve good chemical yield and up to 86% e.e. of the addition product.

3. Experimental

3.1. General methods and materials

^1H and ^{13}C NMR spectra were recorded on a Varian VXR-400 spectrometer and the chemical shifts (δ) reported in ppm relative to TMS. Optical rotations were recorded on a Perkin–Elmer Model 241 polarimeter using a 1.0 dm cell at specific temperature. Infrared spectra were measured on a Hitachi 270-30 IR spectrometer. High-resolution mass spectra were recorded on a JEOL Jms-SX/SX 102A mass spectrometer. Diethylzinc and $Ni(acac)_2$ were purchased from Aldrich Chemical Co. Merck silica gel 60 (70–230 mesh) was used for chromatography. Enantiomeric excess (e.e.) determination was carried out with a Chiralcel OD (150×4.6 mm) column (Daicel Chemical Industries) on a Beckman 168 HPLC instrument with UV detector set at 254 nm.

3.2. General procedure for conjugated addition

In a 10 ml flame-dried flask was added $Ni(acac)_2$ (2.2 mg, 0.00856 mmol) and chiral ligand **1b** (22.8 mg, 0.0826 mmol) in acetonitrile (1 ml). The resulting solution was refluxed for 1 h, then cooled down to −30°C. Chalcone **2** (86.4 mg, 0.415 mmol) in acetonitrile (1 ml) was added to the above mixture followed by addition of diethylzinc (0.9 ml, 0.99 mmol). The resulting mixture was stirred for 12 hours at the same temperature and quenched with 3N NaOH (5 ml). The aqueous layer was extracted with ethyl acetate (5 ml×3). The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by chromatography (silica gel 10 g, 2% ethyl acetate/hexane) to produce 70.2 mg (97% based on conversion of **2**) of the addition product **3**[1b] as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): 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). Enantiomeric excess (e.e.) determination was carried out using 0.3% 2-propanol in hexane (0.7 ml/min) as eluent with a Chiralcel OD (150×4.6 mm) column (Daicel Chemical Industries) on a Beckman 168 HPLC instrument with UV detector set at 254 nm.

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