

Enantioselective Conjugate Addition of Diethylzinc to Chalcones
Using NiCl₂-Chiral β -Diamine Complex as Catalyst

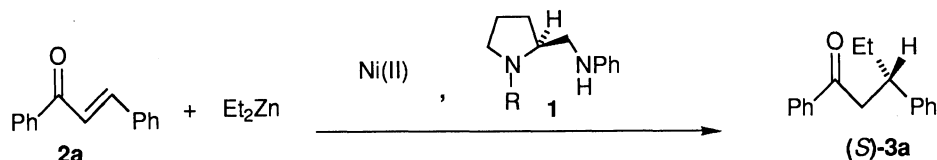
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A chiral catalyst prepared from nickel(II) chloride and chiral β -diamine, (*S*)-1-pentyl-2-anilinomethylpyrrolidine, was found to be effective for the enantioselective conjugate addition of diethylzinc to chalcones to afford corresponding β -substituted ketones in up to 89% ee.

Enantioselective conjugate addition of organometallic reagents to α,β -unsaturated carbonyl compounds provides a useful method for the synthesis of chiral β -substituted carbonyl compounds. A most widely employed approach to this problem has been a modification of organocopper reagents with nontransferable chiral ligands¹⁾ or the use of external ligands for organocopper reagents.²⁾ Recently, the enantioselective conjugate addition of dialkylzinc was found to proceed with rather high selectivity in the presence of Ni(II) catalyst having chiral amino alcohol or amino amide as ligand.³⁾

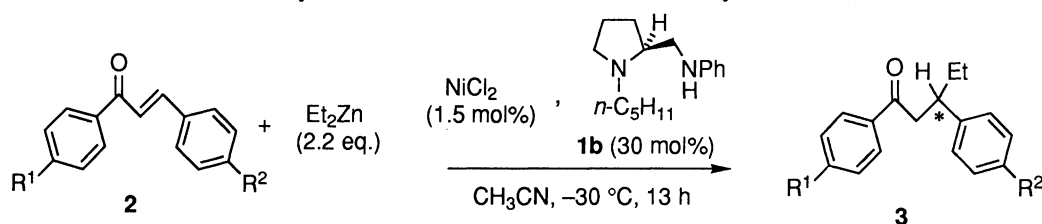
We have been working on asymmetric synthesis using chiral β -diamines prepared from (*S*)-proline and reported several highly stereoselective asymmetric reactions by the use of these chiral auxiliaries.⁴⁾ Though β -diamines are known to form stable chelate complexes with various metals, little is known about asymmetric reaction using chiral β -diamine-transition metal catalyst.⁵⁾ Here we wish to report a new chiral catalyst system prepared from NiCl₂ and the chiral β -diamine for the enantioselective conjugate addition of diethylzinc to chalcones.



In the first place, a conjugate addition to chalcone (**2a**) was carried out in acetonitrile at 0 °C using 1.8 equiv of diethylzinc in the presence of Ni(acac)₂ (3 mol%) and (*S*)-1-methyl-2-anilinomethylpyrrolidine (**1a**) (R = CH₃) (30 mol%), and (*S*)-1,3-diphenylpentan-1-one (**3a**) was obtained in 36% ee (88% yield). After the thorough examination of the substituent of the nitrogen atom of the pyrrolidine ring, (*S*)-1-pentyl-2-anilinomethylpyrrolidine (**1b**) (R = *n*-C₅H₁₁) was found to give the best selectivity (52% ee and 76% yield at 0 °C; 69% ee and 69% yield at -30 °C). Characteristic feature of this Ni(II)-**1b** catalyst was considerable enhancement of the selectivity (82% ee and 72% yield) by the use of NiCl₂ in place of Ni(acac)₂, though Ni(acac)₂ has been used in most studies^{3a,c-g)} in catalytic enantioselective addition of dialkylzinc to conjugated enones. NiBr₂ was also found to be effective (78% ee and 73% yield).

By examination of the molar ratio of the reagents the best result (82% ee and 75% yield) was obtained by

Table 1. Catalytic Enantioselective Addition of Diethylzinc to Chalcones



Entry	2	R ¹	R ²	Yield/% ^{a)}	Ee/% ^{b)}
1	a	H	H	75	82(<i>S</i>)
2	b	H	Cl	48	67 ^{c)}
3	c	Cl	H	55	58 ^{c)}
4	d	H	CH ₃ O	66	80 ^{c)}
5	e	CH ₃ O	H	50	89(<i>S</i>)

a) Isolated yield. b) Determined by HPLC using a chiral column (Waters Optipak-XC) according to the reported method.^{3d)} c) The opposite enantiomer to that obtained predominantly in the literature^{3d)} was formed as the major product.

employing 1.5 mol% of NiCl₂, 30 mol % of **1b**, and 2.2 equiv of diethylzinc. When the reaction was applied to substituted chalcones **2b–e**, corresponding β-substituted ketones **3b–e** were obtained in 58–89% ee (Table 1).

Typical experimental procedure is as follows: Under an argon atmosphere the diamine **1b** (74 mg, 0.3 mmol) and NiCl₂ (2.0 mg, 0.015 mmol) in acetonitrile (4 ml) was stirred at 80 °C for 1 h. The mixture was cooled to room temperature and acetonitrile (2 ml) solution of **2a** (208 mg, 1.0 mmol) was added. Stirring was continued for 20 min and the mixture was cooled to –30 °C. Diethylzinc (2.2 mmol in 2.2 ml hexane) was then added to the mixture over 30 min period and stirring was continued for 13 h at –30 °C. Dichloromethane and 1 M HCl were added and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with brine and dried over anhydrous Na₂SO₄. After removal of the solvent the crude product was purified by preparative TLC to afford (*S*)-**3a** (179 mg, 75% yield). Ee was determined by HPLC analysis using a chiral column (Waters Optipak-XC) according to the reported method.^{3a–e,g)}

It is noted that highly enantioselective conjugated addition of diethylzinc to chalcones was achieved by simple experimental procedure using new chiral catalyst prepared from NiCl₂ and the chiral β-diamine **1b**.

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