CHEMISTRY LETTERS, pp. 297-298, 1994.

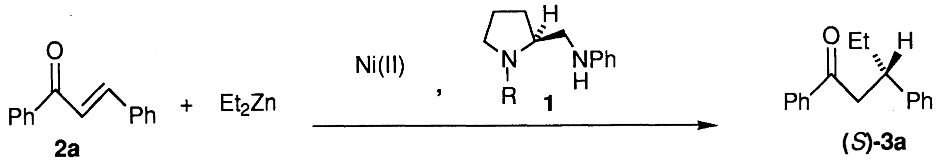
Enantioselective Conjugate Addition of Diethylzinc to Chalcones Using $NiCl_2$–Chiral β-Diamine Complex as Catalyst

Masatoshi ASAMI,* Kenji USUI, Sohmei HIGUCHI, and Seiichi INOUE
Department of Synthetic Chemistry, Faculty of Engineering, Yokohama National University,
Tokiwadai, Hodogaya-ku, Yokohama 240

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)

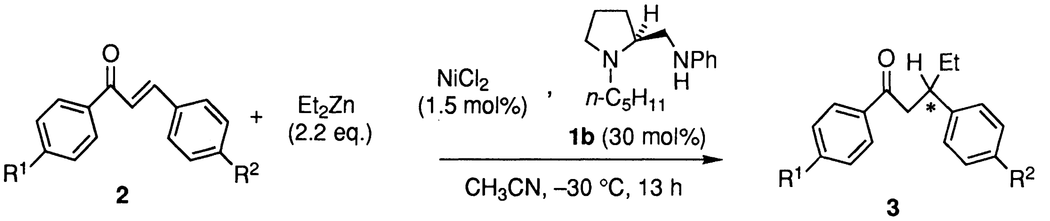
We have been working on asymmetric synthesis using chiral β-diamines prepared from (*S*)-proline and reported several highly stereoselective asymmetric reactions by the use of these chiral auxiliaries.4) Though β-diamines are known to form stable chelate complexes with various metals, little is known about asymmetric reaction using chiral β-diamine–transition metal catalyst.5) Here we wish to report a new chiral catalyst system prepared from $NiCl_2$ 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**) ($R = CH_3$) (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**) ($R = n\text{-}C_5H_{11}$) 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 $NiCl_2$ in place of $Ni(acac)_2$, though $Ni(acac)_2$ has been used in most studies3a,c-g) in catalytic enantioselective addition of dialkylzinc to conjugated enones. $NiBr_2$ 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(*S*)
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(*S*)

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 NiCl$_2$, 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 NiCl$_2$ (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 Na$_2$SO$_4$. 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 NiCl$_2$ and the chiral β-diamine **1b**.

One of the authors (M. A.) gratefully acknowledges the Chisso Award in Synthetic Organic Chemistry, Japan and Kanagawa Academy of Science and Technology for financial support.

References

1) B. E. Rossiter, M. Eguchi, G. Miao, N. M. Swingle, A. E. Hernandez, D. Vickers, E. Fluckiger, R. G.Patterson, and K. V. Reddy, *Tetrahedron*, **49**, 965 (1993) and references cited therein.
2) M. Kanai, K. Koga, and K. Tomioka, *Tetrahedron Lett.*, **33**, 7193 (1992) and references cited therein.
3) a) K. Soai, S. Yokoyama, T. Hayasaka, and K. Ebihara, *J. Org. Chem.*, **53**, 4149 (1988); b) K. Soai, T. Hayasaka, S. Ugajin, and S. Yokoyama, *Chem. Lett.*, **1988**, 1571; c) K. Soai, T. Hayasaka, and S. Ugajin, *J. Chem. Soc., Chem. Commun.*, **1989**, 516; d) C. Bolm, M. Ewald, and M. Felder, *Chem. Ber.*, **125**, 1205 (1992); e) J. F. G. A. Jansen and B. L. Feringa, *Tetrahedron Asymm.*, **3**, 581 (1992); f) A. Corma, M. Iglesias, M. V. Martin, J. Rubio, and F. Sanches, *Tetrahedron Asymm.*, **3**, 845 (1992); g) M. Uemura, R. Miyake, K. Nakayama, M. Shiro, and Y. Hayashi, *J. Org. Chem.*, **58**, 1238 (1993).
4) T. Mukaiyama and M. Asami, *Topics in Current Chemistry*, **127**, 133 (1985).
5) A. Schionato, S. Paganelli, C. Botteghi, and G. Chelucci, *J. Mol. Cat.*, **50**, 11 (1989).

(Received November 1, 1993)