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Synthesis of *N*,*N*-dimethyl-2-amino-1,2-dicyclohexylethanol and its application in the enantioselective conjugate addition of diethylzinc to enones: a convenient upgrade of the chiral ligand via hydrogenation

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Abstract—The effectiveness of *N*,*N*-dimethyl-2-amino-1,2-diphenylethanol as a chiral ligand was significantly improved via simple hydrogenation of the phenyl rings. Both the catalytic activity and the enantioselectivity of the resulting new ligand in the asymmetric conjugate addition of diethylzinc to enones were found to be superior to the original phenyl analog. © 2001 Published by Elsevier Science Ltd.

1. Introduction

The asymmetric conjugate addition of organometallic reagents to prochiral enones is a convenient method for the preparation of optically active β-substituted ketones which are synthetically useful.[1] Traditionally, the asymmetric conjugate addition required a stoichiometric amount of chiral auxiliaries.[2] The first breakthrough, using sub-stoichiometric amounts of chiral auxiliary was achieved by Soai et al.[3] who studied the catalytic asymmetric conjugate addition of diethylzinc to enones with Ni(II)-(1*S*,2*R*)-*N*,*N*-dibutylnorephedrine (DBNE) as a chiral ligand. The method was subsequently modified and higher e.e.s were obtained with moderate yield.[4] Bolm et al.[5] reported the use of homochiral 2,2-dipyridyl ligands for this reaction. Reaction parameters such as the catalyst concentration and the ratios of Ni(II)$(acac)_2$/ligand/substrate were examined. Recently, (+)-camphor-derived tridentate amino alcohol ligands were synthesized by Feringa et al.[6] and were found to give high enantioselectivities in some reactions.

Several reports pointed out that chiral ligands containing cyclohexyl groups are superior to their phenyl analogs.[7] Since the hydrogenation of phenyl rings is relatively easy, expanding the scope of these findings may offer a convenient method for upgrading relevant ligands containing phenyl rings on the chiral backbone. Herein, we wish to report the synthesis of (1*R*,2*S*)-*N*,*N*-dimethyl-2-amino-1,2-dicyclohexylethanol **4** from its phenyl counterpart, (1*R*,2*S*)-*N*,*N*-dimethyl-2-amino-1,2-diphenylethanol **2** via simple hydrogenation. The significant improvement of rate and enantioselectivity of the catalyst containing the new ligand as compared to its phenyl analog is reported.

2. Results and discussion

2.1. Synthesis of (1*R*,2*S*)-*N*,*N*-dimethyl-2-amino-1,2-dicyclohexylethanol 4

Chiral 2-amino-1,2-diphenylethanol **1** was a useful ligand which effectively catalyzed asymmetric borane-reduction[8] and asymmetric transfer hydrogenation[9] with excellent e.e.s. Its *N*,*N*-dimethylated derivative **2** was also found to catalyze the asymmetric addition of diethylzinc to benzaldehyde with very high e.e.[10] To the best of our knowledge, the asymmetric conjugate addition of diethylzinc to enones using homochiral ligand **2** as well as its cyclohexyl analog **4** has not been reported. (1*R*,2*S*)-*N*,*N*-Dimethyl-2-amino-1,2-diphenylethanol **2** was prepared from (1*R*,2*S*)-2-amino-1,2-diphenylethanol **1** in 74% yield by refluxing with formic acid and formaldehyde for 24 h.[11] The cyclohexyl

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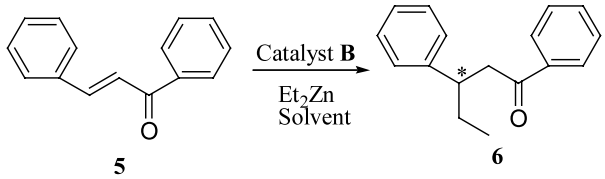
Table 1. Solvent effects on the conjugate addition of diethylzinc to chalcone **5** catalyzed by catalyst **B**



5 **6**

Entry	Solvent	E.e. (%)	Conversion (%)	Configuration
1	THF	/	Trace	/
2	Diethyl ether	/	Trace	/
3	CH_2Cl_2	41.8	30	*S*
4	Toluene	45.8	21	*S*
5	MeCN	82.0	89	*S*

[**5**] = 0.19 M; the molar ratio of substrate: Et_2Zn:Ni(acac)$_2$:ligand **4**:2,2′-dipyridyl = 1:1.2:0.07:0.17:0.07; reaction time = 12 h; reaction temperature = −30°C.

derivative **4** was synthesized by stirring **1** with platinum-(II) oxide in the presence of acetic acid under 3 atmospheres of hydrogen pressure at room temperature for 48 h (88% yield), followed by the reaction with formic acid and formaldehyde under reflux for 24 h (83% yield).

2.2. Application of 2 and 4 as chiral ligands in the nickel-catalyzed conjugate addition of diethylzinc to enones

Catalysts **A** and **B** were prepared via the reactions of the chiral ligands **2** and **4** with 2,2′-dipyridyl and Ni(II)(acac)$_2$ in acetonitrile, respectively.

$$2+\text{Ni(II)(acac)}_2+\text{2,2′-dipyridyl} \xrightarrow[80°C]{\text{MeCN}} \text{catalyst A}$$

$$4+\text{Ni(II)(acac)}_2+\text{2,2′-dipyridyl} \xrightarrow[80°C]{\text{MeCN}} \text{catalyst B}$$

Solvent effects in the conjugate addition of diethylzinc to chalcone **5** using catalyst **B** were examined and the results are listed in Table 1.

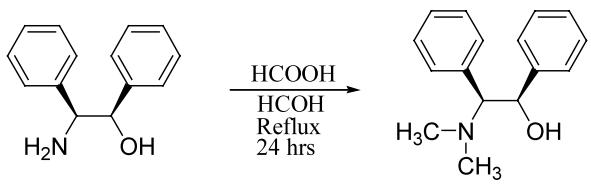
It is clear from Table 1 that faster rate of reaction and higher e.e. were achieved in MeCN than in other common solvents such as CH_2Cl_2 and toluene for the alkylation of chalcone **5** to (*S*)-1,3-diphenylpentane-1-one **6**. When THF and diethyl ether were used as solvents (entries 1 and 2), only trace amounts of **6** were detected, probably due to the poor solubilities of the substrate and the catalyst in these solvents.

A comparison of catalysts **A** and **B** in the asymmetric conjugate addition of diethylzinc to chalcone **5** in both toluene and acetonitrile was carried out and the results are summarized in Table 2.

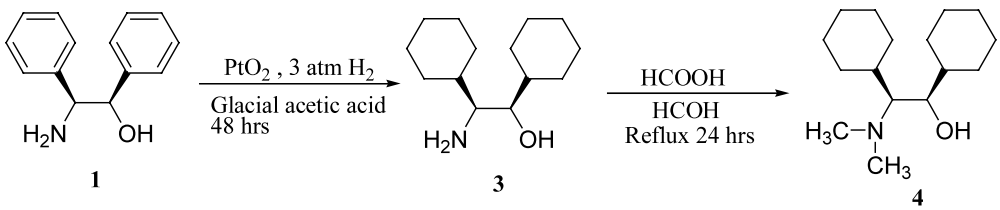
It was observed that the enantioselectivity of catalysts **B** was substantially higher than that of catalyst **A** in both solvent systems. The advantage of using a more sterically-demanding 1,2-dicyclohexyl group in the chiral backbone of catalyst **B** was clearly demonstrated in this reaction. Since MeCN gave the best rate and enantioselectivity, it was chosen as the solvent for the subsequent study.

The effect of the ligand-to-substrate ratio was also studied and the results were summarized in Table 3.

The enantioselectivities of the reactions with both catalysts were found to be relatively insensitive to the



1 **2**



1 **3** **4**

Table 2. Comparison of catalysts **A** and **B** on the asymmetric conjugate addition of diethylzinc to chalcone **5**

Entry	Catalyst	Solvent	Conversion (%)	E.e. (%)	Configuration
1	**A**	Toluene	43	1.6	*S*
2	**B**	Toluene	21	45.8	*S*
3	**A**	MeCN	53	33.2	*S*
4	**B**	MeCN	89	82.0	*S*

[**5**] = 0.19 M; the molar ratio of substrate: Et_2Zn:Ni(acac)$_2$:ligands:2,2′-dipyridyl = 1:1.2:0.07:0.17:0.07; reaction time = 12 h; reaction temperature = −30°C.

Table 3. The effect of ligand-to-substrate ratio on the asymmetric conjugate addition of diethylzinc to chalcone **5**

Entry	Catalyst	L/S (%)	[**5**] (M)	E.e. (%)	Conversion (%)	Configuration
1	**A**	10	0.33	31.2	31	*S*
2	**B**	10	0.33	80.0	42	*S*
3	**A**	17	0.19	33.2	53	*S*
4	**B**	17	0.19	82.0	89	*S*
5	**A**	20	0.16	38.8	69	*S*
6	**B**	20	0.16	80.7	100	*S*
7	**A**	25	0.13	37.2	89	*S*
8	**B**	25	0.13	80.9	100	*S*

The molar ratio of Et_2Zn:Ni(acac)$_2$:ligands:2,2′-dipyridyl = 7.1:0.41:1:0.41; different L/S ratio was performed by varying the amount of chalcone **5**; reaction time = 12 h; reaction temperature = −30°C; solvent = MeCN.

concentration of substrate used in this catalytic reaction (entries 1, 3, 5, 7 and 2, 4, 6, 8). The superiority of catalyst **B** over catalyst **A** was further established by comparing their effectiveness in the asymmetric conjugate addition of diethylzinc to other similar enones as shown in Table 4.

The results in Table 4 again clearly show that catalyst **B** is consistently better than catalyst **A** both in the rate of conversion and enantioselectivity for a variety of conjugate enone substrates.

In conclusion, by simply hydrogenating the phenyl rings of a diphenyl amino alcohol ligand, we are able to develop an effective catalyst for the asymmetric conjugate addition of diethylzinc to enones. Further studies using this catalyst in other reactions are currently in progress.

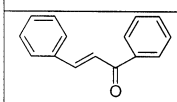
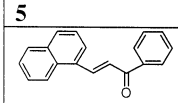
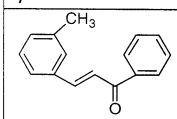
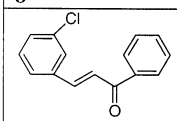
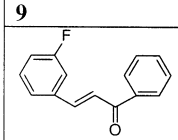
3. Experimental

Unless specified, commercial reagents were used as received. All solvents used were dried according to standard, published methods and were distilled under N_2 atmosphere prior to use.

3.1. Preparation of (1*R*,2*S*)-2-amino-1,2-dicyclohexylethanol 3

A 50 mL autoclave with a magnetic stirring bar was charged with (1*R*,2*S*)-2-amino-1,2-diphenylethanol **1** (0.2 g, 0.9 mmol), PtO_2 (0.02 g, 0.09 mmol) and glacial acetic acid (10 mL). The mixture was stirred for 48 h at ambient temperature under 3 atmospheres of H_2. After releasing the hydrogen gas and removing the solid catalyst by filtration, the mixture was neutralized with aqueous $NaHCO_3$ solution followed by extraction with

Table 4. Application of catalysts **A** and **B** in the asymmetric conjugate addition of diethylzinc to enones

Substrate	E.e. (%)		Conversion (%)		Configuration
	Catalyst **A**	Catalyst **B**	Catalyst **A**	Catalyst **B**	
 **5**	33.2	82.0	53	89	*S*
 **7**	41.5	78.6	28	43	*S*
 **8**	60.0	79.8	14	31	*S*
 **9**	45.2	80.9	45	48	*S*
 **10**	41.1	86.7	28	36	*S*

[Substrate] = 0.19M; the molar ratio of substrate : Et_2Zn : Ni(acac)$_2$: ligands : 2,2'-dipyridyl = 1 : 1.2 : 0.07 : 0.17 : 0.07; reaction time = 12 h.; reaction temperature = -30°C; Solvent = MeCN

ethyl acetate (3×20 mL). The combined extracts were dried over sodium sulfate and the solvent was removed by using a rotory evaporator to give 198 mg of crude product which was purified by crystallization in ethanol to give crystals of (1*R*,2*S*)-**3** (185 mg, 88%). Analytical data for (1*R*,2*S*)-**3**: mp: 144–146°C; +8.0° ($c=1.0$, ethanol); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.28 (dd, 1H, $J=6.2$ and 4.4 Hz); 2.59 (dd, 1H, $J=6.1$ and 4.3 Hz); 1.79–1.10 (m, 22H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 76.94, 57.87, 39.77, 30.85, 27.45, 27.42, 27.08, 26.97, 26.88, 26.71, 26.53 ppm; MS: 226 M^+.

3.2. Preparation of (1*R*,2*S*)-*N*,*N*-dimethyl-2-amino-1,2-dicyclohexylethanol 4

A one neck round bottom flask was charged with (1*R*,2*S*)-2-amino-1,2-dicyclohexylethanol **3** (0.2 g, 0.9 mmol), formic acid (2 mL) and formaldehyde (1 mL of 37% aqueous solution). The mixture was refluxed for 20 h. The solution was cooled to ambient temperature. Sodium hydroxide (40 mL of 10% aqueous solution) was added and white solids precipitated. The solids were filtered and were re-dissolved in ethyl acetate (30 mL). The solution was washed by saturated sodium chloride solution for three times. The organic phase was dried with anhydrous magnesium sulfate. The solvent was removed by rotory evaporation leaving a white solid of pure (1*R*,2*S*)-**4**. (0.19 g, 83% theoretical yield). MHz, $CDCl_3$) δ: 3.73 (dd, 1H, $J=2.5$); 2.79–2.54 (s, 7H); 1.95–0.79 (m, 22H) ^{13}C NMR (101 MHz, $CDCl_3$) δ: 73.62, 69.63, 69.46, 42.41, 41.00, 36.61, 32.60, 31.39, 31.03, 27.74, 27.00, 26.77, 26.68, 26.29 ppm; MS: 254 M^+.

3.3. Typical procedure for asymmetric conjugate addition of diethylzinc to chalcone 5

A mixture of $Ni(acac)_2$ (3.6 mg, 0.014 mmol) and (1*R*,2*S*)-**4** (0.034 mmol) in MeCN (0.2 mL) was stirred at 80°C for 1 h under a nitrogen atmosphere in a 25 mL Schlenck flask. After the reaction, the solvent was removed in vacuo. 2,2′-Dipyridyl (2 mg, 0.014 mmol) and MeCN (0.2 mL) were added, and the mixture was stirred at 80°C for 1 h. The resulting green solution was cooled to room temperature. Chalcone (40 mg, 0.2 mmol) in MeCN (0.4 mL) was added, and the mixture was stirred for 20 min and then was cooled to −30°C. Diethylzinc (1 M solution in toluene, 0.24 mmol) was added dropwise, and the resulting mixture was stirred at −30°C for 12 h. The reaction was quenched with 1 M hydrochloric acid (0.6 mL), and the product was extracted with ethyl acetate (3 mL). The enantioselectivity was determined by HPLC with a Daicel OD column. The conversion was calibrated against standard samples with known composition of substrate and product.

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References

1. (a) *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5; (b) *Asymmetric Catalysis in Organic Synthesis*; Noyori, R., Ed.; Wiley & Sons: New York, 1994; (c) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; (d) *Advanced Asymmetric Synthesis*; Stephenson, G. R., Ed.; Chapman & Hall: London, 1996; (e) *Advances in Catalytic Processes*; Doyle, M. P. Ed.; JAI Press: Greemwich, Connecticut, 1995; Vol. 1.
2. (a) Corey, E. J.; Naef, R.; Hannon, J. F. *J. Am. Chem. Soc*. **1986**, *108*, 7114; (b) Greene, A. E.; Lansard, J. P.; Luche, J. L.; Petrier, C. *J. Org. Chem*. **1984**, *49*, 931.
3. Soai, K.; Yokoyama, S.; Hayasaka, T.; Ebihara, K. *J. Org. Chem*. **1988**, *53*, 4149.
4. (a) Soai, K.; Hayasaka, T.; Ugajin, S. *J. Chem. Soc., Chem. Commun*. **1989**, 516; (b) Soai, K.; Okudo, M.; Okamoto, M. *Tetrahedron Lett*. **1991**, *32*, 95.
5. Bolm, C.; Ewald, M. *Tetrahedron Lett*. **1990**, *31*, 5011.
6. Vries, A.-H. M.; Imbos, R.; Feringa, B. L. *Tetrahedron: Asymmetry* **1997**, *8*, 1467.
7. (a) Riley, D. P.; Shumate, R. E. *J. Org. Chem*. **1980**, *45*, 5187; (b) Oliver, J. D.; Riley, D. P. *Organometallics* **1983**, *2*, 1032; (c) Chan, A. C. S.; Zhang, F. Y.; Yip, C. W. *J. Am. Chem. Soc*. **1997**, *119*, 4081; (d) Chan, A. C. S.; Zhang, F. Y. *Tetrahedron: Asymmetry* **1998**, *9*, 1179.
8. Jiang, Y. Z.; Qin, Y.; Mi, A. Q. *Tetrahedron: Asymmetry* **1994**, *5*, 1211.
9. Takehara, J.; Hashiguchi, S.; Fujii, A.; Inoue, S.; Ikariya, T.; Noyori, R. *Chem. Commun*. **1996**, 234.
10. (a) Li, S. J.; Jiang, Y. Z.; Mi, A. Q. *Tetrahedron: Asymmetry* **1992**, *3*, 1467; (b) Li, S. J.; Jiang, Y. Z.; Mi, A. Q.; Yang, G. S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 885; (c) Li, S. J.; Mi, A. Q.; Yang, G. S.; Jiang, Y. Z. *Synth. Commun*. **1992**, *22*, 1497.
11. Jiang, Y. Z.; Mi, A. Q.; Wang, Z. Y.; Li, S. J. *Youji HuaXue* **1994**, *14*, 68.