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Enantioselective addition of diethylzinc to aldehydes induced by a new chiral Ti(IV) catalyst

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Abstract

A new chiral titanium reagent, derived from optically active *trans*-1,2-dicamphorsulfonamidocyclohexane **2a** and $Ti(O^iPr)_4$, was found to promote the enantioselective addition of diethylzinc to various aldehydes giving rise to the corresponding alcohols in high yields with moderate to high selectivity. © 1998 Published by Elsevier Science Ltd. All rights reserved.

1. Introduction

In recent years, there has been a great deal of interest in the development of metal catalyzed asymmetric reactions[1] and also the synthesis of ligands[2] that result in high enantioselectivity. To design efficient asymmetric catalysts, particularly in the case of nucleophilic addition of an alkyl metal on aldehyde, we became interested in developing a much simpler and readily available ligand possessing electron-withdrawing groups that feature a deep chiral pocket after complexation with $Ti(O^iPr)_4$.[3–5] In such a modified Lewis acid, the chiral ligand will not only provide a chiral environment but also increase the Lewis acidity of the catalyst which we believe to be crucial in order to realize an efficient catalytic process.

2. Results and discussion

2.1. *Preparation of ligands 2a and 2b*

Based on the above considerations, we have developed potentially useful C_2-symmetrical *trans*-1,2-biscamphorsulfonamidocyclohexane **2a, 2b** ligands for used in a catalytic enantioselective alkylation of

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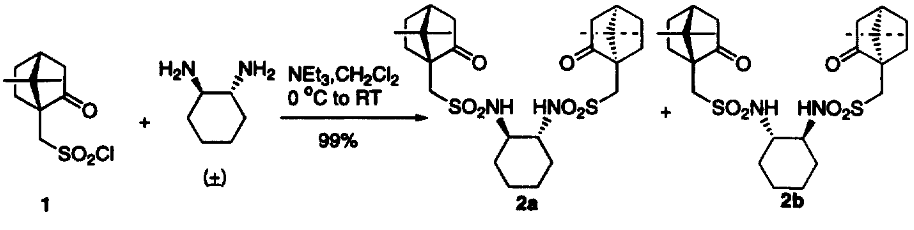
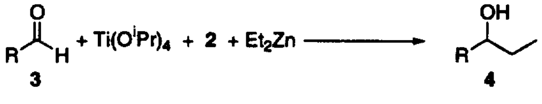
aldehydes by the disulfonamide–Ti(O^{i}Pr)$_4$–dialkylzinc system.[3–5] Compound **2a** and **2b** were synthesized respectively from (+)- and (−)-*trans*-1,2-diaminocyclohexane by reacting with 2 equiv. of (1*S*)-(+)-10-camphorsulfonyl chloride in the presence of triethylamine. Alternatively, by treating (±)-*trans*-1,2-diaminocyclohexane under the same conditions mentioned above (Scheme 1), **2a** and **2b** can be isolated by selective crystallization (*vide infra*).



Scheme 1.

2.2. Enantioselective addition of diethylzinc to aldehydes catalyzed by 2/Ti(O^{i}Pr)$_4$ complex

After the synthesis of **2a** and **2b**, we started a study of the diethylzinc addition reaction catalyzed by a complex conveniently prepared by mixing small amounts of **2a** or **2b** with Ti(O^{i}Pr)$_4$. The catalyst was found to be highly effective for the enantioselective addition of diethylzinc to a variety of aldehydes (Eq. 1). Since benzaldehyde has been extensively studied,[6,7] we focused our efforts on the diethylzinc addition to benzaldehyde in our initial study so that the results can be easily compared with those from previous studies.[3–7] The reaction was found to be quite clean with essentially no byproduct observed (Table 1). By using hexane, dichloromethane and toluene as solvents and 20 mol% of chiral ligand **2a** at −20°C, the addition products were isolated in 96–99% yield with 73–81% enantiomeric excess (ee) in favor of the *S* isomer. However, in THF solution at 27°C the addition product was obtained in 89% yield with 91% ee (entry 5). When ligand **2b** was applied to the same reaction conditions as **2a** using hexane as solvent, the addition product was isolated in 99% yield with 57% ee in favor of the *R* isomer (entry 2). Although, using THF as solvent gave the best enantioselectivity in the case of benzaldehyde, it was not the best solvent for other aldehydes since a slower reaction rate and inferior enantioselectivity was observed; for instance, *p*-methoxybenzaldehyde gave 28% yield and 68% ee of the addition product after reaction at 30°C for 16 h.



(1)

The applicability of the present catalytic system to the diethylzinc addition reaction with various substituted aldehydes was then examined using hexane as the solvent at −20°C. The results are summarized in Table 2. From Table 2, it can be observed that for *para*-substituted benzaldehydes, an electron-donating substituent (e.g. a methoxy group, entry 1) was found to increase the enantioselectivity of the reaction while an electron-withdrawing substituent (e.g. a chloride group, entry 2) was found to decrease it. For the *ortho*-substituted benzaldehyde, significantly lower enantioselectivity was observed. This is probably due to the strong steric interaction between *ortho*-substituent and chiral ligand thus weakening the coordination of the substrate to the chiral catalyst. This would effectively reduce the influence of the chiral environment of the catalyst on the orientation of the substrate, and consequently lower

Table 1
Enantioselective addition of diethylzinc to benzaldehyde (**3a**) catalyzed by **2**/Ti(O^{i}Pr)$_4$ complex[a]

entry	**2** (eq)	Ti(O^{i}Pr)$_4$(eq)	solvent	temp. (°C)	time (h)	yield (%)	ee[b](%)	config.[c]
1	**2a** (0.2)	1.4	Hexane	-20	12	99	81	*S*
2	**2b** (0.2)	1.4	Hexane	-20	12	99	57	*R*
3	**2a** (0.2)	1.4	CH_2Cl_2	-20	12	97	78	*S*
4	**2a** (0.2)	1.4	Toluene	-20	12	96	73	*S*
5	**2a** (0.2)	1.4	THF	27	10	89	91	*S*

(*a*) 3eq. of diethylzinc was used. (*b*) Determined by HPLC with Chiralcel OD column. (*c*) By the comparison of $[\alpha]_D$ with data reported in reference 8.

Table 2
Enantioselective addition of diethylzinc to aldehydes catalyzed by **2a**/Ti(O^{i}Pr)$_4$ complex[a]

entry	aldehyde	time (h)	yield (%)	ee[b](%)	config.	ref.
1	*p*-Methoxybenzaldehyde **3b**	14	91	87	*S*	8
2	*p*-chlorobenzaldehyde **3c**	12	95	77	*S*	8
3	*o*-Methoxybenzaldehyde **3d**	16	95	59	*S*	10
4	2-naphthaldehyde **3e**	14	99	90	*S*	11
5	(*E*)-cinnamaldehyde **3f**	12	93	88	*S*	8
6	3-phenylpropionaldehyde **3g**	12	94	76	*S*	8

(*a*) substrate : **2a** : Ti(O^{i}Pr)$_4$: Et_2Zn=1.0 : 0.2 : 1.4 : 3.0 (molar ratio); solvent=hexane; at -20 °C. (*b*) Determined by HPLC with Chiralcel OD column.

enantioselectivity was observed for the alkylation of 2-methoxybenzaldehyde (entry 3). In comparison with benzaldehyde, the sterically more demanding 2-naphthaldehyde gave better enantioselectivity (entry 4). Additionally, (*E*)-cinnamaldehyde and 3-phenylpropionaldehyde gave addition products in 88 and 76% ee respectively. All addition products are in the *S* configuration by comparison of the $[\alpha]_D$ value with literature data.

In conclusion, a new chiral ligand has been developed and has been shown to catalyze the addition of diethylzinc to a variety of aldehydes with moderate to high enantioselectivity after complexation with Ti(O^{i}Pr)$_4$. Further modification of the ligand and the exploration of potential asymmetric catalysis in other reactions are in progress.

3. Experimental section

3.1. General

All melting points were uncorrected. ^1H and ^{13}C NMR were measured on Varian GEMINI-300, Varian UNITY-400 or Bruker AC-300 MHz NMR spectrometers. HRMS analyses were measured on a JEOL JMS-HX110 mass spectrometer. HPLC analysis were performed on a HITACHI L-6200 chromatography system with L-4200 UV detector at 254 nm. Chiralcel OD column was purchased from Daicel Chemical Industries, Ltd. Optical rotations were measured with a DIP-1000 polarimeter. CH_2Cl_2 was distilled from

CaH_2. THF was distilled from potassium. Hexane and toluene were distilled from sodium. $Ti(O^iPr)_4$ was purchased from Aldrich. Et_2Zn was purchased from STREM.

*3.2. (1*R*,2*R*)-*N,N′*-Bis[(1*S*,4*R*)-7,7-dimethyl-2-oxo-bicyclo[2.2.1]heptylmethanesulfonyl]-1,2-cyclohexyldiamine **2a** and (1*S*,2*S*)-*N,N′*-bis[(1*S*,4*R*)-7,7-dimethyl-2-oxo-bicyclo[2.2.1]heptylmethanesulfonyl]-1,2-cyclohexyldiamine **2b***

(1*S*)-(+)-10-Camphorsulfonyl chloride **1** (5.20 g, 20.8 mmol) in CH_2Cl_2 (25 mL) was added to a stirred solution of triethylamine (3 g, 42 mmol) and racemic *trans*-1,2-diaminocyclohexane (1.14 g, 10 mmol) in CH_2Cl_2 (5 mL) at 0°C over a 1 h period. The reaction was then allowed to come to room temperature and stirred for an additional hour. The reaction was quenched by pouring into saturated $NaHCO_3$ solution (20 mL) then the pH value was adjusted to 7 and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried with Na_2SO_4, then evaporated to give a mixture of **2a** and **2b** (5.37 g, 99%). About 10% of the diastereomer **2a** was crystallized and collected when a boiling solution of ethyl acetate saturated with the mixture of **2a** and **2b** was cooled to 25°C. The remaining solution was added with hexane to the cloudy point. After standing for 12 h, about 10% of the diastereomer **2b** was crystallized and collected. The remaining solution was concentrated and the above procedure was repeated. Thus, about 75% of **2a** and **2b** were separated into pure form by repeating the aforementioned procedure five times. **2a**: mp 242°C; $[\alpha]_D^{26}$ +26.2 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (s, 6H), 1.01 (s, 6H), 1.25–1.45 (m, 6H), 1.65–1.75 (m, 2H), 1.86–2.39 (m, 14H), 2.97 (d, *J*=15 Hz, 2H), 3.15 (m, 2H), 3.47 (d, *J*=15 Hz, 2H), 5.55 (d, *J*=6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.23, 58.71, 57.29, 50.53, 48.29, 42.61, 42.39, 33.54, 26.79, 25.80, 24.16, 19.52, 19.34; HRMS (M^+) calcd for $C_{26}H_{42}O_6N_2S_2$ 542.2484, found 542.2457; IR (KBr) 3362, 1750, 1636 cm^{-1}. **2b**: mp 227°C; $[\alpha]_D^{26}$ +41.0 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.85 (s, 6H), 1.03 (s, 6H), 1.30–1.45 (m, 6H), 1.56–2.10 (m, 10H), 2.20–2.30 (m, 2H), 2.30–2.42 (m, 4H), 2.98 (d, *J*=15 Hz, 2H), 3.20–3.23 (m, 2H), 3.51 (d, *J*=15 Hz, 2H), 5.49 (d, *J*=6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.33, 58.87, 56.56, 51.24, 48.36, 42.73 (2C), 33.89, 26.85, 25.46, 24.27, 19.74, 19.63; HRMS $(M+H)^+$ calcd for $C_{26}H_{43}O_6N_2S_2$ 543.2563, found 543.2570; IR (KBr) 3362, 1750, 1636 cm^{-1}.

3.3. General procedure for the enantioselective addition of diethylzinc to aldehydes

To a stirred solution of compound **2a** (0.11 g, 0.20 mmol) in dichloromethane (5 mL) was added titanium tetraisopropoxide (0.42 mL, 1.4 mmol) under Ar at room temperature. After stirring for 1 h, the mixture was cooled to −78°C and diethylzinc[9] (0.30 mL, 3.0 mmol) was added. The resulting mixture was stirred for 0.5 h, then benzaldehyde (0.1 mL, 1 mmol) was added. The mixture was stirred at −78°C for an additional 0.5 h then warmed to −20°C. The disappearance of the aldehyde was monitored by thin layer chromatography (ethyl acetate/hexane=1/5). The reaction mixture was quenched with 1 N HCl (10 mL), filtered, and the filtrate was extracted with ethyl acetate (3×5 mL). The combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$, then concentrated in vacuo. The residue was distilled under reduced pressure (100°C/0.3 mmHg) to afford (*S*)-1-phenylpronpanol 135 mg (99%).

3.4. Determination of enantiomeric excess (ee) of the corresponding alcohol

*3.4.1. 1-Phenylpropanol **4a***

Crude product was purified by bulb to bulb distillation (100°C/0.3 mmHg) to give *S*-enriched product (99%): $[\alpha]_D^{24}$ −36.6 (*c* 0.99, $CHCl_3$) [lit.[8] $[\alpha]_D^{22}$ −47.6 (*c* 6.11, $CHCl_3$) for *S* enantiomer in 98% ee].

The product was determined as 81% ee by HPLC analysis. The t_R of the *R* isomer is 14.1 min and that for the *S* isomer is 16.6 min [hexane/2-propanol (97.5/2.5), 1.0 mL/min].

3.4.2. 1-(4-Methoxyphenyl)propanol ***4b***

Crude product was purified by bulb to bulb distillation (150°C/0.3 mmHg) to give *S*-enriched product (91%): $[\alpha]_D^{24}$ −28.3 (*c* 2.20, C_6H_6) [lit.[8] $[\alpha]_D^{22}$ −32.1 (*c* 1.25, C_6H_6) for *S* enantiomer in 93% ee]. The product was determined as 87.1% ee by HPLC analysis. The t_R of the *R* isomer is 17.99 min and that for the *S* isomer is 20.0 min [hexane/2-propanol (97.5/2.5), 1.0 mL/min].

3.4.3. 1-(4-Chlorophenyl)propanol ***4c***

Crude product was purified by bulb to bulb distillation (120°C/0.3 mmHg) to give *S*-enriched product (95%): $[\alpha]_D^{24}$ −19.55 (*c* 1.0, C_6H_6) [lit.[8] $[\alpha]_D^{22}$ −23.5 (*c* 0.82, C_6H_6) for *S* enantiomer in 93% ee]. The product was determined as 77% ee by comparison of the $[\alpha]_D$ value with that in the literature.[8]

3.4.4. 1-(2-Methoxyphenyl)propanol ***4d***

Crude product was purified by bulb to bulb distillation (150°C/0.3 mmHg) to give *S*-enriched product (95%): $[\alpha]_D^{24}$ −36.0 (*c* 0.71, $C_6H_5CH_3$) [lit.[10] $[\alpha]_D^{22}$ +37.6 (*c* 3.02, $C_6H_5CH_3$) in 73% ee]. The product was determined as 59% ee by HPLC analysis. The t_R of the *R* isomer is 32.83 min and that for the *S* isomer is 30.35 min [hexane/2-propanol (100/0.8), 1.0 mL/min].

3.4.5. 1-(2-Naphthyl)propanol ***4e***

Crude product was purified by bulb to bulb distillation (150°C/0.3 mmHg) to give *S*-enriched product (99%): $[\alpha]_D^{24}$ −19.2 (*c* 1.79, C_6H_6) [lit.[11] $[\alpha]_D^{22}$ −26.6 (*c* 3.35, C_6H_6) for *S* enantiomer in 97% ee]. The product was determined as 90.7% ee by HPLC analysis. The t_R of the *R* isomer is 33.92 min and that for the *S* isomer is 29.35 min [hexane/2-propanol (97.5/2.5), 1.0 mL/min].

3.4.6. trans-*1-Phenyl-1-penten-3-ol* ***4f***

Crude product was purified by bulb to bulb distillation (110°C/0.3 mmHg) to give *S*-enriched product (91%): $[\alpha]_D^{24}$ −6.3 (*c* 1.73, $CHCl_3$) [lit.[8] $[\alpha]_D^{22}$ −5.7 (*c* 100, $CHCl_3$) for *S* enantiomer in 96% ee]. The product was determined as 87.6% ee by HPLC analysis. The t_R of the *R* isomer is 8.96 min and that for the *S* isomer is 13.02 min [hexane/2-propanol (9/1), 1.0 mL/min].

3.4.7. 1-Phenyl-3-pentanol ***4g***

Crude product was purified by bulb to bulb distillation (110°C/0.3 mmHg) to give *S*-enriched product (94%): $[\alpha]_D^{24}$ +16.8 (*c* 1.2, EtOH) [lit.[8] $[\alpha]_D^{22}$ +23.9 (*c* 1.44, EtOH) for *S* enantiomer in 90% ee]. The product was determined as 76% ee by HPLC analysis. The t_R of the *R* isomer is 21.55 min and that for the *S* isomer is 23.83 min [hexane/2-propanol (97.5/2.5), 1.0 mL/min].

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References

1. (a) Ojima, I. *Catalytic Asymmetric Synthesis*; VCH: Weinhem, 1993. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley: New York, 1994.
2. Brunner, H.; Zettlmeier, W. *Handbook of Enantioselective Catalysis*; VCH: Weinheim, 1993.
3. For disulfonamides as ligands: (a) Takahashi, H.; Kawakita, T.; Yoshioka, M.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 7095. (b) Yoshioka, M.; Kawakita, T.; Ohno, M. *ibid.* **1989**, *30*, 1657. (c) Qiu, J.; Guo, C.; Zhang, X.-M. *J. Org. Chem.* **1997**, *62*, 2665.
4. For TADDOLs as ligands: (a) Schmidt, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 99. (b) Ito, Y. N.; Ariza, X.; Beck, A. K.; Bohac, A.; Granter, C.; Gawley, R. E.; Kuhnle, F. N. M.; Tuleja, J.; Wang, Y. M.; Seebach, D. *Helv. Chim. Acta* **1994**, *77*, 2071.
5. For more related ligands: (a) Ito, K.; Kimura, Y.; Okamura, H.; Katsuki, T. *Synlett* **1992**, 573. (b) Soai, K.; Hirose, Y.; Ohno, Y. *Tetrahedron: Asymmetry* **1993**, *4*, 1473. (c) Dreisbach, C.; Kragl, U.; Wandrey, C. *Synthesis* **1994**, 911. (d) Waldman, H.; Weigerding, M.; Dreisbach, C.; Wandrey, C. *Helv. Chim. Acta* **1994**, *77*, 2111. (e) Langer, F.; Schwink, L.; Devasagayaraj, A.; Chavant, P.-Y.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 8229. (f) Nakai, T.; Mori, M. *Tetrahedron Lett.* **1997**, *38*, 6233. (g) Zhang, F. Y.; Yip, C.-W.; Cao, R.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 585. (h) Zhang, F. Y.; Chan, A. S. C. *ibid.* **1997**, *8*, 3651. (i) Cernerud, M.; Skrinning, A.; Bergere, I.; Moberg, C. *ibid.* **1997**, *8*, 3437.
6. For reviews see: (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.
7. For more recent related works: (a) Bolm, C.; Fernandez, K. M.; Seger, A.; Raabe, G. *Synlett* **1997**, 1051. (b) Asami, M.; Inoue, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1687. (c) Kitajima, H.; Ito, K.; Katsuki, T.; Aoki, Y. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 207. (d) Hu, Q.-S.; Huang, W.-S.; Pu, L. *J. Am. Chem. Soc.* **1997**, *119*, 12454. (e) Nakano, H.; Iwasa, K.; Hongo, H. *Heterocycles* **1997**, *44*, 435. (f) Vidalferran, A.; Moyano, A.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **1997**, *62*, 4970. (g) Prasad, K. R. K.; Joshi, N. N. *J. Org. Chem.* **1997**, *62*, 3770. (h) Williams, D. R.; Fromhold, M. G. *Synlett* **1997**, 523. (i) Fulton, D. A.; Gibson, C. L. *Tetrahedron Lett.* **1997**, *38*, 2019. (j) Wilken, J.; Groger, H.; Kossenjans, M.; Martens, J. *Tetrahedron: Asymmetry* **1997**, *8*, 2761. (k) Chelucci, G.; Pinna, G. A.; Saba, A. *ibid.* **1997**, *8*, 2571. (l) Beliczey, J.; Giffels, G.; Kragl, U.; Wandrey, C. *ibid.* **1997**, *8*, 1529. (m) Cicchi, S.; Crea, S.; Goti, A.; Brandi, A. *ibid.* **1997**, *8*, 293. (n) Goralski, C. T.; Chrisman, W.; Hasha, D. L.; Nicholson, L. W.; Rudolf, P. R.; Zakett, D.; Singaram, B. *ibid.* **1997**, *8*, 3863. (o) Pu, L.; Hu, Q. S.; Huang, W.-S. *J. Org. Chem.* **1998**, *63*, 1364. (p) Brunel, J. M.; Constantieux, T.; Legrand, O.; Buono, G. *Tetrahedron Lett.* **1998**, *39*, 2961. (q) Anderson, J. C.; Harding, M. *Chem. Commun.* **1998**, 393. (r) Cho, B. T.; Chun, Y. S. *Tetrahedron: Asymmetry* **1998**, *9*, 1489. (s) Bringmann, G.; Breuning, M. *ibid.* **1998**, *9*, 667. (t) Ramon, D. J.; Yus, M. *Tetrahedron* **1998**, *54*, 5651.
8. Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071.
9. Diethylzinc (neat) is a flammable and moisture-sensitive liquid, which must be handled with care to avoid a fire upon exposure to air.
10. Soai, K.; Nishi, M.; Ito, Y. *Chem. Lett.* **1987**, 2405.
11. Watanabe, M.; Araki, S.; Butsugan, Y.; Uemura, M. *J. Org. Chem.* **1991**, *56*, 2218.