Pergamon

Tetrahedron Letters 41 (2000) 10263–10266

TETRAHEDRON LETTERS

Chiral ligands for asymmetric synthesis: enantioselective addition of diethylzinc to aromatic aldehydes catalyzed by chiral *N*-α-pyridylmethyl amino alcohols

Hongying Yun, Yangjie Wu,* Yusheng Wu, Kuiling Ding and Ying Zhou

Department of Chemistry, Zhengzhou University, Zhengzhou 450052, PR China

Received 31 May 2000; revised 9 October 2000; accepted 19 October 2000

Abstract

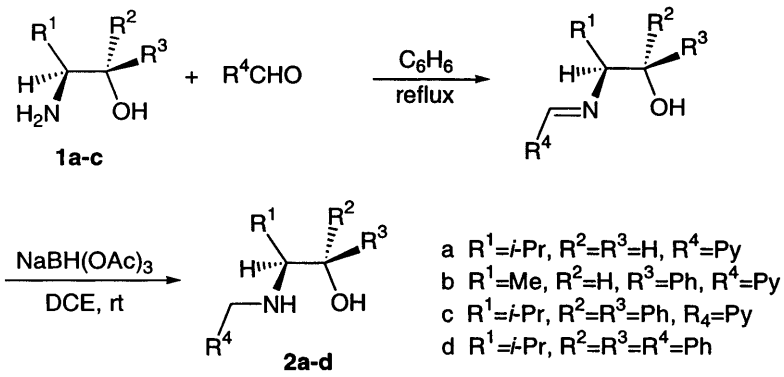
A series of chiral ligands **2a–d** were conveniently prepared from β-amino alcohols through a two-step sequence and applied to catalysis of enantioselective addition of diethylzinc to benzaldehyde. Among them ligand **2c** was found to show the best asymmetric induction for the reaction and catalyze the addition to various aromatic aldehydes to provide (*R*)-secondary alcohols in up to 98.3% ee. © 2000 Elsevier Science Ltd. All rights reserved.

Amongst asymmetric catalysis of C–C bond formation, enantioselective addition of diorganozinc reagents to aldehydes in the presence of catalytic amounts of chiral β-amino alcohols is a convenient method for the preparation of optically active secondary alcohols.[1] Various catalysts derived from β-amino alcohols have been reported to catalyze this kind of reaction with excellent asymmetric induction.[2] Recently, pyridine derived carbinols[3] and plane-extended pyridyl alcohols[4] have been developed as chiral ligands in the enantioselective addition of dialkylzinc to aldehydes, but most of them gave only moderate ee. Herein, we demonstrate an efficient synthesis of novel chiral ligands, *N*-α-pyridylmethyl-β-amino alcohols **2a–c** and *N*-benzyl amino alcohol **2d**, through a two-step reaction approach and their application to the enantioselective addition of diethylzinc to various aromatic aldehydes.

The synthesis of ligands **2a–d** is shown in Scheme 1. The (*S*)-amino alcohol **1** (**1b** is the commercially available (1*R*,2*S*)-(−)-norephedrine) and one equivalent of 2-pyridinecarboxaldehyde or benzaldehyde were mixed in dry benzene and refluxed for 2 hours using a Dean–Stark trap to give the Schiff's base in quantitative yield. Reduction of the Schiff's base was carried out in dry 1,2-dichloroethane with two equivalents of sodium triacetoxyborohydride.[5] After a standard workup, **2a–d** were obtained in high yields (72–98%). All of the new chiral ligands were characterized by elemental analysis, IR and ^{1}H NMR spectra.[6] Some of the results are listed in Table 1. Recently, Christopher et al. have reported the synthesis of **2b** using a similar method.[7]

* Corresponding author. E-mail: wyj@mail.zzu.edu.cn

0040-4039/00/$ - see front matter © 2000 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(00)01842-6



Scheme 1. Synthesis of **2a–d**

Table 1
Some data about synthesis and characterization of **2**

Product	Time[a] (h)	Mp (°C)	Yield[b] (%)	$[\alpha]_D$ ($c=1.0$, CH_2Cl_2)
2a	24	Oil	98	+28.2[c]
2b	24	Oil	98	+3.90[c]
2c	96	119–121	81	−68.0[d]
2d	48	133–134	72	−40.8[e]

[a] Refers to the time of reduction of the Schiff's base.
[b] Isolated yields.
[c] The optical rotation was measured at 20°C.
[d] The optical rotation was measured at 23°C.
[e] The optical rotation was measured at 28°C.

The novel chiral ligands **2a–d** were then evaluated to check their asymmetric induction efficiency for the addition of diethylzinc to benzaldehyde. As shown in Table 2, **2c** shows the best asymmetric induction, 1-phenylpropanol with 91.8% ee was obtained by using 5 mol% **2c** as catalyst (entry 3 versus entries 1, 2 and 4). Obviously, the presence of two bulky phenyl groups at the hydroxy-substituted carbon is crucial for the best asymmetric induction. It is interesting to note that the α-pyridylmethyl group in **2c** also plays a very important role for the enantioselectivity of the reaction (entry 3 versus 4 and 7). Thus, it may be concluded that both bulky groups at the α-carbon and the α-pyridylmethyl group at the β-amino nitrogen contribute to the high asymmetric induction obtained using **2c**. Temperature has little effect on the optical yields (entries 3–5).

The chiral ligand **2c** was then examined for the asymmetric addition of diethylzinc to a series of aromatic aldehydes under the optimized conditions. The results are summarized in Table 3. It was found that **2c** was effective for various aromatic aldehydes, including *ortho*-, *para*- and *meta*-substituted benzaldehydes (entries 1–6), thiophene-2-carboxaldehyde (entry 8) and ferrocenyl aldehyde (entry 7). The best asymmetric induction, as high as 98.3% ee, was obtained by using ferrocenyl aldehyde as substrate.

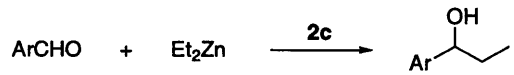
In conclusion, a series of novel chiral ligands **2a–d** has been prepared from β-amino alcohols through a two-step sequence and **2c** was found to be highly efficient for the enantioselective

Table 2
Asymmetric addition of diethylzinc to benzaldehyde in the presence of **2**[a]

Entry	Catalyst	Temp. (°C)	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)	Confign[d]
1	**2a**	rt	T–H[e]	5	69	2.5	*R*
2	**2b**	rt	T–H	5	80	3.3	*S*
3	**2c**	rt	T–H	5	98	91.8	*R*
4	**2d**	rt	T–H	6	85	34.5	*R*
5	**2c**	0	T–H	8	98	90.1	*R*
6	**2c**	−25	T–H	12	94	90.4	*R*
7	**1c**	rt	T–H	12	71	4.7	*R*

[a] The reaction was carried out in toluene with 5 mol% of catalyst and 2.5 equiv. of diethylzinc (4.17 M solution in hexane) relative to benzaldehyde.
[b] Isolated yields.
[c] Determined by HPLC using a chiral OD column.
[d] Configurations were determined by comparison of optical rotations with the literature.[8]
[e] Toluene and hexane, 4:1 (v/v).

Table 3
Asymmetric addition of diethylzinc to aromatic aldehydes in the presence of **2c**



Entry[a]	Aldehyde	Solvent[b]	Time (h)	Yield[c] (%)	ee[d] (%)	Confign[e]
1	*p*-ClC_6H_4CHO	T–H	5	97	91.5	*R*
2	*p*-$MeOC_6H_4CHO$	T–H	6	96	92.3	*R*
3	*p*-MeC_6H_4CHO	T–H	5	98	96.2[g]	*R*
4	*m*-ClC_6H_4CHO	T–H	5	70	90.2	*R*
5	α-Naphthaldehyde	T–H	6	94	80.9	*R*
6	*o*-$MeOC_6H_4CHO$	T–H	5	95	88.1	*R*
7	FcCHO[f]	T–H	5	88	98.3	*R*
8	Thiophene-2-carboxaldehyde	T–H	5	95	94.4	Nd[h]

[a] The reactions were carried out by using 5 mol% **2c** at rt.
[b] Toluene and hexane, 4:1 (v/v).
[c] Isolated yields.
[d] Determined by HPLC using a chiral OD column.
[e] Determined by comparison of optical rotations with the literature.
[f] Ferrocenyl aldehyde.
[g] Determined by comparison of the optical rotation value with the literature value.[9]
[h] Not determined.

addition of diethylzinc to aromatic aldehydes. The excellent asymmetric induction due to **2c** can be attributed to the presence of steric effect due to the diphenyl groups at the hydroxyl substituted carbon and the α-pyridylmethyl group at the β-amino nitrogen. This result provides new information for the design of novel chiral tridentate ligands for this type of reaction. Further work is undergoing to extend the variety of this type of chiral ligand and applications of their metallic complexes to other types of asymmetric reactions.

Acknowledgements

We are grateful to the National Natural Sciences Foundation of People's Republic of China (No. 29872034) for financial support.

References

1. For general discussion and comprehensive reviews, see: (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (b) *Asymmetric Catalysis*; Ojima, I., Ed.; VCH: New York, 1993. (c) Brunner, H.; Zettlmeier, W. *Handbook of Enantioselective Catalysis*; VCH: Weinheim, 1993. (d) Lin, G. Q.; Chen, Y. Q.; Chen, X. Z.; Li, Y. M. *Chiral Synthesis: Asymmetric Reactions and Their Applications*; Science Press: Beijing, 2000. (e) Soai, K.; Niwa, S. *Chem. Rev*. **1992**, *92*, 833. (f) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl*. **1991**, *30*, 49.
2. For recent examples, see: (a) Reddy, K. S.; Sola, L.; Moyano, A.; Pericas, M. A.; Riera, A. *Synthesis* **2000**, 165. (b) Hailes, H. C.; Madden, J. *Synlett* **1999**, 105. (c) Aurich, H. G.; Biesemeier, F.; Geiger M.; Harms, H. *Liebig. Ann*. **1997**, 423. (d) Li, Z.; Upadhyay, V.; DeCamp, A. E.; Dimichele, L.; Reider, P. J. *Synthesis* **1999**, 1453. (e) Kitamura, M.; Suga, S.; Miwa, M.; Noyori, R. *J. Am. Chem. Soc*. **1995**, *117*, 4832. (f) Prasad, K. R. K.; Joshi, N. N. *J. Org. Chem*. **1997**, *62*, 3770.
3. (a) Williams, D. R.; Fromhold, M. G. *Synlett* **1997**, 523. (b) Kotsuki, H.; Nakagawa, Y.; Moriya, N.; Tateishi, H.; Hirotaka, H.; Ochi, M.; Suzuki, T.; Isobe, K. *Tetrahedron: Asymmetry* **1995**, *6*, 1165. (c) Kotsuki, H.; Hayakawa, H.; Tateishi, H.; Wakao, M. *Tetrahedron: Asymmetry* **1998**, *9*, 3203. (d) Chelucci, G.; Soccolini, F. *Tetrahedron: Asymmetry* **1992**, *3*, 1235. (e) Zhang, H.; Xue, F.; Mak, T. C. W.; Chan, K. S. *J. Org. Chem*. **1996**, *61*, 8002. (f) Soai, K.; Niwa, S.; Hori, H. *Chem. Commun*. **1990**, 982. (g) Shibata, T.; Morioka, H.; Tanji, S.; Hayase, T.; Kodaka, Y.; Soai, K. *Tetrahedron Lett*. **1996**, *37*, 8783.
4. Kang, J.; Kim, H. Y.; Kim, J. H. *Tetrahedron*: *Asymmetry* **1999**, *10*, 2523.
5. The use of triacetoxyborohydride in reduction, see: Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem*. **1996**, *61*, 3849.
6. Compound **2a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, $J=6.8$ Hz, 3H, CH_3), 1.02 (d, $J=6.8$ Hz, 3H, CH_3), 1.90 (m, 1H, $CH(CH_3)_2$), 2.55 (m, 1H, CHNH), 3.55 (dd, $J=7.2$ Hz, 1H, CH_AOH), 3.73 (dd, $J=7.2$ Hz, 1H, CH_BOH), 4.07 (m, 2H, CH_2Py), 7.21 (m, 1H, Py*H*), 7.27 (m, 1H, Py*H*), 7.67 (m, 1H, Py*H*), 8.56 (d, $J=4.4$ Hz, 1H, Py*H*-α). Anal. calcd for $C_{11}H_{18}N_2O$: C, 68.00; H, 9.34; N, 14.42. Found: C, 68.21; H, 9.10; N, 14.36. Compound **2b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, $J=6.4$ Hz, 3H, CH_3), 3.09 (m, 1H, CHCH$_3$), 4.14 (s, 2H, CH_2Py), 4.97 (d, $J=2.4$ Hz, 1H, CHPh), 7.24–7.35 (m, 7H, Ph*H*, Py*H*), 7.69 (m, 1H, Py*H*), 8.58 (d, $J=4.4$ Hz, 1H, Py*H*-α). Anal. calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.29; H, 7.32; N, 11.58. Compound **2c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (d, $J=6.8$ Hz, 3H, CH_3), 0.95 (d, $J=6.8$ Hz, 3H, CH_3), 2.02 (m, 1H, $CH(CH_3)_2$), 3.38 (d, $J=14$ Hz, 1H, CH_APy), 3.52 (d, $J=14$ Hz, 1H, CH_BPy), 3.62 (d, $J=1.6$ Hz, 1H, CHNH), 6.89 (d, $J=4.8$ Hz, 1H, Ph*H*), 7.12–7.74 (m, 12H, Ph*H*, Py*H*), 8.52 (d, $J=4.8$ Hz, 1H, Py*H*-α). Anal. calcd for $C_{23}H_{26}N_2O$: C, 79.73; H, 7.56; N, 8.09. Found: C, 79.73; H, 7.63; N, 8.10. Compound **2d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (m, 3H, CH_3), 0.98 (d, $J=7.2$ Hz, 3H, CH_3), 2.06 (m, 1H, $CH(CH_3)_2$), 3.28 (d, $J=12$ Hz, CH_APh), 3.46 (d, $J=12$ Hz, 1H, CH_BPh), 3.65 (s, 1H, CHNH), 7.10–7.19 (m, 4H, Ph*H*), 7.22–7.33 (m, 7H, Ph*H*), 7.57 (d, $J=7.6$ Hz, 2H, Ph*H*), 7.72 (d, $J=8.0$ Hz, 2H, Ph*H*). Anal. calcd for $C_{24}H_{27}NO$: C, 83.44; H, 7.88; N, 4.06. Found: C, 83.43; H, 7.89; N, 4.06.
7. Christopher, G. F.; Paul, M. *Tetrahedron*: *Asymmetry* **2000**, *11*, 1845.
8. Soai, K.; Watanabe, M. *J. Chem. Soc., Chem. Commun*. **1990**, 43.
9. Chaloner, P. A.; Renuka Perera, S. A. *Tetrahedron Lett*. **1987**, *28*, 3013.