(1*R*,5*R*)-1-(1′-Dimethylaminoethyl)-2-isopropylidene-5-methylcyclohexanol as a Chiral Ligand in the Enantioselective Addition of Diethylzinc to Aldehydes

Ashok K. Yadav,* Manoj Kumar, Tripti Yadav, Renuka Jain

Department of Chemistry, University of Rajasthan, Jaipur 302055, India
Fax +91(141)2700364; E-mail: drakyada@yahoo.co.in

Received 13 August 2009

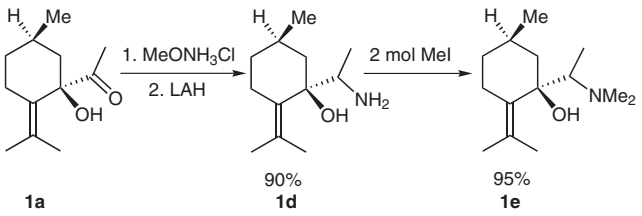
Abstract: An efficient chiral ligand, (1*R*,5*R*)-1-(1′-dimethylaminoethyl)-2-isopropylidene-5-methylcyclohexanol, has been developed for the enantioselective addition of diethylzinc to some prochiral aldehydes to afford *S*-alcohols. The overall conversion rate was 80–98% with excellent enantiomeric excess (79–98%).

Key words: ionic liquid, intermolecular reductive coupling, prochiral aldehydes, chiral ligand, enantioselectivity

Asymmetric addition of diethyl-, diphenyl-, and dialkynylzinc using a catalytic amount of chiral inductor is one of the most active and fascinating research areas for enantioselective additions to prochiral aldehydes.[1] To achieve this goal, diverse chiral ligand structures such as β-amino alcohols,[2] aminothiols,[3] amines,[4] aminonaphthols,[5] pyridyl alcohols,[6] *o*-hydroxybenzyl amines,[7] BINOL,[8] and ligands derived from natural products have been widely been exploited,[9] but the enantiomeric excess is some times disappointing. Metal complexes[10] have also been exploited to achieve this goal.

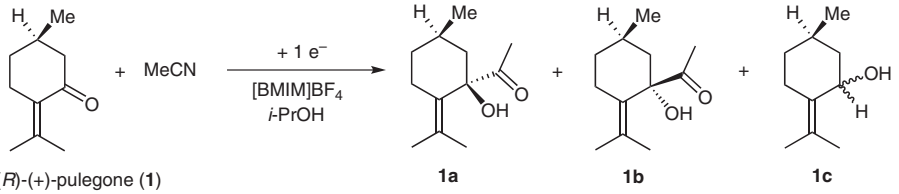
In our strategy for development of new effective chiral ligands, we have performed an intermolecular electroductive coupling[11] of (*R*)-(+)-2-isopropylidene-5-methylcyclohexanone [(*R*)-(+)-pulegone] with acetonitrile in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate propan-2-ol[12] at a smooth copper cathode. A constant current (0.1 A) was passed corresponding to 1.1 F mol^{-1} charge transfer; wherein, three products, (1*R*,5*R*)-1-(1-hydroxy-2-isopropylidene-5-methylcyclohexyl)ethanone (**1a**), (1*S*,5*R*)-1-(1-hydroxy-2-isopropylidene-5-methylcyclohexyl)ethanone (**1b**), and 2-isopropylidene-5-methylcyclohexanol (**1c**) were formed (Scheme 1).

The products were separated employing a swollen triacetyl cellulose column prepared by the reported method.[13] The elution was accomplished by ethanol, when compound **1a** was obtained first followed by **1b** and **1c** in 70%, 20% and 8% yield, respectively. The major stereoisomer **1a** upon treatment with *O*-methyloxime hydrochloride in ethanol and subsequent reduction of oximated product by lithium aluminium hydride afforded (1*R*,5*R*)-1-(1′-aminoethyl)-2-isopropylidene-5-methylcyclohexanol (**1d**) as the sole product in 90% yield. This compound upon N-methylation with methyl iodide (2 mol) furnished the desired chiral ligand, (1*R*,5*R*)-1-(1′-dimethylaminoethyl)-2-isopropylidene-5-methylcyclohexanol (**1e**)[14] in 95% yield (Scheme 2). The chiral ligand obtained, as above, was purified over a silica gel G column by eluting with hexane–ethyl acetate (8:2) and characterized, unambiguously, by elemental analysis, IR, ^{1}H NMR, and ^{13}C NMR. It was employed as chiral inductor for the addition of diethylzinc to a range of prochiral aldehydes.[15]



Scheme 2

In order to evaluate the optimum concentration of this new chiral ligand, we have studied the addition of diethylzinc to benzaldehyde at 3, 5, 8, and 10 mol% concentration. The product upon hydrolysis gave (*S*)-phenylpropan-1-ol (**4a**) in 85–90% yield with 87%, 93%, 90%, and 89% enantiomeric excess. These data clearly suggest that 5 mol% concentration of the chiral ligand **1e** is best suited for this reaction (Scheme 3).



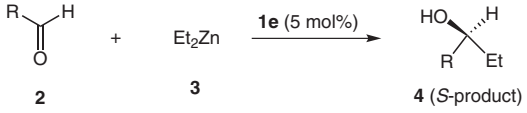
Scheme 1

SYNLETT 2010, No. 5, pp 0712–0714
Advanced online publication: 08.02.2010
DOI: 10.1055/s-0029-1219379; Art ID: D21909ST
© Georg Thieme Verlag Stuttgart · New York

Table 1 Addition of Diethylzinc to Aldehydes Using Ligand **1e** (5 mol%)

Entry	Aldehyde **2**	Product **4**	Conversion (%)	Optical rotation	ee (%)	Config.
1	PhCHO	**4a**	90	$[\alpha]_D^{25}$ –42.10 (*c* 5.3, $CHCl_3$)	93[a]	*S*
2	PhCH=CHCHO	**4b**	82	$[\alpha]_D^{25}$ –5.80 (*c* 3.2, $CHCl_3$)	88[b]	*S*
3	2-$MeOC_6H_4CHO$	**4c**	95	$[\alpha]_D^{25}$ –43.24 (*c* 3.0, $PhCH_3$)	92[c]	*S*
4	4-$MeOC_6H_4CHO$	**4d**	98	$[\alpha]_D^{25}$ –16.16 (*c* 5.1, C_6H_6)	94[d]	*S*
5	*n*-$C_6H_{13}CHO$	**4e**	92	$[\alpha]_D^{25}$ –9.12 (*c* 3.7, $CHCl_3$)	95[e]	*S*
6	*n*-$C_6H_{17}CHO$	**4f**	95	$[\alpha]_D^{26}$ +7.79 (*c* 8.7, EtOH)	96[f]	*S*
7	$PhCH_2CH_2CHO$	**4g**	94	$[\alpha]_D^{25}$ +26.26 (*c* 5.0, EtOH)	98[g]	*S*
8	$C_6H_{11}CHO$	**4h**	80	$[\alpha]_D^{24}$ –6.32 (neat)	79[f]	*S*

[a] $[\alpha]_D$ –45.45 (*c* 5.15, $CHCl_3$).[16]
[b] $[\alpha]_D$ –6.6 (*c* 3.2, $CHCl_3$).[17]
[c] $[\alpha]_D$ –47.0 (*c* 1.2, $PhCH_3$).[18]
[d] $[\alpha]_D$ –17.2 (*c* 5.0, benzene).[19]
[e] $[\alpha]_D$ –9.6 (*c* 8.3, $CHCl_3$).[20]
[f] The e was determined by ^1H NMR analysis of the derived acetates using $Eu(hfc)_3$.
[g] $[\alpha]_D$ –26.8 (C, 5.0, EtOH).[17]



2 **3** **4** (*S*-product)

Scheme 3

Eight prochiral aldehydes **4a**–**h** were studied, and the corresponding products have been assigned *S*-configuration by comparison to the known values in the literature and by derivatization with $Eu(hfc)_3$ and recording ^1H NMR spectra (Table 1). All the products **4a**–**h** have been characterized by IR, ^1H NMR, ^{13}C NMR, and elemental analyses. These data for the representative compounds **4a** and **4e** have been presented.[21]

The observation of the data presented in Table 1 reveals that, with the new chiral ligand **1e**, the overall conversion rate is 80–98% with excellent ee ranging from 79–98%. *o*-Methoxybenzaldehyde afforded lower enantioselectivity than its *para* isomer, probably due to the steric effect exerted by the *ortho* substitutent. Amongst the prochiral aldehydes examined, aliphatic aldehydes gave best enantiomeric excesses with the exception of cyclohexyl carboxaldehye which exhibited the lowest enantioselectivity.

In conclusion, we have demonstrated that the chiral ligand **1e** gave excellent enantiomeric excesses for the addition for diethylzinc to a range of prochiral aldehydes **4a**–**h**. The work on the synthesis of new chiral ligands derived from (+)-dihydrocarvone, (–)-menthone, and (+)-camphor is under investigation and results will be addressed in future in the form of full paper.

Acknowledgment

We thank the Head of the Department of Chemistry, University of Rajasthan, Jaipur for providing laboratory facilities. Analytical data from CDRI, Lucknow are gratefully acknowledged. We are also grateful to DST, New Delhi for financial assistance.

References and Notes

(1) (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. (c) Pu, L.; Yu, H. B. *Chem. Rev.* **2001**, *101*, 757. (d) Zhu, H. J.; Jiang, J. X.; Ren, J.; Yan, Y. M.; Pittman, C. U. *Curr. Org. Synth.* **2005**, *2*, 547. (e) Hatano, M.; Miyamoto, T.; Ishihara, K. *Curr. Org. Chem.* **2007**, *11*, 127.

(2) (a) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071. (b) Cho, B. T.; Chun, Y. S. *Tetrahedron: Asymmetry* **1998**, *9*, 1489. (c) Joshi, S. N.; Malhotra, S. V. *Tetrahedron: Asymmetry* **2003**, *14*, 1763. (d) Parrott, R. W.; Hitchcock, S. R. *Tetrahedron: Asymmetry* **2008**, *19*, 19; and references cited therein. (e) Sachi, P.; Dabiri, M.; Kozehgary, G.; Heydari, S. *Synth. Commun.* **2009**, *39*, 2575. (f) Binder, C.; Bautista, A.; Zaidlewicz, M.; Kizeminski, M. P.; Oliver, A.; Singaram, B. *J. Org. Chem.* **2009**, *74*, 2337; and references cited therein. (g) Ichikawa, Y.; Yamamoto, S.; Kotsuki, H.; Nokano, K. *Synlett* **2009**, 2281; and references cited therein.

(3) (a) Anderson, J. C.; Harding, M. *Chem. Commun.* **1998**, 393. (b) Tseng, S. L.; Yang, T. K. *Tetrahedron: Asymmetry* **2005**, *16*, 773. (c) Tseng, S. L.; Yang, T. K. *Tetrahedron: Asymmetry* **2004**, *15*, 3375.

(4) (a) Chelucci, G.; Conti, S.; Falorni, M.; Giacomelli, G. *Tetrahedron* **1991**, *47*, 8251. (b) Weselinski, L.; Stephiak, P.; Jurczak, J. *Synlett* **2009**, 2261; and references cited therein.

(5) (a) Cardellicchio, C.; Ciccarella, G.; Naso, F.; Perna, F.; Tortorella, P. *Tetrahedron* **1999**, *55*, 14685. (b) Liu, D. X.; Zhang, L. C.; Wang, Q.; Da C, S.; Xin, Z. Q.; Wang, R.; Choi, C. K. M.; Chan, A. S. C. *Org. Lett.* **2001**, *3*, 2733; and references cited therein. (c) Yand, X.; Hirose, T.; Zhang, G. *Tetrahedron: Asymmetry* **2008**, *19*, 1670; and references

cited therein.
(6) (a) Bolm, C.; Zehnder, M.; Bur, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 205. (b) Cheng, Y. Q.; Zheng, B.; Kang, C. Q.; Guo, H. Q.; Gao, L. X. *Tetrahedron: Asymmetry* **2008**, *19*, 1572.
(7) (a) Palmieri, G. *Tetrahedron: Asymmetry* **2000**, *11*, 3361. (b) Yang, X. F.; Wang, Z. H.; Koshizawa, T.; Yasutake, M.; Zhang, G. Y.; Hirose, T. *Tetrahedron: Asymmetry* **2007**, *18*, 1257.
(8) (a) Yang, X. W.; Sheng, J. H.; Da C, S.; Wang, H. S.; Su, W.; Wang, R.; Chan, A. S. C. *J. Org. Chem.* **2000**, *65*, 295. (b) Guo, S.; Judesh, Z. M. A. *Tetrahedron Lett.* **2009**, *50*, 281.
(9) (a) *Chiral Auxilliaries and Ligands in Asymmetric Synthesis*; Seyden, J. P., Ed.; John Wiley and Sons: New York, **1995**. (b) Blaser, H. U. *Chem. Rev.* **1992**, *92*, 935. (c) Dabiri, M.; Salehi, P.; Kozehgary, G.; Heydari, S.; Heydari, A.; Esfandyari, M. *Tetrahedron: Asymmetry* **2008**, *19*, 1970.
(10) (a) Zhang, F. Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 3651. (b) Hwang, C. D.; Uang, B. J. *Tetrahedron: Asymmetry* **1998**, *9*, 3979. (c) Dean, M. A.; Hitchcock, S. R. *Tetrahedron: Asymmetry* **2008**, *19*, 2563; and references cited therein.
(11) **Typical Experimental Procedure for Preparative-Scale Electrosynthesis**
The electrolysis was carried out in a double-walled cell (Metrohm, 100 ml) equipped with cover glass inlet and outlet, thermometer, and magnetic stirrer. This cell was divided by a medium-porosity glass frit into two separate compartments. The catholyte was a 10 mL mixture of [BMIM]BF_4–*i*-PrOH (9:1) containing 0.03 M (*R*)-(+)-pulegone and 0.04 M of MeCN. The anolyte was 5 mL of [BMIM]BF_4–*i*-PrOH (9:1). A smooth copper foil (1 × 1 cm) was used as a cathode and a platinum foil (1 × 1 cm) was used as an anode. Nitrogen gas was bubbled for 10 min and the electroreductive coupling was carried out by passing current 0.1 A for the time corresponding to charge-transfer equivalent to 1.1 F/mol.
The catholyte was extracted with EtOAc (3 × 10 mL), the extract dried over anhyd $MgSO_4$, filtered, and the solvent was removed by distillation under reduced pressure. The product so obtained was purified by chromatography on a swollen triacetyl cellulose(microcrystalline) column, and elution was performed by EtOH to afford **1a** in pure form in 70% yield. R_f = 0.55 (hexane–EtOAc, 10:1). IR (neat): ν = 3460, 1700, 1640, 880 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.05 (d, 3 H, *J* = 6.5 Hz, CH_3) 1.28 (m, 2 H, CH_2), 1.60 (m, 1 H, CH), 1.65 (m, 2 H, CH_2), 1.70 (s, 6 H, 2 × CH_3), 1.95 (m, 2 H, CH_2), 2.10 (s, 3 H, $COCH_3$), 3.80 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.60, 19.20, 20.50, 21.60, 25.60, 38.40, 42.40, 92.50, 125.30, 142.70, 207.10. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.41; H, 10.27. Found: C, 73.62; H, 10.12.
(12) 1-Butyl-3-methylimidazolium tetrafluoroborate was synthesized according to the reported method, see: Palimkar, S. S.; Siddiqui, S. A.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *J. Org. Chem.* **2003**, *68*, 9371.
(13) Hesse, G.; Hagel, R. *Chromatographia* **1976**, *9*, 62.
(14) Compound **1a** was heated to reflux with *O*-methyloxime hydrochloride in the presence of 0.03 M Et_3N in EtOH. Removal of the solvent gave the oximated product which, upon lithium aluminium hydride reduction, afforded compound **1d** in 90% yield. Compound **1d**, when refluxed with 2 mol of MeI resulted in the desired chiral ligand **1e** in 95% yield; bp 150–153 °C (67 mbar); R_f = 0.4 (hexane–EtOAc, 1:1). IR (neat): ν = 3855, 2780, 1645, 886 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.05 (d, 3 H, *J* = 6.5 Hz, CH_3), 1.12 (d, 3 H, *J* = 7.1 Hz, CH_3), 1.30–1.42 (m, 4 H, 2 × CH_2), 1.62 (m, 1 H, CH), 1.75 (m, 6 H, 2 × CH_3), 1.95 (m, 2 H, CH_2), 2.30 (s, 6 H, 2 × CH_3), 2.95 [q, 1 H, *J* = 7.1 Hz, $CHN(CH_3)_2$], 3.85 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.10, 19.20, 20.60, 22.40, 26.20, 37.25, 39.50, 44.15, 66.50, 78.30, 125.20, 142.70. Anal. Calcd for $C_{14}H_{27}ON$: C, 74.59; H, 12.08; N, 6.21. Found: C, 74.43; H, 11.84; N, 5.96.
(15) Kitamura, M.; Okada, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028.
(16) Picard, R. H.; Kenyon, J. *J. Chem. Soc.* **1914**, 1115.
(17) Sato, T.; Gotoh, Y.; Wakebayashi, Y.; Fugisawe, T. *Tetrahedron Lett.* **1983**, *24*, 4123.
(18) Smaardijk, A. A.; Wynberg, H. *J. Org. Chem.* **1987**, *52*, 135.
(19) Capillon, J.; Guette, J. *Tetrahedron* **1979**, *35*, 1817.
(20) Mukaiyama, T.; Hojo, K. *Chem. Lett.* **1976**, 893.
(21) **Representative Spectroscopic Data**
(*S*)-1-phenylpropan-1-ol (4a)
Bp 94–95 (13.3 mbar); R_f = 0.35 (hexane–EtOAc, 8:2). IR (neat): ν = 3400, 3020, 2990, 1600, 1100 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 6.0 Hz, 3 H, CH_3), 1.40–1.55 (m, 2 H, CH_2CH_3), 3.60 (br s, 1 H, OH), 4.50 (t, *J* = 7.0 Hz, 1 H, CHOH), 7.10–7.40 (m, 5 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.10, 33.10, 78.20, 124.60, 128.40, 128.80, 139.20. Anal. Calcd for $C_9H_{12}O$: C, 79.36; H, 8.88. Found: C, 79.55; H, 8.70.
(*S*)-3-Nonanol (4e)
Bp 192–194 °C; R_f = 0.40 (hexane–EtOAc, 8:2). IR (neat): ν = 3600, 2970, 1350, 1100 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 6.0 Hz, 3 H, CH_3), 0.95 (t, *J* = 6.0 Hz, 3 H, CH_3), 1.20–1.62 (m, 12 H, 6 × CH_2), 2.20 (br s, 1 H, OH), 3.25 (t, *J* = 7.0 Hz, 1 H, CHOH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.00, 15.30, 22.40, 25.20, 29.80, 30.60, 33.10, 38.40, 75.50. Anal. Calcd for $C_9H_{20}O$: C, 74.92; H, 13.98. Found: C, 74.75; H, 13.80.

Copyright of Synlett is the property of Georg Thieme Verlag Stuttgart and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.