Published in final edited form as:

Tetrahedron Asymmetry. 1997 March 27; 8(6): 821–824. doi:10.1016/S0957-4166(97)00065-7.

Asymmetric alkylations and aldol reactions: (1*S*,2*R*)-2-aminocyclopentan-1-ol derived new chiral auxiliary

Arun K. Ghosh*, Hanna Cho, and Masanobu Onishi

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607-7061, USA

Abstract

Asymmetric alkylation and aldol reaction of optically active (1*S*,2*R*)-2-aminocyclopentan-1-ol derived chiral auxiliary proceeded with excellent diastereofacial selectivities (>99%) and isolated yields.

The α -amino acid derived amino alcohols have been conveniently utilized in numerous efficient asymmetric syntheses.¹ The development of new chiral auxiliaries that are not derived from natural aminoacids, however offers opportunities in terms of manipulation of structural properties and conformational rigidities necessary for a particular asymmetric process.² Recently, we have reported a number of efficient asymmetric processes involving conformationally constrained optically active *cis*-1-aminoindan-2-ols both as covalently bound chiral auxiliaries³ as well as ligands in asymmetric catalysis⁴. Conformationally constrained cyclic aminoalcohols are of particular interest to us because of their utilities as amino acid surrogates as well as ligands and chiral auxiliaries for various asymmetric synthesis. As part of our continuing interest in the design and synthesis of hydrolytically stable peptide isosteres for the HIV protease substrate binding site, we required a number of cyclic aminoalcohols that are not derived from natural aminoacids. In this context, we have prepared quantities of (1*S*,2*R*)-2-aminocyclopentan-1-ol conveniently from commercially available ethyl 2-oxocyclopentanecarboxylate and examined its ability to function as an aminoacid surrogate as well as chiral template for asymmetric synthesis. Herein, we report convenient synthesis and utilities of (4*R*,5*S*)-cyclopentano[d]oxazolidin-2-one as a highly effective chiral auxiliary in asymmetric alkylations⁵ and asymmetric syn-aldol reactions.⁶

Enantiomerically pure (4*R*,5*S*)-cyclopentano[d]oxazolidin-2-one **3** was conveniently prepared in multigram quantities by a known baker's yeast reduction⁷ of β -ketoester **1** (Scheme 1), ester hydrolysis with aqueous sodium hydroxide followed by Curtius rearrangement⁸ of the resulting β -hydroxy acid with diphenylphosphoryl azide in refluxing benzene for 12 h to afford **3** in 71% yield after silica gel chromatography. Oxazolidinone **3** was lithiated with **1** equiv of *n*BuLi in dry THF and subsequent reaction with 1.1 equiv of propionyl chloride at -78°C furnished the propionyl imide **4** in quantitative yield, $[\alpha]_{\text{D}}^{25} -183$ ($c=0.46$, CHCl_3). Enolization of imide **4** was effected⁹ by reaction of **4** with 1.1 equiv of dibutylboron triflate and 1.2 equiv of *N,N*-diisopropylethylamine at 0°C for 1 h affording

*Corresponding author. Arun.Ghosh@UIC.EDU.

the corresponding boron enolate. Condensation of the above enolate with various aldehydes at -78°C to 0°C for several hours as monitored by TLC (4–6 h), resulted in only diastereomer **5** after workup and silica gel chromatography. No other diastereomers were detected by 400 MHz ^1H -NMR spectroscopy or by HPLC analysis.¹⁰ The results of the aldol reaction of the oxazolidinone **4** with four different aldehydes are summarized in Table 1. As can be seen, conformationally constrained oxazolidinone **5** has provided almost complete diastereofacial selectivity ($>99\%$ de) and good isolated yields (70–80%) with various aldehydes. The removal of the chiral auxiliary was effected by exposure to lithium hydroperoxide in aqueous THF under standard reaction conditions¹¹ to provide the corresponding β -hydroxy acid (68–75% yield) and good recovery (80–85%) of the chiral auxiliary **3**. The absolute configuration of the aldol products was assigned by comparison of the optical rotation of the resulting β -hydroxy acid with the literature values.¹² For example, acid **7** was obtained (from aldol product **5**, entry 4) in 86% yield after silica gel chromatography, observed $+33.6$, $c=0.7$; CHCl_3 , lit.¹² $[\alpha]_{\text{D}}+31.03$, $c=1.07$; CHCl_3 . Similarly, acid **8** (from aldol product **5**, entry 2) was obtained in 88% yield, $[\alpha]_{\text{D}}+9.8$, $c=0.31$; CHCl_3 ; lit.¹² $[\alpha]_{\text{D}}+10.54$, $c=1.4$; CHCl_3 .

Asymmetric alkylation of imide **4** with benzyl bromide and allyl iodide as electrophiles was also examined. Deprotonation of the imide **4** was carried out with lithium hexamethyldisilazide in THF at -78°C for 1 h to afford the lithium enolate which upon reaction with benzyl bromide or allyliodide at -78° to -20°C for 6 h furnished **6** ($\text{R}=\text{Ph}$, vinyl) in good yields (65–72%) after silica gel chromatography.¹³ In both cases, only one diastereomer was detected by HPLC analysis and only one isomer was revealed by ^1H -NMR (400 MHz) and by ^{13}C -NMR (100 MHz) spectroscopy. Removal of the chiral auxiliary with lithium hydroperoxide furnished the acid **9**, $[\alpha]_{\text{D}}+24.6$, $c=0.95$; CHCl_3 ; lit.¹⁴ $[\alpha]_{\text{D}}+25$, CHCl_3 , and **10**, $[\alpha]_{\text{D}}+10.1$, $c=0.54$; CHCl_3 ; lit.¹⁵ $[\alpha]_{\text{D}}+10.3$, CHCl_3 , in excellent yield.

In conclusion, readily prepared (4*R*,5*S*)-cyclopentano[d]oxazolidin-2-one **3** can be utilized as a highly effective chiral auxiliary in asymmetric alkylations and asymmetric syn-aldol reactions. From a synthetic standpoint, cis-2-aminocyclopentan-1-ol derived new chiral auxiliaries should find a broad range of further applications in asymmetric synthesis.

Preparation of (4*R*,5*S*)-cyclopentano[d]oxazolidin-2-one **3**

To a stirred solution of ethyl ester **2**⁷ (2.08 g, 13.1 mmol) in a mixture of THF (2 mL) at 23°C , was added 1 M aqueous NaOH solution (26.2 mL). The resulting mixture was stirred for 1 h and then cooled down to 0°C and carefully acidified with 1 N aqueous HCl to pH 3. The mixture was thoroughly extracted with ethyl acetate (3×25 mL). The combined layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to provide the corresponding acid (1.27 g). Above acid was suspended in dry benzene (60 mL) and to it were added diphenylphosphoryl azide (3.5 mL, 16.2 mmol) and triethylamine (2.3 mL, 16.5 mmol). The resulting mixture was stirred at 23°C for 15 min and then heated at reflux for 24 h. After this period, the reaction was cooled to 23°C and the solvents were evaporated under reduced pressure to give a residue which was chromatographed over silica gel (50% EtOAc in hexane as eluent) to furnish the chiral oxazolidinone **3** (1.18 g, 71%) as a white

foam (m.p. 130–132). $[\alpha]_D -41.8$ (c 1.4, CHCl_3); lit⁷; $[\alpha]_D -42.4$ (c 0.98, CHCl_3)•, ¹H-NMR (400 MHz, CDCl_3) δ •, 5.35 (br s, 1 H), 5.05 (dd, 1 H, J=5.5, 6.5 Hz), 4.27 (t, 1 H, J=6.5 Hz), 2.15 (m, 1 H), 1.9–1.5 (m, 5 H).

Acknowledgements

Financial support of this work by the National Institute of Health (GM 53386) is gratefully acknowledged. M. O. is a visiting scientist from Nihon Nohyaku Co. Ltd, Japan.

References

1. For a recent review see: Ager DJ; Prakash I; Schaad DR *Chemical Reviews* 1996, 96, 835. [PubMed: 11848773]
2. (a) Curran DP Jeong K-S; Heffner TA; Rebek J, Jr. *J. Am. Chem. soc.* 1989, 111, 9238;(b)stack JG Curran DP; Rebek J, Jr.; Ballester P *J. Am. Chem. soc.* 1991, 113, 5918;(c)Stack JG; Curran DP; Geib SV; Rebek J, Jr.; Ballester P *J. Am. Chem. soc.* 1992, 114, 7007;(d)Boeckman RK, Jr.; Johnson AT; Musselman RA. *Tetrahedron Letters* 1994, 35, 8521;(e)Boeckman RK, Jr.; Connell BT *J. Am. Chem. soc.* 1995, 117, 12368;(f)Boeckman RK, Jr.; Liu YJ *Org. Chem.* 1996, 61, 7984; (g)Palomo C; Oiarbide M; Gonzalez A; Garcia JM; Berree F *Tetrahedron Letters* 1996, 37, 4565; (h)Chiral Auxiliaries and Ligands in Asymmetric Synthesis; SeydenPenne J Eds.; John Wiley & Sons, Inc.: New York, 1995.
3. (a) Ghosh AK; Chen Y. *Tetrahedron Letters* 1995, 36, 6811;(b)Ghosh AK; Ohnishi MJ *Am. Chem. soc.* 1996, 118, 2527;(c)Ghosh AK; Liu W; xu Y; Chen Z *Angew Chem. Int. Ed.* 1996, 35, 74; (d)Ghosh AK; Mathivanan P *Tetrahedron: Asymmetry* 1996, 7, 375;(e)Ghosh AK; Liu W *J. org. Chem.* 1996, 61, 6175. [PubMed: 11667452]
4. (a) Ghosh AK; Mathivanan P; Cappiello J. *Tetrahedron Letters* 1996, 37, 3815;(b)Ghosh AK; Mathivanan P; Cappiello J; Krishnan K *Tetrahedron: Asymmetry* 1996, 7, 2165.
5. (a) Evans DA; Britton TC; Eliman JA; Dorow RL. *J. Am. Chem. soc.* 1990, 112, 4011;(b)Myers A Yoon T. *J. Am. chem. soc.* 1994, 116, 9361;(c)Myers AG; McKinsty L J. *org. Chem* 1996, 61, 2429.
6. (a) Evans DA; Bartoli, Shih TL. *J. Am. Chem. soc.* 1981, 103, 2127;(b) Evans DA. *Aldrich. Acta* 1982, 15, 23;(c)Roder H; Helmchen G; Peters E-M; von Schmering H-G *Angew. Chem. Int. Ed. Engl.* 1984, 23, 898;(d)Masamune S; Choy W; Peterson JS; Sita LR *Angew. Chem. Int. Ed. Engl.* 1985, 24, 1;(e)Paterson I; Lister MA; McClure CK *Tetrahedron Letters* 1986, 27, 4787;(f)Braun M *Angew Chem. Int. Ed. Engl.* 1987, 26 24;(g)Corey EJ; Imwinkelreid R; Pikul S; Xiang YB *J. Am. Chem. Soc.* 1989, 111, 5493;(h)Oppolzer W'Blagg J; Rodriguez I; Walther E. *J. Am. Chem. soc.* 1990, 112, 2767;(i)Sankhavasi W; Yamamoto M'Kohmoto S; Yamada K. *Bull. Chem. soc. Jpn.* 1991, 64, 1425;(j)Drewes SE; Malissar DS; Roos GP *Chem. Ber* 1991, 124, 2913;(k)Ghosh A Duong TT; McKee SP *J. Chem. soc., Chem. Commun.* 1992, 1673; [PubMed: 30364406] (l)Yan T-H; Tan C Lee H-C; Lo H-C. *J. Am. Chem. soc.* 1993, 115, 2613;(m)Franklin AS; Paterson I *Contemporary Organic Synthesis* 1994, 317.
7. (a) Kometani T; Kitatsuji E; Matsuno R. *Chemistry Letters* 1989, 1465;(b)Didier E; Loubinoux B; Ramos Tombo GM; Rihs G *Tetrahedron* 1991, 47, 4941.
8. (a) Shiori T; Ninomiya K; Yamada S. *J. Am. Chem. soc.* 1972, 94, 6203; [PubMed: 5054412] (b)Ninomiya K; Shiori T; Yamada S *Tetrahedron* 1974, 30, 2151;(c)Grunewald GL; Ye QJ *Org. Chem.* 1988, 53, 4021;(d)Ghosh AK; McKee SP; Thompson WJ; Darke P Zugay JC *J. org. Chem.* 1993, 58, 1025. [PubMed: 30310240]
9. Evans DA; Dow RL; Shih TL; Takacs JM; Zahler RJ *Am. Chem. soc.* 1990, 112, 5290.
10. ¹H-NMR (400 MHz) spectroscopy and HPLC analysis of the product 5 (entry 2; R=Me₂CH) before silica gel chromatography has also revealed one diastereomer.
11. Evans DA; Britton TC; Ellman JA *Tetrahedron Letters* 1987, 28, 6141.
12. Masamune S; Choy W; Kerdesky FA; Imperiali BJ *Am. Chem. Soc.* 1981, 103, 1566.
13. All new compounds gave satisfactory spectroscopic and analytical results.

14. (a) Oppolzer, Philippe L. *Helv. Chim. Acta* 1992, 75, 2572;(b)Helmchen G; Niii Flockerzi D; Youssef MSK. *Angew Chem. Int. Ed. Engl.* 1979, 18, 63.
15. Rao AV; Gurjar MK; Nailaganchu BR; Bhandari A *Tetrahedron Letters* 1993, 34, 7081.

Scheme 1.

(a) Baker's yeast, sugar, H₂O; (b) aqueous NaOH, THE 23°C; (c) (PhO)₂P(O)N₃, Et₃N, PhH, reflux, 12 h; (d) *n*BuLi, THE 0°C then MeCH₂COC1, -78°C, 1 h; (e) *n*Bu₂BOTf, *i*Pr₂NEt, CH₂Cl₂, -78 to 0°C the RCHO, -78°C, 4–6 h; (f) LiOH, H₂O₂, THF-H₂O, 0°C•, (g) LiHMDS, THE -78°C, 1 h then PhCH₂Br or CH₂=CHCH₂I, -78 to -40°C, 6 h.

Table 1.Aldol reaction of oxazolidinone **4** with aldehydes

Entry	Aldehydes	Yields(%) ^a	[α] _D (5)	%de(5) ^b
1.	MeCHO	70	−121.3	>99
2.	Me ₂ CHCHO	71	−106.9	>99
3.	Me ₂ CHCH ₂ CHO	73	−124.4	>99
4.	PhCHO	80	−76.3	>99

^aYield of pure products after silica gel chromatography.^bDetermined by HPLC and 400 MHz ¹H NMR spectroscopy before and after chromatography.