# New synthesis of Evans chiral oxazolidinones by using Sharpless AA reaction

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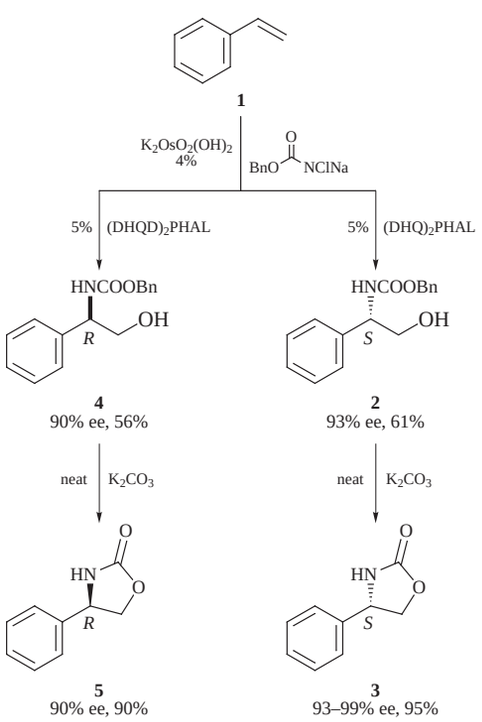
1 PERKIN COMMUNICATION

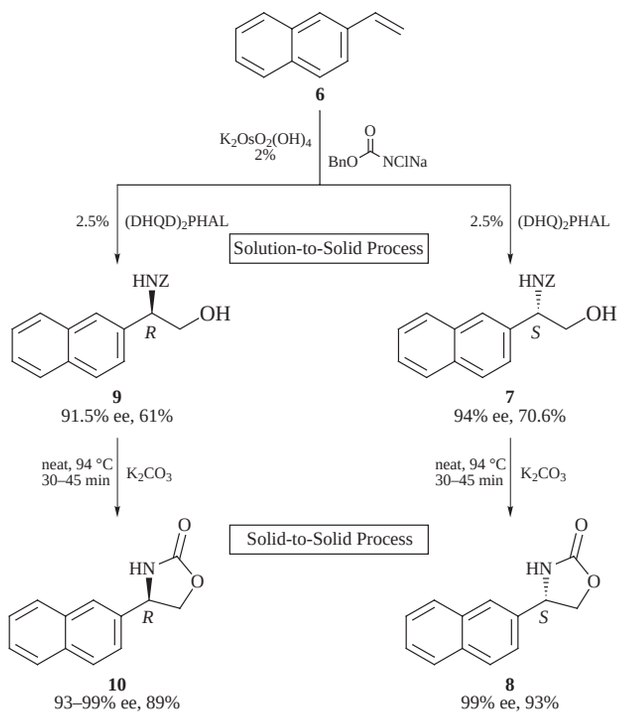
**Optically pure new Evans auxiliary analogs, (4*R*)- and (4*S*)-4-(2-naphthyl)oxazolidin-2-one, have been synthesized by using the Sharpless catalytic asymmetric aminohydroxylation reaction (Sharpless AA). The concise two-step synthesis involves a unique solution-to-solid Sharpless AA process and new neat cyclization conditions.**

Evans chiral auxiliaries have been successfully used in many asymmetric organic reactions,[1–5] such as the aldol condensation reaction,[2] Diels–Alder reaction,[3] alkylation,[4] Michael addition,[5] *etc*. These auxiliaries can be synthesized from optically pure D- or L-α-amino acids,[6] amino alcohols,[7] glycidol[8] and carboxylic acid derivatives.[9] Chiral oxazolidinones can also be synthesized from diols[10] and allylic alcohols.[11] Modifying the R group on position 4 of the oxazolidinone ring can conceivably improve diastereoselectivities in some cases,[12–14] especially when the R group is replaced by rigid and extended aromatic moieties. So far, the synthesis of unnatural 4-aryl- or 4-alkyloxazolidin-2-one is limited by the availability of the unnatural precursors and their trivial preparations. Here, we would like to report a novel method for the synthesis of Evans auxiliaries, especially the new 'unnatural' (4*R*)- and (4*S*)-4-(2-naphthyl)-oxazolidin-2-one by using the Sharpless asymmetric aminohydroxylation reaction.[15,16]

Our synthetic procedures and results are described in Scheme 1 and Scheme 2. Common petroleum olefins, styrene and 2-vinylnaphthalene, were subject to the carbamate-based




**Scheme 1** Asymmetric synthesis of (4*R*)- and (4*S*)-4-phenyloxazolidin-2-one




**Scheme 2** Solution-to-solid AA/neat cyclization for the synthesis of 4-(2-naphthyl)oxazolidin-2-one

Sharpless asymmetric aminohydroxylation reaction[16] and followed by a neat cyclization process in which no solvent was needed. Benzyl carbamate/styrene-based Sharpless AA was applied to the synthesis of (4*R*)- and (4*S*)-4-phenyloxazolidin-2-one of which the $^1$H and $^{13}$C NMR spectra are identical to those of the commercially available authentic samples. They were also confirmed by HPLC co-injection determinations.[17] Ethyl carbamate was also used as the nitrogen source for styrene-based AA with 4 mol% of $K_2OsO_2(OH)_4$ and 5 mol% of phthalazine ligands. This modification resulted in only a little improvement in enantiomeric selectivity [94% ee for $(DHQ)_2PHAL$ and 92% ee for $(DHQD)_2PHAL$ respectively], but gave lower yields (50–55%) than the benzyl carbamate-based AA process. The synthesis of (4*R*)- and (4*S*)-4-(2-naphthyl)oxazolidin-2-one was achieved by using benzyl carbamate/2-vinylnaphthalene-based AA in which 2 mol% of $K_2OsO_2(OH)_4$ and 2.5 mol% of $(DHQ)_2PHAL$ and $(DHQD)_2$-PHAL ligands were employed. The reduced load of potassium osmate and phthalazine ligands gave almost identical yields to the original catalyst loading conditions, but resulted in amino alcohol benzyl carbamates with lower enantiomeric excesses (91.5–93.5% ee). Interestingly, these *N*-Z protected amino alcohols with their lower enantiomeric excesses gave optically pure (4*R*)- and (4*S*)-4-(2-naphthyl)oxazolidin-2-one after cyclization processes.[17]

The ethyl carbamate derivatives of vicinal amino alcohols, which were synthesized from the reduction of amino esters, can

be cyclized to oxazolidinones by reacting them with potassium carbonate at *ca*. 110 °C in a boiling toluene solution.[18] We found that the amino alcohol benzyl carbamates of Sharpless AA reactions can be easily cyclized to oxazolidinones by a new solid-to-solid process without using any solvent. In this process, the *N*-Z protected amino alcohols were mixed with well ground dry potassium carbonate and then heated at 94 °C in a hot water bath. A vacuum was imposed on the reaction vessel so that the benzyl alcohol produced from the cyclization could be distilled off. The cyclization reaction took *ca*. 45 minutes to complete. No racemization was observed in this basic solid-to-solid cyclization process.

## Conclusion

The solution-to-solid Sharpless AA and the new neat solid-to-solid cyclization process provide a very convenient and concise route to the synthesis of chiral 4-phenyloxazolidin-2-ones and 4-(2-naphthyl)oxazolidin-2-ones. The described method can be applied for the synthesis of many other 4-aryloxazolidin-2-one analogs. (4*R*) and (4*S*)-(2-naphthyl)oxazolidin-2-one, the novel Evans auxiliary analogs, could be very efficient in controlling stereochemistry in the asymmetric induction processes because of the rigid and extended aromatic moiety on the 4-position of the oxazolidinone ring. The applications of (4*R*)- and (4*S*)-4-(2-naphthyl)oxazolidinone as chiral auxiliaries to asymmetric reactions, such as Baylis–Hillman related processes, will be carried out in this laboratory in the future.

## Experimental

### Sharpless AA

To a stirred solution of benzyl carbamate (4.69 g, 31.0 mmol) in *n*-propanol (37 ml) was added a freshly prepared solution of sodium hydroxide (1.22 g, 30.5 mmol) in water (37 ml), followed by recently prepared *tert*-butyl hypochlorite (3.31 g, 30.5 mmol, *ca*. 3.5 ml). Then the $(DHQ)_2PHAL$ ligand (400 mg, 0.5 mmol, 2.5 mol%) was added into the above solution. The resulting mixture should be vigorously stirred until a homogeneous solution is obtained. The reaction vessel was immersed in a 0 °C ice-bath, and 2-vinylnaphthalene **6** (1.54 g, 10 mmol) was added, followed by $K_2OsO_2(OH)_4$ (147 mg, 0.4 mmol, 2 mol%). The green homogeneous solution was stirred at 0 °C with appearance of a colorless slurry in about 2 h. The second portion of 2-vinylnaphthalene **6** (1.54 g, 10 mmol) was added to the above mixture when the green color almost disappeared. The reaction mixture was stirred at 0 °C for another 4 hours to completion. The product precipitates were obtained simply by filtration. The solid was then washed with cold (*ca*. 5 °C) *n*-propanol–$H_2O$ (1 : 1, 15 ml) and dried in a vacuum to yield the product that was determined by $^1$H NMR spectroscopy to be nearly pure (*S*)-**8** (4.67 g, 94% ee, 70.6%).[19] The dried product was directly subjected to the following cyclization reaction.

### Neat cyclization

To the above crude AA product (*S*)-**8** (4.54 g, 13.8 mmol, 94% ee), well ground potassium carbonate powder (1.91 g, 13.8 mmol) was added.[20] The resulting mixture was ground together thoroughly and then transferred to a 50 ml round bottom flask equipped with a vacuum adapter which was connected to a vacuum system. The vial was immersed in a boiling water bath for *ca*. 20 min at which time benzyl alcohol, the side product of the cyclization reaction, started to appear as the liquid. The heating was then continued for 20 more min to completion. The reaction was monitored by TLC (EtOAc–hexane, 1 : 1, v/v). Purification was conducted by flash silica gel filtration by which less polar impurities were washed away by EtOAc–hexane (1 : 9, v/v), the remaining polar (4*S*)-4-(2-naphthyl)oxazolidin-2-one was washed out by ethyl acetate, and then condensed by rotary evaporation to give the pure product (2.73 g, 99% ee, 93%)[21] as a colorless solid; mp 164–167 °C; $[a]_D^{25}$ +41.8 ($c$ = 0.39 in 95% EtOH); $\delta_H$(200 MHz, $CDCl_3$) 4.27 (dd, $J$ 8.60 Hz, 6.7 Hz, 1 H), 4.80 (t, $J$ 8.7 Hz, 1 H), 5.12 (t, $J$ 7.03 Hz, 1 H), 5.89 (s, 1 H), 7.42–7.93 (m, 7 H); $\delta_C$(50 MHz, $CDCl_3$) 56.5, 72.3, 123.1, 125.4, 126.6, 126.8, 127.8, 127.9, 129.4, 133.1, 133.3, 136.6, 159.7; *m*/*z* (EI) 214.20 (214.16 calc. for $C_{13}H_{11}NO_2$).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## References and notes


1 D. J. Ager, I. Prakash and D. Schaad, *Aldrichimica Acta*, 1997, **30**, 3.
2 D. A. Evans, J. Bartroli and T. L. Shih, *J. Am. Chem. Soc.*, 1981, **103**, 2127.
3 (*a*) D. A. Evans, K. T. Chapman, D. T. Hung and A. T. Hawaguchi, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 1184; (*b*) I. W. Davies, C. H. Senanayake, L. Castonguay, R. D. Larsen, T. R. Verhoeven and P. J. Reider, *Tetrahedron Lett.*, 1995, **36**, 7619.
4 M. A. Walker and C. H. Heathcock, *J. Org. Chem.*, 1991, **56**, 5747.
5 (*a*) D. A. Evans, M. T. Bilodeau, T. Somers, J. Clardy, D. Cherry and Y. Kato, *J. Org. Chem.*, 1991, **56**, 5750; (*b*) G. Li, K. C. Russell, M. A. Jarosinski and V. J. Hruby, *Tetrahedron Lett.*, 1993, **34**, 2565.
6 (*a*) J. R. Cage and D. A. Evans, *Org. Synth.*, 1990, **68**, 77; (*b*) M. Sudharshan and P. G. Hultin, *Synlett*, 1997, **2**, 171.
7 (*a*) W. Lubell and H. Rapoport, *J. Org. Chem.*, 1989, **54**, 3824; (*b*) T. P. Curren, M. P. Pollastri, S. M. Ablelleira, R. J. Messier, T. A. McCollum and C. G. Rowe, *Tetrahedron Lett.*, 1994, **35**, 5409.
8 S. Iwama and S. Katsumura, *Bull. Chem. Soc. Jpn.*, 1994, **67**, 3363.
9 J. Takacs, M. R. Jaber and A. S. Vellekoop, Abstracts of Papers, 214th ACS National Meeting, Las Vegas, September 7th–11th, 1997, ORG 206.
10 D. Xu and K. B. Sharpless, *Tetrahedron*, 1993, **34**, 951.
11 J. D. Blas, J. C. Carretero and E. Domingurez, *Tetrahedron Lett.*, 1994, **35**, 4603.
12 E. Nicolas, K. C. Russell and V. J. Hruby, *J. Org. Chem.*, 1993, **58**, 766.
13 A. K. Ghosh and W. Liu, *J. Org. Chem.*, 1996, **61**, 6175.
14 M. P. Sibi, D. Rutherford and R. Sharma, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1675.
15 (*a*) G. Li, H.-T. Chang and K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 451; (*b*) J. Rudolph, P. C. Sennhenn, C. P. Vlaar and K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2810.
16 G. Li, H. H. Angert and K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2813.
17 HPLC determinations for 4-aryloxazolidin-2-ones [chiralcel OD-H, $Pr^iOH$–hexane (3 : 7), 0.7 ml $min^{-1}$]: 12.98 min (**3**, *S*), 12.18 min (**5**, *R*); 21.97 min (**9**, *S*), 26.91 min (**10**, *R*).
18 N. Lewis, A. McKillop, R. J. K. Taylor and R. J. Watson, *Synth. Commun.*, 1995, **25**, 561.
19 HPLC determinations for ethyl carbamate/styrene-based AA products: chiralcel OD-H, $Pr^iOH$–hexane (3 : 17), 0.7 ml $min^{-1}$, 8.44 min (*S*), 10.70 min (*R*). The enantiomeric excesses of benzyl carbamate-based AA products (**2**, **4**, **7** and **9**) were determined by using the HPLC conditions as described in ref. 16.
20 The neat cyclization can be conducted by using a catalytic amount of $K_2CO_3$ (10 mol%) and gave a lower yield of 82%.
21 99% ee indicates that only one enantiomer was observed in HPLC analysis.



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