Supporting Information

Small Organic Molecule in Enantioselective, Direct Aldol Reaction "In Water"

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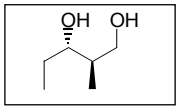
Typical procedure of asymmetric self-aldol reaction of propanal (Table 1, entry 19)

To a mixture of L-proline carboxamide (17 mg, 0.15 mmol) and water (0.33 mL) added propanal (216 μL, 3.0 mmol) successively at room temperature. After stirring the reaction mixture for 3 hours at that temperature, the reaction mixture was cooled at 0 °C and MeOH (3 mL) and $NaBH_4$ (284 mg, 7.5 mmol) were added. The reaction mixture was stirred for 1 hour at 0 °C. The reaction was quenched with pH 7.0 phosphate buffer solution and the organic materials were extracted with ethyl acetate three times and the combined organic extracts were dried over anhydrous Na_2SO_4, and concentrated in vacuo after filtration. Purification by silica gel column chromatography (ethyl acetate:hexane=1:2 ~ 1:1) gave (2*R*, 3*R*)-2-methylpentane-1,3-diol and (2*R*, 3*S*)-2-methylpentane-1,3-diol (diastereomer ratio;1.1:1, 73 mg, 0.6 mmol) in 41% yield.

(2*R*, 3*R*)-2-Methylpentane-1,3-diol (1)[1]
(2*R*, 3*S*)-2-Methylpentane-1,3-diol (2)[2]
are known compounds.



Enantiomeric excess was determined by HPLC with a Chiralpak IA column (100:1 hexane:2-propanol, λ=254 nm), 1.0 mL/min; major enantiomer(*syn*) tr =24.6 min, minor enantiomer(*syn*) tr =29.9 min, major enantiomer(*anti*) tr =31.5 min, minor enantiomer(*anti*) tr =34.4 min, after conversion to the mono benzoyl ester.

The absolute stereochemistry of the *syn* aldol adduct was determined by the chiral HPLC analysis by comparing the retention time of the mono benzoyl ester of present aldol product with that synthesized by Cane's procedure[3].
The absolute stereochemistry of the *anti* aldol adduct was determined by the chiral HPLC analysis by comparing the retention time of the mono benzoyl ester of present aldol product with that synthesized by L-proline in DMF by MacMillan's procedure[4].

References

1) Bartoli, G.; Bellucci, M. C.; Basco, M.; Dalpozzo, R.; Marcantoni, E.; Sambri, L. *Chem. Eur. J.* **2000**, *6*, 2590.
2) Kayano, A.; Akazome, M.; Fujita, M.; Ogura, K. *Tetrahedron* **1997**, *53*, 12101.
3) Cane, D. E.; Lambalot, R. H.; Prabhakaran, P. C.; Ott, W. R. *J. Am. Chem. Soc.* **1993**, *115*, 522.
4) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798.