Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 289–291

TETRAHEDRON: *ASYMMETRY*

Lipase-catalyzed stereoselective resolution and desymmetrization of binaphthols

Marcela Juárez-Hernandez, Dean V. Johnson, Herbert L. Holland,* James McNulty and Alfredo Capretta

Department of Chemistry, Brock University, St Catharines, Ontario L2S 3A1, Canada

Received 18 September 2002; accepted 11 November 2002

Abstract—We have investigated the use of lipoprotein lipase enzymes from *Pseudomonas* sp. and *Pseudomonas fluorescens* for the enantioselective resolution and desymmetrization of racemic binaphthols. The reactions were carried out using a non-aqueous environment (iPr_2O/acetone/vinyl acetate), and yielded mono-acetate ester products of the parent unsubstituted substrate, the 6,6′-dibromo-substrate, and the 6,6′-dimethoxy-substrate with high enantiomeric selectivity.

Optically active 1,1′-binaphthyl-2,2′-diol (BINOL) has provided a versatile template for a plethora of chiral catalysts and auxiliaries which have been employed with great success in asymmetric synthesis.[1] Illustrative of this are reports of the use of BINOL in asymmetric Michael additions,[2] epoxidations,[3] aldol condensations,[4] oxidations,[5] reductions,[6] alkylations,[7] Diels–Alder reactions[8] and addition reactions involving trimethylsilylcyanide (TMSCN).[9] Additionally, BINOL has proven useful when applied into the synthesis of HIV-protease inhibitors,[10] chiral stationary phases,[11] polymeric chiral ligands[12] and has also been used as a chiral resolving agent.[13]

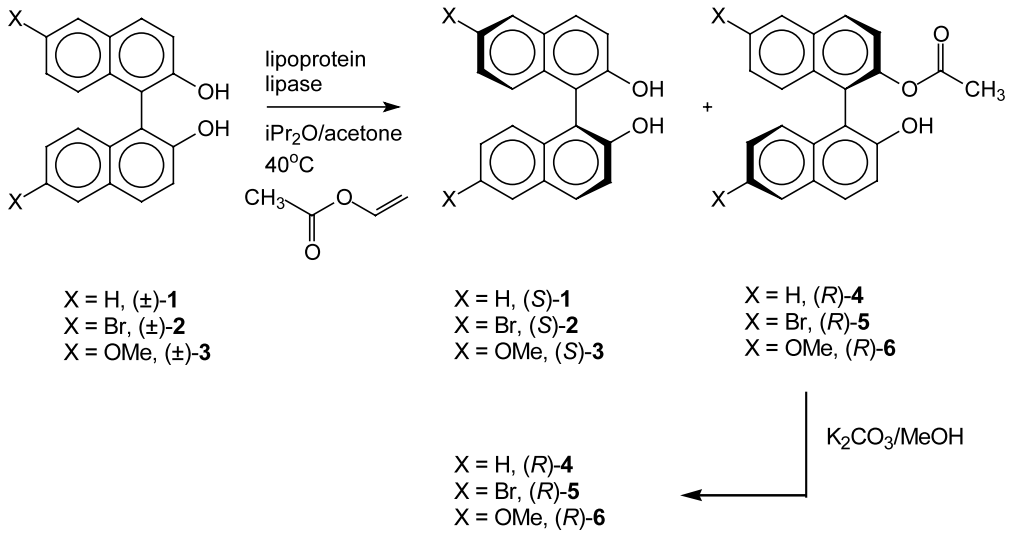
Direct asymmetric approaches to enantiomerically enriched binaphthols (and analogs) include oxidative couplings, which employ chiral amines,[14] oxovanadium complexes[15] or bile acid,[16] or the resolution of racemic mixtures.[17] Though enzymatic approaches to chiral binaphthols (through oxidation and resolution) have been reported, they are more limited.[18] Only a single report of a biocatalyst for the formation of one such compound ((*S*)-**1**) has been previously reported,[18c] but the description of the type of enzyme was incomplete. Indeed, in a more recent report on such a biocatalytic reaction, the authors reported that 'all attempts failed'.[18g]

We have now investigated the use of a series of enzymes[19] not only for selective esterification of unsubstituted BINOL (X = H), but also for its 6,6′-disubstituted derivatives (X = Br, OMe): the chiral bromine moiety can be a key to further functionalization using the Suzuki reaction with boronic acids under the influence of a palladium catalyst, and the chiral methoxy products may provide other such reaction opportunities.[8a] We have been able for the first time to elaborate on the lipoprotein enzymes that allow the enantioselective preparation of BINOLs (e.g. *S*-**1**–**3**) and of their corresponding desymmetrized monoester (e.g. (*R*)-**4**–**6**), Scheme 1.

When vinyl acetate was employed as the acyl donor in acetylation, a preliminary examination of ten Celite-immobilized[18c] lipases or lipoprotein lipases[19] revealed that only the lipoprotein lipase from *Pseudomonas* sp. efficiently catalyzed the conversion of 1,1′-binaphthyl-2,2′-diol (±)-**1** to its corresponding monoacetate (*R*)-**4** (Table 1, entry a), yielding unreacted (*S*)-**1**. In comparison to chiral compound **1**, chiral 6,6′-dibromo-1,1′-binaphthyl-2,2′-diol **2** (98% ee) has been reported to be a superior chiral catalyst for synthesis.[20] In our hands, (±)-**2** proved to be a suitable substrate for the lipoprotein lipases from both *Pseudomonas* sp. and *Pseudomonas fluorescens*. In both cases the monoacylation and desymmetrization proceeded with excellent selectivity (to yield (*R*)-**5**, 94 and 93% ee, respectively, Table 1 entries b and c) and (*S*)-6,6′-dibromo-1,1′-binaphthyl-2,2′-diol (*S*)-**2** (80 and 69% ee, respectively). In contrast to (±)-**2**, 6,6′-dimethoxy-1,1′-binaphthyl-2,2′diol ((±)-**3**) proved to be a substrate for only the lipoprotein lipase from *P. fluorescens*, and acylation (to yield (*R*)-**6**)

* Corresponding author. Tel.: +1-905-688-5550, ext. 3403; fax: +1-905-682-9020; e-mail: holland@chemiris.labs.brocku.ca

0957-4166/03/$ - see front matter
PII: S0957-4166(02)00792-9



Scheme 1.

Table 1.

Entry	Substrate	Lipoprotein lipase	Reaction time (h)	Binol[21]				Mono-acetate[21]			
				Product	Yield (%)[a]	$[\alpha]_D^{25}$ THF	ee (%)[b]	Product	Yield (%)[a]	$[\alpha]_D^{25}$ THF	ee (%)[c]
a	(±)-**1**	*Pseudomonas* sp.	120	(*S*)-**1**	30	−15.3[d]	55	(*R*)-**4**	32	+28.0[e]	96
b	(±)-**2**	*Pseudomonas* sp.	126	(*S*)-**2**	46	+33.1[f]	80	(*R*)-**5**	44	−35.7[g]	94
c	(±)-**2**	*P. fluorescens*	126	(*S*)-**2**	56	+29.5[h]	69	(*R*)-**5**	30	−38.8[j]	93
d	(±)-**3**	*P. fluorescens*	120	(*S*)-**3**[22]	52	+29.8[k]	58	(*R*)-**6**	31	−23.8[l]	78

Biotransformations were typically carried out as follows: a mixture of binaphthol **1** (100 mg), vinyl acetate (600 mg), di-*iso*-butyl ether (4.6 mL), acetone (dry, 0.5 mL), and a suspension of lipase (400 mg) was stirred at 240 rpm, 40°C, for 120–126 h. The final mixture was analyzed by silica gel (8:2 toluene/ethyl acetate) and purified by evaporation followed by chromatography using fractional solvent changes of toluene/hexane (90:10) to toluene (100) to toluene/ethyl acetate (80:20) in 2% graded solvent changes.

[a] Isolated yields based on either (±)-**1**, **2** or **3**.

[b] Determined by HPLC analysis (Astec Chirobiotic V chiral column with 6 cm phenomex C-18 guard column, hexane:ethanol (95:5) for (*S*)-**1** and (*S*)-**2** or 93:7 for (*S*)-**3**, 1 mL/min, 254 nm).[23]

[c] Determined by HPLC analysis (conditions, see note b) of (*R*)-**1**, (*R*)-**2** or (*R*)-**3** derived from (*R*)-**4**, (*R*)-**5** and (*R*)-**6,** respectively (using K_2CO_3/methanol).[24]

[d] *c* 1.47.

[e] *c* 0.95.

[f] *c* 1.36.

[g] *c* 1.14.

[h] *c* 1.72.

[j] *c* 1.55.

[k] *c* 1.26.

[l] *c* 1.84.

occurred with only moderate selectivity (78% ee, Table 1, entry d). In all cases of substrates **1**–**3** no diacetate was observed in the biocatalytic reaction. For the binaphthol products (e.g. (*S*)-**1**–**3**) the enantiomeric excesses (ee's) were determined by chiral HPLC analysis. To determine the enantiomeric purities of the products (*R*-**4**–**6**) (the enantiomers of which were not easily separated by chiral HPLC), the monoesters were hydrolyzed to their corresponding binaphthols with K_2CO_3/methanol prior to chiroptical analysis of the latter chiral products.

As both biocatalysts are immobilized they can be easily recovered by filtration, which facilitates their re-use, as enzyme deactivation is marginal. We have therefore developed two new biocatalytic reactions for the enantioselective resolution and desymmetrization of racemic binaphthols, namely the used of lipoprotein lipases from *Pseudomonas* sp. and *P. fluorescens*, and applied these reactions to generate two new chiral binaphthol products in this way, the enzymes for which are of known commercial availability, and which are recoverable under the reaction conditions described in Table 1.

References

1. For recent reviews, see: (a) Pu, L. *Chem. Rev*. **1998**, *98*, 2405–2494; (b) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 1236–1256.
2. Sasai, H.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc*. **1994**, *116*, 1571–1572.
3. Bougauchi, M.; Watanabe, S.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc*. **1997**, *119*, 2329–2330.
4. Ishitani, H.; Yamashita, Y.; Shimizu, H.; Kobayahsi, S. *J. Am. Chem. Soc*. **2000**, *122*, 5403–5404.
5. Reetz, M. T.; Merk, C.; Naberfeld, G.; Rudolph, J.; Griebenow, N.; Goddard, R. *Tetrahedron Lett*. **1997**, *38*, 5273–5276.
6. Fu, I.-P.; Uang, B.-J. *Tetrahedron: Asymmetry* **2001**, *12*, 45–48.
7. (a) Tanaka, F.; Node, M.; Tanaka, K.; Mizuchi, M.; Hosoi, S.; Nakayama, M.; Taga, T.; Fuji, K. *J. Am. Chem. Soc*. **1995**, *117*, 12159–12171; (b) Tanaka, K.; Ahn, M.; Watanaba, Y.; Fuji, K. *Tetrahedron: Asymmetry* **1996**, *7*, 1771–1782.
8. (a) Kobayahi, S.; Kusakabe, K.; Ishitani, H. *Org. Lett*. **2000**, *2*, 1225–1227; (b) Simonsen, K. B.; Svenstrup, N.; Roberson, M.; Jørgensen, K. A. *Chem. Eur. J*. **2000**, *6*, 123–128; (c) Wipf, P.; Jung, J.-K. *J. Org. Chem*. **2000**, *65*, 6319–6337.
9. (a) Quin, C.; Zhu, C.; Huang, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2131–2132; (b) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc*. **2000**, *122*, 6327–6328; (c) Sellner, H.; Faber, C.; Rheiner, P. B.; Seebach, D. *Chem. Eur. J*. **2000**, *6*, 3692–3705.
10. Reetz, M. T.; Merk, C.; Mehler, G. *J. Chem. Soc., Chem. Commun*. **1998**, 2075–2076.
11. Sudo, Y.; Yamaguchi, T.; Shinbo, T. *J. Chromatogr. A* **1998**, *813*, 35–45.
12. Fan, Q.-H.; Liu, G.-H.; Deng, G.-J.; Chen, X.-M.; Chan, A. S. C. *Tetrahedron Lett*. **2001**, *42*, 9047–9050.
13. Nakajima, M.; Sasaki, Y.; Shiro, M.; Hashimoto, S. *Tetrahedron: Asymmetry* **1997**, *8*, 341–344.
14. Nakajima, M.; Miyoshi, I.; Kanayama, K.; Hashimoto, S.; Noji, M.; Koga, K. *J. Org. Chem*. **1999**, *64*, 2264–2271.
15. Chu, C.-Y.; Hwang, D.-R.; Wang, S.-K.; Uang, B.-J. *J. Chem. Soc., Chem. Commun*. **2001**, 980–981.
16. Bandyopadhyaya, A. K.; Sangeetha, N. M.; Maitra, U. *J. Org. Chem*. **2000**, *65*, 8239–8244.
17. (a) Brunel, J.-M.; Buono, G. *J. Org. Chem*. **1993**, *58*, 7313–7314; (b) Pakulski, Z.; Zamojski, A. *Tetrahedron: Asymmetry* **1995**, *6*, 111–114; (c) Periasamy, M.; Venkatraman, L.; Thomas, K. R. *J. Org. Chem*. **1997**, *62*, 4302–4306; (d) Shan, Z.; Xiong, Y.; Weizhong, L.; Zhao, D. *Tetrahedron: Asymmetry* **1998**, *9*, 3985–3989; (e) Shan, Z.; Xiong, Y.; Zhao, D. *Tetrahedron* **1999**, *55*, 3893–3896; (f) Periasmay, M.; Vankatraman, L.; Sivakumar, S.; Sampathkumar, N.; Ramanathan, C. R. *J. Org. Chem*. **1999**, *64*, 7643–7645; (g) Daqing, C.; Andersen, N. G.; Lau, S. Y. W.; Parvez, M.; Keay, B. A. *Tetrahedron: Asymmetry* **2000**, *11*, 1919–1925.
18. (a) Wu, S.-H.; Zhang, L.-Q.; Chen, C.-S.; Girdaukas, G.; Sih, C. J. *Tetrahedron Lett*. **1985**, *26*, 4323–4326; (b) Fujimoto, Y.; Iwadate, H.; Ikekawa, N. *J. Chem. Soc., Chem. Commun*. **1985**, 1333–1334; (c) Inagaki, M.; Hiratake, J.; Nishioka, T.; Oda, T. *J. Agric. Biol. Chem*. **1989**, *53*, 1879–1884; (d) Kawahara, K.; Matsumoto, M.; Hashimoto, H.; Miyano, S. *Chem. Lett*. **1988**, 1163–1164; (e) Kazlaukas, R. J. *J. Am. Chem. Soc*. **1989**, *111*, 4953–4959; (f) Sridhar, M.; Vadivel, S. K.; Bhalerao, U. T. *Tetrahedron Lett*. **1997**, *38*, 5695–5696; (g) Furutani, T.; Hatsuda, M.; Imashiro, R.; Seki, M. *Tetrahedron: Asymmetry* **1999**, *10*, 4763–4768.
19. The lipase extension kit from Fluka (62323) was employed and contains samples of the following lipases: *Aspergillus oryzae*, *Candida lipolytica*, *Mucor javanicus*, *Penicillium roqueforti*, *Pseudomonas fluorescens*, *Rhizomucor miehei*, wheat germ and lipoprotein lipases from *Chromobacterium vicosum*, *Pseudomonas* sp. and *P. fluorescens*.
20. Terada, M.; Motoyama, Y.; Mikami, K. *Tetrahedron Lett*. **1994**, *35*, 6693–6696.
21. Literatures values: (*S*)-**1** $[\alpha]_D^{25}$ −28.0 (*c* 1.05, THF),[18c] (*R*)-**4** $[\alpha]_D^{25}$ +31.0 (*c* 1.10, THF),[18c] (*R*)-**2** $[\alpha]_D^{25}$ −52.3 (*c* 1.15, THF).[20]
22. The configuration has been provisionally assigned from the elution order observed on chiral HPLC, which is identical to that observed for (±)-**1** or **2** (i.e. *R*-enantiomer first eluting, *S*-enantiomer second eluting).
23. The retention times in the given solvent are: (*R*)-**1** 26.8 min, (*S*)-**1** 29.7 min, (*R*)-**2**, 31.5 min, (*S*)-**2** 35.3 min, (*R*)-**3** 41.1 min, (*S*)-**3** 45.2 min.
24. (*R*)-**2** $[\alpha]_D^{25}$ −32.4 (*c* 1.25, THF), (*R*)-**3** $[\alpha]_D^{25}$ −21.7 (*c* 0.97, THF) measured from the hydrolysis of (*R*)-**5** and (*R*)-**6**, respectively.