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Enantioselective synthesis using crude enzymes

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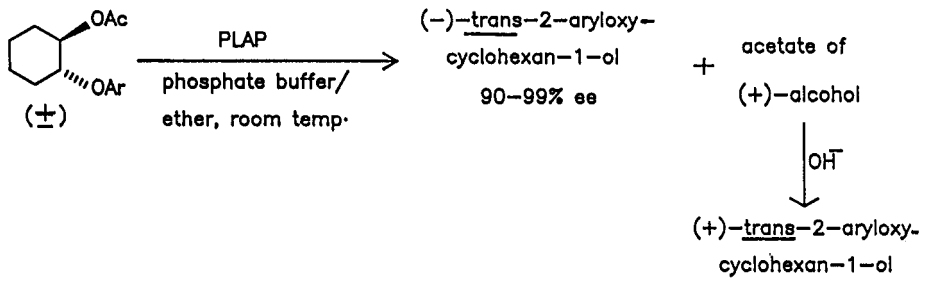
Abstract: Chiral trans-2-aryloxycyclohexan-1-ols, trans-2-alkoxy cyclohexan-1-ols, trans-2-arylcyclohexan-1-ols, homoallyl alcohols, 1-aryl-1-alkanols, 1,2-diphenylethane-1,2-diol are prepared in high optical purities via enantioselective hydrolysis of acetates of the corresponding racemic alcohols using crude enzymes such as pig liver acetone powder (PLAP), goat liver acetone powder (GLAP), chicken liver acetone powder (CLAP) and bovine liver acetone powder (BLAP).

Synthesis of enantiomerically pure molecules is one of the fascinating and challenging areas in organic chemistry (ref. 1-4). Chemico-enzymatic methodology for this purpose has grown to such a level that it has become one of the most useful methods for preparation of optically pure molecules (ref. 5-9). Despite the useful applications of enzymatic reactions, there exists some apprehension amongst organic chemists particularly with respect to experimental techniques and handling of enzymes. Also most of the enzymes are very expensive. With an objective of providing an easy means of handling enzymes and developing inexpensive procedures we have been working for the last 3 years on the applications of crude enzymes such as pig liver acetone powder (PLAP), goat liver acetone powder (GLAP), chicken liver acetone powder (CLAP) and bovine liver acetone powder (BLAP) for enantioselective synthesis of organic molecules. We,herein,report our results on enantioselective hydrolysis using these crude enzymes.

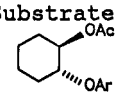
Chiral auxiliaries play an important role in bringing latitude to organic synthesis. Enantiomerically pure molecules with cyclohexanol substructures like (+)/(-) menthol (ref. 10), (-)-8-phenyl menthol (ref. 11), (+)/(-)-trans-2-phenylcyclohexan-1-ol (ref. 12,13) are commonly used chiral auxiliaries for preparation of enantiomerically enriched molecules. With a view that structurally similar trans-2-aryloxycyclohexan-1-ols would offer promise as chiral auxiliaries, we have investigated the enantioselective hydrolysis of trans-1-acetoxy-2-aryloxycyclohexanes using pig liver

Scheme 1

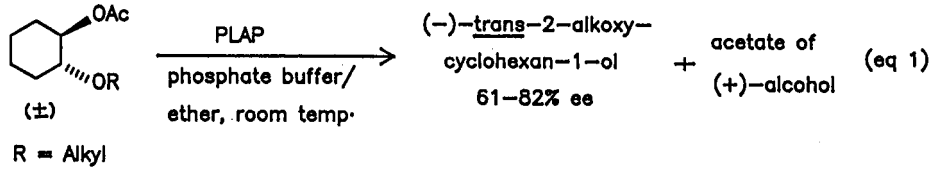


acetone powder (PLAP). Best results were obtained when the hydrolysis was carried out in a two phase medium (ether and aqueous phosphate buffer) (Scheme 1) and a variety of trans-1-acetoxy-2-aryloxycyclohexanes have been hydrolyzed to produce the desired (-)-trans-2-aryloxycyclohexan-1-ols in high optical purities (ref. 14), (Table 1).

Table 1: Enantioselective hydrolysis of (±)-trans-1-acetoxy-2-aryloxycyclohexanes using crude PLAP.

Substrate  (±) Ar =	Hydrolysis time in hrs	Conversion ratio OH:OAc	(-)-Alcohol Yield %	(-)-Alcohol ee %	Recovered acetate Yield %	Recovered acetate ee %
Phenyl	22	44:56	73	98	75	85
4-Tolyl	40	41:59	72	>99	70	70
4-t-Butylphenyl	84	47:53	70	>99	68	90
4-Phenylphenyl	96	47:53	72	>99	69	88
2-Methoxyphenyl	96	45:55	76	92	75	77
2,4-Dimethylphenyl	50	37:63	65	90	60	60
3-Methylphenyl	45	41:59	78	90	92	53
4-Methoxyphenyl	11	48:52	92	95	96	83
3-Methoxyphenyl	23	49:51	96	94	88	90

After obtaining encouraging results in the synthesis of chiral trans-2-aryloxycyclohexan-1-ols, we have directed our studies towards the preparation of chiral trans-2-alkoxycyclohexan-1-ols (eq 1). A variety of racemic trans-1-acetoxy-2-alkoxycyclohexanes were hydrolyzed enantioselectively with PLAP to produce the resulting (-)-trans-2-alkoxycyclohexan-1-ols in 61-82% enantiomeric purities (ref. 15). [R = methyl (ee 80%), ethyl (ee 76%), isopropyl (ee 79%), isobutyl (ee 61%), 2-(2-methoxyethoxy)ethyl (ee 82%), benzyl (ee 79%)].



PLAP hydrolyzes trans-2-phenylcyclohexyl acetate to produce the corresponding (-)-trans-2-phenylcyclohexan-1-ol in optically pure form (ref. 16). Our attempts to hydrolyze other 2-arylcyclohexyl acetates with PLAP resulted in failure. Our efforts with BLAP also met with failure. However, when we employed chicken liver acetone powder (CLAP) (ref. 17) for enantioselective hydrolysis of 2-arylcyclohexyl acetates, encouraging results were obtained (eq 2), thus producing the desired (-)-trans-2-arylcyclohexan-1-ols in 99% optical purities though the rate of hydrolysis is slow (Table 2)

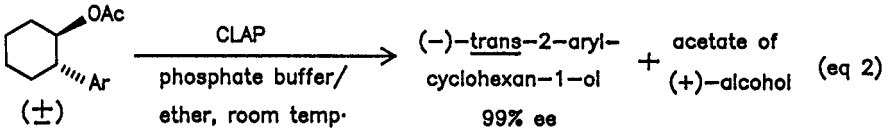


Table 2. Enzymatic resolution of the racemic acetates of trans-2-arylcyclohexan-1-ols with CLAP.

Substrate (±) Ar =	Hydrolysis time in days	Conversion ratio OH:OAc	(-)-Alcohol Yield %	(-)-Alcohol ee %	Recovered acetate Yield %	Recovered acetate ee %
Phenyl	10	35:65	85	99	86	50
4-Tolyl	10	40:60	82	99	88	65
Mesityl	12	25:75	84	99	87	30
4-Anisyl	10	37:63	86	99	89	55
4-Bromophenyl	12	28:72	80	99	85	42
α-Naphthyl	12	26:74	83	99	91	39

We next examined the enantioselective hydrolysis of racemic acetates of homoallyl alcohols with PLAP. The resulting (+)-homoallyl alcohols are obtained in 50-72% enantiomeric purities (ref. 18). However, chicken liver acetone powder (CLAP) provided better results in the hydrolysis, thus the required homoallyl alcohols are obtained in high optical purities (Table 3) (ref. 19) (eq 3).

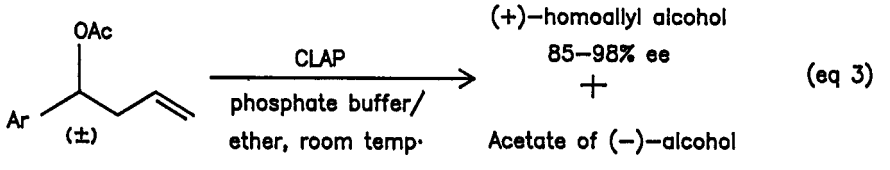
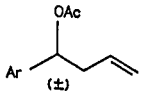


Table 3. Enzymatic hydrolysis of racemic acetates of 1-aryl-3-buten-1-ols using crude CLAP.

Substrate  Ar =	Hydrolysis time in hrs	Conversion ratio OH:OAc	(+)-Alcohol Yield %	(+)-Alcohol ee %	Recovered acetate Yield %	Recovered acetate ee %
4-Tolyl	40	41:59	90	98	91	73
4-Chlorophenyl	22	32:68	75	95	89	51
2,4-Dichlorophenyl	40	42:58	92	85	93	56
3,4-Dichlorophenyl	20	31:69	88	92	91	46
α-Naphthyl	20	28:72	89	96	93	32

With a view to expand the applications of crude enzymes, we have carried out enantioselective hydrolysis of 1-acetoxy-1-arylalkanes with crude enzymes PLAP, GLAP and BLAP in two phase medium (ether:phosphate buffer). PLAP and GLAP provided the desired (R)-1-aryl-1-alkanols in 55-95% optical purities (ref. 20). Better results are obtained with BLAP, thus producing the (R)-alcohols in 90->99% optical purities (ref. 21) (Table 4) (eq 4).

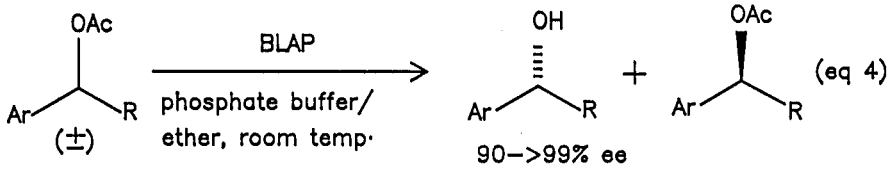
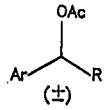
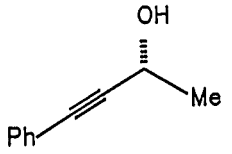


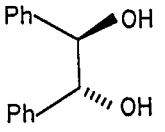
Table 4: Enzymatic hydrolysis of the racemic acetates of 1-arylalkan-1-ols with crude BLAP.

Substrate  Ar =	R =	Hydrolysis time (hrs)	conversion ratio OH:OAc	(+)-Alcohol Yield %	(+)-Alcohol ee %	Recovered acetate Yield %	Recovered acetate ee %
Phenyl	Ethyl	35	45:55	75	95	85	84
p-Methylphenyl	Methyl	12	35:65	79	93	90	52
p-i-Propylphenyl	Methyl	48	37:63	83	90	83	62
p-Chlorophenyl	Methyl	30	37:63	89	94	91	58
p-Bromophenyl	Methyl	36	35:65	87	92	89	55
β-Naphthyl	Methyl	12	33:67	81	93	85	58
α-Naphthyl	Methyl	65	40:60	77	>99	90	70

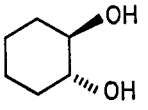
We also utilized PLAP for possible enantioselective hydrolysis of(±)-4-phenyl-2-acetoxybut-3-yne. The resulting (+)-4-phenylbut-3-yn-2-ol was obtained in 88% optical purity (ref. 19). We have synthesized (+)-(R,R)-1,2-diphenylethane-1,2-diol in 98% optical purity using CLAP though the rate of hydrolysis of racemic 1,2-diacetoxy-1,2-diphenylethane is very slow (15 days for 15% hydrolysis) (ref. 15). Similarly (-)-(R,R)-cyclohexane-1,2-diol was prepared in 70% ee using PLAP via enantioselective hydrolysis of the corresponding racemic diacetate (ref. 15).



88% ee



98% ee



70% ee

In conclusion, crude enzymes offer reasonable selectivities in enantioselective hydrolysis of racemic acetates thus providing useful, economical and operationally simple procedures for the preparation of enantiomerically enriched molecules. Work towards the synthesis of biologically active molecules using crude enzymes is now in progress in our laboratory.

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REFERENCES

1. J.D. Morrison, (Editor) Asymmetric synthesis, vol 1-5, Academic press, New York (1985).
2. J.M. Brown, Nature 350, 191 (1991).
3. D.A. Evans, Science 240, 420-426 (1988).
4. J.K. Whitesell, Chem.Rev. 89, 1581-1590 (1989).
5. G.M. Whitesides, C-H. Wong, Angew. chem. Int. Ed. Engl. 24, 617-638 (1985).
6. J.B. Jones, Tetrahedron 42, 3351-3403 (1986).
7. C.S. Chen, C.J. Sih, Angew. Chem. Int. Ed. Engl. 28, 695-707 (1989).
8. C-H. Wong, Science 244, 1145-1152 (1989).
9. A.M. Klibanov, Acc. Chem. Res. 23, 114-120 (1990).
10. A. Misumi, K. Iwanaga, K. Furuta, H. Yamamoto, J. Am. Chem. Soc. 107, 3343-3345 (1985).
11. J.K. Whitesell, A. Bhattacharya, K. Henke, J. Chem. Soc. Chem. Commun. 988-989 (1982).

12. J.K. Whitesell, H.H. Chen, R.M. Lawrence, J. Org. Chem. 50, 4663-4664 (1985).
13. J. Castro, H. Sorensen, A. Riera, C. Morin, A. Moyano, M.A. Pericas, A.E Greene, J. Am. Chem. Soc. 112, 9388-9389 (1990).
14. D. Basavaiah, P. Rama Krishna, T.K. Bharathi, Tetrahedron lett. 31, 4347-4348 (1990).
15. D. Basavaiah, P. Rama Krishna, Unpublished results.
16. PLAP hydrolyzes 2-phenylcyclohexyl acetate. Ref: J.K. Whitesell, R.M. Lawrence, Chimia 40, 318-321 (1986).
17. D. Basavaiah, P. Dharma Rao, Manuscript submitted for publication.
18. D. Basavaiah, P. Dharma Rao, Synth. Commun. 20, 2945-2949 (1990).
19. D. Basavaiah, P. Dharma Rao, Unpublished results.
20. D. Basavaiah, S. Bhaskar Raju, Synth. Commun. 21, 1859-1863 (1991).
21. D. Basavaiah, S. Bhaskar Raju, Manuscript submitted for publication.