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Preparation of Optically Active Aziridine Carboxylates by Lipase-Catalyzed Alcoholysis

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Abstract: Aziridine carboxylates alcoholysis by lipases depends of the N-substitutent. N-alkyl and N-aryl compounds have been resolved with medium to good enantiomeric purity by enzymatic alcoholysis catalyzed by pig pancreatic (PPL) or *Candida cylindracea* lipase (CCL).

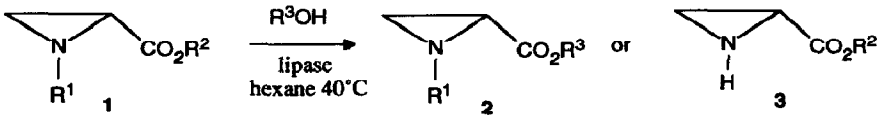
Aziridines, like epoxides, possess a large synthetic potential. In a recent review, Tanner[1] reported different uses of optically active aziridines:
- as chiral synthons for the enantioselective synthesis of aminoacids,[2] β-lactams,[3] pyrrolidines,[4] polymers,[5]
- as chiral auxiliaries or ligands.[6]

Transformation of chiral epoxides,[7] dehydration of optically active aminoalcohols,[8] condensation of metal enolates with chiral imines,[9] asymmetric aziridination of alkenes,[10] resolution of the racemic compound by complexation[11] are the main ways to synthesize optically active aziridines.

Our previous studies on the resolution of cyclopropylcarbinols by means of lipases[12] led us to apply the same strategy in order to prepare optically active aziridine carboxylates. Surprisingly, despite their intensive use for the resolution of a wide array of racemic organic structures or in asymmetric synthesis,[13] hydrolases did not receive the same attention regarding the resolution of aziridines.[14]

Thus, we have first studied the reactivity of various aziridine carboxylates[15] in lipase-catalyzed alcoholyses (Scheme 1) which were preferred to hydrolyses because of the inherent instability of aziridine carboxylic acids.[16]

Scheme 1



With respect to the enzymes used in this study (PPL and CCL), the results summarized in Table 1 show that:
- while N-alkyl and N-aryl aziridine carboxylates **1** give esters **2**, N-tosyl, N-mesyl and N-dimethyl(1,1,2-trimethylpropyl)silyl **1** are recovered unchanged after 10 days,
- the N-acyl and N-carboxyalkyl aziridines undergo instead the alcoholysis of the amide bond to give N-H aziridines **3**. In the case of the *iso*-propyl N-acetyl aziridine carboxylate, contrary to the results reported by Moretti *et al.* for hydrolyses of the methyl ester,[14e] we isolated only racemic **3** when reactions were stopped before completion.

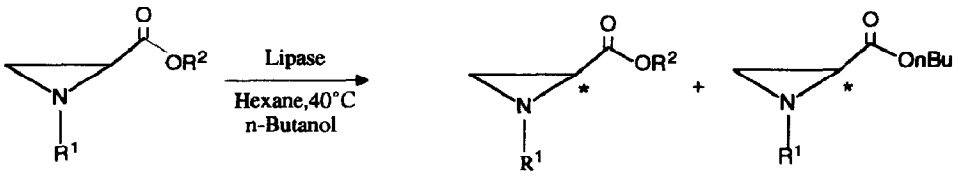
Table 1

R^1	R^2	R^3	Lipase	Reaction times (hours)	Products (Yield %)
CH_3	CH_3	nC_4H_9	CCL	15	**2** (43)*
nC_3H_7	CH_3	nC_4H_9	PPL	170	**2** (50)*
allyl	CH_3	nC_4H_9	PPL	204	**2** (70)*
cyclohexyl	CH_3	nC_4H_9	PPL	240	**2** (60)*
tosyl	nC_4H_9	nC_8H_{17}	PPL	240	-
mesyl	nC_4H_9	nC_8H_{17}	PPL	240	-
HCO	nC_4H_9	nC_8H_{17}	PPL	6.5	**3** (84)
CH_3CO	iC_3H_7	nC_4H_9	PPL	42	**3** (50)*
CH_3CO	nC_4H_9	nC_8H_{17}	PPL	42	**3** (98)
$COOCH_3$	iC_3H_7	nC_5H_{11}	PPL	50	**3** (70)
PhCO	nC_4H_9	nC_8H_{17}	CCL	43	**3** (90)
dimethyl(1,1,2-trimethylpropyl)silyl	nC_4H_9	nC_8H_{17}	CCL	240	-
H	nC_4H_9	nC_8H_{17}	PPL	240	-
Br	nC_4H_9	CH_3	PPL	15	**3** (86)

* Yield for incomplete conversion of the substrate.

Accordingly, we decided to study the efficiency of the kinetic resolution using N-alkyl aziridine carboxylates as substrates (Scheme 2). All the enantiomeric excesses of the aziridines reported in Table 2 were determined by chromatographic analysis on chiral HPLC or GC columns .[17]

Scheme 2



4 $R^1 = CH_3$ $R^2 = CH_3$ **6a** R^1 = tert-Bu $R^2 = CH_3$

5a R^1 = iso-Pr $R^2 = CH_3$ **6b** R^1 = tert-Bu $R^2 = CH_2CF_3$

5b R^1 = iso-Pr $R^2 = CH_2CF_3$ **7** R^1 = Bn $R^2 = CH_3$

As shown by the initial rates, the enzymatic reaction is very sensitive to the bulk of the N-alkyl substituent:
- with PPL, N-Me esters react faster than N-*tert*-Bu, N-Bn and N-*iso*-Pr esters which have similar initial rates
- with CCL, the following order of decreasing reactivity was observed: N-*iso*-Pr > N-*tert*-Bu > N-Bn.

It has been shown previously[13c] that the use of irreversible conditions can allow to dramatically improve the stereoselectivity of lipase-catalyzed resolutions. In the butanolysis of N-*iso*-Pr or N-*tert*-Bu aziridine carboxylates, the best enantioselectivity is indeed obtained with trifluoroethyl esters (entries 4,5 and 8,9). Moreover, in this case, the reaction rate is higher than that observed with methyl esters (entries 2,3 and 6,7).

As can be seen by comparing the respective E values, under irreversible conditions, the two enzymes display similar enantiselectiviies toward N-*iso*-Pr aziridine (entries 4 and 5) while CCL appears more enantioselective than PPL toward N-*tert*-Bu aziridine (entries 8 and 9).

Table 2

Entry	Subtrate	Lipase	Reaction time (days)	Conversion (%)	ee substrate	ee product	Total yield* (%)	E product **	Initial rate ***
1	**4**	PPL	2	42	62.3	66	95	7.2	139
2	**5a**	PPL	42	5	5	54.5	50	5.8	2.37
3	**5a**	CCL	4	48	21	32	61	2.5	1.11
4	**5b**	PPL	12	10	10	>95	73	>100	16.5
5	**5b**	CCL	5 h	73	91	68	90	>100	32.4
6	**6a**	PPL	14	5	5	0	42	-	4.7
7	**6a**	CCL	14	24	5	17	70	1.5	0.11
8	**6b**	PPL	28	20	23	75	75	3.3	14.17
9	**6b**	CCL	20 h	68	53	47	79	36	7.88
10	**7**	PPL	20	6	6	54	80	3.5	3.17
11	**7**	CCL	20	25	0	7	82	1.2	0.06

All the experiments were performed at 40°C in hexane with 150mg of enzyme for 1mmol of substrate.
Pig pancreatic lipase (Fluka) PPL 3.5 U/mg, *Candida cylindracea* lipase (Sigma) CCL 750 U/mg.

* Total yield after purification

** The enantiomeric ratio E was calculated as reported in ref. 13a

*** Initial rate in µm substrate transformed/min/U.

So far, we have shown that lipase-catalyzed alcoholysis gives both enantiomers of aziridine carboxylates in good yield and medium to high e.e, the best e.e. being obtained with PPL and N-Me, N-*iso*-Pr and N-Bn aziridine carboxylates. The use of other lipases and esterases, combined with variation in the substitution pattern of the starting aziridines, should allow to improve the efficiency of the resolution. The determination of the absolute configuration of the optically active products obtained in this study is currently in progress in order to compare the experimental results of the resolution and the theoretical predictions using active site models.[18]

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References and Notes

1- Tanner D., *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599-619.

2- a Baldwin, J.E.; Adlington, R.M.; O'Neil, I.A.; Schofield, C.; Spivey, A.C.; Sweeney, J.B. *J. Chem. Soc., Chem. Commun.* **1989**, 1852-1854.

b Legters, J.; Willems, J.G.H.; Thijs, L.; Zwanenburg, B. *Rec. Trav. Chim. Pays-Bas* **1992**, *111*, 59-68.

c Dubois, L.; Dodd, R.H. *Tetrahedron* **1993**, *49*, 901-910 and references cited therein.

3- a Deyrup, J.A.; Clough, S.C. *J. Org. Chem.* **1974**, *39*, 902-907.

b Cainelli, G.; Panunzio, M.; Giacomini, D. *Tetrahedron Lett.* **1991**, *32*, 121-124.

c Van der Steen, F.H.; van Koten G. *Tetrahedron* **1991**, *47*, 7503-7524.

4- a Woller, P.B.; Cromwell, N.H. *J. Org. Chem.* **1970**, *35*, 888-898.

b Hassan, M.E. *Gazz. Chim. Ital.* **1992**, *122*, 7-9.

5- Tsuboyama, K.; Tsuboyama, S.; Yanagati, M. *Bull. Chem. Soc. Japan* **1967**, *40*, 2954-2957.

6- Tanner D. *Pure & Appl. Chem.* **1993**, *65*, 1319-1328.

7- a Ittah, Y.; Sasson, Y.; Shahak, I.; Tsaroom, S.; Blum, J. *J. Org. Chem.* **1978**, *43*, 4271-4273.

b Le Merrer, Y.; Duréault, A.; Greck, C.; Micas-Languin, D.; Gravier, C.; Depezay, J.C. *Heterocycles* **1987**, *25*, 541-548.

c Tanner, D.; Somfai, P. *Tetrahedron* **1988**, *44*, 619- 624.

d Legters, J.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1989**, *30*, 4881-4884.

8- a Nakagawa, Y.; Tsuno, T.; Nakajima, K.; Iwai, M.; Kawai, H.; Okawa, K. *Bull. Chem. Soc. Japan* **1972**, *45*, 1162-1167.

b Chakraborty, T .K.; Gangakhedkar, K.K. *Tetrahedron Lett.* **1991**, *32*, 1897-1898.

c Berry, M.B.; Craig, D. *Synlett* **1992**, 41- 44.

9- Fujisawa, T.; Hayakawa, R.; Shimizu, M. *Tetrahedron Lett.* **1992**, *33*, 7903-7906.

10- a Li, Z.; Conser, K.R.; Jacobsen, E.N. *J. Amer. Chem. Soc.* **1993**, *115*, 5326-5327.

b Evans, D.A.; Faul, M.M.; Bilodeau, M.T.; Anderson, B.A.; Barnes, D.M. *J. Amer. Chem. Soc.* **1993**, *115*, 5328-5329.

11- Mori, K.; Toda, F.; *Tetrahedron Asym.* **1990**, *1*, 281-282.

12- Poitou, F.; Dr. thesis, University of Aix-Marseille, March 1992.

13- a Chen, C.S.; Sih, C.J. *Angew. Chem. Int. Ed.* **1989**, *28*, 695-707.

b Boland, W.; FröBl, C.; Lorenz, M. *Synthesis* **1991**, 1049-1072.

c Faber, K.; Riva, S. *Synthesis* **1992**, 895-910.

14- a Bucciarelli, M.; Forni, A.; Moretti, I.; Prati, F. *Tetrahedron Asym.* **1990**, *1*, 5-8.

b Fuji, K.; Kawabata, T.; Kiryu, Y.; Sugiura, Y. *Tetrahedron Lett.* **1990**, *31*, 6663-6666.

c Bucciarelli, M.; Forni, A.; Moretti, I.; Prati, F.; Torre, G. *Tetrahedron Asym.* **1993**, *4*, 903-906.

d Renold, P.; Tamm, C. *Tetrahedron Asym.* **1993**, *4*, 2295-2298.

e Bucciarelli, M.; Forni, A.; Moretti, I.; Prati, F.; Torre, G. *J. Chem. Soc., Perkin Trans. I* **1993**, 3041-3045.

15- a Deyrupand, J.A.; Moyer, C.L. *J. Org. Chem.* **1970**, *35*, 3424-3428.

b Harada, K.; Nakamura, I. *J. Chem. Soc, Chem. Comm.* **1978**, 522-523.

c Wenbert, D.; Fergusson, S.B.; Porter, B.; Quarnström, A. *J. Org. Chem.* **1985**, *50*, 4114-4119.

16- Lambert, C.; Viehe, H.G. *Tetrahedron Lett.* **1985**, *26*, 4439-4442.

17- Separation of the enantiomers using HPLC on Chiralcel OD-H (Daicel Company) for aziridines **4** (data presented at the "18th International Symposium of Column Separation, 8-13 May 1994 Minneapolis- USA), using GC on FS-Hydrodex β-PM (Macherey-Nagel) for the others.

18- a Ehrler, J.; Seebach, D. *Liebigs Ann. Chem.* **1990**, 379-388.

b Hultin, P.G.; Jones, J.B. *Tetrahedron Lett.* **1992**, *33*, 1399-1402.

c Wimmer, Z. *Tetrahedron* **1992**, *48*, 8431-8436.

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