Enzymatic Kinetic Resolution of Secondary Alcohols in a Homemade Continuous-Flow System

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Abstract

Optically active secondary alcohols were obtained via enzymatic kinetic resolution in a homemade continuous-flow system.

Introduction

Continuous-flow systems in biocatalysis offer some advantages, such as no degradation of enzyme support and, mainly, removing the product from the reaction media.[1] On the other hand, high costs of commercial equipment can be a prohibitive factor in the popularization of continuous-flow methods. However, anyone can build their own equipment, which implies in a significant cost reduction.[2] In this context, we report here the application of a homemade continuous-flow system in enzymatic kinetic resolution reactions of secondary alcohols.

Results and Discussion

Our continuous-flow system is shown in Figure 1.

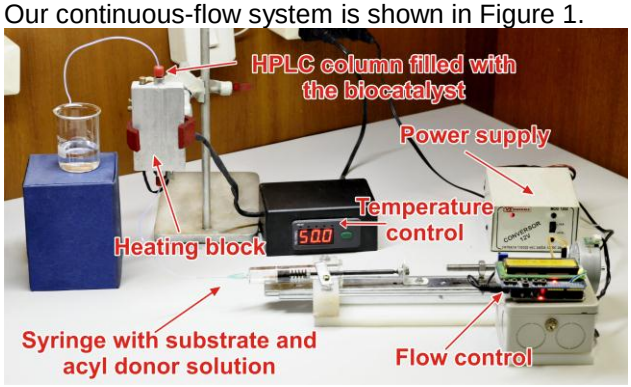
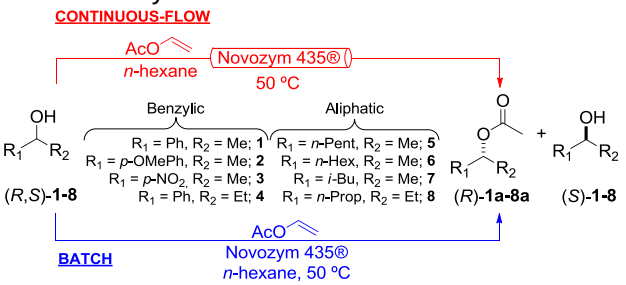


Figure 1. Continuous-flow system

This system was applied to the enzymatic kinetic resolution of well-known lipase-substrates, alcohols **1**-**8**. Batch mode reactions were carried out in parallel to compare the results (Table 1).

A multigram scale reaction was also performed in order to evaluate the reproducibility of results and reuse of the biocatalyst. A solution of 2.0 g of alcohol **1** (0.1 mol L^{-1}) was eluted through the column at 1 mL min^{-1} and it was collected 4 mL aliquots. It was not observed any decrease of conversion even after the elution of entire solution (Figure 2).

Table 1. Enzymatic kinetic resolution of alcohols **1**-**8**



Alcohol	Flow					Batch			
	Rate / mL min^{-1}	Time[a] / min	c^b / %	e.e.[c] / % (*S*)-alcohol	e.e.[c] / % (*R*)-ester	Time / min^{-1}	c^b / %	e.e.[c] / % (*S*)-alcohol	e.e.[c] / % (*R*)-ester
1	1.0	0.5	50	>99	>99	1	50	>99	>99
2	0.5	1	50	>99	>99	6	50	>99	>99
3	0.7	0.7	50	>99	>99	3	50	>99	>99
4	0.1 0.1[d]	5 10	45 50	80 >99	>99 >99	9	50	>99	>99
5	0.1[e]	5	48	92	98	2	50	>99	>99
6	0.1[e]	5	51	99	95	1	50	>99	>99
7	0.1[e]	5	50	98	98	1	50	>99	>99
8	0.1[d,e]	10	57	>99	75	2	50	>99	>99

Reaction conditions: Flow mode: substrate (0.1 mmol mL^{-1}), vinyl acetate (0.4 equivalents) and *n*-hexane (5 mL) and Novozym 435® (200 mg); Batch mode: substrate (0.1 mmol), vinyl acetate (0.4 mmol), *n*-hexane (2 mL) and Novozym 435® (20 mg). Temperature for both 50 °C; [a] Residence time: reactor volume / flow rate; [b] Conversion: ee_s / (ee_s + ee_p); [c] Enantiomeric excess: (*R* – *S*) / (*R* + *S*) x 100; [d] 2 cycles; [e] 100 mg of Novozym 435®

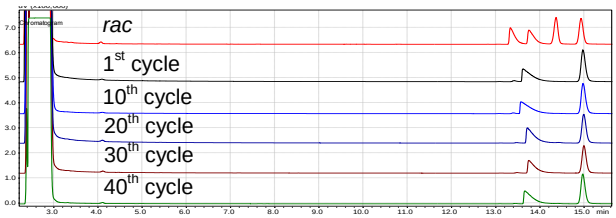


Figure 2. Racemic mixture and reaction aliquots

Conclusion

The combination of our homemade continuous-flow system and biocatalysis was very successful, since all compounds were obtained with high optically purity (75 up to >99%) and reproducibility was very high.

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