Universität Rostock

Traditio et Innovatio

Alcohol Dehydrogenase-catalyzed Enantioselective Synthesis of α-Halogenated Alcohols Bearing a Pyridine Ring

Timo Broese[a, b], Peter Ehlers[b], Peter Langer[b]*, Jan von Langermann[a]*

[a] University of Rostock | Institute of Chemistry, Albert-Einstein-Str. 3a | Biocatalysis group | 18059 Rostock, Germany
[b] University of Rostock | Institute of Chemistry, Albert-Einstein-Str. 3a | Organic Chemistry | 18059 Rostock, Germany

Introduction

The substrate range of the (*R*)-selective alcohol dehydrogenase evo-1.1.270 towards prochiral α-halogenated ketones that are linked via a methylene group with a pyridine ring was investigated. In contrast to the intensively studied acetophenone and pyridine derivates[1] this kind of structural motive is rarely investigated for biocatalytic reduction reactions. High conversions with excellent enantioselectivities were found for relatively small substrates with two or less halogen substitutions. Substrates with even larger heterocycles and more halogen substitutions were not converted.

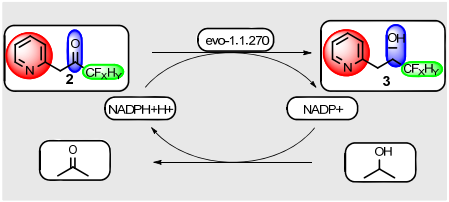


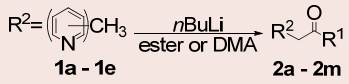
Figure 1. evo-1.1.270-catalyzed synthesis of enantiopure pyridinylpropanols

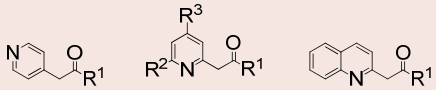
Results

The investigated ketones were synthesized starting from the respective picoline 1a-d or quinanzoline derivatives 1e using the lithium bases *n*-butyllithium (*n*BuLi) or lithium diisopropyl amide (LDA). The different α-halogenated acyl moieties were introduced through the use of different esters or the use of dimethylacetamide (DMA). The straight-forward one pot synthesis was followed by simple workup consisting of an aqueous extraction, while in some examples an additional column chromatography step was required.

Substrates 2a-c and 2e-g were converted with yields between 36% and 98% and very high values for the enantiomeric excesses of up to > 99%. The positive effect of α-halogenation (CFH_2 and CF_2H groups) is clearly shown by high equilibrium yields, even for complex substrates. The introduction of an CF_3 group or substitution on the heterocycle causes a full loss of reactivity (3d, 3h-3o). A similar behavior was also reported recently for α-halogenated acetophenone derivatives.[2]

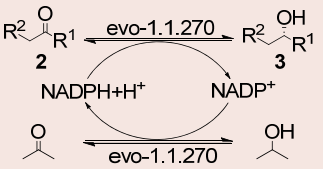
Table 1. Substrate range for subsequent enzymatic reduction





1,2	R^1	R^2	1,2	R^1	R^2
a	CH_3	4-(NC_5H_4)	j	CH_3	2-($NC_5H_3CH_3$)
b	CH_2F	4-(NC_5H_4)	k	CF_3	2-($NC_5H_3CH_3$)
c	CHF_2	4-(NC_5H_4)	l	CH_3	2-($NC_5H_2(CH_3)_2$)
d	CF_3	4-(NC_5H_4)	m	CF_3	2-($NC_5H_2(CH_3)_2$)
e	CH_3	2-(NC_5H_4)	n	CH_3	2-(NC_9H_6)
f	CH_2F	2-(NC_5H_4)	o	CF_3	2-(NC_9H_6)
g	CHF_2	2-(NC_5H_4)			
h	CF_3	2-(NC_5H_4)			
i	$CClF_2$	2-(NC_5H_4)			

Table 2. Conversion of prochiral ketones 2a-2o to the corresponding chiral alcohols 3a-3o.



2,3	R^1	R^2	Y [%]	*ee*
a	CH_3	4-(NC_5H_4)	93	>99(R)
b	CH_2F	4-(NC_5H_4)	98	n.d.
c	CHF_2	4-(NC_5H_4)	95	>99(*S*)
d	CF_3	4-(NC_5H_4)	0	-
e	CH_3	2-(NC_5H_4)	36	>99(R)
f	CH_2F	2-(NC_5H_4)	70	95(*S*)
g	CHF_2	2-(NC_5H_4)	60	n.d
h	CF_3	2-(NC_5H_4)	0	-
i	$CClF_2$	2-(NC_5H_4)	0	-

The shown library of synthesized ketones (table 1) was converted to the corresponding alcohols with very high *ee* and good yields. The obtained results of the enzymatic reduction show that almost half of the investigated substrates were successfully transformed into chiral alcohols, while especially larger substrates were not accepted as substrates (table 2).

Limitations:

- Only small heterocyclic moieties are accepted (2a-c; 2e-g).
- The reactivity increases with increasing number of substitutions. $CH_3 < CH_2X < CHX_2$.
- Full loss of reactivity was obtained with CX_3 substitution (2d; 2h-i).

Summary and Outlook

The aim of this study was to examine the reduction of α-halogenated ketones that are linked via a methylene group with a pyridine ring by a commercially available (*R*)-selective alcohol dehydrogenase. The investigation showed that α-halogenation has a positive effect on the equilibrium yield. Furthermore this study shows that large heterocyclic moieties as well as CF_3 substitution on the ketone remain challenging substrates. Taking this limitations into account we found a series of CH_3, CH_2F and CHF_2 α-substituted pyridine derivates that are easily converted from the methyl ketones to the corresponding chiral alcohol. The obtained alcohols exhibit high *ee* values of up to >99%.

[1] a) C. W. Bradshaw, W. Hummel, C. H. Wong, *J. Org. Chem.* 1992, *57*, 1532–1536. b) S. Choudhury, J.-O. Baeg, N.-J. Park, R. K. Yadav, *Green Chem.* 2014, *16*, 4389. c) T. T. Tolea, J. H.L. Jordaana, H. C.M. Vosloo, Curr. Org. Synth. 2015, 12, 261–304.
[2] b) C. Rodríguez, W. Borzęcka, J. H. Sattler, W. Kroutil, I. Lavandera, V. Gotor, *Org. Biomol. Chem.* 2014, *12*, 673–681.

Acknowledgements
Financial support by Bundesministerium für Bildung und Forschung, Germany (project number: 031A123) is gratefully acknowledged.

Bundesministerium für Bildung und Forschung

Scan this for PDF!