DOI: 10.1002/adsc.201100466

An Efficient Dynamic Kinetic Resolution of N-Heterocyclic 1,2-Amino Alcohols

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Received: June 8, 2011; Published online: August 26, 2011

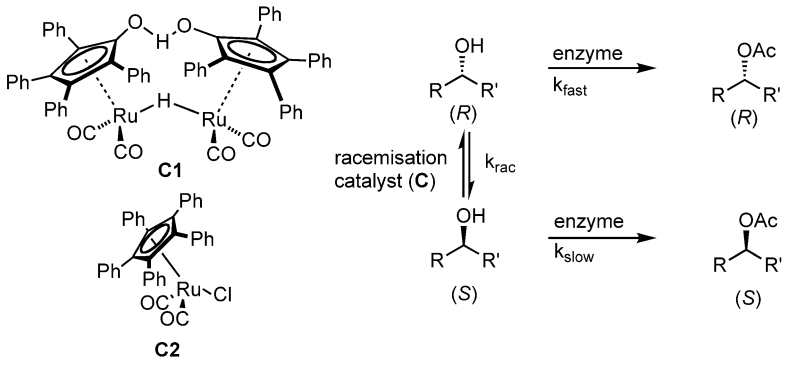
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adcs.201100466.

Abstract: A chemoenzymatic dynamic kinetic resolution (DKR) of N-heterocyclic amino alcohols is described. Various lipases were studied as biocatalysts for the kinetic resolution of N-heterocyclic 1,2-amino alcohols. The influence of the support of the enzymes on the enantioselectivity in the resolution of different substrates is highlighted. Various 3-acetoxypyrrolidines and -piperidines were obtained in high yield and high enantiomeric excess in efficient DKR reactions.

Keywords: amino alcohols; biocatalysis; dynamic kinetic resolution; enzymatic catalysis; lipase

N-Heterocyclic chiral molecules are highly attractive compounds for industry and academic research.[1] Among them, molecules bearing chiral secondary alcohols such as 3-hydroxypiperidines or 3-hydroxypyrrolidines constitute an important class of molecules. They have a wide application scope ranging from intermediates for the synthesis of biologically active compounds to chiral ligands and organocatalysts in asymmetric synthesis.[1,2,3] Various methods have been described for the preparation of N-heterocyclic alcohols in an optically active form[4]; however, only a few of those involve enzymatic resolution.[5]

Enzymatic kinetic resolution (KR) is a highly powerful tool for obtaining enantiopure alcohols and amines.[6] It remains however limited by a theoretical maximum yield of 50%. To overcome this limitation, *in situ* racemisation, using an additional catalyst, has been integrated with the KR protocol (Scheme 1). This integrated system, known as dynamic kinetic resolution (DKR)[7], enables the reaction to proceed beyond the 50% yield barrier and reach a theoretical yield of 100% with high enantiomeric excess. The number of substrate classes suitable for chemoenzymatic DKR with transition metal racemisation catalysts has increased during the past decade from the early examples of simple benzylic alcohols with aliphatic substituents to more functionalised substrates such as chlorohydrins,[8] cyanohydrins,[9] diols,[10] amines,[11] axially chiral allenes,[12] and amino alcohols.[13]



Scheme 1. Two examples of ruthenium-based racemisation catalysts (**C1** and **C2**) and a schematic picture of an (*R*)-selective dynamic kinetic resolution (DKR).

In order to further explore the limitations of chemoenzymatic DKR, we have now investigated the use of this method for transforming racemic 1,2-amino alcohols into enantiomerically pure forms.[14]

Tomori et al.[5c] reported highly selective enzymatic hydrolysis and transesterification processes for the KR of N-heterocyclic acetates and alcohols, respectively, employing lipase PS. However, the transesterification reaction required a large amount of biocatalyst (500 wt%) making it unsuitable for large-scale synthesis. Horiguchi et al.[5d] described a similar resolution in a flow reactor employing supported lipase PS, which increased the catalytic activity of the enzyme. Inspired by these results we decided to investigate the possibility of applying dynamic kinetic resolution to a variety of substituted N-heterocyclic alcohols.

To prove the utility of the DKR process we envisioned to study substrates with various groups attached to the nitrogen of the heterocycle. Electron-withdrawing N-protecting groups, electron-donating aliphatic substituents, and N-aryls were considered valuable to investigate. This range of substrates would illustrate the viability of the protocol both before and after a desired synthetic transformation.

As a model substrate we chose to start by investigating the kinetic resolution of *N*-benzylpiperidin-3-ol (**1a**).

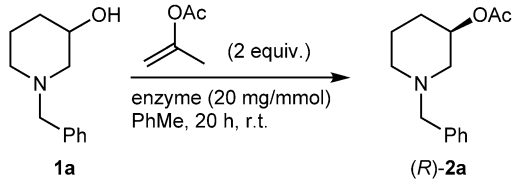
As previously reported,[5c] non-immobilized PS (*Burkholderia cepacia*, previously *Pseudomonas cepacia*) showed very low activity in the transesterification of **1a** (Table 1, entry 1). When an immobilised PS enzyme was employed the activity was increased and an enantioselective reaction was obtained. Commercially available lipases PS-IM (*Burkholderia cepacia* immobilised on diatomaceous earth) and PS-C (*Burkholderia cepacia* immobilised on ceramic particles) showed moderate enantioselectivity with E values ranging from 20 to 25 (Table 1, entries 2 and 3). On the other hand IL1-PS[16] (*Burkholderia cepacia* coated with ionic liquid) showed an E value of 290 determined at 48% conversion. This was the highest E value observed for this substrate in the study (Table 1, entry 4). A high activity with a good enantioselectivity was observed in the KR with CALB (*Candida antarctica* lipase B immobilized on acrylic resin, Novozyme 435®), which afforded an E value of 67 at 51% conversion (Table 1, entry 5). Even though the selectivity was not as high as for IL1-PS this result was promising since CALB was not known to be able to resolve these types of cyclic secondary alcohols.

Next a dynamic kinetic resolution was set up using Shvo's catalyst **C1** for the racemisation and IL1-PS for the resolution (Scheme 2).

The reaction proceeded to full conversion within 24 h at 70 °C giving acetate **2a** in 90% *ee*. Under the same conditions, *N*-benzylpyrrolidin-3-ol (**3a**) afforded acetate **4a** with a dramatic drop in *ee* (4% *ee* at full conversion). During the reaction, *N*-benzylpyrrole was formed in approximately 10%. The decrease in enantioselectivity was confirmed to be due to a severe loss of selectivity in the enzymatic resolution (*vide infra*, Table 2) and highlighted the importance of looking for the most suitable enzyme for each substrate.

For *N*-isopropylpiperidin-3-ol (**1b**), which has a smaller substituent on the nitrogen, PS-IM showed the best selectivity with an E value of >400 (810) at room temperature (Scheme 3, Table 2, entry 5). In the case of the *N*-cyclohexyl alcohol **1c** (Cy = cyclohexyl) an E value of >600 (1143) was obtained with IL1-PS (Table 2, entry 9). With a cyclohexylmethyl group on the nitrogen (**1d**), both PS-IM and IL1-PS lost all activity while CALB displayed high selectivity (Table 2,

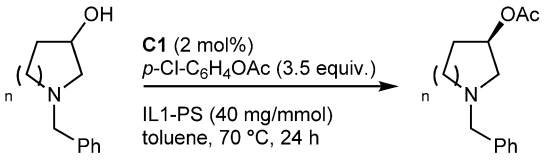
Table 1. Kinetic resolution of **1a** with various enzymes.[a]



1a (*R*)-**2a**

Entry	Enzyme	Conv. [%][b]	ee_{OH} [%][c]	ee_{OAc} [%][c]	Evalue[d]
1	PS	0	–	–	–
2	PS-C	13	13	89	20
3	PS-IM	19	16	91	25
4	IL1-PS	48	88	98	>200 (290)
5	CALB	51	96	89	67

[a] The reactions were run at room temperature for 20 h on a 0.25-mmol scale under argon using 5 mg of enzyme, 2 equiv. of isopropenyl acetate in 1 mL of toluene.
[b] Calculated from the ee_{OH} and ee_{OAc} according to the formula: Conv. = $ee_{OH}/(ee_{OAc}+ee_{OH})$.
[c] Determined by chiral HPLC (see Supporting Information for more details).
[d] Calculated from the ee_{OH} and ee_{OAc} according to formula.[15]

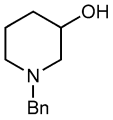
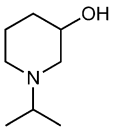
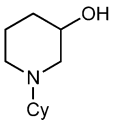
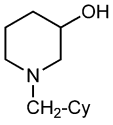
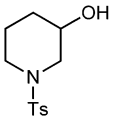
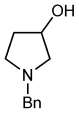
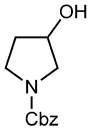
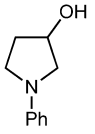


1a, n = 2
3a, n = 1

(*R*)-**2a**, n = 2, *ee* 90%
(*R*)-**4a**, n = 1, *ee* 4%

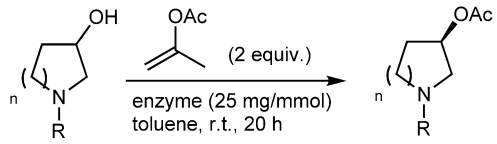
Scheme 2. First DKR attempt employing **C1** as racemisation catalyst.

Table 2. Kinetic resolution of various 1,2-cyclic amino alcohols employing different lipases.[a]

Entry	Substrate	Enzyme	Conv. [%][b]	ee_{OH} [%][c]	ee_{OAc} [%][c]	E value[d]
1	 **1a**	PS	0	–	–	–
2		PS-IM	19	16	91	25
3		IL1-PS	48	88	98	>200 (290)
4		CALB	51	96	89	67
5	 **1b**	PS-IM	18	20	99.7	>400 (810)
6		IL1-PS	11	9	99.4	>200 (363)
7		CALB	41	64	96	95
8	 **1c**	PS-IM	26	36	99.0	>200 (283)
9		IL1-PS	48	93	99.4	>600 (1143)
10		CALB	50	94	93	98
11	 **1d**	PS-IM	5	nd[e]	–	–
12		IL1-PS	5	nd[e]	–	–
13		CALB	42	nd[e]	98	>200
14	 **1f**	PS-IM	9	12	99	200
15		IL1-PS	34	50	99	>200 (327)
16		CALB	47	90	99	>300 (617)
17	 **3a**	PS-IM	53	nd[e]	89	nd[f]
18[g]		PS-IM	20.5	nd[e]	99.8	>600 (1285)
19		IL1-PS	65	nd[e]	52	11
20		CALB	100	–	–	–
21[g]	 **3b**	PS-IM	45	80	>98	>200 (244)
22[g]		IL1-PS	55	99.8	82	67
23	 **3c**	PS-IM	20	23	94	40
24		IL1-PS	51	92	90	62
25		CALB	73	46	-	10

[a] *Typical conditions:* substrate (0.25 mmol), lipase (25 mg mmol^{-1}), isopropenyl acetate (2 equiv.) in toluene (1 mL) at room temperature for 20 h. Cy = cyclohexyl.
[b] Calculated from both *ee*, Conv. = $ee_{OH}/(ee_{OAc}+ee_{OH})$ or determined by ^{1}H NMR.
[c] Determined by chiral GC or chiral HPLC (see Supporting Information for more details).
[d] Calculated from both *ee* or from conversion and *ee* according to formula.[15]
[e] No chiral separation methods for the alcohol were found.
[f] Conversion was too close to 50% to allow accurate determination of E value.
[g] Reaction time 3 h.

entries 11–13). Substrate **1f** seemed to be within the optimal size range for all three biocatalysts screened since good enantioselectivity was observed for all of them (Table 2, entries 14–16). CALB was considered as the best enzyme for the resolution of this substrate due to its high activity.



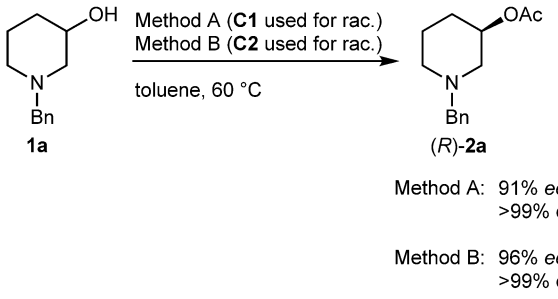
1 n = 2
a: R = Bn, **b**: R = *i*-Pr, **c**: R = Cy, **d**: R = CH_2Cy,
e: R = cyclohexen-2-yl, **f**: R = Ts
2 n = 1
a: R = Bn, **b**: R = Cbz, **c**: R = Ph

Scheme 3. KR conditions of various cyclic amino alcohols.

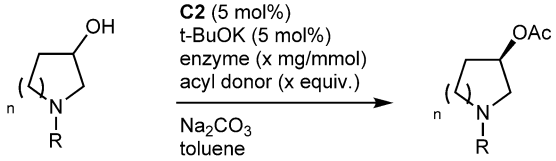
Turning our attention to the substituted 3-pyrrolidinols, once again the support of the enzyme appeared to play a major role in the activity and selectivity of the enzyme. IL1-PS showed a low selectivity for substrate **3a** ($E = 11$, Table 2, entry 19), thus explaining the low *ee* obtained previously (*vide supra*). However, in this case, lipase PS-IM showed the highest enantioselectivity with an E value of 125 (Table 2, entry 18). The *N*-Cbz-pyrrolidin-3-ol (**3b**) showed the same results with the lipase PS-IM being more selective than IL1-PS (Table 2, entries 21 and 22). Finally, the *N*-phenylpyrrolidin-3-ol (**3c**) was resolved in more moderate enantioselectivity by both PS-IM and IL1-PS (Table 2, entries 23 and 24). The results from these kinetic resolutions also illustrate the general trend that IL1-PS displays a faster catalysis of the transesterification than PS-IM.

These kinetic resolutions highlight the impact that the support of an enzyme can play in such processes. The same lipase can show dramatic variations in enantioselectivity for the same substrate simply due to the immobilisation technique used.

Both racemisation catalyst **C1** and **C2** were compared in the DKR of **1a** at 60 °C (Scheme 4). The reaction with **C2** as racemisation catalyst gave a product with a higher *ee* (96% *ee*) than that with **C1** (91% *ee*). This slight difference is due to a more efficient racemisation with **C2** as the catalyst. This is advantageous since it enables the reaction to be run at lower temperatures which is crucial for the PS selectivity and stability.



Scheme 4. DKR of substrate **1a**. *Method A:* **1a** (0.25 mmol), **C1** (6.6 mg), IL1-PS (10 mg), PCPA (3.5 equiv.); *Method B:* **1a** (0.5 mmol), **C2** (16 mg), *t*-BuOK (3.4 mg), Na_2CO_3 (53 mg), IL1-PS (12.5 mg), isopropenyl acetate (2 equiv.).



1 n = 2
a: R = Bn, **b**: R = *i*-Pr, **c**: R = Cy, **d**: R = CH_2Cy, **e**: R = cyclohexen-2yl, **f**: R = Ts
2 n = 1
a: R = Bn, **b**: R = Cbz, **c**: R = Ph

Scheme 5. General scheme for DKR of *N*-substituted pyrrolidin-3-ols and piperidin-3-ols.

The conditions used for resolution of alcohol **1a** were applied in a first attempt for the DKR of alcohol **1b**, but full conversion was not reached within 24 h. The reaction also yielded a slightly lower *ee* than expected.[17] Prolongation of the reaction time from 24 to 36 h did not bring the reaction to completion since the PS lipase loses its activity after long reaction times at these temperatures. The reaction conditions for **1b** and also for the remaining substrates therefore needed to be optimised in terms of enzyme loading, acyl donor amount, and temperature (Scheme 5).

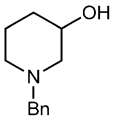
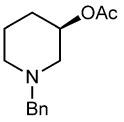
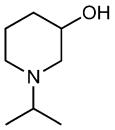
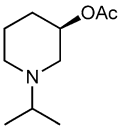
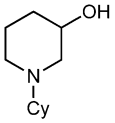
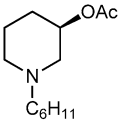
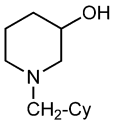
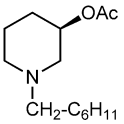
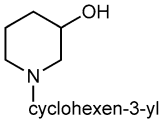
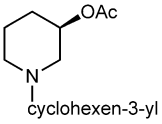
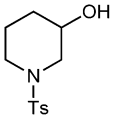
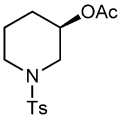
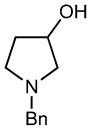
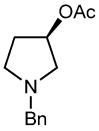
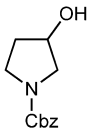
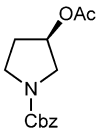
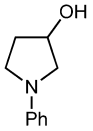
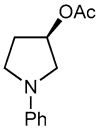
For substrates bearing an aliphatic substituent on the nitrogen (**1b–1e**) an increase of the amount of acyl donor was needed due to low reactivity, and this resulted in a decrease in enantioselectivity under the reaction conditions. This decrease was hypothesised to occur due to chemical acylation facilitated by the tertiary amine. However, a background experiment run at 70 °C for substrate **1b** failed to show any significant chemical acylation. Furthermore, higher yield and somewhat better *ee* were obtained when the reaction was run at 50 °C instead of 60 °C (Table 3, entries 3 and 4). *N*-Cyclohexyl-3-acetoxypiperidine (**2c**) was isolated in a 89% yield and an excellent *ee* of 99% (Table 3, entry 5). The resulting *ee* and conversion of **1d** was lower than expected under the optimised conditions and further elaboration with the reaction conditions failed to improve the results (Table 3, entry 6).

Acetate **2e** was obtained in a 1:1 diastereomeric mixture with a high *ee*. In order to determine the *ee* the double bond was reduced, affording the known acetate **2c** in an *ee* above 98% (Scheme 6).

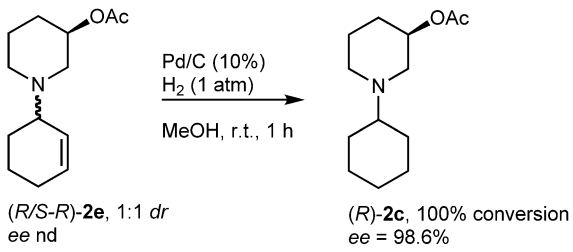
N-Tosyl-3-acetoxypiperidine (**2f**) was obtained in 88% yield and 96% *ee* (Table 3, entry 9).

N-Benzyl- and Cbz-protected pyrrolidinols **3a** and **3b** were efficiently converted to the enantioenriched acetates **4a** and **4b**, respectively, in more than 95% *ee* and yields above 80% (Table 3, entries 10 and 11).

Table 3. Dynamic kinetic resolution of substrates **1a–f** and **3a–3c**.[a]

Entry	Substrate	Enzyme (x mg mmol^{-1})	Isopropenyl acetate	Product	Yield [%][b]	ee_{OAc} [%][c]
1	 **1a**	IL1-PS (25 mg mmol^{-1})	2 equiv.	 (*R*)-**2a**	91	96
2[d]	 **1b**	PS-IM (40 mg mmol^{-1})	2 equiv.	 (*R*)-**2b**	(84)	92
3		PS-IM (80 mmol)	4 equiv.		76	95.4
4[d]		PS-IM(80 mg mmol^{-1})	4 equiv.		86	96.4
5[d]	 **1c**	PS-IM (80 mg mmol^{-1})	6 equiv.	 (*R*)-**2c**	89	99
6	 **1d**	CALB (40 mg mmol^{-1})	4 equiv.	 (*R*)-**2d**	73	90
7[d]	 **1e**	PS-IM (80 mg mmol^{-1})	4 equiv.	 (*R/S-R*)-**2e**	(70)	nd
8[d]		PS-IM (80 mg mmol^{-1})	6 equiv.		(83)	98.6[e]
9[f]	 **1f**	CALB (25 mg mmol^{-1})	2 equiv.	 (*R*)-**2f**	88	96
10	 **3a**	PS-IM (25 mg mmol^{-1})	2 equiv.	 (*R*)-**4a**	80	95
11	 **3b**	PS-IM (25 mg mmol^{-1})	2 equiv.	 (*R*)-**4b**	87	95
12	 **3c**	IL1-PS (40 mg mmol^{-1})	2 equiv.	 (*R*)-**4c**	(>99)	28
13		PS-IM (25 mg mmol^{-1})	4 equiv.		82	86

[a] *Typical conditions:* substrate (0.5 mmol), **C2** (5 mol%), *t*-BuOK (6 mol%), Na_2CO_3 (1 equiv.), lipase (25–80 mg mmol^{-1}), isopropenyl acetate (2.6 equiv.) in toluene (1 mL). See Supporting Information for more details. Cy = cyclohexyl.
[b] Isolated yield, in parenthesis ^{1}H NMR conversion.
[c] Determined by chiral GC or chiral HPLC (see Supporting Information for more details).
[d] Reaction run at 50 °C.
[e] The *ee* was determined after hydrogenation of a 1:1 mixture of diastereomers.
[f] 6 mol% of **C2** used.



Scheme 6. Enantiomeric excess of **2e** determined after hydrogenation of (*R/S-R*)-**2e** to (*R*)-**2c**.

Under these conditions no traces of *N*-benzylpyrrole were detected.

DKR for *N*-phenylpyrrolidin-3-ol (**3c**) was first conducted with IL1-PS, which was the most selective enzyme in the KR study. The result was discouraging since the *ee* of the acetate **4c** was as low as 28%. However, PS-IM was able to deliver the desired acetate in 86% *ee* and 82% yield (Table 3, entry 13).

In summary, DKR has been successfully applied to various vicinal amino alcohols with a 3-hydroxypyrrolidine or -piperidine structure. A variety of electron-withdrawing and electron-donating substituents on the cyclic amine can be used. We also pinpointed the importance of the effect of the immobilisation technique on the outcome of the enzymatic resolution.

Experimental Section

General Procedure for Dynamic Kinetic Resolution of *N*-Benzyl-3-hydroxypiperidine 1a

Ruthenium complex **C2** (η^5-C_5Ph_5)Ru(CO)$_2$Cl (16 mg, 0.025 mmol), IL1-PS (12.5 mg, 25 mg mmol^{-1} substrate) and Na_2CO_3 (53 mg, 0.5 mmol) were added to a dry Schlenk tube. Dry toluene (0.5 mL) was added and the resulting yellow solution was stirred. A THF solution of *t*-BuOK (60 μL, 0.5 M in dry THF, 0.03 mmol) was added to the reaction mixture. The reaction mixture turned orange. After approximately 5 min of stirring, *rac*-**1a** (95,6 mg, 0.5 mmol) dissolved in dry toluene (0.5 mL), was added to the reaction mixture. After an additional 5 min, isopropenyl acetate (110 μL, 1 mmol) was added. The reaction mixture was heated to 60 °C. After 24 h the reaction mixture was filtered and concentrated. Purification by Kugelrohr distillation (0.6 mmHg, 130 °C) afforded (*R*)-**2a** in 96% *ee*; yield: 106 mg (46 mmol, 91%). Spectral data were in accordance with those reported in the literature.[5c]

Acknowledgements

We gratefully acknowledge Dr. Allan Svendsen, Novozymes A/S for a generous gift of CALB (Novozym 435). We also thank Dr. Yoshihiko Hirose, Amano Enzyme Inc. Gifu R&D Center for kindly providing us with enzymes (PS-IM, PS-C, PS-D) and Prof. Itoh for providing IL1-PS. The authors thank INTENANT for financial support. R.M is gratefully acknowledging the Swiss National Science Foundation for a postdoctoral stipend.

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[17] See Supporting Information for more details.

