Tetrahedron: *Asymmetry* 19 (2008) 2374–2377

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

DNA-based hydrolytic kinetic resolution of epoxides

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ARTICLE INFO

Article history:
Received 15 August 2008
Accepted 9 October 2008
Available online 19 November 2008

ABSTRACT

DNA-bound copper(II) complexes serve as catalysts for the hydrolytic kinetic resolution of 2-pyridyloxiranes in water. Selectivity factors of up to 2.7 were achieved, indicating a chirality transfer of DNA to epoxides via a coordinated metal ion.

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1. Introduction

Water is increasingly recognised as a special solvent for asymmetric catalysis.[1] Many catalysts not only tolerate the presence of water, but also in many cases water is beneficial for the rate and enantioselectivity of the catalysed reactions.[2] The use of hybrid catalysts represents a powerful, emerging approach towards aqueous phase catalysis. A hybrid catalyst is created by incorporation of a catalytically active transition metal complex into a protein[3] or oligonucleotide[4] host. The well-defined chiral environment provided by the host is used to induce enantioselectivity in the catalysed reaction.

We have introduced the concept of DNA-based asymmetric catalysis, in which DNA is used as a chiral scaffold.[5] Using a noncovalently bound metal–ligand complex as a cofactor, the chirality of DNA was transferred to the copper(II) catalysed Diels–Alder reaction in water. Two generations of catalyst have been developed; the first contains an acridine-based intercalator moiety that is connected via a spacer to a metal-binding domain. The ligands of the second generation are based on simple polyaromatic or bipyridine-type molecules that combine the DNA- and metal-binding properties into a single moiety (Fig. 1). The latter DNA–metal 0conjugate catalysts yielded the Diels–Alder product in excellent diastereoselectivity and enantioselectivity.[5b] In addition to the Diels–Alder reaction, DNA-based asymmetric catalysis has also been successfully applied in enantioselective Michael additions[6] and electrophilic fluorination[7] reactions.

Kinetic resolution is a powerful method for obtaining enantiomerically enriched chiral compounds.[8] By virtue of the unequal reactivity of both enantiomers in a racemic mixture with a chiral reagent or catalyst, kinetic resolution results in enantiomeric enrichment in the slow-reacting compound. A variety of enzymes and synthetic catalysts have been developed for the kinetic resolution of many classes of compounds.[9] In this regard, the hydrolytic kinetic resolution (HKR) of epoxides is particularly useful, since it results in enantiomerically pure epoxides, which represent very attractive building blocks for organic synthesis. A very efficient and stereoselective catalyst for the HKR of terminal epoxides was reported by Jacobsen et al.[10] By using chiral cobalt–salen com-

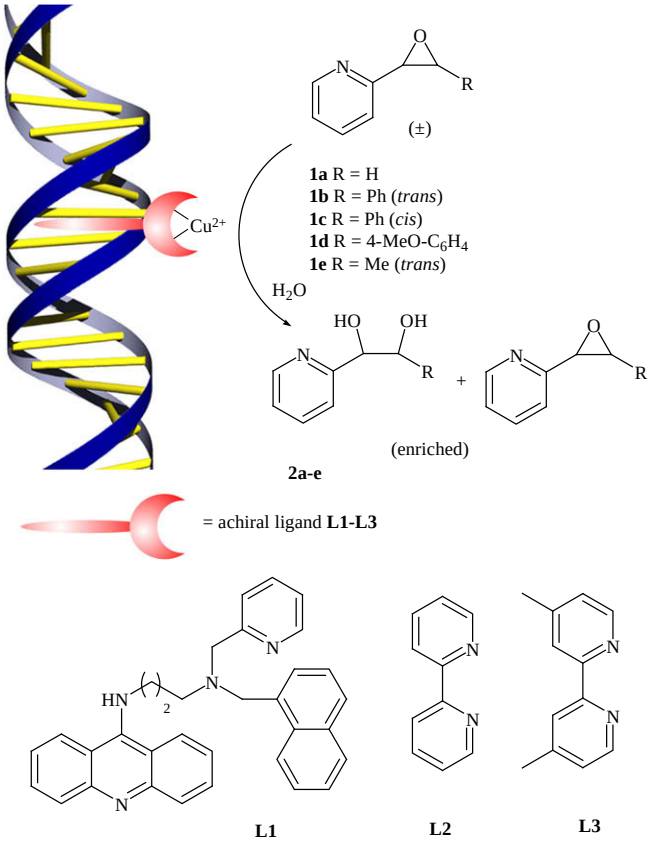

Figure 1. Schematic representation of the DNA-based hydrolytic kinetic resolution of 2-pyridyloxiranes **1a**–**e**.

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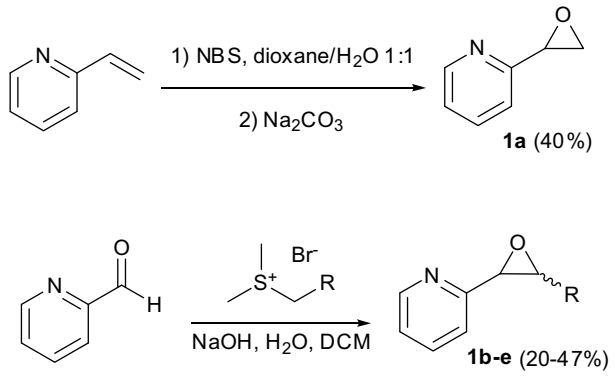
doi:10.1016/j.tetasy.2008.10.004

plexes, *S* values of up to >400 were obtained by reaction with 0.55 equiv of water. Alternatively, highly selective enzymatic catalysts have been developed for the HKR of epoxides in aqueous environments.[11,12]

Herein, we report the first examples of DNA-based kinetic resolution, that is the hydrolytic kinetic resolution of epoxides (Fig. 1).

2. Results and discussion

2-Pyridyloxiranes (2-POs) were selected as substrates for HKR, to ensure efficient bidentate coordination of the substrate to the metal centre. Monodentate binding oxiranes were found not to be good substrates.[13] Lewis acid-promoted ring opening of 2-pyridyloxiranes in water has been reported,[14] making them viable candidates for the HKR catalysed by our hybrid catalyst. 2-Pyridyloxiranes are readily accessible via ring closure of the corresponding halohydrin[15] or the Corey–Chaykovsky reaction.[16] Thus, (±)-2-pyridyloxirane **1a** was synthesised from 2-vinylpyridine in reasonable yield, and β-substituted pyridyloxiranes **1b–e** were synthesised from 2-pyridinecarboxaldehyde and the corresponding dimethylsulfonium ylide (Scheme 1). In this case, yields were limited due to a competing Cannizzaro reaction of the aldehyde.



Scheme 1. Synthesis of epoxide substrates **1a–e.**

In order to establish the optimal metal ion for the DNA-based HKR of 2-pyridyloxirane **1a**, the substrate (initial concentration 3.0 mM) was added to a buffered solution of salmon testes DNA (st-DNA) (1.3 mg mL^{-1}), **L2** (0.39 mM) and various metal ions (0.30 mM, Table 1) at 5 °C.

Hydrolytic conversions of epoxide **1a** were determined, after 72 h of continuous inversion, by rp-HPLC with caffeine as the external standard. From the data in Table 1, it can be concluded that of the metal ions tested, only Cu^{2+} and Ni^{2+} significantly enhance the rate of the hydrolysis of **1a**. In both cases, however, the ee of remaining epoxide **1a** was negligible (<5%; Table 2, entries 2 and 5).

Table 1
The influence of metal ions on the conversion in the HKR of **1a**[a]

Salt	Conv. %
$Sc(OTf)_3$	<10
$FeSO_4$	<10
$Co(NO_3)_2$	<10
$Ni(NO_3)_2$	13 ± 5
$CuSO_4$	43 ± 7
$ZnSO_4$	<10
None	<10

In all cases, **L2** was used as the ligand.
[a] The product of the reaction is the corresponding diol.

Subsequently, the kinetic resolution of **1a** was attempted using the first-generation ligand **L1** with $Ni(NO_3)_2$ and $CuSO_4$ under the conditions described above. The observed conversion after 48 h, 62 ± 1% and 20 ± 6% for the Cu^{2+} and Ni^{2+} catalysed reactions, respectively, (Table 2, entries 1 and 4) were significantly higher using this ligand than using **L2**. With Cu^{2+} as the Lewis acid, the ee of remaining epoxide **1a** was determined to be 21%, leading to an *S* factor of 1.5. Using Ni^{2+} as the Lewis acid, the ee of remaining **1a** was only 5%, and because of the low activity of the Ni^{2+}-based catalyst, Cu^{2+} was the metal ion of choice in further experiments. Finally, as a result of this preliminary screening, when using **L3** as the ligand, 2-pyridyloxirane **1a** could be resolved with *S* = 1.5, giving 10% ee after 42 ± 4% conversion (Table 2, entry 3).

Table 2
Conversions, ees and selectivity factors for the kinetic resolution of substrates **1a–e**[a]

Entry	Substrate	Ligand	Time (h)	Conv. (%)[e]	ee (%)[f]	*S*
1	**1a**	**L1**	48	62 ± 1	21	1.5
2		**L2**	72	43 ± 7	<5	n.d.[g]
3		**L3**	48	42 ± 4	10	1.5
4		**L1**[b]	48	20 ± 6	5	1.6
5		**L2**[b]	72	13 ± 5	<5	n.d.
6	**1b**	**L1**	4.75	91 ± 2	12 (*S*,*S*)	1.1
7		**L2**	16	53 ± 7	21 (*S*,*S*)	1.9
8		**L3**	4	80 ± 1	52 (*S*,*S*)	2.0
9			5	85 ± 2	61(*S*,*S*)	2.0
10		**L3**[c]	2.5	67 ± 1	45 (*S*,*S*)	2.4
11		**L3**[d]	2.5	74 ± 5	63 (*S*,*S*)	2.7
12		None	1.25	80 ± 1	32 (*S*,*S*)	1.5
13	**1c**	**L2**	22	57 ± 2	<5	n.d.
14		**L3**	5	31 ± 4	4	1.2
15	**1d**	**L2**	11	85 ± 1	<5	n.d.
16		**L3**	4	66 ± 3	7	1.2
17	**1e**	**L1**	47	25 ± 4	<5	n.d.
18		**L2**	63	55 ± 4	11	1.3
19		**L3**	47	49 ± 5	<5	n.d.

[a] Conditions: 1.3 mg mL^{-1} st-DNA, 0.3 mM Cu^{2+}/ligand complex, 3 mM substrate, 20 mM MOPS buffer pH 6.5, unless noted otherwise.
[b] $Ni(NO_3)_2$ was used as the metal salt.
[c] 1.5 mM initial substrate concentration.
[d] 0.30 mM initial substrate concentration.
[e] Determined by reversed-phase HPLC.
[f] Ee values were reproducible within 2%.
[g] Not determined.

The optimal buffer and pH for the kinetic resolution of **1a** were determined for Cu^{2+}/**L1**. Both reaction rate and selectivity showed negligible dependence on the nature and pH of the buffer between pH 4.0 and 7.0. For practical reasons, a 30 mM MOPS buffer at pH 6.5 was used in all further experiments.[17]

Next, the effect of β-substituents at the oxirane ring was studied. *trans*-2-(3-Phenyloxiranyl)pyridine **1b** was tested as a substrate in the DNA-based HKR. After only 4 h with **L3** as the ligand, the reaction had proceeded to 80% conversion, with an ee of 52% (*S* = 2.0, Table 2, entry 8) in the remaining substrate. In this case, the corresponding diol formed had an ee of 16%. To exclude Lewis acid-catalysed racemisation of the substrate and/or the product, the reaction was allowed to proceed further. After 5 h, the remaining substrate was present in 61% ee (85% conversion, entry 9), and the corresponding diol had 12% ee. Since the ee increased and the *S* factor stayed the same, this demonstrates that the reaction is not reversible and racemisation of the epoxide does not take place. The selectivity of the HKR using **L2** as the ligand was similar, but the reaction was considerably slower (entry 7). Interestingly, with **L1** as the ligand, the *S* factor was only 1.1 (entry 6). The use of DNA from an alternative source (calf thymus) gave identical results as with st-DNA, which demonstrates that DNA is indeed the source of chirality in the HKR.

For the best catalyst, the substrate/catalyst ratio was lowered to 5:1 and 1:1 by decreasing the substrate concentration (entries 10 and 11, respectively). After 2.5 h, the conversions were slightly lower compared to the reaction with a substrate/catalyst ratio of 10:1. However, the ee of the recovered starting material was higher (up to 63%), resulting in *S* values of up to 2.7. This suggests that the uncatalysed reaction is not negligible, and can give rise to decreased selectivity factors in the case of lower catalyst loadings. Comparison of the specific rotation of the major enantiomer,[18] which was resolved by preparative chiral HPLC, to the literature value, established that the (*S*,*S*)-enantiomer of **1b** remained in excess in all cases, that is, the (*R*,*R*)-enantiomer is preferentially hydrolysed under the influence of the DNA-based catalyst. Interestingly, in the absence of a ligand for Cu^{2+}, the reaction was considerably faster (Table 2, entry 12). However, the observed selectivity factor is significantly lower in this case.

Using the *cis*-isomer **1c** instead of the *trans*-isomer **1b** resulted in a considerable decrease in selectivity, whereas the rate of hydrolysis was approximately the same (entries 13 and 14). Apparently, the DNA-based catalyst could not discriminate efficiently between the enantiomers of **1c**. Substituents at the 2-position of the phenyl ring (2-bromo and 2-nitro) made these substrates insoluble in the buffer, and hence no conversion or kinetic resolution occurred, even at elevated temperatures (data not shown). A 4-methoxyphenyl substituent at the oxirane **1d** gave rise to a sluggish reaction and many unidentified side-products. Furthermore, hardly any enantioenrichment of the substrate was observed (entries 15 and 16). Substitution of 2-PO at the β-carbon with a methyl group (substrate **1e**) considerably decreased the resolution selectivity (entries 17–19).

3. Conclusion

In conclusion, we have presented the first examples of DNA-based catalytic kinetic resolution in water. Using DNA as the source of chirality in the hydrolytic kinetic resolution of 2-pyridyloxiranes, *S* values of up to 2.7 were achieved, and the remaining epoxide was recovered with up to 63% ee. Although to date the resolution selectivity is not high enough for synthetic applications and the substrate scope is limited, these results demonstrate for the first time that the concept of DNA-based catalysis can be applied to achieve kinetic resolution of chiral substrates in water.

4. Experimental

Salmon testes and calf thymus DNA were purchased from Sigma. Reagents and buffer salts were used as supplied without further purification. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian AS400 Mercury Plus spectrometer, operating at 400 and 100.6 MHz, respectively. Chemical shifts are reported in δ units (ppm) relative to the residual solvent signals of $CHCl_3$ (^{1}H NMR: 7.26 ppm; ^{13}C NMR: 77.0 ppm), *J* values are given in Hertz. Thin layer chromatography was performed on Merck Silica gel 60 TLC plates, flash column chromatography was performed on Silicycle Silia P 60 Å silica gel. Mass spectra were recorded on a Jeol JMS-600H mass spectrometer. Reversed-phase and normal-phase HPLC analyses were performed on Shimadzu LC-10AD-VP HPLC instruments equipped with a Shimadzu SPD-M10A-VP diode array detector. Conversions were determined on a Vydac C4 MS or Waters Xterra Phenyl column using methanol/Na-phosphate (25 mM, pH 2.0 or 6.5) as an eluent. Chiral HPLC analyses were performed on a Daicel Chiralpak AD column using heptane/2-propanol as eluent. Chiral GC analysis was performed on a HP-6890 chromatograph using a flame ionisation detector. Optical rotations were determined on a Schmidt + Haensch Polartronic MH8 polarimeter.

4.1. General procedure for the HKR of epoxide substrates

A freshly prepared 1.0 M stock solution of the epoxide in acetonitrile (31.5 μL, 31.5 μmol) was added to 10.5 mL of a solution of st-DNA (1.3 mg mL^{-1}), the metal salt (0.30 mM) and the ligand (0.39 mM) in MOPS buffer (20 mM, pH 6.5) at 5 °C. Mixing was performed by continuous inversion. After the time indicated in Table 2, a 200 μL sample of the reaction mixture was thoroughly mixed with 200 μL of acetonitrile, leading to the precipitation of DNA. After brief centrifugation (13,000 rpm), 200 μL of this mixture was added to 200 μL of a 1.50 mM caffeine solution in water and the conversion of the sample was determined by rp-HPLC analysis. Absolute amounts of remaining epoxide were determined by correlation to a calibration curve. The remaining reaction mixture was extracted with diethyl ether (5 mL, substrate **1a**) or ethyl acetate (2 × 5 mL, substrates **1b**–**e**), the solution dried over Na_2SO_4 and the ee of remaining epoxide was determined by GC (**1a**) or chiral HPLC (**1b**–**e**).

4.2. Synthesis of substrates and ligand L1

2-Pyridyloxirane **1a**[15] (Chiral GC: Chrompack CP Chirasil Dex CB; 110 °C; He flow 1.0 mL min^{-1}, T_r = 7.1; 7.7 min; rp-HPLC: Vydac C4 MS; MeOH/Na-phosphate 25 mM pH 2.0 30/70; flow 0.3 mL min^{-1}; T_r = 15.2 min; caffeine: T_r = 11.3 min) and ligand **L1**[5a] were synthesised following literature procedures. *trans*-2-(3-Phenyl-2-oxiranyl)pyridine **1b** and its diastereomer **1c** were synthesised by the method described by Solladié-Cavallo et al.[16] and were separated by column chromatography (SiO_2, $CHCl_3$/Et_2O 4:1). Compound **1b** was obtained in 30% yield from pyridine-2-carboxaldehyde, and had all analytical data as reported. HPLC: Daicel Chiralpak AD; heptane/*i*-PrOH 95:5; flow 1.0 mL min^{-1}; T_r = 8.9; 16.8 min; rp-HPLC: Waters XTerra Phenyl; MeOH/Na-phosphate 25 mM pH 2.0 30/70; flow 0.5 mL min^{-1}; T_r = 9.5 min; caffeine: T_r = 3.6 min. The *cis*-diastereomer **1c** was obtained in 5% yield, and was recrystallised from pentane, yielding colourless crystals, mp 46–47 °C (lit.[19] 45–47 °C); δ_H (400 MHz; $CDCl_3$) 4.45 (2H, m), 7.02–7.05 (1H, m), 7.06–7.10 (1H, m), 7.11–7.20 (3H, m), 7.20–7.26 (2H, m), 7.41–7.47 (1H, m), 8.41–8.47 (1H, m); δ_C (100.6 MHz; $CDCl_3$) 59.64 (d), 59.99 (d), 121.13 (d), 122.40 (d), 126.79 (d), 127.55 (d), 127.76 (d), 133.81 (s), 135.61 (d), 148.87 (d), 154.56 (s). HPLC: Daicel Chiralpak AD; heptane/*i*-PrOH 99:1; flow 1.0 mL min^{-1}; T_r = 16.2; 22.3 min; rp-HPLC: Waters XTerra Phenyl; MeOH/Na-phosphate 25 mM pH 2.0 20/80; flow 0.5 mL min^{-1} T_r = 8.8 min; caffeine: T_r = 5.5 min.

4.3. *trans*-2-[3-(4-Methoxyphenyl)-2-oxiranyl]pyridine 1d

To a cooled (0 °C) suspension of 4-methoxybenzyldimethylsulfonium hydrogen sulfate[20] (8.16 g, 22.6 mmol) in dichloromethane (36 mL) were added tetrabutylammonium hydrogen sulfate (384 mg, 1.13 mmol, 0.05 equiv) and freshly distilled pyridine-2-carboxaldehyde (2.8 mL, 29.5 mmol, 1.3 equiv). A 50% aqueous solution of sodium hydroxide (22 mL) was added dropwise over 15 min. The reaction mixture was slowly warmed to room temperature and stirring was continued overnight. The reaction mixture was diluted with water and ethyl acetate, the layers separated and the aqueous phase extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated. Crude yield: (4.55 g, 20 mmol, 89%) of a brownish oil. The diastereomers were separated by flash column chromatography (SiO_2, pentane/diethyl ether 1:2). The *trans*-isomer (R_f 0.34) was isolated as an off-white solid (1.01 g, 4.4 mmol, 20%), mp 52–53 °C (lit.[21]: 51–53 °C); δ_H (400 MHz; $CDCl_3$) 3.80 (3 H, s), 4.00 (1H, d, *J* 1.8), 4.05 (1H, d, *J* 1.8), 6.88–6.92 (2H, m), 7.21–7.33 (4H, m), 7.67–7.71 (1H, m), 8.57–8.59

(1H, m); δ_C (100.6 MHz; $CDCl_3$) 55.19 (q), 61.67 (d), 62.52 (d), 113.91 (d), 119.87 (d), 123.02 (d), 126.99 (d), 128.49(s), 136.65 (d), 149.40 (d), 156.50 (s), 159.77 (s); *m*/*z* (EI) 227 (22, M^+), 198(100), 121(74); HRMS for $C_{14}H_{13}NO_2$: calcd 227.0952, found 227.0946. HPLC: Daicel Chiralpak AD; heptane/*i*-PrOH 9:1; flow 1.0 mL min^{-1}; T_r = 9.7; 18.1 min; rp-HPLC: Waters XTerra Phenyl; MeOH/Na-phosphate 25 mM pH 6.5 40/60; flow 0.5 mL min^{-1}; T_r = 15.9 min; caffeine: T_r = 2.9 min.

4.4. *trans*-2-(3-Methyl-2-oxiranyl)pyridine 1e

To a cooled (0 °C) suspension of triethylsulfonium bromide[22] (1.45 g, 7.28 mmol) in dichloromethane (12 mL) were added tetrabutylammonium hydrogen sulfate (124 mg, 0.364 mmol) and freshly distilled pyridine-2-carboxaldehyde (0.77 mL, 8.0 mmol). A 50% aqueous solution of sodium hydroxide (7 mL) was added dropwise over 15 min. The reaction mixture was slowly warmed to room temperature and stirring was continued overnight. The reaction mixture was diluted with water and ethyl acetate, the layers separated and the aqueous phase extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated. Crude yield: (856 mg, 6.3 mmol, 87%) of a dark brown oil. The diastereomers were separated by flash column chromatography (SiO_2; pentane/diethyl ether 1:1). The *trans*-isomer was obtained as a pale yellow oil (136 mg, 1.0 mmol, 14%). δ_H (400 MHz; $CDCl_3$) 1.47 (3H, d, *J* 5.1), 3.12–3.16 (1H, m), 3.74 (1H, d, *J* 2.2), 7.18–7.21 (2H, m), 7.63–7.67 (1H, m), 8.53–8.55 (1H, m); δ_C (100.6 MHz; $CDCl_3$) 17.64 (q), 58.26 (d), 59.67 (d), 119.40 (d), 122.77 (d), 136.60 (d), 149.09 (d), 157.26 (s); m/z (EI) 135 (3.8, M^+), 120 (27), 79 (100); HRMS for C_8H_9NO: calcd 135.0684, found 135.0681. HPLC: Daicel Chiralpak AD; heptane/*i*-PrOH 99:1; flow 1.0 mL min^{-1}; T_r = 11.8; 16.5 min; rp-HPLC: Vydac C4 MS; MeOH/Na-phosphate 25 mM pH 7.0 30/70; flow 0.5 mL min^{-1}; T_r = 12.8 min; caffeine: T_r = 9.8 min.

Acknowledgements

We are grateful to Nanoned and NWO-CW for the financial support. Mrs. T. Tiemersma-Wegman is acknowledged for technical assistance with HPLC separations.

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