Biocatalytic Dynamic Kinetic Resolution for the Synthesis of Atropisomeric Biaryl *N*-Oxide Lewis Base Catalysts

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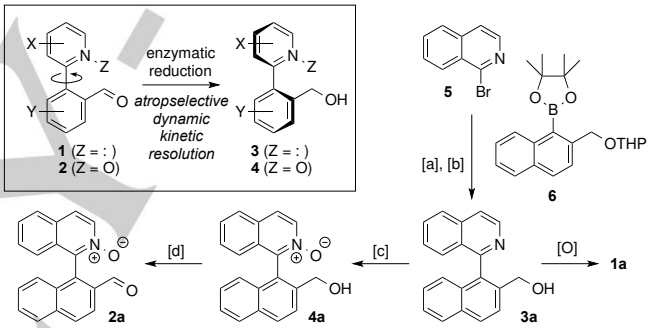
Abstract: *Atropisomeric biaryl pyridine and isoquinoline N-oxides were synthesized enantioselectively by dynamic kinetic resolution (DKR) of rapidly racemising precursors exhibiting free bond rotation. The DKR was achieved by ketoreductase (KRED) catalysed reduction of an aldehyde to form a configurationally stable atropisomeric alcohol, with the substantial increase in rotational barrier arising from the loss of a bonding interaction between the N-oxide and the aldehyde. Use of different KREDs allowed either the M or P enantiomer to be synthesized in excellent enantiopurity. The enantioenriched biaryl N-oxide compounds catalyse the asymmetric allylation of benzaldehyde derivatives with allyltrichlorosilane.*

Biaryl atropisomers provide an important class of structure with extensive utility in asymmetric synthesis, particularly as ligands inducing asymmetric catalysis by metals.[1] Atropisomers are also used as catalysts in their own right. BINOL derived phosphoric acids have been utilised as Brønsted acid catalysts[2] and atropisomeric quinoline *N*-oxides such as QUINOX[3] are excellent Lewis base catalysts for various asymmetric transformations incuding asymmetric allylation of substituted benzaldehydes,[4,5] asymmetric desymmetrisations of *meso* epoxides[6] and asymmetric aldol reactions.[7]

The need for efficient methods for the enantioselective synthesis of atropisomers[8] has encouraged the development of atroposelective transition metal couplings,[9] kinetic resolution by metal catalysis[10] and organocatalytic methods,[11] and desymmetrisation.[12] The potential for subtle control of racemisation rates in atropisomeric and near-atropisomeric structures allows the efficient use of dynamic kinetic[13] or thermodynamic[14] resolution. Although biocatalytic methods are particularly effective for achieving kinetic resolution and dynamic kinetic resolution,[15] biocatalytic dynamic kinetic resolution (DKR) has never been used to synthesise atropisomers enantioselectively.[16] In this paper we describe the first use of biocatalytic DKR for the asymmetric synthesis of some novel catalytically active biaryl atropisomers.

In an effective DKR,[17] an enantioselective transformation must take place more slowly than the racemisation of the starting materials but faster than the racemisation of the products. This requirement makes DKR a particularly appealing strategy for the synthesis of atropisomers, since their racemisation entails a simple bond rotation that may be fine-tuned using steric or electronic substituent effects. For a practical biocatalytic DKR this substrate racemisation must take place on a timescale of minutes or less within a temperature range at which the enzyme can operate (typically 20-50 °C), while the product must be atropisomerically stable over at least hours at this temperature. We reasoned that such a substantial decrease in racemisation rate could be achieved by a functional group interconversion in which a small, planar substituent such as an aldehyde is converted to a larger, tetrahedral substituent.[18] Atropisomeric alcohols of general structure **3** are useful chiral ligands for asymmetric synthesis,[19] so we set out to explore the possibility of making them enantioselectively by dynamic kinetic resolution of the biaryl aldehydes **1**.



Scheme 1. Biaryl aldehyde substrates for KR and DKR. [a] PdRuPhos (3 mol%), CsF (3.0 equiv), THF, reflux, 86%; [b] PPTS (0.6 equiv), EtOH, 73%; [c] MnO_2 (10.0 equiv), CH_2Cl_2, r.t. 86%.; [d] *m*-CPBA (1.5 equiv), CH_2Cl_2, r.t., 74%

Initial studies focused on aldehyde **1a**, but this turned out to be unstable towards an oxidative cyclisation (see SI), so its isoquinoline nitrogen atom was protected in the form of the *N*-oxide derivative **2a**. Suzuki coupling of boronate ester **6** with 1-bromoisoquinoline **5** in 86% yield was followed by THP ether deprotection to give **3a** in 73% yield (Scheme 1). Oxidation to the *N*-oxide **4a** in 74% yield and a second oxidation with MnO_2 in 86**%** yield gave aldehyde **2a**. The stability of **2a** towards racemisation was estimated by micropreparative separation of its enantiomers by HPLC on a chiral stationary phase, monitoring their subsequent decay in ee of **2a** over time. No loss in ee was observed after 5 h in xylenes at 100 °C, and at 138 °C decomposition occurred faster than racemisation. A substrate racemising this slowly is not a suitable candidate for a DKR process, so **2a** was used instead as a model to determine the ability of commercially available ketoreductase enzymes (KREDs) to distinguish the enantiomers of this family of biaryl aldehydes in a non-dynamic kinetic resolution. Aldehyde **2a** was incubated at 30 °C for 16 h with a series of KREDs in the presence of a glucose/glucose dehydrogenase (GDH)/NADP cofactor recycling system,[20] and the results are shown in Table 1.

KREDs (Codexis) 113, 110, 112 and 114 (Entries 5, 7, 8 and 9) gave excellent results, selectively reducing one enantiomer of aldehyde **2a** to give the alcohol **4a** in 98 to >99%

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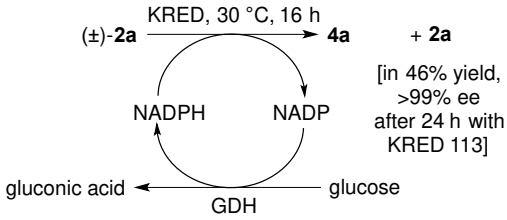
ee respectively and with yields of 46-51%. KRED 130 by contrast (Entry 13) showed high reactivity but low enantioselectivity, producing alcohol **4a** in 93% yield with 20% ee. These high enantioselectivities indicated that the enzyme active site was able to distinguish highly effectively the two enantiomeric atropisomers of a 2-arylisoquinoline-*N*-oxide, so we set about modifying the substrates in order to increase the rate of racemisation of these substrates.

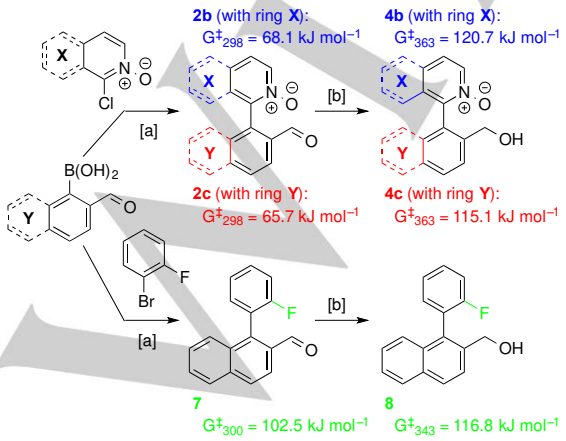
Table 1. Kinetic resolution of racemic aldehyde **2a** using a panel of KREDs.



Entry	KRED	**4a** [%][a]	**4a** ee[b] [%]	**2a** [%]	**2a** ee[b] [%]
1	102	4	22	96	0
2	105	0	-	100	-
3	107	0	-	100	-
4	108	3	60	97	3
5	110	54	63	46	98
6	111	0	-	100	-
7	112	51	67	49	99
8	113	54	65	46	>99
9	114	49	77	51	98
10	119	40	87	60	72
11	123	31	72	69	45
12	124	62	44	38	99
13	130	93	1	7	20
14	none[c]	13	100	87	23

[a] % conversion determined by HPLC. [b] Absolute configuration not known. [c]Reaction mixture still contains GDH.

Two less hindered biaryl *N*-oxides, the 1-phenylisoquinoline-*N*-oxide **2b** and the 2-(1-naphthyl)pyridine-*N*-oxide **2c**, were made by Suzuki coupling (Scheme 2). Preliminary analysis by HPLC suggested that both aldehydes were unstable towards racemisation at room temperature: attempted resolution on a chiral stationary phase at 30 °C resulted in a single broad peak in both cases. By contrast, racemic samples of the corresponding alcohols **4b** and **4c** each clearly showed two distinct enantiomeric peaks on the same chiral stationary phase (see SI), indicating that, as hoped, both **4b** and **4c** had a substantially higher barrier to rotation than the corresponding aldehydes.

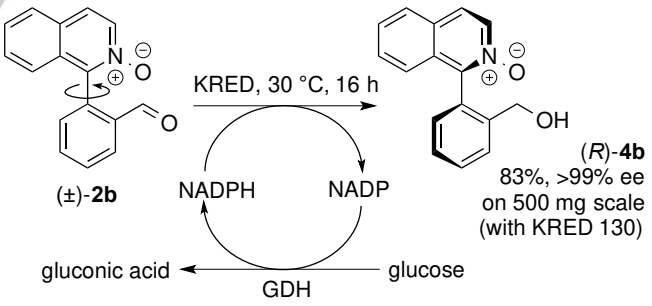


Scheme 2. Synthesis of less hindered biaryl *N*-oxide aldehydes **2b, 2c** and alcohols **4b, 4c**, along with models **7** and **8**.. $\Delta G^{\ddagger}_{T}$ indicates the barrier to enantiomerisation (Ar–Ar bond rotation) at *T* K. [a] $Pd(PPh_3)_4$ (10 mol%), K_2CO_3 (3.0 equiv), dioxane, reflux; [b] $NaBH_4$, MeOH.

The rotational barriers of the configurationally unstable aldehydes **2b** and **2c** were determined more accurately by VT ^{1}H NMR analysis in toluene-d_8 in the presence of the chiral solvating reagent, (*R*)-1-anthracen-9-yl-2,2,2-trifluoroethanol (1 equiv.). VTNMR and line-shape analysis of the resulting pair of diastereoisomeric aldehyde CHO resonances (see SI) gave values for the barrier to enantiomerisation of $\Delta G^{\ddagger}_{298\,K}$ = 68.1 kJ mol^{-1} for **2b** and $\Delta G^{\ddagger}_{298\,K}$ = 65.7 kJ mol^{-1} for **2c**, both corresponding to half-lives of seconds or less at ambient temperatures. The barriers to Ar–Ar bond rotation in the alcohols **4b** and **4c** were calculated from the rate of first-order decay in ee over time at 90 °C in xylenes (see SI) of samples resolved by semi-preparative HPLC on a chiral stationary phase. For **4b** $\Delta G^{\ddagger}_{363\,K}$ = 120.7 kJ mol^{-1}, corresponding to a half-life to racemisation at 90 °C of 2.9 h; for **4c**, $\Delta G^{\ddagger}_{363\,K}$ = 115.1 kJ mol^{-1}, corresponding to a half-life to racemisation at 90 °C of 45 min. The substantially greater configurational stability of the alcohols over the aldehydes allows a usefully large window for a potential dynamic kinetic resolution on a time scale intermediate between the two time scales of racemisation.

The panel of KREDs were screened against substrates **2b** and **2c** on an analytical scale (1 mL, 2.5 mg substrate). Remarkably, KREDs 108, 112, 119 and 130 (Table 2, Entries 4, 7, 9 and 12) performed almost perfect DKR of **2b**. The atropisomeric alcohol (*S*)-**4b** was obtained in 100% yield (based on full conversion by HPLC), with enantioselectivities of 96, 98 and 94% ee. Furthermore, KRED 130, (Entry 12) showed opposite selectivity to KREDs 108, 112 and 119 (Entries 4, 7 and 9), giving (*R*)-**4b** enantiomer in excellent ee (>99%). The ability to access both enantiomers of the product is an attractive feature of the method, and scaling the reaction to 500 mg of substrate (entry 12) returned a preparatively useful quantity of (*R*)-**4b**. This result represents the first example of a biocatalytic DKR for the asymmetric synthesis of an enantiopure axially chiral biaryl. A control experiment in the absence of KRED (Entry 13) confirmed that background reduction by the glucose dehydrogenase (GDH) used for cofactor recycling was not responsible for the DKR.

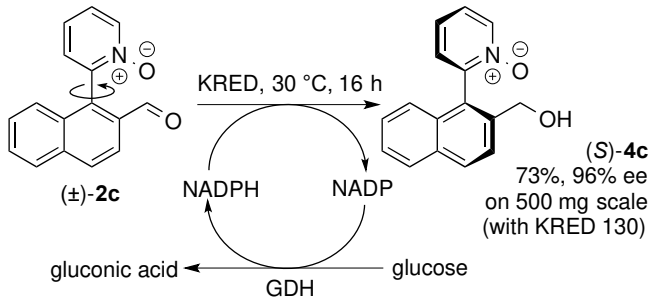
Table 2. Dynamic Kinetic resolution of aldehyde **2b** using a panel of KREDs.



Entry	KRED	**4b** [%][a]	**4b** ee [%]	Configuration[b]
1	102	21	7	*R*
2	105	4	>99	*R*
3	107	5	>99	*R*
4	108	100	96	*S*
5	110	59	99	*S*
6	111	5	>99	*R*
7	112	100	98	*S*
8	113	93	95	*S*
9	119	100	94	*S*
10	123	22	16	*S*
11	124	73	68	*S*
12	130	100, 83[c]	>99	*R*
13	none	0	-	-

[a] % conversion determined by HPLC. [b] Configuration assigned by comparing experimental and calculated circular dichroism spectra (see Fig. 1). [c] Isolated yield on 500 mg scale.

Table 3. Dynamic Kinetic resolution of aldehyde **2c** using a panel of KREDs.



Entry	KRED	**4c** [%][a]	**4c** ee [%]	Configuration.[b]
1	102	21	55	*S*
2	105	5	76	*S*
3	107	11	33	*R*
4	108	21	82	*S*
5	110	100	4	*R*
6	111	25	74	*S*
7	112	100	54	*S*
8	113	100	8	*R*
9	119	77	23	*S*
10	123	7	11	*S*
11	124	100	73	*R*
12	130	100, 73[c]	96	*S*
13	none	3	36	*S*
14	none[d]	0	-	-
15	130[d]	42	96	*S*

[a] % conversion determined by HPLC. [b] Configuration assigned by comparing experimental and calculated circular dichroism spectra (see Fig. 1). [c] Isolated yield on 500 mg scale. [d] Formate dehydrogenase (FDH) used instead of GDH, with formic acid as reductant.

Substrate **2c** was screened with the same series of KREDs and again excellent conversions (100%) were obtained, this time with KREDs 110, 112, 113, 124 and 130 (Table 3, entries 5, 7, 8, 11 and 12). In general the enantioselectivities were lower than with **2b**, but nonetheless KRED 130 (entry 12) produced (*S*)-**4c** in 96% ee and 100% yield. In this case, a background reaction occurred in the absence of the KRED (entry 13) suggesting that GDH was able to catalyse the reduction in 3% yield and 36% ee. GDH is known to have some substrate promiscuity,[21] so the reaction was repeated using formate dehydrogenase (FDH) and formic acid as the co-factor recycling system. No background reaction was observed (entry 14). The enantioselectivity with KRED 130 with FDH recycling remained high (96% ee), so any background reaction from using GDH can be disregarded. Again, the reaction performed well on scale-up, giving 73% of (*S*)-**4c** (96% ee) on a 500 mg scale (entry 12).

The absolute configuration of alcohols **4b** and **4c** was assigned by comparison of their electronic circular dichroism spectra (Figure 1, solid lines) with CD spectra calculated by time-dependent DFT (Figure 1, dashed lines: see SI). Intriguingly, KRED 130 reduced **2b** to give (*R*)-**4b** but reduced **2c** to give (*S*)-**4c**.

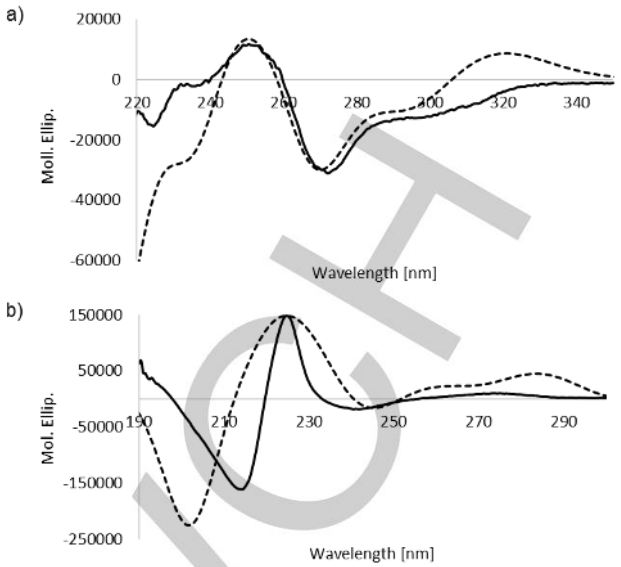


Figure 1. Experimental (solid line) and calculated (dashed line) electronic circular dichroism spectra (a) of (*R*)-**4b** and (b) of (*S*)-**4c.**

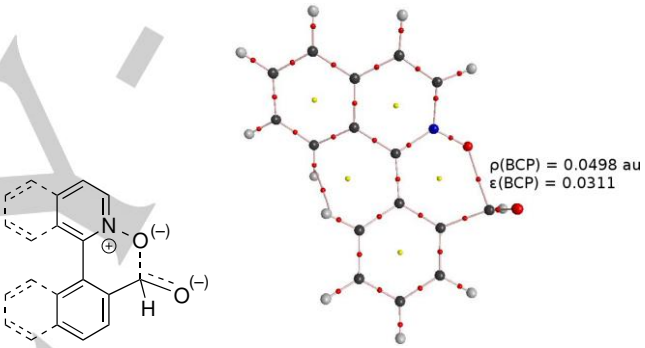
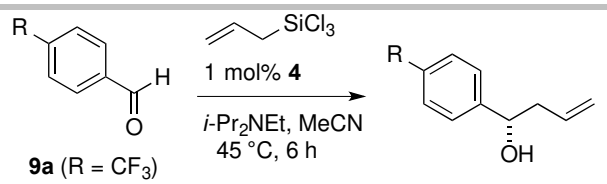


Figure 2. Bonding interaction at the transition state for enantiomerisation of **2.**

The successful DKR is made possible by the substantial difference in barriers to Ar–Ar bond rotation between the aldehydes **2** and the alcohols **4**. To explore the possibility that a bonding interaction between the *N*-oxide substituent and the formyl group in **2** accelerates its racemisation (Figure 2),[22] isosteric fluorinated compounds **7** and **8** were made (Scheme 2) in which this possibility is greatly reduced. While the barrier to bond rotation in alcohol **8** is similar to that in alcohols **4**, the barrier to bond rotation in **7** is significantly higher than that in **2**, suggesting that the transition state for enantiomerisation of **2** benefits from the stabilising bonding interaction illustrated in Figure 2. Molecular modelling (described in full in the SI) supports this interpretation, indicating pyramidalisation of the aldehyde at the transition state (Fig 2) as a consequence of this interaction.[23]

In common with biaryl *N*-oxides such as QUINOX,[3] the biaryl *N*-oxides formed by biocatalytic DKR turned out to be effective Lewis base organocatalysts for the asymmetric allylation of aldehydes. Using the method of Hayashi *et al.*[4], allyltrichlorosilane (1.1 equiv.) and the aldehyde (1.0 equiv.) were stirred in either acetonitrile or dichloromethane at −45 °C in the presence of 0.1-1 mol% *N*-oxide catalyst for 6 h. Three substituted benzaldehydes were employed (**9a-c**), and enantiomeric excesses of up to 80% were obtained in the presence of (*S*)-**4c** (0.1 mol%).

Table 4: Allylation of benzaldehydes using **4** as organocatalysts.



9a (R = CF_3)
9b (R = H)
9c (R = OMe)

(*S*)-**10**

Entry	Catalyst	R =	**10** [%]	**10** ee [%]	Configuration
1	(*R*)-**4b**	CF_3	15	32	*S*
2	(*R*)-**4b**	H	22	34	*S*
3	(*R*)-**4b**	OMe	17	17	*S*
4	(*S*)-**4c**[a]	CF_3	28	50	*R*
5	(*S*)-**4c**[a]	H	66	48	*R*
6	(*S*)-**4c**[a]	OMe	50	76	*R*
7	(*S*)-**4c**[a, b]	OMe	27	80	*R*

[a] Catalyst has 96% ee. [b] 0.1 mol% catalyst loading.

In summary, the first asymmetric synthesis of atropisomers by dynamic kinetic resolution using biocatalysis gives access to new biaryl *N*-oxide scaffolds in excellent ee and yields in three steps from commercially available starting materials. Structural features in the aldehydes facilitate rapid racemisation at ambient temperatures required for the asymmetric biocatalytic transformation. The *N*-oxides act as Lewis base organocatalysts for the asymmetric allylation of aldehydes. Biocatalytic DKR offers rich possibilities for the synthesis of atropisomers without recourse to traditional resolution.

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Keywords: atropisomer • ketoreductase • dynamic kinetic sesolution • biaryl • *N*-Oxides • organocatalysis.

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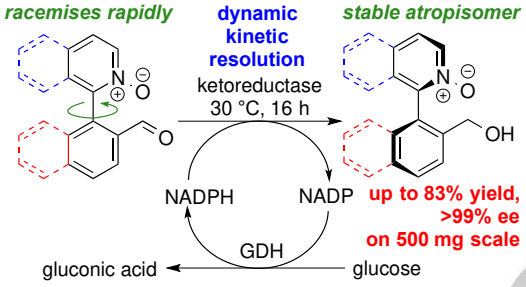
COMMUNICATION

Enzymatic reduction of rapidly racemising biaryl aldehydes yields, by highly selective dynamic kinetic resolution (DKR), single enantiomers of atropisomeric biaryls in high yield and high ee. This first atropselective enzymatic DKR gives products that contain pyridine-N-oxide and primary alcohol groups and function as catalysts of asymmetric aldehyde allylation.



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Biocatalytic Dynamic Kinetic Resolution for the Synthesis of Atropisomeric Biaryl *N*-Oxide Lewis Base Catalysts