Biocatalytic Atroposelective Synthesis of Axially Chiral *N*-Arylindoles via Dynamic Kinetic Resolution

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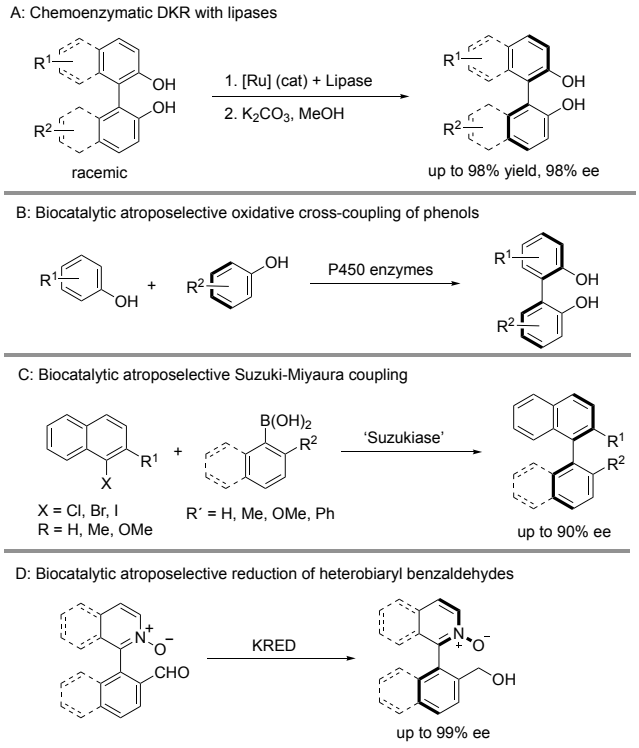
ABSTRACT: A highly enantioselective biocatalytic dynamic kinetic resolution (DKR) of configurationally labile *N*-arylindole aldehydes is described. The DKR proceeds by atroposelective bioreduction of the carbonyl group catalyzed by commercial ketoreductases (KREDs), thus affording the corresponding axially chiral *N*-arylindole aminoalcohols, with excellent conversions and optical purities. The strategy relies on the racemization of the stereogenic axis that takes place thanks to a transient Lewis pair interaction between the NMe_2 and the aldehyde groups. This protocol features a broad substrate scope under very mild conditions.

Axial chirality is an fascinating property present in a variety of natural products, biologically active substances, privileged chiral ligands and smart materials.[1] In the past two decades, enormous advances have been achieved toward the construction of various axially chiral scaffolds, especially for the synthesis of atropisomers containing a C–C axis.[2] In contrast, the asymmetric synthesis of C–N axially chiral compounds remains much less explored, and is more challenging because the structural properties of the C–N axis often led to a decrease in their configurational stability.[3] Among the catalytic methodologies developed for the atroposelective synthesis of (hetero)biaryls, biocatalysis has been scarcely applied in relative terms, but there is an increasing interest in the methodology.[4] An overview of the state of the art reveals that hydrolytic enzymes (lipases) are the most common type of enzymes, often applied to kinetic resolution (KR),[5] desymmetrization,[6] and, more recently, to an elegant dynamic kinetic resolution (DKR) of BINOL derivatives, using a ruthenium complex as cocatalyst to facilitate the required. racemization[7] (Scheme 1A). Oxidative cross-coupling of phenol derivatives,[8] which is the main biosynthetic route in nature for the of atroposelective formation of axially chiral biaryls, is also a challenging target in the field of biocatalytic transformations. Recently, the group of Narayan demonstrated that both wild-type and engineered P450 enzymes are capable to perform regio- and atroposelective unnatural oxidative cross-couplings while avoiding dimerization[9] (Scheme 1B). Notably, the biotin–avidin technology has been applied to design a Pd-containing artificial metalloenzyme named 'Suzukiase', optimized by site-directed mutagenesis to catalyze Suzuki-Miyaura couplings with moderate-to-good atroposelectivities (up to 90% *ee*)[10] (Scheme 1C). Finally, Turner, Clayden and co–workers developed an elegant atroposelective bioreduction of heterobiaryl *N*-oxides (Scheme 1D),[11] providing the first and unique example of a biocatalytic Dynamic Kinetic Resolution (DKR) on heterobiaryl systems employing ketoreductases (KREDs) as biocatalysts.[12]

Scheme 1. Biocatalytic atroposelective transformations



Key in this last strategy is the stereochemical lability of the starting *N*-oxide **1**, facilitated by a bonding interaction between the *N*-oxide and the carbonyl group in a 6-membered cyclic transition state $\mathbf{TS_I}$ (C···O distance = 1.96 Å, Scheme 2A). On the other hand, we have recently developed a DKR strategy for the atroposelective synthesis

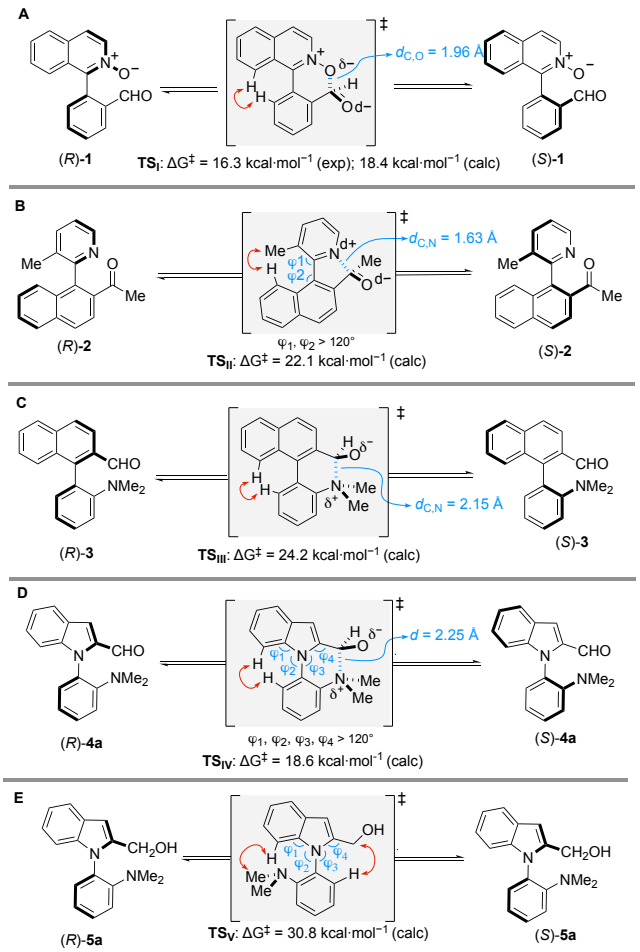
of heterobiaryl carbinols bearing central and axial chirality elements through the zinc-catalyzed hydrosilylation of heterobiaryl ketones **2**.[13] In this this case, the Lewis pair in the transition state $\mathbf{TS_{II}}$ forces a cyclic five-member geometry that results in a widening of the φ_1 and φ_2 angles involved in the configurational stability of the axis, making possible to racemize *ortho*,*ortho´*-disubstituted substrates (Scheme 2B). On this basis, we decided to explore the resolution of biaryls decorated with formyl and *N*-dimethylamino groups as Lewis acidic and basic functionalities. We initially considered the resolution of biphenyl derivatives **3**, envisioning racemization through a transition state $\mathbf{TS_{III}}$ which is *a priori* similar to $\mathbf{TS_I}$ (Scheme 2C). In this case, however, the $NMe_2\cdots CHO$ interaction might be less efficient due to the bigger size of the dimethylamino group, generating also repulsive steric interactions, in particular between the carbonyl oxygen atom and the nearest N-Me group. These concern, supported later by DFT calculations (vide infra) made it doubtful that **3** are suitable substrates in any transformation *via* DKR, at least under conditions compatible with biocatalysis. To overcome this limitation, we envisioned the resolution of *N*-aryl indole analogues **4a**, assuming that the racemization would be significantly facilitated by two concomitant factors:

1) In the predicted structure of the corresponding transition state $\mathbf{TS_{IV}}$ (Scheme 2D), the presence of a five-membered heterocycle (pyrrole unit of the indole fragment) instead of a phenyl ring makes the angles φ_1, φ_2, φ_3, and φ_4 significantly wider than the prototypical 120° angles in the former. Consequently, the distances between the *ortho* groups, on one side, and the interacting $NMe_2\cdots CHO$ groups, on the other, are significantly longer.

2) It is assumed that the lower aromaticity of the indole ring[14] confers a higher flexibility to the system (for example, by a partial pyramidalization of the N atom) that should also alleviate, in relative terms, the steric interactions in $\mathbf{TS_{IV}}$

Moreover, a computational study [DFT/B3PW91-D/6-311++g(2d,p)/CPM -*n*-hexane-; see the SI for details] was performed to assess the validity of these hypothesis. As expected, a longer $NMe_2\cdots CHO$ distance was measured in $\mathbf{TS_{IV}}$ than in $\mathbf{TS_{III}}$ (d_{CN} = 2.25 Å versus 2.15 Å) and, while ability of the N atom to pyramidalize at a low energy cost alleviate steric H–H contacts in $\mathbf{TS_{IV}}$,[15] the same requirement in $\mathbf{TS_{III}}$ involves a marked deviation from planarity of the napthyl rings (see 3d structures in the Supporting information). Combined, these differences facilitate, as predicted, a much easier racemization of formyl indole **4a**, with a calculated barrier of 18.6 kcal·mol^{-1}, while the calculated barrier for the naphthyl analogue **3** is 24.2 kcal·mol^{-1}, more than 5 kcal·mol^{-1} higher and in agreement with the experimental data. For the sake of comparison, the rotation about the C–C stereogenic axis of the reduced alcohol **5a** was also calculated (Scheme 2E). Lacking the stabilizing interaction shown in the precedent cases (see the SI for a detailed discussion), the calculated barrier of 30.8 kcal·mol^{-1} for the corresponding transition structure $\mathbf{TS_V}$ is, as expected, significantly higher and grants the configurational stability of the products. With this information in hand, we decided to explore the biocatalytic reduction of formyl indole amines **4** for the synthesis of the corresponding alcohols **5**. This study is further motivated by the growing interest in this family of compounds,[16] which exist in a variety of alkaloids,[17] bioactive molecules[18] and chiral phosphine ligands.[19] Available methods for their synthesis include both enantioselective metal-catalyzed transformations[20] and organocatalytic approaches[21] but the use of biocatalysis in this topic remains unexplored.

Scheme 2. Racemization of (hetero)biaryls.

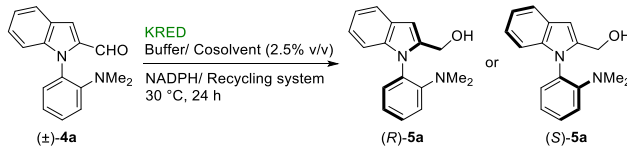


A-D: Racemization based in Lewis acid-Lewis base interactions (marked as blue dashed bonds). **E**: Racemization of indol-derived alcohol **5a**. Red arrows denote repulsive steric interaction

Initial studies were performed with aldehyde **4a**[22] as a model substrate, and a set of commercially available ketoreductases (KRED, Codexis)[23] were tested to perform bioreduction by DKR at analytical scale (1.0 mL, 10 mM substrate). Thus, **4a** was incubated at 30 °C for 24 hours in buffer containing 2.5% v/v DMSO, employing the biocatalysts both in presence of isopropanol or glucose/glucose dehydrogenase (GDH) for the NAD(P)H cofactor recycling (Table 1). Bioreduction catalyzed by P1-B12 afforded axially chiral alcohol (*S*)-**5a** in nearly full conversion, although in moderate enantioselectivity (entry 1). KRED P2-H07 performed better in the DKR, affording 91% of (*S*)-**5a** with 96% *ee*.

Additionally, high enantiomeric excess could also be obtained by using KREDs P3-B03, P3-H12, P3-G09 and P1-A04 (entries 3, 4, 6, and 8) but the conversions were moderate in all these cases. Interestingly, the use of glucose/GDH dependent KREDs 101, 119 and 130 afforded the opposite enantiomer (*R*)-**5a** in good conversions (from 67 to 88%) and high enantiomeric excesses (90-92%) (entries 9-12). In particular, the use of KRED 119 afforded (*R*)-**5a** in 88% conversion and 92% *ee* (entry 10). The ability of obtaining both atropoisomers of heterobiaryl alcohol **5a** with excellent conversion and optical purities constitute an important feature of this methodology. These results could be further improved by slightly modifying the co-solvent employed. Thus, higher conversion was achieved by using 2.5% v/v THF in presence of P3-H12 and P3-G09 (entries 5

Table 1. Screening of commercial KREDs for the DKR of 4a.



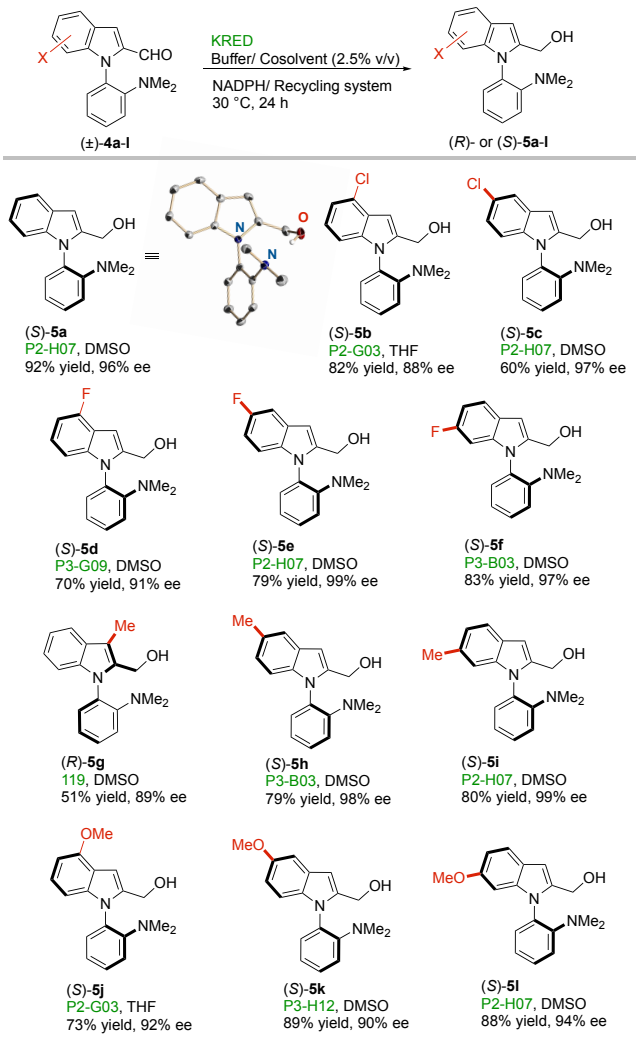
Entry[a]	KRED	Cosolvent	Conv. [%][a]	*ee* [%][b]
1	P1-B12	DMSO	95	81 (*S*)
2	P2-H07	DMSO	91	96 (*S*)
3	P3-B03	DMSO	57	95 (*S*)
4	P3-H12	DMSO	65	97 (*S*)
5	P3-H12	THF	88	94 (*S*)
6	P3-G09	DMSO	76	91 (*S*)
7	P3-G09	THF	94	94 (*S*)
8	P1-A04	DMSO	56	97 (*S*)
9	101	DMSO	84	92 (*R*)
10	119	DMSO	88	92 (*R*)
11	130	DMSO	67	90 (*R*)
12	NADH 101	DMSO	83	91 (*R*)

[a]Conversion determined by GC. [b]The enantiomeric excesses were determined by HPLC on a chiral stationary phase. [c]The absolute configuration of (*S*)-**5a** was assigned by X-ray diffraction analysis (CCDC 2184007).

and 7, respectively). Under these conditions, the enantiomeric excess of (*S*)-**5a**, using enzyme P3-G09 could also be increased (94% *ee*, entry 7), whereas a slight decrease in the enantioselectivity was observed in the reaction catalyzed by P3-H12 (94% *ee*, entry 5).

With the most efficient KREDs in hands, we explored the extension of this biocatalytic atroposelective reduction strategy to a range of 2-formylindoles **4b-l** bearing different substituents in the indole structure (Scheme 3). Bioreductions were scaled up to 15 mg of substrate to obtain synthetically useful amounts of chiral alcohols for further transformations. Satisfyingly, we found out that use of KREDs P2-H07, P2-G03, P3-G09, P3-H12, P3-B03 and KRED 119 led to the desired axially chiral alcohols **5b-l** with high isolated yields and excellent optical purities in nearly all cases, using DMSO or THF as cosolvents (see also Supporting Information), at 20 mM substrate concentration. Halogenated derivatives **4b-f** were converted into the (*S*)-alcohols in high yields and optical purities. Aldehydes bearing a chlorine or a fluorine atom at 5- or 6-position of the indole ring afforded higher enantioselectivity when compared with the 4-substituted ones. Thus, (*S*)-**5c**, (*S*)-**5e** and (*S*)-**5f** were obtained with enantiomeric excesses higher than 97%, while a lower optical purity (88% *ee*) was observed for (*S*)-**5b**. Both 5-methyl and 6-methyl derivatives were also suitable substrates affording the corresponding alcohols (*S*)-**5h,i** in excellent selectivities (98-99% *ee*) and yields around 80%. Methoxy substituted (*S*)-alcohols **5j-l** were also obtained in high enantioselectivities although a lower yield (73%) was observed for alcohol (*S*)-**5j**. As a limitation of the

Scheme 3. DKR of heterobiaryl aldehydes 4b-l catalyzed by ketoreductases.



[a]Reactions performed at 2 mM scale, using DMSO or THF as cosolvents. [b]Isolated overall yields after chromatography. [c]The enantiomeric excesses were determined by HPLC on a chiral stationary phase.

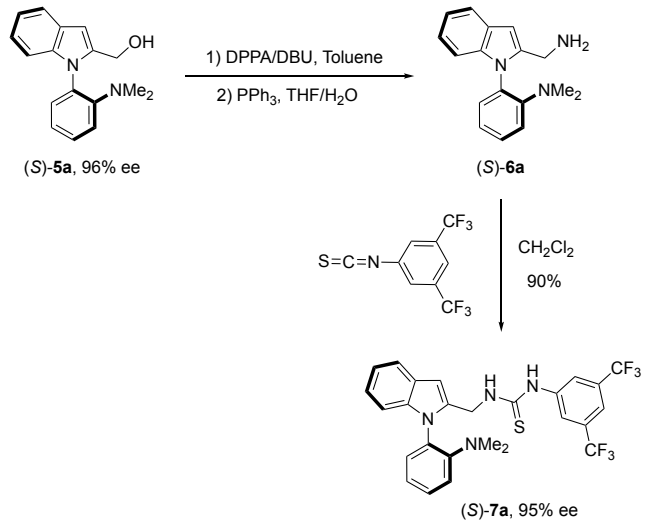
methodology, we found that substitutions at 3 position of the indole ring was not well tolerated, although a 51% yield and 89% *ee* could be obtained for the bioreduction of 3-methyl derivative **4g** using KRED 119. In general, the presence of a substituent at 4-position of the indole ring has a negative effect on conversion and/or selectivity of the process, whereas if this substituent is placed at 5- or 6-position, excellent results were obtained. This effect seems not to be dependent of the electronic nature of the substituent but associated to steric factors. The absolute configuration of (*S*)-**5a** was determined by X-ray diffraction analysis,[24] and those of the other alcohols **5b-l** were tentatively assigned by assuming a uniform atropisomer elution order. These assignments were further confirmed by comparison of the HPLC traces with those obtained for the same products **5** obtained by Zn-catalyzed enantioselective hydrosilylation[13] (See the Supporting Information for details).

The configurational stability of the alcohol product **5a** was experimentally calculated by measuring the kinetics of racemization at 60 °C. In this way, the barrier to racemization was determined to be 28 kcal·mol^{-1}, with a half-life $t_{1/2rac}$ = 42 h at this temperature. This data are in agreement with the above discussed hypothesis and

calculations, and grants the required configurational stability for further application.

To further demonstrate the potential of this new methodology, alcohol **5a** was used as a platform for derivatization (Scheme 4). For instance, the displacement of the primary alcohol in (*S*)-**5a** using diphenylphosphoryl azide (DPPA) and DBU followed by Staudinger reaction gave axially chiral diamine (*S*)-**6** with excellent yield. Further condensation of the latter with 1-isothiocyanato-3,5- bis(trifluoromethyl)benzene afforded a novel class of bifunctional thiourea catalysts (*S*)-**7** (81% global yield, 95% *ee*) with potential utility in asymmetric organocatalysis.

Scheme 4. Transformation from (*S*)-5a to the bifunctional thiourea (*S*)-7a.



In conclusion, a highly efficient enantioselective biocatalytic DKR of configurationally labile *N*-arylindole aldehydes has been developed, which afforded a series of axially chiral *N*-arylindole aminoalcohols with excellent conversions and optical purities under very mild reaction conditions. A weak Lewis acid-base interaction between the NMe_2 and the aldehyde carbonyl groups is responsible of the racemization of the substrates through the formation of 6-membered cyclic transition states.

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information

Experimental details, spectroscopic and analytical data for new compounds and computational data (pdf)
Crystallographic data of (*S*)-**5a** (CIF)

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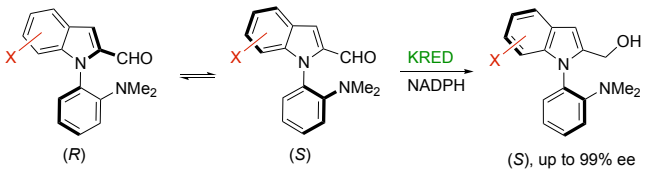

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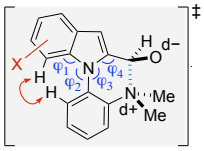

$\varphi_1, \varphi_2, \varphi_3, \varphi_4 > 120°$

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