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Atroposelective Synthesis of 2-(Quinolin-8-yl)benzyl Alcohols by Biocatalytic Dynamic Kinetic Resolutions

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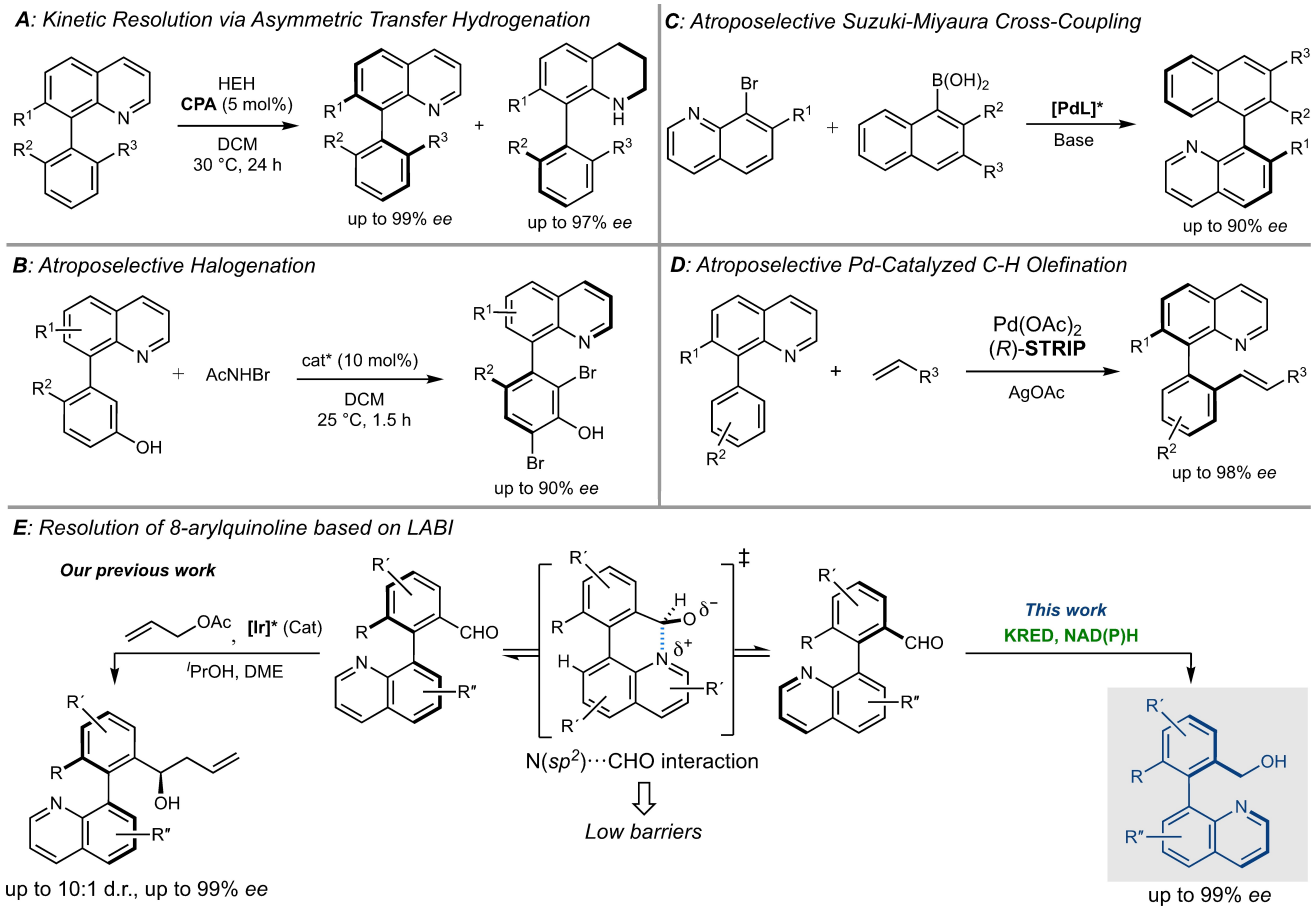
Abstract: A highly enantioselective biocatalytic dynamic kinetic resolution (DKR) of 2-(quinoline-8-yl) 3-methylbenzaldehydes and 1-naphthaldehydes is described. The reaction proceeds by atroposelective carbonyl reduction catalyzed by commercial ketoreductases (KREDs), generally reaching high conversions and excellent enantiomeric excesses. Both atropoisomers of the final alcohols can be obtained by a proper selection of the biocatalyst. The DKR strategy relies in the racemization of the stereogenic axis that takes place thanks to a transient Lewis acid-base interaction (LABI) between the nitrogen in the quinoline and the carbonyl group.

Keywords: Axial chirality; Asymmetric catalysis; Ketoreductases; Dynamic kinetic resolution; Quinolines

Introduction

Axially chiral (hetero)biaryls, particularly those containing nitrogen atoms, are key structural motifs in several natural products, biologically active compounds, chiral ligands and catalysts.[1] Several approaches have been established for the synthesis of biaryl compounds.[2] However, methods detailing the preparation of heterobiaryl systems, especially (iso)quinoline derivatives, remain relatively limited.[3] This scarcity becomes particularly evident when considering the synthesis of chiral 8-arylquinoline atropisomers, where a short handful of methods has been reported. Thus, in 2016, Zhou and coworkers described the kinetic resolution of 8-substituted quinolines by chiral phosphoric acid-catalysed asymmetric transfer hydrogenation (Scheme 1A).[4] Later, the group of Miyaji described an enantioselective aromatic electrophilic halogenation reaction to afford chiral 8-arylquinoline derivatives, using a bifunctional Cinchona-derived organocatalyst (Scheme 1B).[5] More recently, the groups of Shi[6a] and Zhu[6b] have reported Pd-catalysed cross-coupling strategies suitable for the synthesis of quinoline derivatives (Scheme 1C). Finally, axially chiral 8-arylquinoline derivatives have also been prepared by enantioselective C–H functionalization using a Pd/chiral phosphoric acid as a catalyst (Scheme 1D).[3f,7]

Over the past few years, our group has successfully showcased the utilization of transient Lewis pairs (LABI) formed through the subtle interplay between an acidic moiety (even as weak as a carbonyl group)



Scheme 1. Catalytic enantioselective synthesis of axially chiral quinolines. EHE: Diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate. CPA: Chiral phosphoric acid. STRIP: [6,6′-bis(2,4,6-triisopropylphenyl)-1,1-spirobiindan-7,7-diyl hydrogen phosphate.

and a basic counterpart. This innovative approach has proven to be highly effective in promoting the racemization of stereogenic axes in heterobiaryl systems. The formation of quasi-zwitterionic transition states plays a pivotal role in facilitating racemization by substantially reducing the barrier to atropisomerization, which would otherwise be significantly higher in the absence of the stabilizing LABI interactions. In this scenario, we designed transformations aimed at eliminating the acidic nature of the carbonyl group through quaternization, thereby raising the barrier to atropisomerization, ultimately leading to configurationally stable enantioenriched compounds.

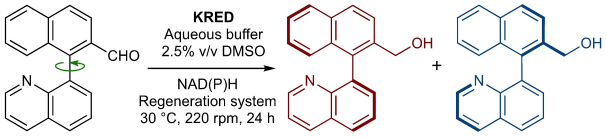
We first implemented this strategy in the atroposelective synthesis of chiral heterobiaryl carbinols through an asymmetric Zn-catalysed hydrosilylation of configurationally labile heterobiaryl ketones.[8] The racemization of the substrate relied on a LABI interaction between the isoquinolyl nitrogen atom and the carbonyl group through the formation of 5-membered cyclic transition states. Furthermore, we developed the DKR of N- and 3-arylindole aldehydes that proceed by atroposelective bioreduction,[9] and Rh-catalysed intermolecular reductive aldol reaction,[10] respectively. In this case, racemization is expedited through a transient Lewis pair interaction occurring within a 6-membered cyclic transition state. The key factor for an efficient interaction was the presence of a five-membered heterocycle within the indole fragment that effectively elongates the distances between the Lewis base (NMe_2 or SR) and the carbonyl fragment. This adjustment served to mitigate repulsive interactions between them, thus optimizing the overall process. More recently, the DKR of axially chiral 2-(quinolin-8-yl)benzaldehydes has been developed using Ir-catalysed transfer hydrogenative coupling with high yields and diastereoselectivities, and excellent levels of enantioselectivity (Scheme 1E).[11] The racemization, facilitated by a LABI between the nitrogen in the quinoline and the aldehyde group, becomes more challenging in this case, since the cyclic structure enclosing the bonding interaction and both aryl rings are all six-membered.

Given the prevalence of axially chiral 8-arylquinolines in a wide range of bioactive compounds, natural products,[12] and ligands,[13] the advancement of more effective methods for their synthesis is of great importance and continues to be a significant research goal. Therefore, in this study, we have employed our LABI strategy to synthesize a range of chiral 2-(quinolin-8-yl)benzyl alcohols via a dynamic kinetic resolution (DKR) catalysed by commercially available ketoreductases under mild reaction conditions (KREDs, Scheme 1E).[14] It is worth noting that achieving high enantioselectivity in this scenario presents a greater challenge, as there is only a single stereogenic axis contributing to the overall stereoselectivity.

Results and Discussion

Heterobiaryl quinoline aldehydes employed as KREDs substrates were prepared as previously described.[11] Initial experiments were performed using commercially available libraries of ketoreductase from Codexis Inc (see Supporting Information). (Codexis KRED Screening Kit) and from Evoxx Technologies. Bioreduction of 1-(quinolin-8-yl)-2-naphthaldehyde **1 a** (5.0 mM) was carried out in phosphate buffer pH 7.0 containing 2.5% v/v DMSO for substrate solubilization and NAD(P)H (0.2–1.1 mM). Nicotinamide cofactor was regenerated either by a coupled-substrate approach in presence of 10% v/v *iso*-propanol (IPA) as cosubstrate, or by a coupled-enzyme approach using glucose/glucose dehydrogenase (GDH). Table 1 includes the most compelling results, demonstrating the capacity to achieve both high conversions and enantioselectivities of atropisomeric heterobiaryl alcohol **2 a**, depending on the specific KRED employed. Most of the studied biocatalysts, including P1-B12, P1-H08, P2-G03, P1-B10, and P1-C01 from Codexis, yielded (*S*)-**2 a** with *ee's* exceeding 90%, with Evoxx 442, Evoxx 40, and P1-B12 achieving an excellent 97% *ee* (entries 2 to 8). These biocatalysts consistently achieved conversions of approximately 90%, although the Evoxx biocatalysts exhibited diminished activity compared to the others, resulting in lower conversion rates. A smaller subset of the tested KREDs displayed an opposite enantiopreference, resulting in the formation of the *R*-atropisomer. Notably, Evoxx 440 yielded (*R*)-**2 a** with a conversion rate of 86% and a 92% *ee* (entry 11). Conversely, P1-B05 from Codexis and Evoxx 430 could reduce the aldehyde to the (*R*)-alcohol **2 a** as well, although they exhibited significantly lower conversion rates and enantioselectivities (entries 9 and 10). Reactions catalyzed by both P2-G03 and Evoxx 440 were scaled up (10.6 mg, 10 mM) to obtain (*S*)-**2 a** and (*R*)-**2 a** with isolated yields of 82 and 80% and enantiomeric excesses of 97% and 92%, respectively.

Table 1. Screening of biocatalysts for the DKR of heterobiaryl aldehyde **1 a**.

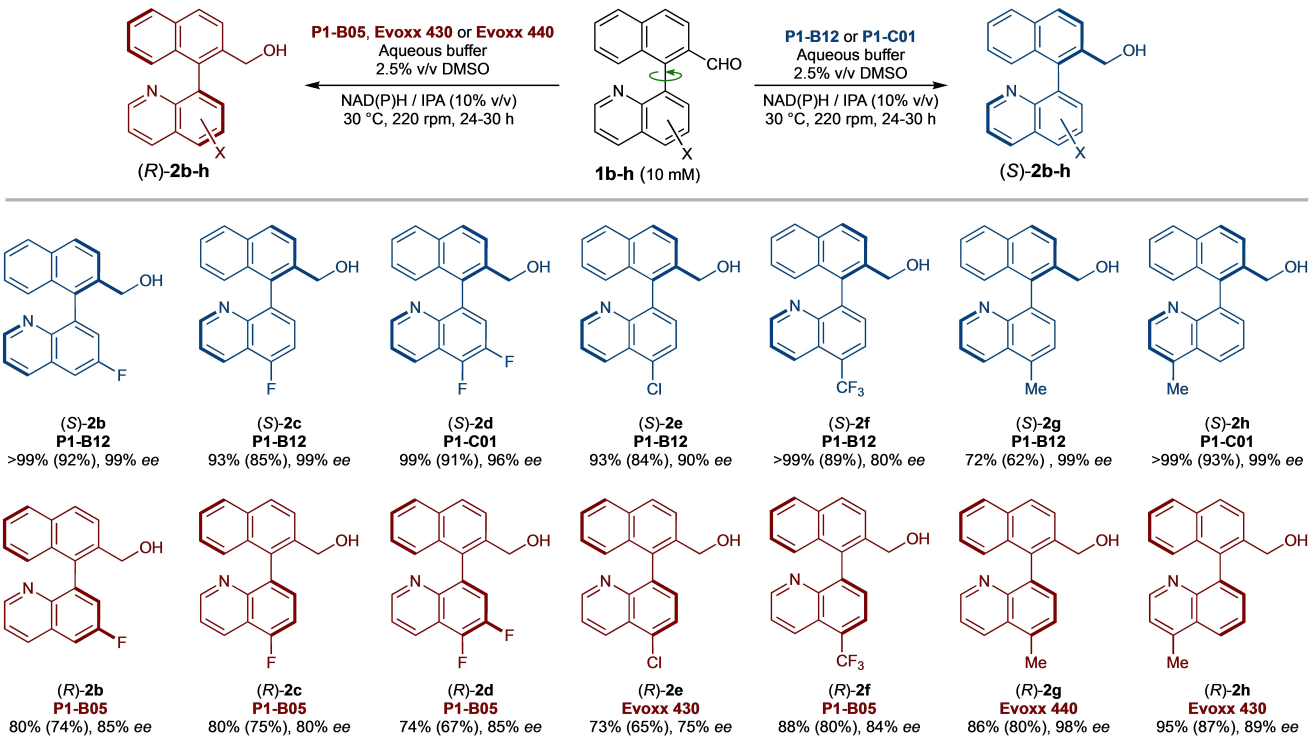


1a (*R*)-**2a** (*S*)-**2a**

Entry	KRED	Conv. (%)[a]	*ee* (%)[b]	Config.
1	**P1-A04**	≥99	27	*S*
2	**P1-B12**	90	97	*S*
3	**P1-H08**	95	94	*S*
4	**P2-G03**	90	92	*S*
5	**P1-B10**	85	93	*S*
6	**P1-C01**	92	95	*S*
7	**Evoxx 442**	65	97	*S*
8	**Evoxx 40**	77	97	*S*
9	**P1-B05**	55	64	*R*
10	**Evoxx 430**	64	73	*R*
11	**Evoxx 440**	86	92	*R*

[a] Conversions determined by GC/MS.
[b] The enantiomeric excesses were determined by HPLC on a chiral stationary phase.

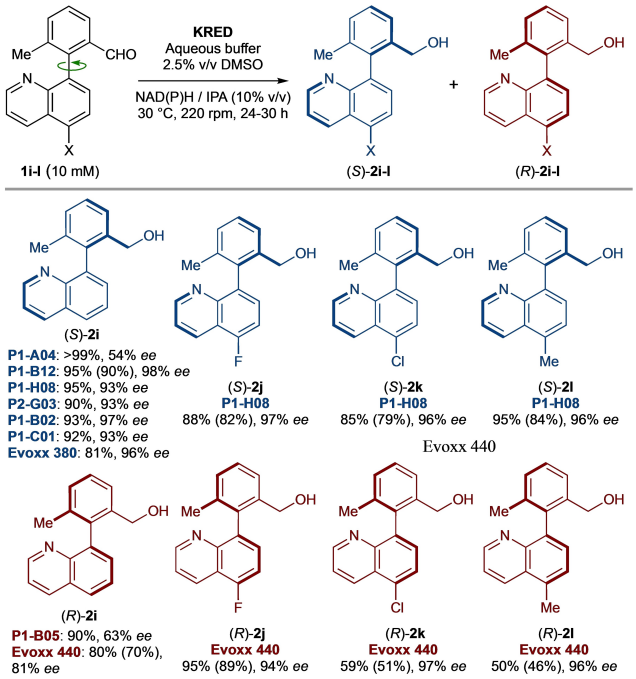
With the best biocatalysts for the selective transformation of substrate **1 a** in hand, the reduction of 2-(quinolin-8-yl)benzaldehydes containing different substituents in the quinoline moiety was analyzed. Bioreductions were performed at 0.04 mmol scale to achieve synthetically useful amounts of the chiral alcohols. As shown in Scheme 2, P1-B12 and P1-C01 were used to obtain the (*S*)-atropisomers (in blue at Scheme 2), whereas P1-B05, Evoxx 430 and Evoxx 440 were used for the synthesis of the (*R*)-alcohols (in red at Scheme 2). The corresponding (*S*)-products could be obtained with high conversions and enantiomeric excesses for almost all the substrates tested. For instance, the 6- and 5-fluorine derivatives (*S*)-**2 b–c** were synthesised with high conversion and 99% *ee*, when employing biocatalyst P1-B12. The bioreduction of the difluorinated aldehyde **1 d** led to a complete conversion and a high 96% *ee* using KRED P1-C01. The 5-chloro derivative **1 e** proved to be a suitable substrate for P1-B12. However, the synthesis of the 5-trifluoromethyl alcohol (*S*)-**2 f** resulted in a slightly lower enantioselectivity (80% *ee*) with complete conversion, whereas both methylated alcohols (*S*)-**2 g–h** were obtained enantiopure by using P1-B12 and P1-C01, respectively. For the 5-methylated aldehyde, the conversion was moderate (72%), being observed a complete conversion for **1 h**. In the case of (*R*)-products, the achieved enantioselectivities remained at values from 75% to 89% *ee*, with minimal influence observed on the electronic nature of the substituent. The best result was achieved for the 5-methyl



Scheme 2. Scope of 2(quinoline-8-yl)benzaldehydes bioreductions. Conversions determined by GC/MS and enantiomeric excesses were determined by HPLC on a chiral stationary phase. In brackets, the isolated yields of the chiral alcohols.

derivative (*R*)-**2 g**, which was recovered with 86% conversion and 98% *ee* in the bioreduction catalysed by Evoxx 440. A complete conversion was observed in the bioreduction of **1 h** in presence of Evoxx 430, whereas for the rest of substrates, conversion values from 73% to 95% were measured.

To further expand the scope of the reaction, the DKR of quinolines featuring a 2-formyl-6-methylphenyl group at the 8 position was also studied. Various KREDs were investigated for the bioreduction of 3-methyl-2-(quinolin-8-yl)benzaldehyde **1 i** in buffer solution at 30 °C. The most notable results are summarized in Scheme 3. The use of enzyme P1-A04 led to full conversion but exhibited modest selectivity (54% *ee*). Fortunately, several ADHs from Codexis, including P1-B12, P1-C01, P1-H08, P2-G03, and P1-B02, rendered alcohol (*S*)-**2 i** with conversions exceeding 90% and enantioselectivities ranging from 93% to 98% *ee*, with the optimal results provided by biocatalysts P1-B12 and P1-B02. Additionally, the use of Evoxx 380 yielded the desired product with a remarkable 96% *ee* and 81% conversion. Notably, the (*R*)-enantiomer of the desired alcohol could also be obtained with alternative biocatalysts, although lower enantioselectivities were observed. Evoxx 440 emerged as the most effective enzyme in this regard, with an 80% conversion and 81% *ee* of the desired alcohol. A variety of 2-formyl-6-methylphenyl derivatives with varying substituents at the 5-position of the

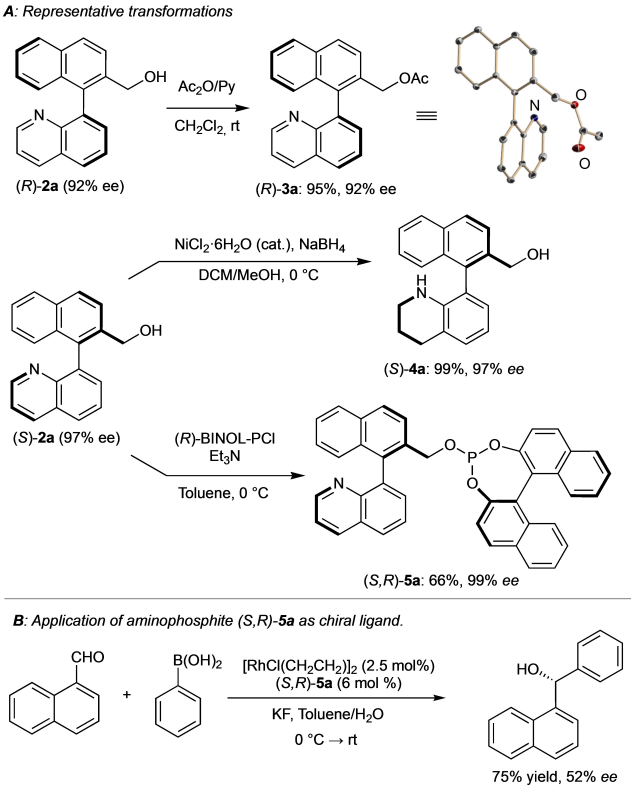


Scheme 3. Biocatalysed reduction of heterobiaryl aldehydes **1 i-l** employing KREDs. Conversions determined by GC/MS and enantiomeric excesses were determined by HPLC on a chiral stationary phase. In brackets, isolated yields of the chiral alcohols.

quinoline ring were also investigated as substrates. KRED P1-H08 yielded the best results for the synthesis of (*S*)-alcohols, while Evoxx 440 proved optimal for (*R*)-alcohol synthesis. For 5-fluoro-, 5-chloro- and 5-methyl substituted aldehydes, the resulting alcohols, (*S*)-**2 j–l** were obtained with excellent enantioselectivities (96-97% *ee*), being observed a lower conversion for the 5-chloro and 5-methyl derivatives.

The effect of some parameters that can affect to the biocatalysts properties was analyzed for some selected biotransformations. Thus, the bioreduction of **1 e** catalyzed by P1-B12 to yield (*S*)-**2 e** and that of **1 d** in presence of P1-B05 to achieve (*R*)-**2 d** were studied at different temperatures. For both processes, chiral alcohols were obtained with lower conversions and almost the same enantioselectivities at 20 °C than when working at 30 °C, whereas the bioreductions performed at 45 °C led to higher conversions but with a high drop in the enantiomeric excesses (see Supporting Information). The influence of the substrate concentration (**1 d**) on the activity and stereoselectivity of KRED P1-C01 was studied (Supporting Information). Although apparent conversions were lower at elevated substrate concentrations, the reaction rates (expressed as mmoles of aldehyde **1 d** consumed per L of solution per hour) increased from 10 mM to 20 mM, reaching a maximum value of 45.7 mmol L^{-1} h^{-1}. Higher substrate concentrations led to slightly lower values, but still high values were achieved at 100 mM concentration. No effect of the substrate concentration was observed in the enantioselectivity of (*S*)-**2 d**, being recovered in all cases with excellent enantiomeric excesses.

The absolute configuration of (*R*)-**2 a** was determined by X-ray diffraction analysis of its acetylated derivative (*R*)-**3 a** (Scheme 4A).[15] Additionally, chiral alcohol (*S*)-**2 a** was employed as starting material for the preparation of potential ligands or catalysts for asymmetric synthesis. First, the quinoline moiety was selectively hydrogenated to obtain axially chiral aminoalcohol (*S*)-**4 a** quantitatively and without erosion of the enantiomeric excess. Additionally, treatment of (*S*)-**2 a** with (*R*)-BINOL chlorophosphite provided enantiomerically pure compound (*S*,*R*)-**5 a** with moderate yield and 99% *ee*. In order to explore the potential applicability of the new compounds in asymmetric catalysis, axially chiral amino-phosphite (*S*,*R*)-**5 a** was employed as ligand for the rhodium catalysed addition of phenylboronic acid to 1-naphthaldehyde. The (*R*)-enantiomer of the addition product was obtained with 75% isolated yield and a promising 52% *ee* (Scheme 4B).



Scheme 4. Transformations of alcohol (*S*)-**2 a** (A) and application of aminophosphite (*S*,*R*)-**5 a** in catalysis (B).

Conclusion

In summary, a Dynamic Kinetic Resolution methodology has been developed for the atroposelective preparation of a set of quinoline-based alcohols, employing commercially available ketoreductases. The racemization mechanism for the DKR was promoted by the Lewis acid-base interaction (LABI) between the nitrogen in the quinoline and the aldehyde group. Depending on the KRED employed, both atropoisomers of the final alcohols can be obtained, generally in high conversions and enantioselectivities. Derivatizations of the products and the application in a rhodium catalysed 1,2-addition, showcase the versatility of the resulting products as a chiral ligands for asymmetric synthesis.

Experimental Section

General procedure for the biocatalysed reduction of 2-(quinolin-8-yl)benzaldehydes (1 a-l) employing KREDs. Codexis KRED P1-B12, P1-C01, P1-H08 P1-B05, Evoxx 430 or Evoxx 440 (20 mg) was added to a glass vial with 3.5 mL of NaPi buffer 100 mM pH 7.0 containing $NAD(P)^+$ (0.2–1.1 mM), and the tube was shaken until KRED was dissolved. To this mixture, a solution of racemic heterobiaryl aldehyde **1 a–l** (10.6–13.4 mg, 0.04 mmol) in IPA (400 µL) and DMSO (100 µL) was added. The reactions were shaken at 220 rpm and 30 °C for 24–30 hours. After this time, the product was extracted with ethyl acetate (3×1.0 mL), the combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated and the conversion and the enantiomeric

excess of alcohols (*S*)-**2a–l** (when using KRED P1-B12, P1-C01 or P1-H08) or (*R*)-**2a–l** (when employing P1-B05, Evoxx 430 or Evoxx 440) were measured by GC/MS and HPLC, respectively. Crude reactions were purified by chromatography employing *n*-hexane:EtOAc 1:1 as eluent, recovering the final alcohols with yields ranging from 46–93%.

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[15] CCDC-2306279 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures. The absolute configuration of all other compounds **2** was assigned by analogy assuming a uniform elution order.