AN ABSTRACT OF THE DISSERTATION OF

Somdev Banerjee for the degree of Doctor of Philosophy in Chemistry presented on May 9, 2017.
Title: Scaffold Reactivity and Large Scale Synthesis of Organocatalyzed Yamada-Otani Condensation Product and Investigation of the Synthesis and Properties of Axially Chiral 8,8'-Biquinolyls and 8-(Naphtha-1-yl)quinolines

Abstract approved:

Paul R. Blakemore

In Part I, (4*S*,5*R*)-4,5-dimethyl-4-phenylcyclohex-2-enone (**19a**) was prepared in 73% yield with high enantio- and diastereo-selectivity (er > 98:2, dr > 20:1) on a multigram scale by a Yamada-Otani condensation between (*E*)-pent-3-en-2-one and 2-phenylpropanal catalyzed by a sulfonimide derivative of (*S*)-proline (**18**, HuaCat®). Synthetically useful transformations of the cyclohexenone product **19a** were demonstrated, as follows: (a) alpha-alkylation via Li-enolate formation (e.g., LDA, DMPU, MeI, THF, –78 °C, 2 h; 86% yield, dr > 20:1), (b) 1,2-addition of organolithiums (e.g., PhLi, THF, –78 °C, 2 h; 82% yield, dr > 20:1), and (c) 1,4-addition of cyanocuprates (e.g., *n*-BuLi, CuCN, THF, –78 °C, 2 h; 90% yield, dr > 20:1).

In Part II, an azaanalog of 1,1′-bi-2-naphthol (BINOL, **38**), 7-hydroxy-8-(2-hydroxynaphth-1-yl)quinoline (8-azaBINOL, **67**), was prepared in 3 steps and 49% yield from *N,N*-diethyl *O*-(7-hydroxy-8-iodoquinolyl) carbamate via Suzuki coupling with 1-naphthyl-boronic acid followed by Sanford oxidation and saponification. 8-

AzaBINOL (**67**) was resolved into (–)-(*aS*) and (+)-(*aR*) atropisomers by enzymatic hydrolysis of its racemic divalerate derivative with bovine pancreas acetone powder. The configurational stability of 8-azaBINOL (**67**) was found to be intermediate to that of 7,7′-dihydroxy-8,8′-biquinolyl ('8,8′-diazaBINOL', **50**, least stable) and BINOL (**38**, most stable). Eyring plot analysis of the enantiomerization kinetics of **50**, **67**, and **38**, in DMSO solution revealed activation parameters of $\Delta H^{\ddagger}$ = +27.4, +19.9, +23.2 kcal mol^{-1}, and $\Delta S^{\ddagger}$ = +3.8, –27.9, –25.3 cal mol^{-1} K^{-1}, respectively. The unique character of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values for biquinolyl **50** suggests that the enantiomerization mechanism for **50** is distinct to that for naphthalenes **67** and **38**. Monohydroxy analogs of **67**, 7-hydroxy-8-(naphth-1-yl)quinoline (**71**) and 8-(2-hydroxynaphth-1-yl)quinoline (**75**), were similarly prepared and their racemization half-lives at rt were determined; $\tau_{1/2(rac.)}$ was strongly dependent on solvent for naphthol **75** ($\tau_{1/2(rac.)}$ at 24 °C: in $CHCl_3$ = 2.7 h, in MeOH = 89 h) but not for the quinol **71** ($\tau_{1/2(rac.)}$ at 24 °C: in $CHCl_3$ = 106 h, in MeOH = 120 h).

8-AzaBINOL (**67**) and its tosylic acid salt (**67**•TsOH) were evaluated as potential hydrogen-bonding / Brønsted acid organocatalysts for enantioselective carbon-carbon bond forming processes. Neither form of the compound was an effective catalyst for the Henry reaction between nitromethane and benzaldehyde nor the conjugate addition of acetylacetone to *beta*-nitrostyrene; however, these quinols did promote the addition of nucleophilic arenes to pyruvate esters (albeit with low enantioselectivity). For example, addition of indole to ethyl trifluoropyruvate (Et_2O, –78 °C) gave the expected *beta*-substituted indole product [(*S*)-**87**] in 98% yield and with 5% ee in the presence

of free base (*S*)-**67** (10 mol%). The same organocatalyst did not promote addition of indole to ethyl pyruvate (Et_2O, –40 °C) but its more reactive tosylate salt (*S*)-**67**•TsOH did, resulting in an 82% yield of the addition product with 3% ee.

In a collaborative study (with R. Overacker and S. Loesgen), a 45-member library of 8-azaBINOL and 8,8′-diazaBINOL derivatives was evaluated for biological activity in cytotoxicity/cell viability and HIV viral entry inhibition assays. The isopropyl ether of 7-hydroxy-8-(naphth-1-yl)quinoline (**92**) and the analogous *N,N*-diethyl carbamate (**69**) exhibited the most significant bioactivity with respective IC_{50} = 4.74 μM and 5.18 μM for inhibition of HIV-1 entry into TZM-b1 cells. Comparable 8,8′-diazaBINOLs did not inhibit viral entry. Specific binding of isopropyl ether **92** to purified and immobilized HIV-1 glycoprotein 120 with a K_D = 22 ± 2.9 μM was established using biolayer interferometry.

Scaffold Reactivity and Large Scale Synthesis of Organocatalyzed Yamada-Otani Condensation Product and Investigation of the Synthesis and Properties of Axially Chiral 8,8'-biquinolyls and 8-(Naphtha-1-yl)quinolines

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Somdev Banerjee

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APPROVED:

Major Professor, representing Chemistry

Chair of the Department of Chemistry

Dean of the Graduate School

I understand that my dissertation will become part of the permanent collection of Oregon State University libraries. My signature below authorizes release of my dissertation to any reader upon request.

Somdev Banerjee, Author

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Thank you!

CONTRIBUTION OF AUTHORS

Dr. Hua Yang synthesized the stereogenic all-carbon quaternary center containing cyclohexenones **19** using organocatalyzed multicomponent coupling, as noted in the text.

Mr. Brian Riggs precipitated crystals for the X-Ray crystal structure of compound **75**, as noted in the text.

Mr. Ross Overacker and Dr. Sandra Loesgen performed all the bioassays mentioned.

Dr. Lev. N. Zakharov performed all X-ray crystallographic studies.

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PREFACE

I worked in Prof. Carter's research group for almost a year before joining Dr. Blakemore's research group. Hence I divided my thesis into two different parts. Part I of the thesis describes my work in the Carter group and Part II of the thesis describes my work in the Blakemore group.

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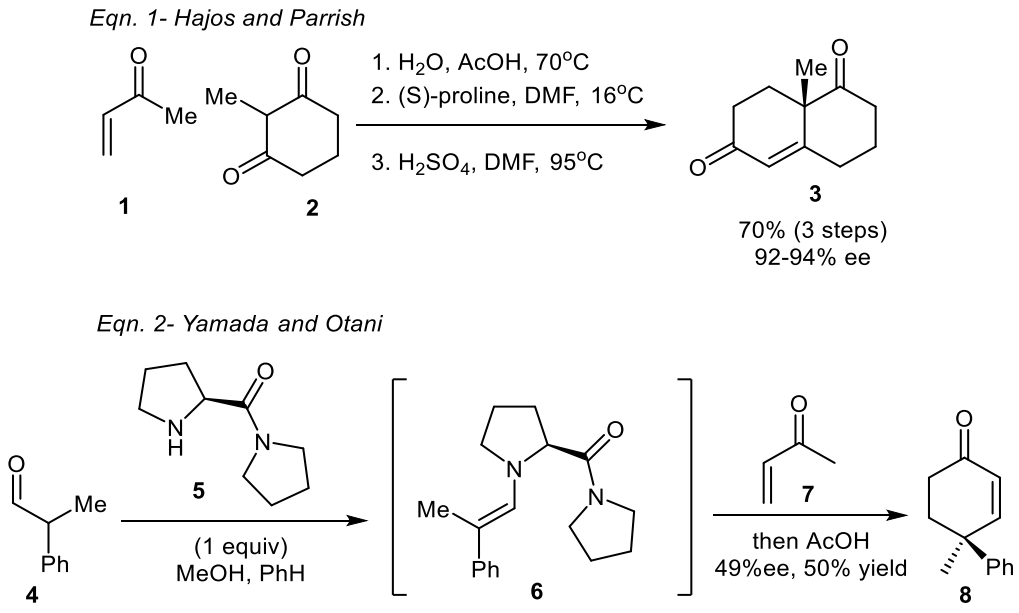
Part I. Organocatalyzed Yamada-Otani Condensation: Large Scale Synthesis and Scaffold Reactivity

1. Introduction

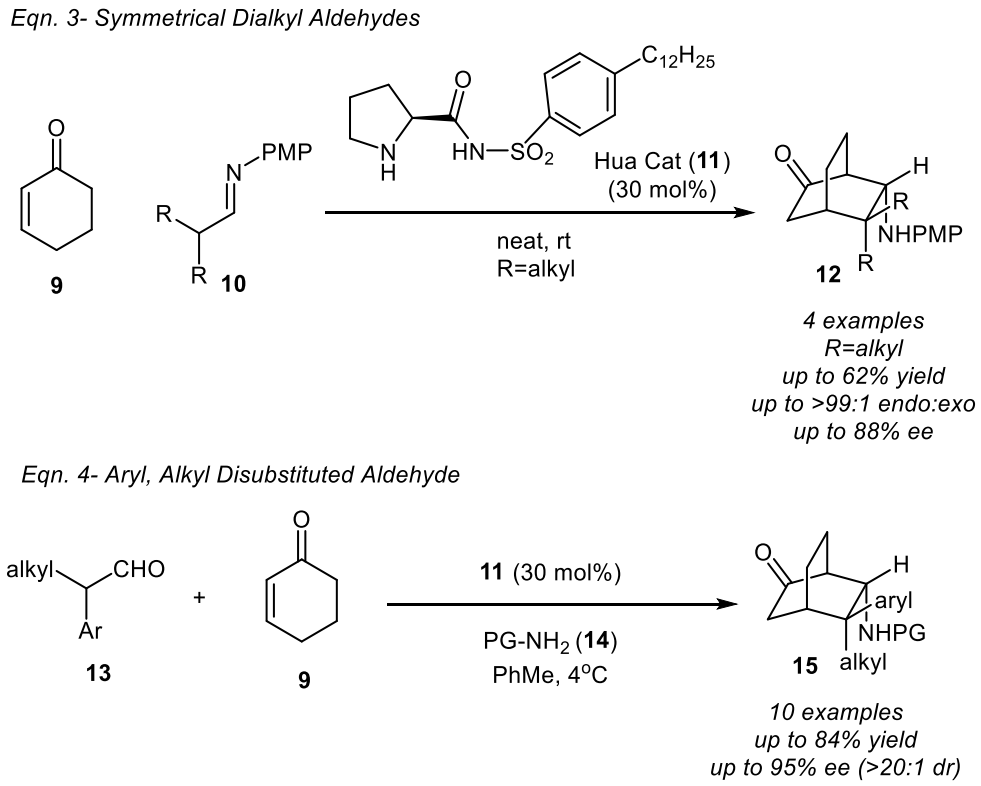
Stereogenic all-carbon quaternary centers are widely present in natural products and their construction is relatively challenging. Hence, new methods for their construction continue to be needed[1] and the efficient synthesis of all-carbon quaternary centers is a central focus of organic chemistry.[1a,2] As a specific example, stereogenic, γ,γ-disubstituted cycloalkenones embody a potentially powerful building block in natural product synthesis. An important method for accessing this structural motif is the Hajos–Parrish reaction,[3] which typically generates bicyclic enone systems and employs a cyclic β-di-ketone starting material (Scheme 1, eqn (1)). Examples from several laboratories have utilized the Michael addition itself as the enantiodetermining step via transition metal,[4] Brønsted acid[5] or phase-transfer catalysis.[6] In order to access stereogenic, γ,γ-disubstituted cycloalkenones, aldehyde-based nucleophiles are needed; however, this functional group has not been widely used to date. Yamada and Otani reported a traceless auxiliary-based approach in this area in the late 1960s and early 1970s (Scheme 1, eqn (2)).[7] This concept essentially lay dormant over the next four decades[8], likely due to difficulties related to catalytic turnover and disappointing levels of enantioselectivity. Advances by the Carter laboratory,[9] as well as others,[8,10] towards methods for controlling stereochemistry using α,α-disubstituted aldehydes prompted a reinvestigation of the Yamada–Otani reaction.



Scheme 1. Pioneering work in synthesis of γ,γ-disubstituted cycloalkenones

Intital forays into this area were based on prior work with cyclic enones (primarily cyclohexenone) as shown in Scheme 2.[9] In these reactions, reaction conditions were successfully developed for facilitating the enantioselective construction of [2.2.2] bicyclic systems using a proline sulfonamide[11] organocatalyst (nicknamed Hua Cat-®) developed in the Carter laboratory.[12] Both enantiomers of this catalyst have now been commercialized through Sigma and Synthetech, Inc. In Equation 3, the utility of symmetrical aldehydes was first studied where R = alkyl using a preformed imine (e.g. **10**). These transformations were performed neat using excess (5 equivalents) of the enone to provide the bicyclic ketone products in excellent endo/exo selectivity but in modest chemical yield (Eq. 3).[9a] The reactivity of this system could be greatly improved by substitution of one of the two alkyl substituents on the aldehyde or imine for an aryl moiety (Eq. 4).[9b] This modification also allowed the change to a multi-component coupling process in which the pre-formed enamine

is not isolated prior to addition of the enone and proline sulfonamide organocatalyst.

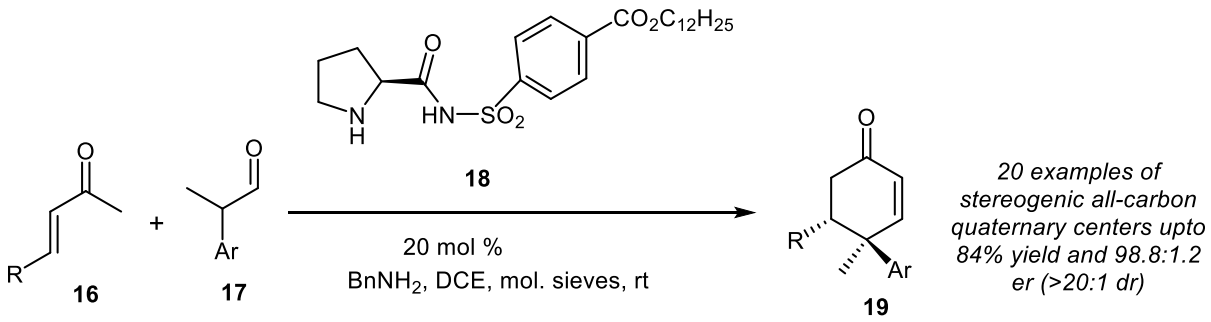


Scheme 2. Prior work from Carter Laboratory using α,α-disubstituted aldehydes / imines

In a preliminary communication, Carter et al. disclosed the development of an organocatalyzed method facilitating Yamada–Otani-type reactivity on systems containing β-substitution on the enone moiety (Scheme 3).[13] Concurrently to these discoveries, the Kotsuki laboratory reported a dual catalysis method using enones not containing β-substitution.[8] Complementary to the protocols for systems containing β-substitution, a full account was published on the development of proline sulfonamide-catalyzed method for facilitating the annulation of α-aryl, α-alkyl-disubstituted

aldehydes with acyclic enones to generate highly functionalized cyclohexenones in excellent levels of diastereoselectivity and enantioselectivity.[12]

The cyclohexenone scaffold synthesized by this method was further reacted to produce various highly diastereoselective derivatives.[12c] A large-scale synthesis of the cyclohexenone moiety using this protocol was also achieved.



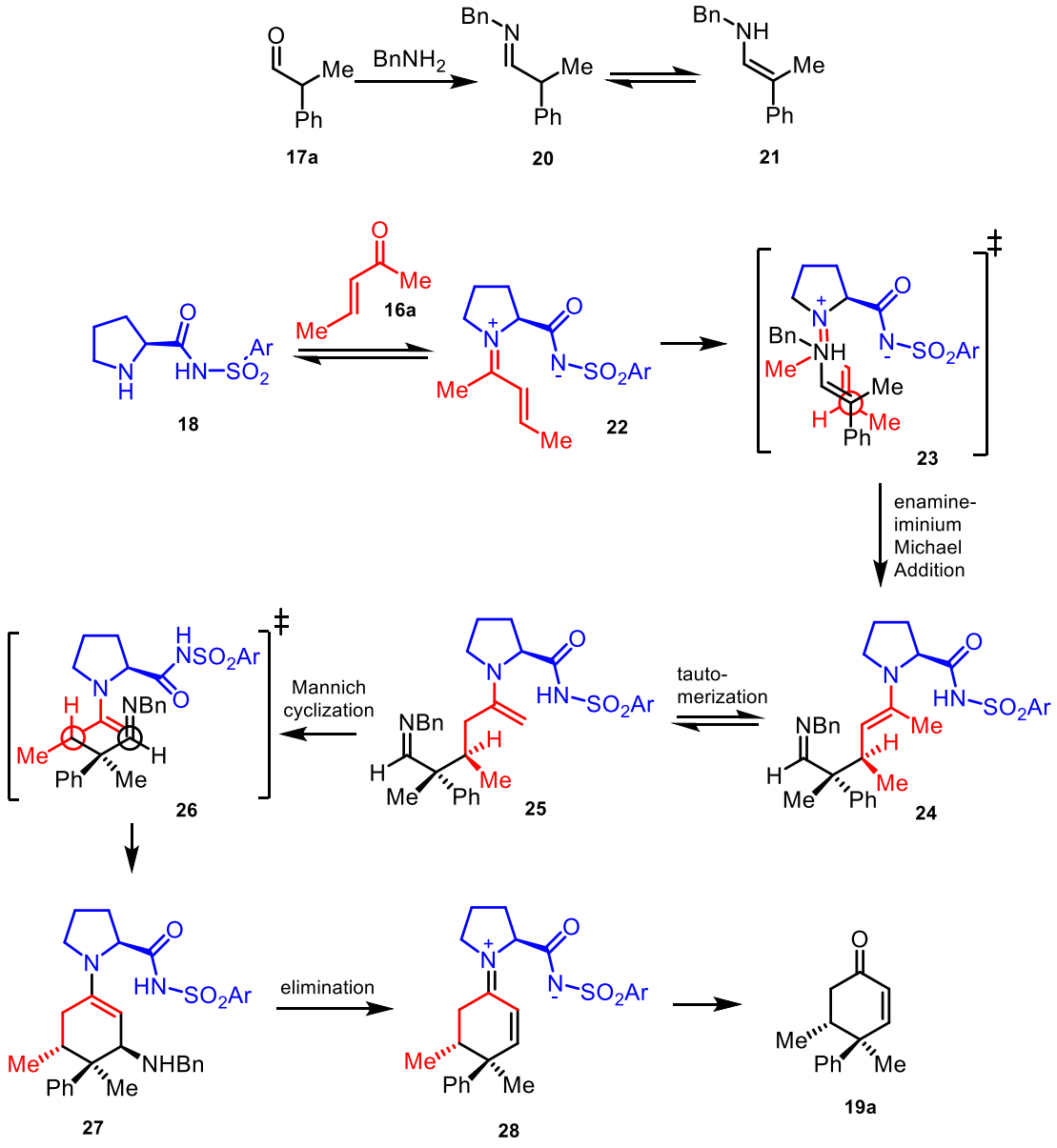
Scheme 3. Proline sulphonamide-catalyzed Yamada-Otani Condensation

2. Results and Discussions

The cyclohexenone **19a** with an all-carbon-quaternary stereogenic center was synthesized on a larger scale (2 g scale) with comparable yield (73%) and diastereoselectivity (>20:1 dr) to demonstrate the successful application of the synthetic protocol in large scale synthesis.

A likely mechanism for this transformation is illustrated in Scheme 4. An in-depth computational analysis of the mechanism can be found elsewhere.[14] The experimental procedure developed calls for premixing the aldehyde and benzylamine prior to addition of the enone or catalyst. Consequently, it is hypothesized that the imine / enamine mixture **20**-**21** is preformed and the enamine (*E*)-**21** is the reactive nucleophile in the key enamine-iminium ion dual-catalyzed Michael addition to form the key quaternary stereogenic centre and the vicinal stereocenter. Additional support for this hypothesis can be found in the products derived from the cyclohexenone series **15** described in Scheme 2 in which the benzyl amine moiety is incorporated in the product **15** where subsequent elimination is not viable. The important role of the mol. sieves in the reaction is likely to remove the water from the reaction media, which would possibly disrupt the key hydrogen bonding network present in transition state **23**. After enamine tautomerization, an intramolecular Mannich cyclization followed by elimination of benzyl amine would yield zwitterion **28**. The presence of molecular sieves in the reaction complicates any mechanistic explanation for the proline sulfonamide hydrolysis step. If water

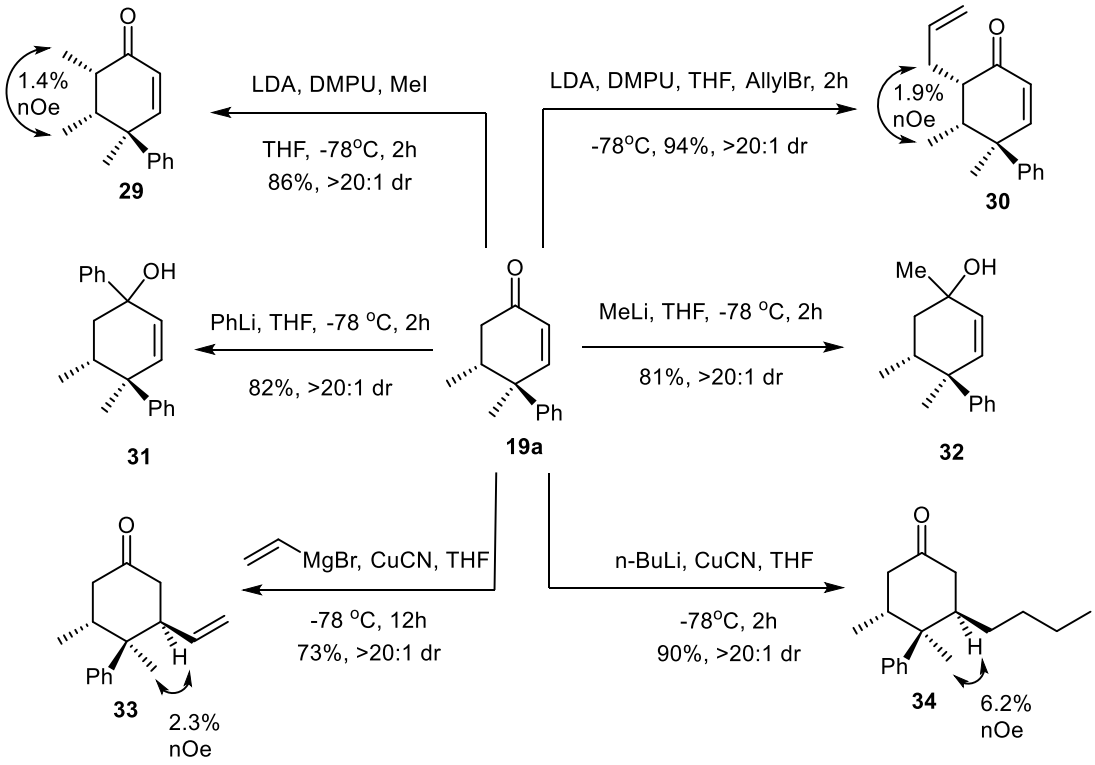
is not the nucleophile for catalyst cleavage, it is possible that the by-product benzylamine could undergo iminium ion / imine exchange with **28** after its elimination from intermediate **27**. If this iminium ion / imine exchange is operative, it would require that a subsequent imine hydrolysis step occur to reveal the enone product **19a**.



Scheme 4. Possible mechanism for the catalytic cycle

The stereochemically rich cyclohexenone scaffold **19a** can potentially serve as a key intermediate for various functionalized products with diastereoselectivity dictated by the substrate. Wise choice of incoming functional groups would lead to synthetically useful building blocks which can be further derivatized. Compound **19a** was hence derivatized with high levels of diastereoselectivity (Scheme 5) to synthesize densely functionalized six-membered carbocyclic moeties. NOe (Nuclear Overhauser Effect) experiments were performed to determine the relative stereochemistry of the products (as indicated in Scheme 5).

Enolization using LDA and DMPU followed by the addition of a suitable electrophile would produce the α-functionalized products. Methyl (**29**) and allyl (**30**) groups were introduced in this way to produce cyclohexenones with three contiguous stereogenic centers. Nucleophilic addition to the enone scaffolds was possible in both a 1,2- and a 1,4-pathway. 1, 2-Addition of methyl and phenyllithium to compound **19a** provided the 3° alcohol products **32** and **31** in high selectivity and chemical yield. We were unable to determine the relative stereochemistry of the newly formed 3° alcohol moiety. The conjugate addition[15] of vinyl and n-butyl groups was undertaken to produce cyclohexanones with three contiguous stereogenic centers. These reactions mediated by cuprous cyanide also proceeded equally well with high levels of diastereoselectivity being observed in products **33** and **34**. The vinyl and allyl functional handles in derivatives **33** and **30** can potentially lead to various other functionalized products of synthetic utility.



Scheme 5. Derivatization of cyclohexenone scaffold

3. Conclusion

The extension of the Hajos-Parrish reaction[3] to include aldehyde components with acyclic enones represents one of the first major advances since its discovery nearly forty years ago. This proline sulfonamide-catalyzed protocol of rapid multi-component coupling generates useful cyclohexenone building blocks with two contiguous stereogenic centers in a highly stereoselective fashion. One of the two stereocenters generated is an all-carbon quaternary stereocenter, which is relatively challenging to obtain. We have demonstrated that this protocol can be easily applied to large scale synthesis of densely functionalized cyclohexenone moieties. We have diastereoselectively derivatized the cyclohexenone scaffold to illustrate the utility of the building block for chemical synthesis. The essentially stereochemically pure derivatives obtained contain up to three contiguous stereogenic centers (including the all-carbon quaternary stereocenter) and the new functional groups (like vinyl and allyl groups) introduced can potentially be further functionalized to other useful synthetic building blocks.

Part II. Investigation of the Synthesis and Properties of Axially Chiral 8,8'-biquinolyls and 8-(Naphtha-1-yl)quinolines

IIA. Introduction to the 'azaBINOL' class of Heterocyclic Biaryl Compounds

1. Carbocyclic versus Heterocyclic Biaryl Compounds

Two aromatic rings linked by a carbon-carbon single bond form a biaryl compound. In such a molecule, when all atoms of the cyclic conjugated pi systems are carbon, it is called a carbocyclic biaryl compound; but when at least one of those atoms is a heteroatom (e.g., O, N, S), it is called a heterocyclic biaryl compound. Carbocyclic biaryl compounds have been well described in the literature for a long time. They form significant structural motifs of various natural products (e.g. knipholone (**37**)[16], schizandrin (**35**)[17], etc.) and other biologically active compounds.[18] Biaryl compounds can also be found in some advanced materials such as conductive polymers,[19] liquid crystals,[20] and supramolecular hosts[21]. Restricted rotation about the central C-C bond of biaryl molecules (due to steric hindrance) can result in atropisomers with axial chirality, a property which can be used to affect stereoinduction in enantioselective synthesis (e.g., chiral ligands BINOL **38** and BINAP **39**).[22]

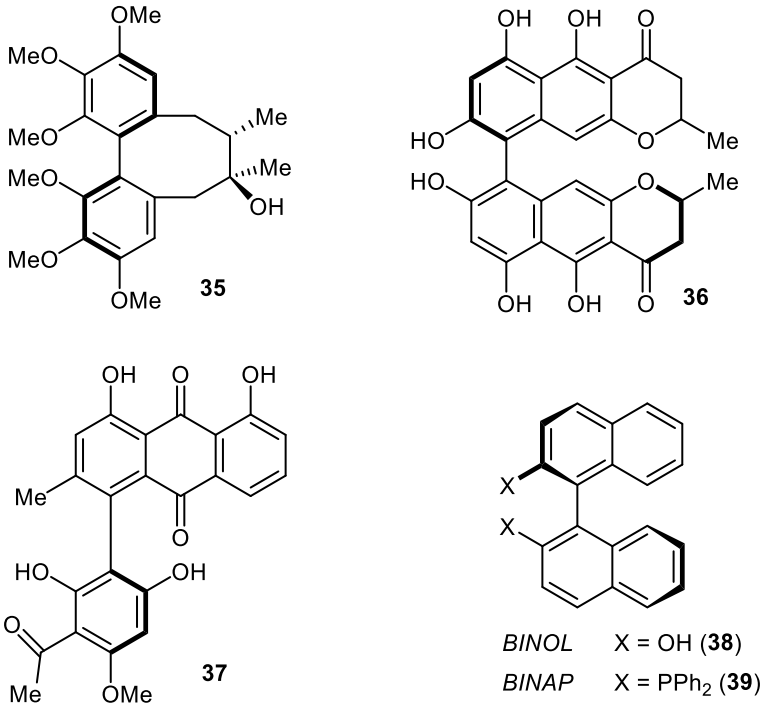
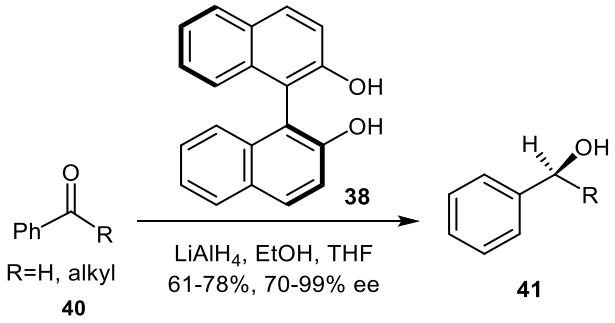


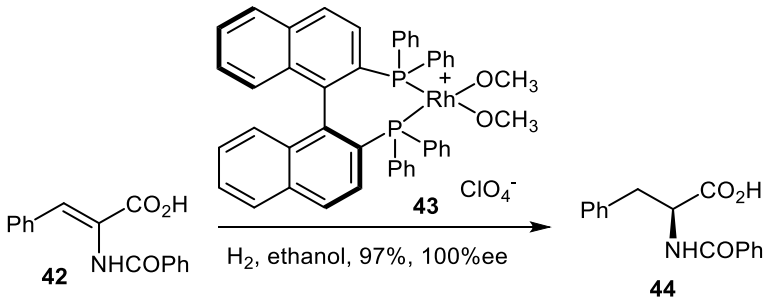
Figure 1. Some examples of carbocyclic biaryl molecules

One of the most well-known axially chiral molecules and a popularly used metal ligand for both stoichiometric and catalytic asymmetric reactions is 1,1'-bi-2-naphthol (BINOL, **38**). This compound was first demonstrated in 1979 by Noyori and coworkers to be an excellent chiral ligand in the enantioselective reduction of ketones to alcohols with very high enantioselectivity (99% ee) using stoichiometric $LiAlH_4$ (scheme 6).[23] BINOL has since then been utilized as a stereocontrol element in Diels-Alder reactions, Friedel-Crafts reactions and in various other enantioselective transformations.[24]



Scheme 6. Application of BINOL in enantioselective reduction

In 1980, Noyori introduced 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP, **39**) as a conformationally flexible atropisomeric C_2-symmetric diphosphine. This well-known carbocyclic biaryl ligand has the capacity to accommodate a wide range of transition metals with insignificant increase of torsional strain. Chelation of BINAP with metals to form structurally unambiguous seven-membered rings leads to the 'chirality transfer' of this ligand to the metal coordination sites[25] rendering high chiral recognition to BINAP based metal catalysis. BINAP has been used as an efficient catalyst in highly enantioselective asymmetric hydrogenation of various substrates (e.g., Scheme 7) as well as C–C bond formation.



Scheme 7. Application of BINAP in enantioselective asymmetric hydrogenation

Heterocyclic biaryl compounds have received much less attention as compared to their carbocyclic analogues. Aromatic heterocycles can provide considerable structural diversity and offer varied types of functionalities with simple modification techniques. Therefore, these molecules can potentially catalyze a wide variety of chemical transformations. Furthermore, such heterocycles can be placed in axially chiral scaffolds and used in the discovery of novel and potentially enantioselective processes.[26] In fact, axially chiral molecules having multiple functionalities have a wide range of applications in many areas of contemporary interest including enantioselective catalysis,[27] chiral recognition[28] and materials chemistry.[29] Although chiral phosphines (e.g. **39**, Figure 1) have been widely used for a long time as enantioselective catalysts, their azacyclic variants can provide more versatile opportunities. Biaryl compounds containing aromatic N-atom(s) offer a few advantages over their carbocyclic analogues.[30] Firstly, they can be used in reactions where the required reaction conditions are not compatible with phosphines. Secondly, the ligands binding through N-atom(s) can coordinate and form complexation to a large variety of metal ions. A lot of studies have been done to comprehend the catalytic modes of action of these ligands in reactions.[31] The third advantage is the easy availability of many nitrogen-based ligands in enantiomerically pure form. The best studied group of heterocyclic biaryl molecules so far constitute 2,2'-bipyridyls (e.g. **45**) and the atropisomeric ligand 1-(2′-diphenylphosphino-1′-naphthyl)-isoquinoline (QUINAP, **46**) (Figure 2). QUINAP is an N,P-ligand widely used in various types of asymmetric catalytic reactions[32], such as asymmetric hydroboration,[33] allylic alkylation,[34] and the copper-catalyzed enantioselective three-component synthesis of chiral propargyl amines.[35]

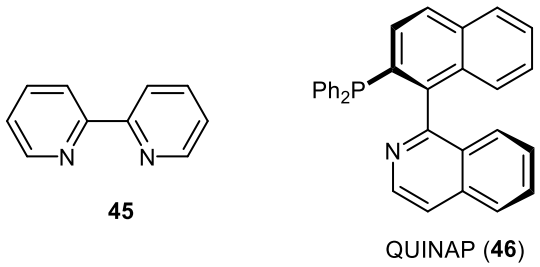


Figure 2. Two examples of heterocyclic biaryl molecules

Quaternization of the pyridyl *N*-atoms in 2,2´-bipyridyls and similar systems provides configurationally stable chiral metal ligands. In the enantioselective addition of allyltrichlorosilane to aldehydes, *atropos* (restricted rotation) *N,N´*-dioxide derivatives of 2,2´-bipyridyls have been used as chiral Lewis base promoters.[36] Similarly, *N,N´*-dioxides of 2,2´-biquinolyls and 1,1´-biisoquinolyls have also been utilized (Figure 3).

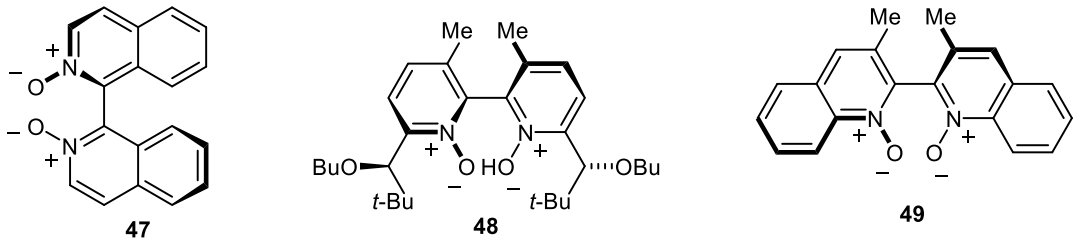


Figure 3. Examples of configurationally stable quaternized 2,2´-bipyridyl type molecules

2. The Chemistry of 8,8′-Biquinolyls

The search for a topologically distinct but highly functionalizable heterocyclic biaryl template with a broad range of potential applications resulted in the identification of 7,7'-dihydroxy-8,8'-biquinolyls (previously known as ‘azaBINOLs’ and now colloquially referred to as 8, 8’-diazaBINOLs, e.g. **50**) as an intriguing and promising group of molecules for study.

8,8'-DiazaBINOL **50** could be a useful ligand and a chiral catalyst in its own right and could also serve as a crucial intermediate to produce other 8,8'-biquinolyls of interest. It has an intriguing juxtaposition of sp^2-hybridized N-atoms (basic, nucleophilic, and 'soft'-metal ion coordination properties) and phenolic OH groups (acidic and 'hard'-metal ion coordination properties). Given that these types of molecules had been little explored as compared to the analogous carbacyclic biaryl systems like BINOL,[23, 24] and that no significant study of their atropisomerism had been reported, Blakemore and coworkers pursued extensive studies on these molecules (8,8’-diazaBINOLs).[37, 38a-c, 39]

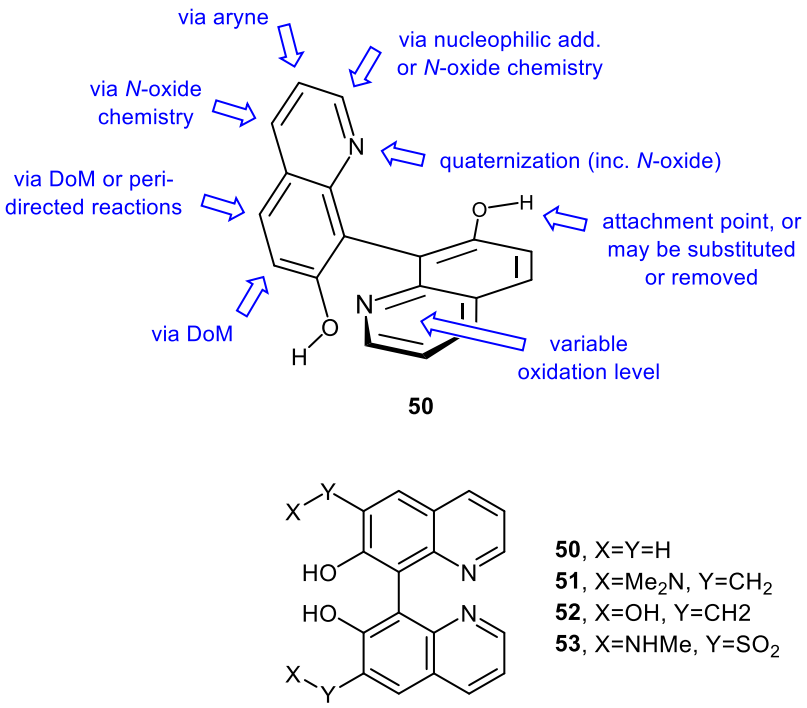
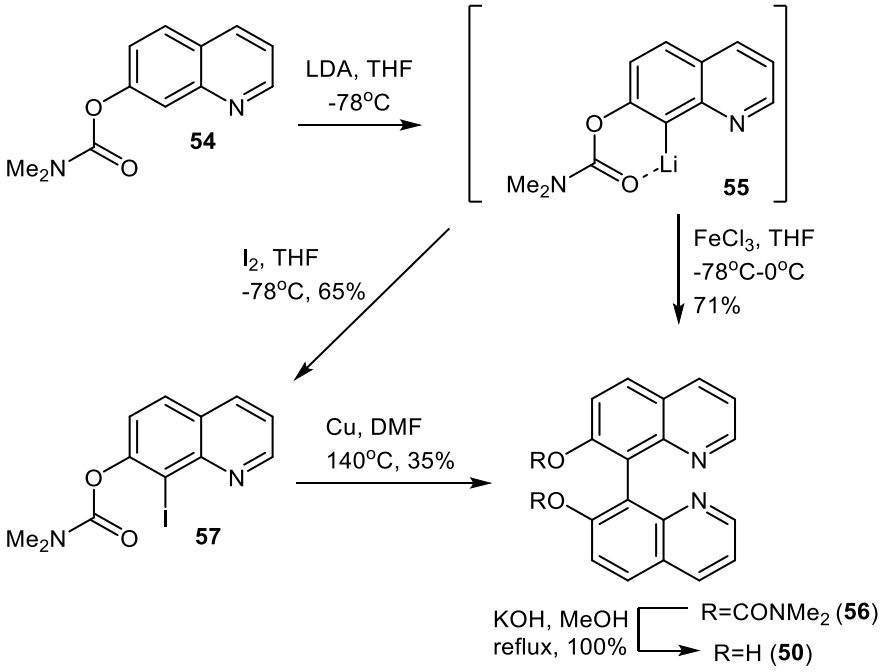


Figure 4. 8,8'-DiazaBINOL (**50**) with indication of possible derivatization tactics and some functionalized derivatives (**51**-**53**)

Syntheses of 8,8'-diazaBINOL and its derivatives have been reported by Blakemore and coworkers,[37,38] and other groups.[38d] These biaryl compounds have been resolved into their enantiomeric atropisomers and physical organic studies have been conducted to investigate their key properties like enantiomerization kinetics and effects of pH on conformation. This work will now be reviewed to place the novel studies reported herein in context.

The first synthesis of 8,8'-diazaBINOL by Blakemore and coworkers was based on oxidative dimerization of an 8-lithio-7-(carbamoyloxy)quinoline intermediate.[38a] In this approach, *N*,*N*-dimethyl *O*-quinol-7-yl carbamate (**54**) was subjected to

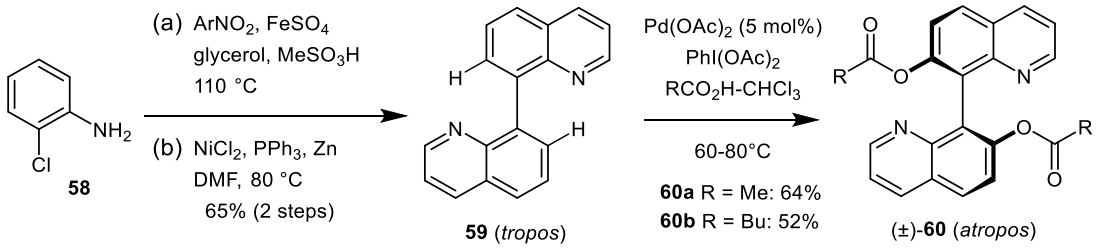
regioselective directed ortho metalation (DoM) with LDA. Addition of the resultant metalate **55** to a solution of iodine to produce 8-iodoquinoline **57** (65% yield), followed by subsequent Ullmann coupling of iodide **57** proceeded in a moderate yield (30-40%). However, direct oxidative coupling of aryllithium **55** with anhydrous ferric chloride was carried out later to improve the formation of the biquinolyl bond. The method was subsequently adopted by Loh and Xiao for their synthesis of octahydro diazaBINOLs.[38d]



Scheme 8. Two syntheses of 8,8'-diazaBINOL (**37**) based on directed ortho-metallation of carbamate **46**

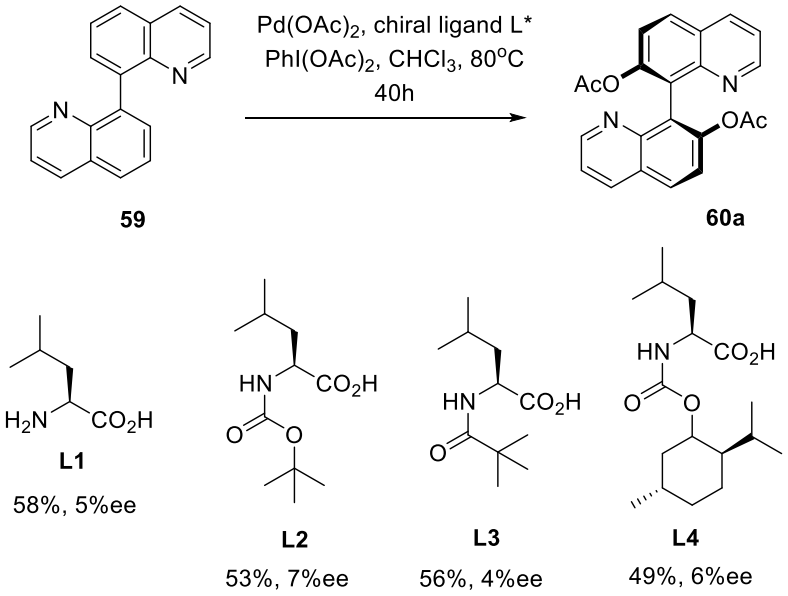
Because it was a lengthy method (7 steps from 3-aminophenol to **50**) that hindered later studies, a much improved second generation route to **50** via Pd(II)-catalyzed directed double CH functionalization of 8,8´-biquinolyl (**59**) was developed leaving the original

method with little practical utility (Scheme 9).[39] In this improved synthesis, commercially available 2-chloroaniline (**58**) is subjected to Skraup reaction followed by Ni-catalyzed reductive dimerization of 8-chloroquinoline to obtain 8,8´-biquinolyl (**59**), which then underwent Sanford oxidation[46a,46b] in AcOH-$CHCl_3$ to form diacetate **60a**. The product is isolated by simple trituration making the short sequence from **58** chromatography free. The Sanford oxidation in a mixture of $BuCO_2H$-$CHCl_3$ provided the dipentanoate of **50** (**60b**, R = Bu), a substrate for enzymatic resolution.[38b] 8,8'-DiazaBINOL (**50**) is obtained in high yield via straightforward saponification of its diester derivatives **60**.



Scheme 9a. A concise chromatography-free synthesis of 8, 8'-diazaBINOL diesters **60**

Following the report of Yu and coworkers[46c], L-Leucine and three N-protected L-Leucine derivatives were synthesized and their role in the enantioselective Sanford oxidation step was investigated. All of them produced decent yields but low *ee* from 4-7% (Scheme 9b).[46d]



Scheme 9b. Enantioselective Sanford oxidation using Yu's ligands

Two successful methods have been developed[37, 38b, 40] for the resolution of 8,8'-diazaBINOL (**50**). The first protocol was based on C18-HPLC separation of diastereomeric bismenthylcarbonate derivatives,[37] but it provides only a limited amount of enantioenriched material and it therefore has limited usefulness. The second more practical approach was based on enzymatic kinetic resolution of dipentanoate (±)-**60b** with inexpensive bovine pancreas acetone powder (Scheme 10).[38b, 40] Though the former method is inferior, it successfully established the absolute stereochemical assignment for the optical isomers of **50**.[37] Enantioenriched isomers of **50** have modest configurational stability. Hence the conversion of both enantiomers into their diesters **60** provided precursors to scalemic samples of biquinolyl **50**.

Eyring plot analysis of the enantiomerization kinetics of 8,8'-diazaBINOL in water over the temperature range of 316-366 K revealed activation parameters of $\Delta H^{\ddagger}$ = +34.0

kcal mol^{-1} and $\Delta S^{\ddagger}$ = +18.7 cal mol^{-1} K^{-1}.[37] Thus, **50** is significantly less configurationally stable than its carbocyclic congener 1,1´-bi-2- nathphthol (BINOL, **38**). The kinetic experimental data for **50** was supported by a molecular modelling study (AM1) of the rotational dynamics of **50** which indicated a *syn* pathway for enantiomerization (calculated rotational barrier, $\Delta H^{\ddagger}$ = 34.1 kcal mol^{-1}).[37] The *greater* configurational stability of **50** at extremes of pH, i.e., in alkoxide and quinolinium ionic forms, in comparison to its neutral form, further backed up the hypothesis of *syn* pathway. The increase in barrier for the interannular rotation observed for compound **50** in highly acidic and basic media may be attributed to the electrostatic repulsion of like charges in the corresponding transition states for *syn*-enantiomerization pathways. BINOL (**38**), in contrast, racemizes quicker in acidic or basic aqueous solutions as compared to neutral conditions.[41] Density Functional Theory (DFT) applied to calculate the racemization barrier of BINOL shows that racemization occurs via *anti* pathway (though *syn-C2* TS is only 17kJ/mol over *anti-Ci* TS).[22, 42] However, the mechanism of BINOL racemization under acidic and basic conditions should not be oversimplified based on these results. It has been shown by computational studies that

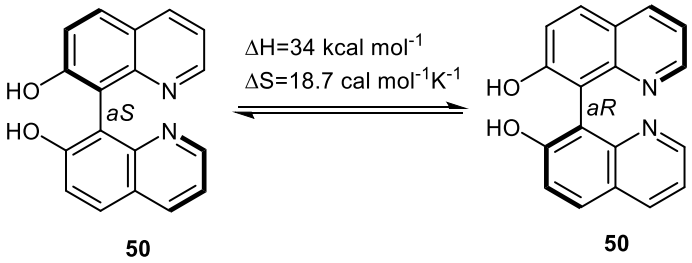


Figure 5. Enthalpy and entropy of activation for the enantiomerization of 8,8'-diazaBINOL in water

acid-catalyzed atropisomerization of BINOL can take place via protonation of C-1 atom to ensure rotation of the monoprotonated naphthyl ring around the $C(sp^2)$-$C(sp^3)$ bond.[41] A recent publication shows detailed NMR studies and DFT calculations to indicate that the atropisomerization of BINOL in acidic medium proceeds via $C(sp^3)$-$C(sp^3)$ single bond rotation in monoprotonated or diprotonated diketo forms depending on the acidity level.[43] For example, in superacid medium, different 'minimum energy' geometries of dication **38c** can be viable intermediates, while under moderate acidic conditions, monocation **38b** is the most feasible intermediate.

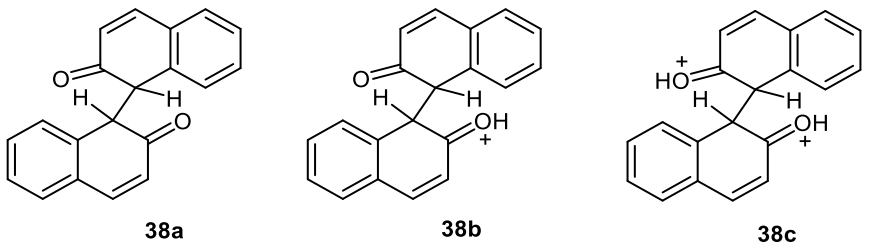
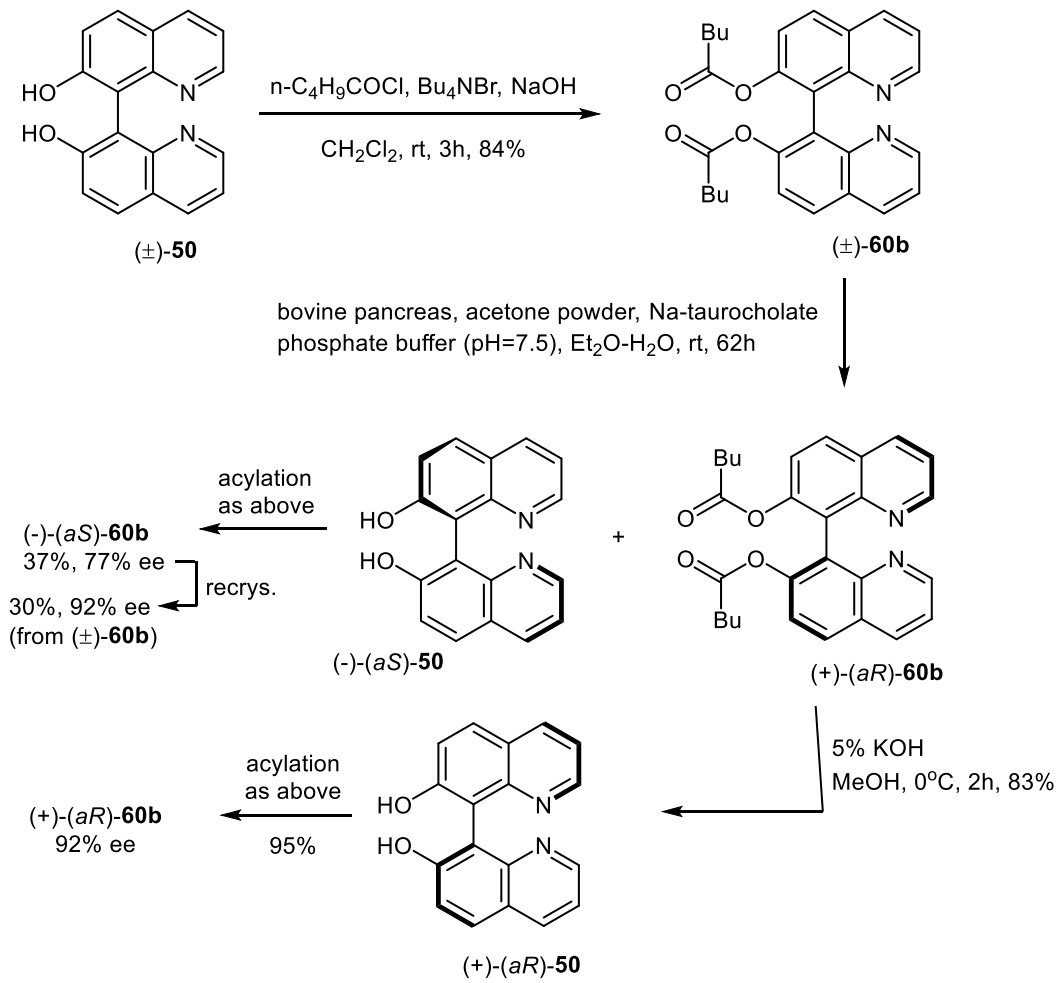


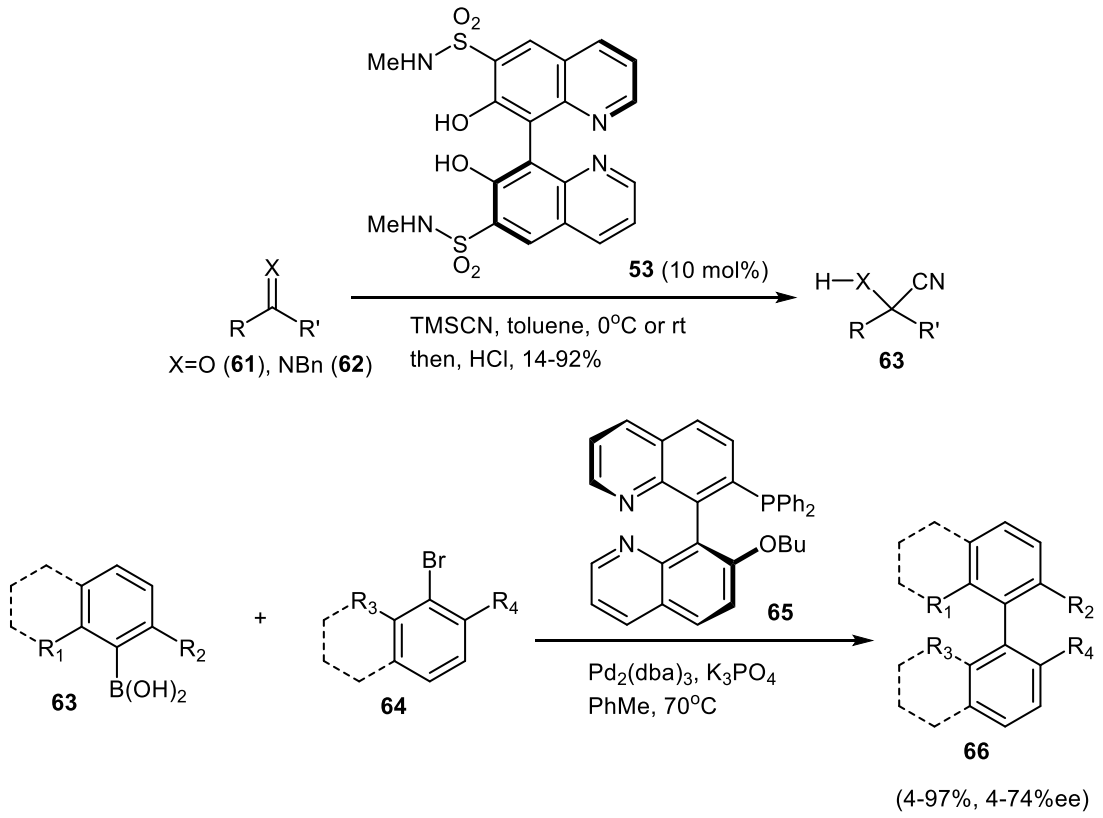
Figure 6. Possible intermediates for BINOL racemization



Scheme 10. Enzymatic kinetic resolution of dipentanoate derivative of (±)-8,8´-diazaBINOL (**50**)

As discussed earlier (indicated in Figure 4), all sites within the molecule **50** are potentially amenable to decoration with ancilliary functionality allowing for the synthesis of derivatives with a diverse range of properties.[39] For example, a 6,6´-bissulfonamide derivative of **50** (**53**) is an effective organocatalyst for the addition of TMSCN to C=X bonds (X = O, NR),[44] while a monophosphine derivative **65** was found to be a useful ligand for the enantioselective synthesis of biaryls by Suzuki cross-coupling.[27a] Hence functionalized 8,8'-diazaBINOL scaffolds provide a versatile

platform for the investigation of inherently chiral interannular proximity effects that may form the basis of significant new catalysis modes.



Scheme 11. Applications of 8,8'-diazaBINOL derivatives in synthesis

Although 8,8'-diazaBINOL has many favorable attributes, some of its physical properties are less than desirable and may hinder further develpment (Figure 7), e.g., poor solubility and relatively low configurational stability. Activation parameters for the enantiomerization of biquinolyl **50** are such that it begins to racemize fairly rapidly above 50 °C (e.g., $\tau_{1/2(rac.)}$ = 2.4 h at 75 °C in H_2O),[37] compromising any potential applications in enantioselective catalysis that might require heating. In addition, diol **50** is very polar and has low solubility in standard organic solvents, such as

tetrahydrofuran, dichloromethane, and toluene, which may again limit its utility. To avoid the detractions inherent to **50** while retaining key elements of its polyfunctionality, a hybrid naphthyl/ quinolyl azaBINOL molecule (**67**) was envisioned that would most likely exhibit solubility and configurational stability properties intermediate to those of **50** and **38**. This new molecule, 8-azaBINOL (**67**), was the focus of the study described herein.

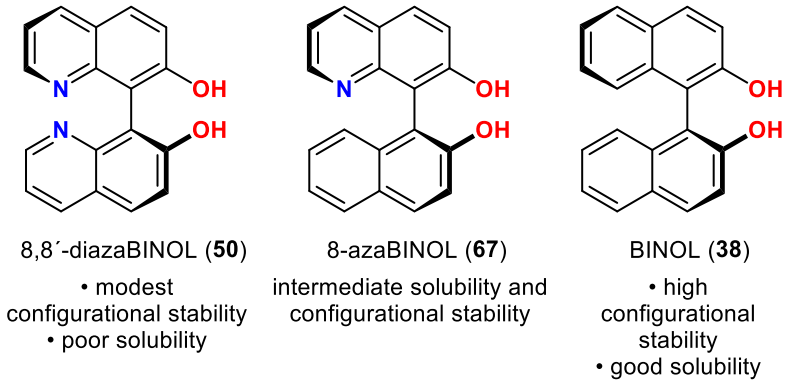


Figure 7. The original 'azaBINOL' molecule, 7, 7´-dihydroxy-8, 8´-biquinolyl (8, 8´-diazaBINOL, **50**), its monofunctional carbocyclic archetype 1, 1´-bi-2-naphthol (BINOL, **38**), and the hybrid naphthyl/ quinolyl 'azaBINOL', 7-hydroxy-8-(2-hydroxynaphth-1-yl)quinoline (8-azaBINOL, **67**).

Note: It is proposed that as a generic class the azaanalogs of BINOL (**50**) continue to be referred to as 'azaBINOLs' and that specific family members are colloquially identified by replacement nomenclature such that their distinction and relationship to the familiar BINOL molecule can be readily appreciated. Thus, 7,7´-dihydroxy-8,8´-biquinolyl (**50**) is being referred as '8,8´-diazaBINOL' and 7-hydroxy-8-(2-hydroxynaphth-1-yl)quinoline (**67**) as '8-azaBINOL.'

The new azaBINOL molecule (**67**) and its derivatives could be used for potential applications in both chemistry and biology. While the molecule itself and its Bronsted acid salts can potentially be utilized for enantioselective catalysis in various chemical transformations involving H-bonding interactions, a library of these compound derivatives can also be tested for antiviral and anti-cancer activities. The discussion here will mainly focus on three different research projects. Firstly, the synthesis, properties, and enantiomerization behavior of axially chiral phenolic derivatives of 8-(naphth-1-yl)quinoline were investigated and compared to 7, 7´-dihydroxy-8, 8´-biquinolyl and 1, 1´-bi-2-naphthol (IIB). Secondly, the study of enantioselective catalysis in chemical reactions involving C-H activation was conducted (IIC). Thirdly, in collaboration with the Loesgen research group, viral entry inhibition assays and MTT assays for anticancer activity were run for a library of these compounds to investigate biological activity (IID).

IIB. Synthesis, Properties, and Enantiomerization Behavior of Axially Chiral Phenolic Derivatives of 8-(Naphth-1-yl)quinoline and Comparison to 7,7´-Dihydroxy-8,8´-biquinolyl and 1,1´-Bi-2-naphthol*

1. Background and aims

Biquinolyl **50** is a diazaanalog of the chiral ligand BINOL (**38**) with significantly poor solubility as compared to BINOL. It also has a significantly lower configurational stability than binaphthyl **38**, a fact previously attributed to the formal replacement of peri CH bonds in **38** with lower steric demanding N-atom lone-pairs. The mixed hybrid version of compounds **38** and **50** bearing quinoline/naphthalene moiety, 8-azaBINOL (**67**), was expected to overcome the aforesaid limitations. With one less N-atom than its 8,8'-diazaBINOL congener, the polarity of this new compound was expected to be considerably reduced resulting in higher solubility. The replacement of one of the two less sterically demanding N-atom lone pairs in 8, 8'-diazaBINOL **50** by a peri CH bond was expected to impart greater configurational stability to the new azaBINOL.

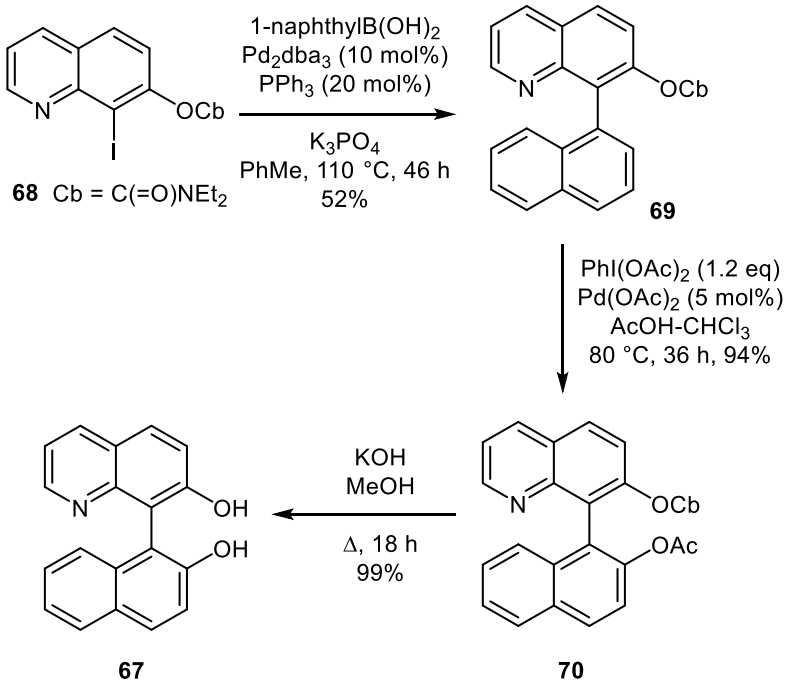
*Adapted from the peer-reviewed publication of the same title by S. Banerjee, B. E. Riggs, L. N., Zakharov, P. R. Blakemore, *Synthesis* **2015**, *47*, 4008-4016

2. Results and Discussions

The above intuitive assumptions about the properties of 8-azaBINOL (**67**) were proven to be correct by experiments and we recently reported the synthesis of (±)-8-azaBINOL (**67**), resolution of diol **67** by enzyme mediated hydrolysis of a diester derivative, determination of the activation enthalpy and entropy of enantiomerization for **67** by Eyring plot analysis and comparison of these data to those measured likewise for congeners **38** and **50**, and measurement of solubility and chiroptical data for **67**.[45]

2.1 Synthesis of Phenolic Derivatives of 8-(Naphth-1-yl)quinoline

8-AzaBINOL (**67**) was prepared in racemic form from the diethyl carbamate of 8-iodo-7-hydroxyquinoline (**68**)[38a] by a route that blended elements of both the first-generation[38a] and the second-generation[39] syntheses of (±)-8,8´-diazaBINOL (**50**) (Scheme 12). Suzuki cross-coupling of iodide **68** with 1-naphthylboronic acid gave the expected naphthylquinoline **69** which was subjected to Pd(II)-catalyzed substrate directed CH oxidation[46] to afford acetoxy derivative **70** in an excellent yield. Base mediated hydrolysis of **70** resulted in clean conversion to the desired target molecule **67** which was found to be more soluble in tetrahydrofuran, dichloromethane, and toluene than biquinolyl **50** (Table 1).



Scheme 12. Synthesis of 8-azaBINOL

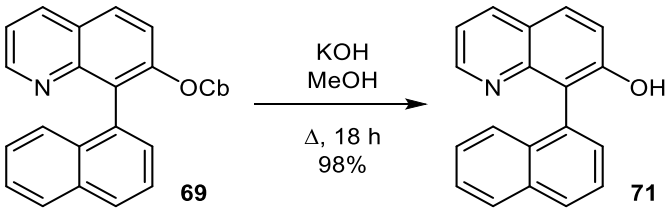
Table 1. Comparison of solubility of (±)-8,8′-diazaBINOL (**50**) and (±)-8-azaBINOL (**67**) in three common organic solvents.[a]

Solvent	Solubility of (±)-**50**	Solubility of (±)-**67**
PhMe	2.3 mM (0.67 g L^{-1})	280 mM (80.0 g/L)
THF	8.7 mM (2.5 g L^{-1})	>700 mM (>200 g/L)
CH_2Cl_2	16.3 mM (4.7 g L^{-1})	>700 mM (>200 g/L)

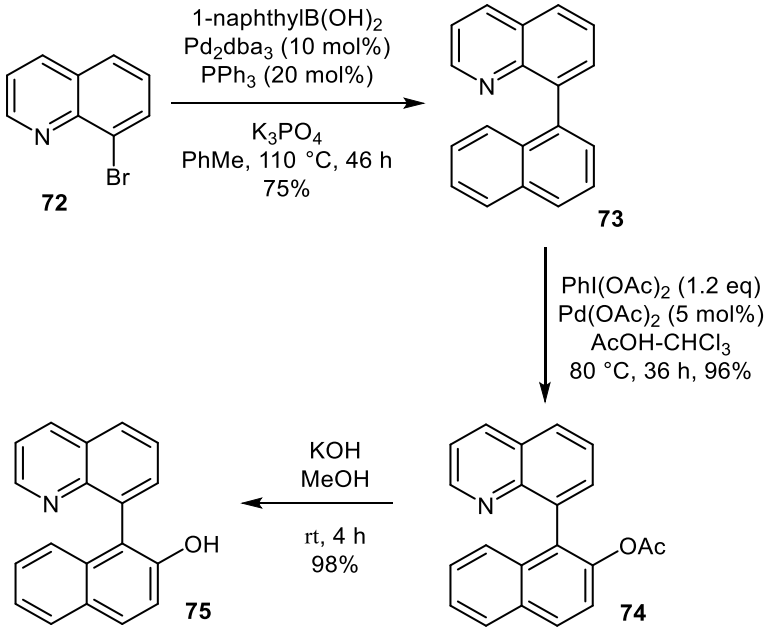
[a]Maximum solubility of racemates at ambient temperature (24 °C).

To have a better understanding of the influence of each hydroxyl group in compound **67** on its enantiomerization behavior, monophenols **71** and **75** were also prepared. The

first compound was accessed from synthetic intermediate **69** by hydrolysis and the second compound was realized in three steps from 8-bromoquinoline **72**. Single-crystal X-ray diffraction (XRD) analysis of the crystalline naphthylquinoline **75** revealed a slightly transoid conformational preference but no obvious intramolecular interaction was present between the quinoline N-atom and the phenolic OH group (Figure 8).[47]



Scheme 13. Synthesis of monophenol **71**



Scheme 14. Synthesis of monophenol **75**

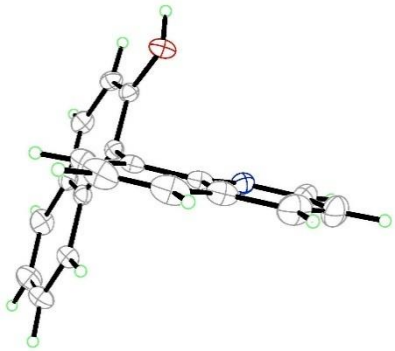


Figure 8. ORTEP diagram for naphthylquinoline (±)-**75** showing one of the two independent molecules present within the unit cell. Both molecules are transoid; the angles between least-squares fitted aryl ring planes are 101.18° and 99.11°. 50% Probability ellipsoids are plotted for non-hydrogen atoms.[47]

2.2 Enantiomerization Behavior and Other Properties of Phenolic Derivatives of 8-(Naphth-1-yl)quinoline and Comparison to 8,8'-diazaBINOL and BINOL

Monophenolic naphthylquinolines **71** and **75** were straightforwardly resolved by semi-preparative chiral stationary phase (CSP) HPLC using Daicel Chiralcel® OD column. Both compounds spontaneously racemized at rt with quinol **71** exhibiting higher configurational stability than its naphthol isomer **75**. The rate of racemization of **71** was only modestly sensitive to solvent; however, for **75**, racemization occurred approximately 30 times faster in chloroform as compared to methanol (Table 2). A similar solvent effect was noted for 2,2´-di-*tert*-butyl-7,7´-dihydroxy-8,8´-biquinolyl, which racemizes 15 times faster in chloroform as compared to methanol (at 23 °C).[38b] One plausible explanation is that an intramolecular hydrogen-bond interaction may lower the barrier for racemization in those biaryls in which a quinolyl N-atom and a phenolic OH group flank one another across the interannular axis. Disruption of such

an interaction by a hydrogen- bonding acceptor/ donor protic solvent like methanol would be expected to raise the racemization barrier.

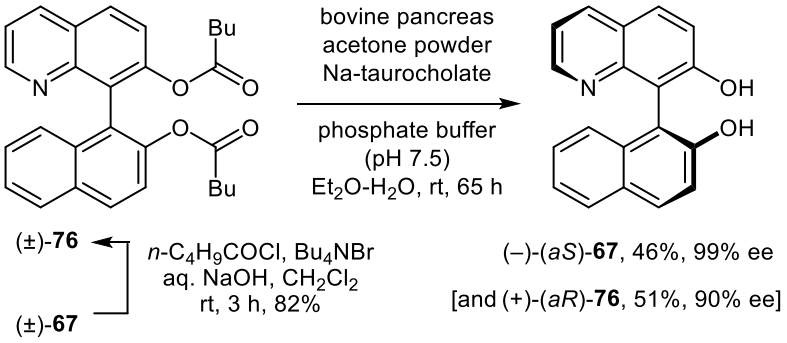
Table 2 Solvent effects on the racemization half-lives of mono- (**71**, **75**) and bis- (**67**) phenolic derivatives of 8-(naphth-1-yl)quinoline.

Solvent	τ1/2(rac.) **71** at 24 °C	τ1/2(rac.) **75** at 24 °C	τ1/2(rac.) **67** at 56 °C
$CHCl_3$	106 h[a]	2.7 h[a]	257 h[a]
MeOH	120 h[a]	89 h[a]	70 h[a]
DMSO	nd	nd	293 h[b]

[a] Determined experimentally. [b]Calculated from the Eyring equation using experimentally determined activation parameters for enantiomerization (ΔH‡, ΔS‡) as shown in Figure 4.

With the relative effects of naphthol- and quinol-type OH groups on configurational stability thus dissected, a means to affect the resolution of diol **67** was sought. Direct resolution of **67** by CSP HPLC was not effective although its dipentanoate **76** was readily resolved into enantiomeric atropisomers using this method. Optical rotation values for scalemic samples of diester **76** were found to be invariant after 18 h at 110 °C in toluene, revealing the excellent configurational stability of this material. The racemic dipentanoate esters of BINOL (**38**)[40] and its diazaanalog **50**[38b] are both well resolved

by hydrolytic kinetic resolution with the esterase found in bovine pancreas acetone powder. Given the isosteric character of **50**, **67**, and **38**, it was not surprising to find that the dipentanoate derivative (**76**) of the intermediate member of the series (**67**) was also efficiently resolved using the same enzymatic method (Scheme 4). For the diesters of (±)-**50** and (±)-**38**, it has been determined that the (*aS*)-configured biaryl atropisomer is processed by the enzyme.[38b, 40] It is reasonable to assume that the hydrolysis of diester (±)-**76** proceeds likewise; thus, the levorotatory diol **67**, $[\alpha]_D^{24°C}$ = –142 (c = 0.10, acetone, 99%ee), obtained via enzymatic hydrolysis is assigned as the (*aS*)-isomer. Pleasingly, 8-azaBINOL (**67**) was found to be configurationally stable in the solid state at rt (no change in $[\alpha]_D$ for an optically active sample during 30 d) and it was established that saponification of diester **76** to return diol **67** can be achieved without racemization. The residual dextrorotatory biaryl diester (+)-(*aR*)-**76**, $[\alpha]_D^{24°C}$ = +173 (c = 0.12, $CHCl_3$, 90% ee), obtained from the enzymatic kinetic resolution of (±)-**76**, is therefore a viable source of (+)-(*aR*)-**67**. Reconversion of enantioenriched samples of **67** into diester **76** via Schotten-Baum conditions (as in Scheme 15) was also found to proceed without a detectable degree of racemization.



Scheme 15. Preparation of enantioenriched diol 2 by hydrolytic enzymatic kinetic resolution of
its dipentanoate derivative (±)-**46**

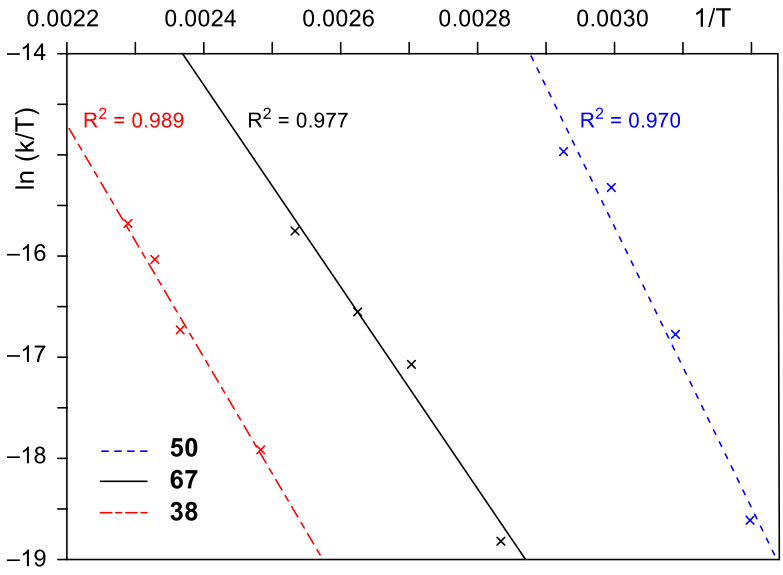
The electronic circular dichroism (CD) spectrum of (–)-(*aS*)-**67** was comparable to those previously obtained[37] for (–)-(*aS*)-**50** and (–)-(*aS*)-**38** and it served to confirm the absolute configuration assignment for this material made previously based on the outcome of enzymatic resolution of (±)-**76**.[48] The levorotatory isomer of diol **7** displays a bisignate exciton couplet of positive chirality in methanol with a negative minimum at 235 nm and a positive maximum at 255 nm and a band intensity of $\Delta\Delta\epsilon$ = +135 M^{-1} cm^{-1}. The (*aS*)-isomers of biquinolyl **50** (in H_2O) and binaphthyl **38** (in MeOH) also exhibit positive exciton chirality albeit with lower [$\Delta\Delta\epsilon$ (**50**) = +63 M^{-1} cm^{-1}] and higher [$\Delta\Delta\epsilon$ (**38**) = +476 M^{-1} cm^{-1}] respective band intensities as compared to the hybrid molecule **67**.

With ready access to scalemic samples of **67** secured, a comparative analysis of the enantiomerization kinetics for this compound and its symmetrical biquinolyl (**50**) and binaphthyl (**38**) analogs was conducted in DMSO solution (Figure 9). Eyring plot analyses have been reported previously for the enantiomerization of **50** in water ($\Delta H^{\ddagger}$ = +34.0 kcal mol^{-1}; $\Delta S^{\ddagger}$ = +18.7 cal mol^{-1} K^{-1})[37] and **38** in diglyme ($\Delta H^{\ddagger}$ = +32.2 kcal mol^{-1}; $\Delta S^{\ddagger}$ = –15.6 cal mol^{-1} K^{-1})[49] but for a truly meaningful comparison, it was important for all three compounds (**38, 50, 67**) to be examined in the same vehicle. DMSO was chosen for this purpose because of its high boiling point (189 °C) and its ability to dissolve all of the biaryls of interest. Four first order rate constants for enantiomerization were experimentally determined for each biaryl **50, 67** and **38** over an appropriate 30-40 °C temperature range (Figure 9). To monitor the enantiopurity of **50** and **67** as a function of time, aliquots were removed from the isothermally incubated DMSO solutions and the diols converted to their dipentanoate derivatives (e.g., **76**) for

ease of ee determination by CSP HPLC analysis. Enantiopurity of BINOL (**38**) was directly determined by CSP HPLC analysis without a derivatization step. Eyring plots gave acceptable linear regression results in all cases ($R^2 \geq 0.97$) and activation enthalpy ($\tau H^{\ddagger}$) and entropy ($\Delta S^{\ddagger}$) values for enantiomerization were extracted as indicated (Figure 9). To aid comparison, racemization half-lives and the associated $\Delta G^{\ddagger}$ values for the enantiomerization of **50**, **67** and **38** in DMSO from 25-200 °C were calculated from the Eyring equation using the measured $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values (Table 3).[50a] The illustrated data support the original hypothesis that the configurational stability of **67** is intermediate to that of **50** and **38**; however, an examination of the individual activation parameters reveals that the mechanism for enantiomerization of **50** is quite different to that for the other two diols, which likely share a similar mode of enantiomer interconversion. As compared to biquinoyl **50**, the naphthalene ring containing biaryls **67** and **38** owe their greater configurational stability to negative $\Delta S^{\ddagger}$ values rather than to larger $\Delta H^{\ddagger}$ values, as had initially been assumed would be the case. Indeed, biquinolyl **50** possesses the *largest* $\Delta H^{\ddagger}$ value for enantiomerization within the series of biaryl diols studied but a small and positive $\Delta S^{\ddagger}$ value for **50** results in lower overall $\Delta G^{\ddagger}$ values than for naphthols **67** and **38** (since $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$). This finding suggests that it may be erroneous, or at the very least an over simplification, to attribute the lower configurational stability for **50** *vs.* **38** to the steric effect of formally replacing peri-CH bonds in binaphthyl **38** with N-atom lone-pairs in biquinolyl **50**. It is possibly due to a different racemization mechanism of **50** as compared to **67** and **38** (which appear to share similar racemization mechanism) involving certain specific reorganization in dipolar aprotic solvent DMSO.[50b]

Finally, to investigate how solvent might influence the configurational stability of diol **67**, racemization half-lives for this material in chloroform and methanol were measured at 56 °C and the values compared to that calculated for **67** in DMSO at the same temperature using the Eyring equation and the previously obtained activation parameters (Table 2). The configurational stability of diol **67** was less sensitive to solvent effects than that for naphthol **75** (both **67** and **75** possess flanking N and OH groups), but, curiously, **67** racemized faster in methanol than in chloroform (by a factor of 3.7), a trend opposite to that found for both quinol **71** and naphthol **75** (and to that previously reported for 2,2´-di-*tert*-butyl-7,7´-dihydroxy-8,8´-biquinolyl).[38b]

Some comments on the role that solvent plays in the configurational stability of the azaanalogous series of compounds investigated are warranted. That solvent effects can alter activation parameters ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) for the enantiomerization of biaryls has been long appreciated;[51] however, the net effect of a change in solvent on $\Delta G^{\ddagger}_{(ent.)}$ [and therefore also $\tau_{1/2(rac.)}$] is often found to be surprisingly small (e.g., $\Delta\Delta G^{\ddagger}_{(ent.)}$ <2 kcal mol^{-1}) because of a poorly understood 'compensation' mechanism in which any solvent induced changes in $\Delta H^{\ddagger}$ are largely balanced out by associated changes in $\Delta S^{\ddagger}$.[52] The kinetic data obtained herein demonstrate that solvent effects can induce changes in the rate of biaryl racemization more significant than the factor of ca. 5 usually expected.[53]



Data for **50**	T / K	313	324	334	342
	$k / 10^{-7}$ s^{-1}	26.8	169	749	1090

$\Delta H^{\ddagger}$ = +27.4 kcal mol^{-1} $\Delta S^{\ddagger}$ = +3.84 cal mol^{-1} K^{-1}

Data for **67**	T / K	353	370	381	395
	$k / 10^{-7}$ s^{-1}	24.2	144	249	571

$\Delta H^{\ddagger}$ = +19.9 kcal mol^{-1} $\Delta S^{\ddagger}$ = –27.9 cal mol^{-1} K^{-1}

Data for **38**	T / K	403	423	430	437
	$k / 10^{-7}$ s^{-1}	68.0	234	470	687

$\Delta H^{\ddagger}$ = +23.2 kcal mol^{-1} $\Delta S^{\ddagger}$ = –25.3 cal mol^{-1} K^{-1}

Figure 9. Eyring plot analysis and rate constant data for the enantiomerization of 8,8´-diazaBINOL (**50**), 8-azaBINOL (**67**), and BINOL (**38**) in DMSO solution (3.5-7.0 mM). Eyring equation: ln (k/T) = $\Delta S‡/R$ – ln (h/kB) – $\Delta H‡/(RT)$.

Table 3 Racemization half-lives for **50**, **67** and **38** and associated ΔG‡(ent.) values in DMSO solution at various temperatures calculated from the Eyring equation using experimentally determined activation parameters for enantiomerization (ΔH‡, ΔS‡) as shown in Figure 9.

Temp.	τ1/2(rac.) **50** / ΔG‡(ent.) **50**[a]	τ1/2(rac.) **67** / ΔG‡(ent.) **67**[a]	τ1/2(rac.) **38** / ΔG‡(ent.) **38**[a]
25 °C	12 d / 26.3	0.87 y / 28.2	120 y / 30.7
50 °C	7.2 h / 26.2	22 d / 28.9	5.5 y / 31.4
75 °C	19 min / 26.1	2.2 d / 29.6	140 d / 32.0
100 °C	73 s / 26.0	7.1 h / 30.3	14 d / 32.6
150 °C	0.82 s / 25.8	16 min / 31.7	7.2 h / 33.9
200 °C	23 ms / 25.6	69 s / 33.1	10 min / 35.2

[a] Free energy of activation for enantiomerization [ΔG‡(ent.)] given in units of kcal mol^{-1}.

For example, racemization of the well-known ligand BINOL (**38**) was observed here to be significantly faster in DMSO than in the ethereal solvent previously used for an Eyring plot analysis of its configurational stability; *viz.*, racemization half-life for **38** in diglyme at 150 °C is 101 days[49] while it is only 7.2 hours in DMSO at the same temperature, a >330 fold increase in rate representing a reduction in $\Delta G^{\ddagger}_{(ent.)}$ of 4.9 kcal mol^{-1} (n.b., at rt the difference in rates exceeds a factor of 32,000!). The very different responses of the mono- (**71** and **75**) and bis-phenolic (**67**) derivatives of 8-(naphth-1-yl)-quinoline to a change in solvent from chloroform to methanol (see Table 2)

illustrates the dramatic impact that subtle structural variations may have on the solvent dependence of racemization rates and the difficulty of extrapolating behavior seen in one series of related compounds to another. Taken together these findings caution against the common practice of neglecting solvent effects in computational studies intended to accurately model enantiomerization barriers for biaryls,[52, 54] particularly if the compounds of interest contain functional groups that may interact strongly with solvent molecules.

3. Conclusion

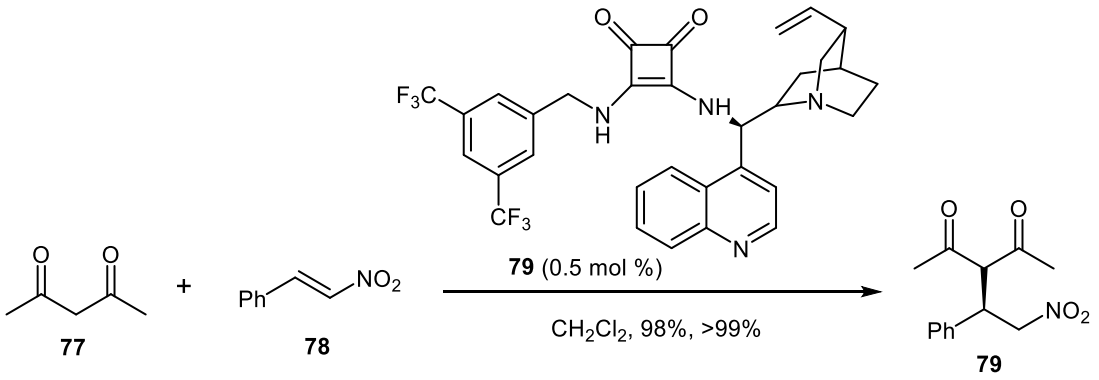
In summary, a new azaBINOL molecule (**67**) that is a structural chimera of 8,8´-diazaBINOL (**50**) and its better known carbocyclic counterpart BINOL (**38**), was prepared and resolved and found to exhibit better solubility and higher configurational stability than **50**. Eyring plot analyses of the enantiomerization kinetics for **50**, **67**, and **38** revealed that the enantiomerization of biquinolyl **50** likely occurs by a different mechanism to that for naphthylquinoline **67** and binaphthyl **38** but that the relative configurational stability of these three compounds falls into the expected sequence (**50**<**67**<**38**). The rate of racemization of BINOL was found to be significantly faster in DMSO than in ethereal solvent, a hitherto unrecognized fact highlighting that solvent effects must be factored into consideration when one contemplates the configurational stability of biaryl compounds. With the completion of this work a new member of the azaBINOL family, 8-azaBINOL (**67**), is available for exploratory studies in enantioselective catalysis, chiral recognition, and materials chemistry.

IIC. Study of 8-AzaBINOL and its Acid Salts in Enantioselective Catalysis

1. Introduction

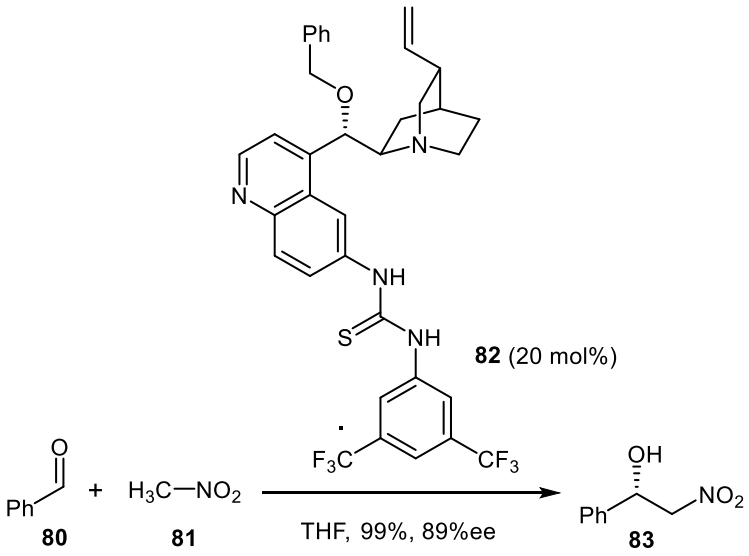
Due to considerably higher configurational stability as compared to 8, 8'-diazaBINOL **50** ($t_{1/2}$(rac.) being 12 d for **50** and 0.87 y for **67** at rt in DMSO), 8-azaBINOL **67** can be better used as a potential enantioselective catalyst in chemical reactions even in those ones requiring relatively higher temperatures. Due to the H-bonding interactions possible with the molecule, enantioselective transformations potentially utilizing these interactions could be targeted using enantiopure 8-azaBINOL **67** and its acid salts as organocatalysts.

Rawal and coworkers demonstrated the use of H-bonding catalysts (TADDOLs, squaramide scaffolds, etc.) in various enantioselective transformations (conjugate addition reactions, Diels-Alder reactions, etc.).[57] For example, they used chiral squaramide derivative **79** as an H-bond donor catalyst to produce the conjugate addition product of 2,4-pentanedione and β-nitrostyrene in high yield and enantioselectivity (Scheme 16).[57c]



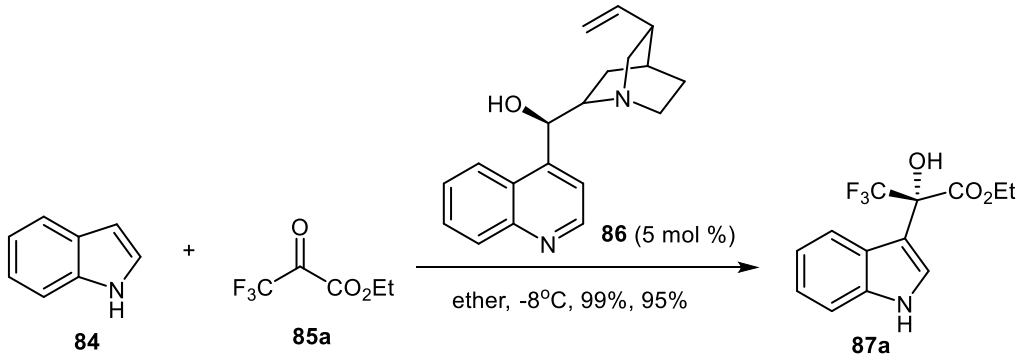
Scheme 16. Conjugate addition catalyzed by chiral squaramide

Hiemstra and coworkers utilized a thiourea derivative of cinchona alkaloid to catalyze an enantioselective nitroaldol reaction with aromatic and heteroaromatic aldehydes and nitromethane (an example shown in Scheme 17).[61] The strong H-bond donor properties make the catalyst more powerful and enantioselective.



Scheme 17. Enantioselective nitroaldol reaction

There are enantioselective Friedel-Crafts reactions[58] involving cinchona alkaloids as organocatalysts[59, 60] that also rely on H-bond activation. For example, Torok and coworkers reported highly enantioselective organocatalytic Friedel-Crafts hydroxyalkylation reaction of indole (**84**) and ethyl 3,3,3 trifluoro pyruvate (**85a**) catalyzed by cinchona alkaloid **86** (Scheme 18). In our study, a set of chemical reactions was chosen for screening of the targeted compounds (**67**, **67**·TsOH, **67**·HBF_4) as potential enantioselective catalysts for similar processes.

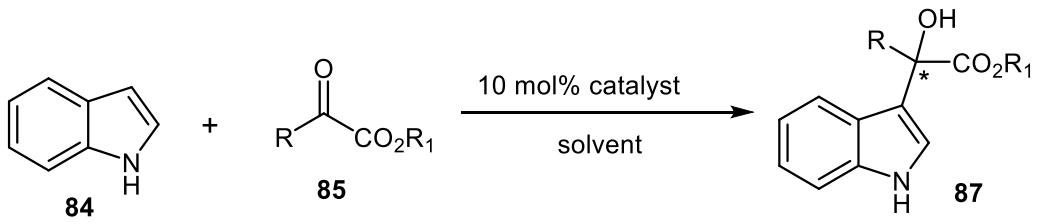


Scheme 18. Enantioselective Friedel-Crafts hydroxyalkylation

2. Results and Discussions

Torok et al. published the enantioselective hydroxyalkylation of indole with ethyl 3,3,3-trifluoropyruvate catalyzed by cinchona alkaloids.[59] Our attempt to screen this reaction with different catalysts showed that the background reaction is too fast to recognize any possible catalysis (Table 4). A negligible ee of 5% was observed in the product (S)-**87** with (-)-(S)-8-azaBINOL **67** as a catalyst (Table 4, entry 3). The reaction was screened in three different solvents, e.g. diethyl ether, toluene and dichloromethane, but similar results were obtained. The reaction was attempted with methyl pyruvate with no effect of catalysts from **67** (entry 7). Treatment of the reaction with catalytic **67**·TsOH provided the product in 82% yield in a much shorter time (entry 8), although negligible ee was observed with (-)-(S)-8-azaBINOL **67**·TsOH (entry 9).

Table 4. Hydroxyalkylation of indole



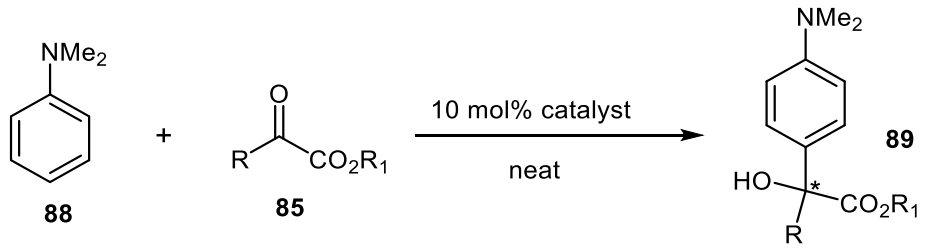
entry	catalyst	R, R_1	solvent	temperature	time	%yield[a]	%ee[b]
1	none	CF_3, Et	Et_2O	-78°C	2	97	-
2	(±)-**67**	CF_3, Et	Et_2O	-78°C	2	98	-
3	(-)-(S)-**67**	CF_3, Et	Et_2O	-78°C	2	98	5 (S)-**87**
4	(-)-(S)-**67**	CF_3, Et	toluene	-78°C	2	96	4 (S)-**87**
5	(-)-(S)-**67**	CF_3, Et	CH_2Cl_2	-78°C	2	97	5 (S)-**87**
6	none	CH_3, CH_3	Et_2O	-40°C	12	<2	-
7	(±)-**67**	CH_3, CH_3	Et_2O	-40°C	12	<2	-
8	(±)-**67**·TsOH	CH_3, CH_3	Et_2O	-40°C	1.75	82	-
9	(-)-(S)-**67**·TsOH	CH_3, CH_3	Et_2O	-40°C	1.75	80	3

[a] isolated yield. [b] Determined by chiral stationary phase HPLC analysis.

Dimethyl aniline and anisole[63] were chosen as less reactive nucleophiles with the same two pyruvate electrophiles (Table 5 and 6). While dimethyl aniline reacted with ethyl trifluoropyruvate without showing any catalysis by **67** and **67**·TsOH (table 5, entries 1-3), it did not react with methyl pyruvate at all with or without the presence of prospective catalysts (Table 5, entries 6-8). Anisole initially showed little more interesting results. While the uncatalyzed reaction did not proceed at all, it reacted with ethyl trifluoropyruvate to form 60% of the product when treated with catalytic **67**·TsOH (Table 6, entry 3). But a negligible ee of 3% was observed in this reaction when treated with (-)-(S)-8-azaBINOL **67**·TsOH as a catalyst (Table 6, entry 4). Both anisole and dimethyl amine were screened in diethyl ether, toluene and dichloromethane as solvents in their reactions with ethyl trifluoropyruvate with similar results (as neat).

Attempted nitroaldol reaction[61] (Scheme 19), conjugate addition reaction to nitrostyrene[57c] (Scheme 20), and hetero-Diels-Alder reaction using Danishefsky-type diene and benzaldehyde[62] were not successful with 8-azaBINOL and its acid salts (e.g., **67**·TsOH).

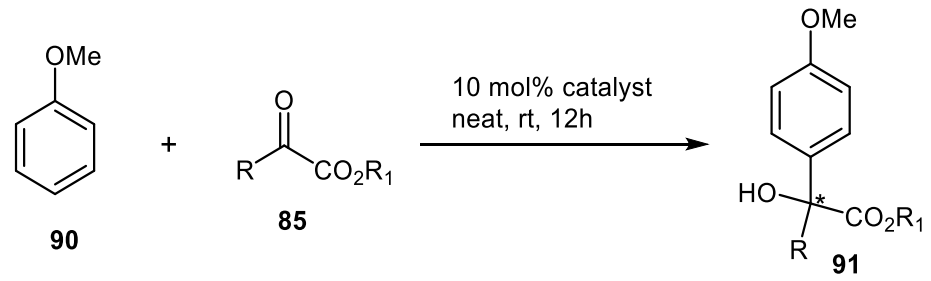
Table 5. Hydroxyalkylation of dimethyl aniline



entry	catalyst	R, R_1	temperature	time	%yield[a]	%ee[b]
1	none	CF_3, Et	-78°C	2.5	55	-
2	(±)-**67**	CF_3, Et	-78°C	2.5	53	-
3	(±)-**67**·TsOH	CF_3, Et	-78°C	2.5	56	-
4	(-)-(S)-**67**·TsOH	CF_3, Et	-78°C	2.5	55	2
5	none	CH_3, CH_3	rt	11	<2	-
6	(±)-**67**	CH_3, CH_3	rt	11	<2	-
7	(±)-**67**·TsOH	CH_3, CH_3	rt	11	<2	-
8	(±)-**67**·HBF_4	CH_3, CH_3	rt	11	<2	-

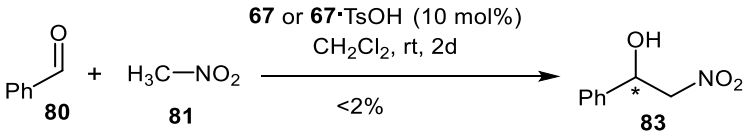
[a] isolated yield. [b] Determined by chiral stationary phase HPLC analysis.

Table 6. Hydroxyalkylation of anisole

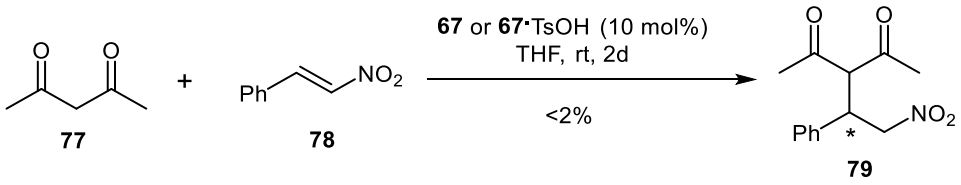


Entry	Catalyst	R, R_1	%yield[a]	%ee[b]
1	none	CF_3, Et	<2	-
2	(±)-**67**	CF_3, Et	<2	-
3	(±)-**67**·TsOH	CF_3, Et	65	-
4	(-)-(S)-**67**·TsOH	CF_3, Et	68	3
5	none	CH_3, CH_3	<2	-
6	(±)-**67**	CH_3, CH_3	<2	-
7	(±)-**67**·TsOH	CH_3, CH_3	<2	-
8	(±)-**67**·HBF_4	CH_3, CH_3	<2	-

[a] isolated yield. [b] Determined by chiral stationary phase HPLC analysis.



Scheme 19. Attempted nitroaldol reaction



Scheme 20. Attempted conjugate addition reaction

3. Conclusion

Enantioenriched 8-azaBINOL and its acid salts contain H-bond donor and acceptor sites in a chiral scaffold and were used to study potential organocatalytic enantioselective transformations. Following literature references of various cinchona-based organocatalysts catalyzing different types of chemical reactions by H-bond activation, a few reactions were chosen and examined. Though no remarkable enantioselectivity was obtained, it was at least a start at considering the application of this new hybrid 8-azaBINOL class of molecules in enantioselective synthesis. Change of solvents did not seem to change the outcome of transformations. Further derivatization of 8-azaBINOL (potentially, introduction of bulky substituents in the quinoline and/or naphthaline ring) could potentially lead to more interesting compounds to examine for organocatalysis.

IID. Inhibition of HIV-1 Entry into TZMBl Cells by Ether and Carbamate Derivatives of 7-Hydroxy-8-(naphth-1-yl)quinoline: A Biological Evaluation of Molecules of the 'azaBINOL' Class

1. Introduction

Numerous ostensibly artificial organic molecules have been introduced as metal ligands and/or organocatalysts for the purpose of facilitating catalytic enantioselective synthesis. The structural features present in such molecules that are necessary for their intended function, e.g., chiral scaffolds with few rotatable bonds, donor sites (atoms with lone pairs), hydrogen-bond acceptors and donors, sites of localized charge density, zones of steric encumbrance, etc., could also lead to meaningful and potentially specific interactions with proteins and other classes of biomolecules. In spite of this fact, comparatively few investigations of the biological activity of libraries of chiral ligands and organocatalysts have taken place. Axially chiral biaryl compounds based on 1,1´-binaphthyl scaffolds are considered a 'priviledged' class of reagents for enantioselective synthesis and the principal member of this group, 1,1´-bi-2-naphthol (BINOL, **38**),[42a] has been found to show modest bioactivity. Nitrogenous analogs of BINOL based on isostructural 8-(naphth-1-yl)quinoline (**67**, '8-azaBINOL')[45] and 8,8'-biquinolyl (**50**, '8,8´-diazaBINOL')[38, 39] core nuclei have been a focus of interest both from a fundamental standpoint[45, 37, 38c] and for potential utility in enantioselective synthesis,[27a, 44] but studies of any aspect of the biological activity of such 'azaBINOLs' have yet to

be reported.[64] Accordingly, and when given that these simple polyfunctional compounds and related structures could conceivably interact with biomolecules in a variety of ways, we set out to screen a library of 'azaBINOL' derivatives in cell viability and HIV-1 entry inhibition assays. Herein, are mentioned, a few significant results of this investigation and our discovery that ether and carbamate derivatives of 2´-desoxy-8-azaBINOL are effective non-cytotoxic inhibitors of HIV-1 entry into TZMBl cells.

2. Results and Discussions

In collaboration with Dr. Sandra Loesgen, a library of compounds of the biquinolyl and the naphthyl quinoline family was tested for viral entry inhibition assays using HIV viruses against TZMBl cells, which is a strain of HeLa cells modified to express the necessary HIV-1 receptors CD4 and CCR5/CXCR4. For pseudovirus production, HEK 293T cells (Human embryonic kidney cells) were used. The MTT cell viability assay is being used to study cytotoxicity/anticancer activities. While the synthesis part of the project was conducted by me, the bioassays were run by Ross Overacker. From the obtained results, compounds in Figure 10 are the compounds of interest. Ethers and carbamates of the naphthyl quinoline rings (e.g. **92**, **93**, **69**, **94**) have the possibility of positioning those functional groups in either the naphthaline or the quinoline ring. Study of biological activities for substituents in each ring could potentially lead to interesting structure-activity relationships. The isopropyl ether of 7-hydroxy-8-(naphth-1-yl)quinoline (**92**) and the analogous *N*,*N*-diethyl carbamate (**69**) exhibited the most significant bioactivity with respective IC_{50} = 4.74 μM and 5.18 μM for inhibition of HIV-1 entry into TZMB1 cells. Comparable 8,8´-diazaBINOLs did not inhibit viral entry. Specific binding of isopropyl ether **92** to purified and immobilized HIV-1 glycoprotein 120 with a K_D = 22 ± 2.9 μM was established using biolayer interferometry.

plate map for azaBINOL library

= compounds of current interest

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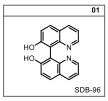
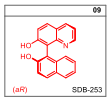
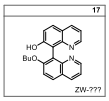
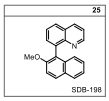
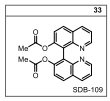
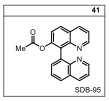
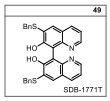
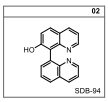
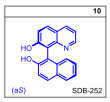
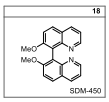
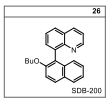
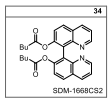
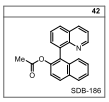
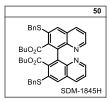
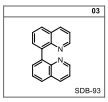
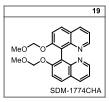
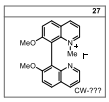
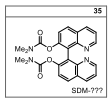
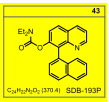
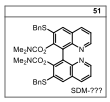
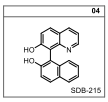
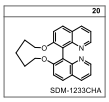
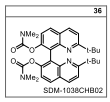
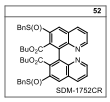
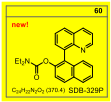
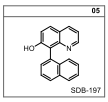
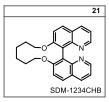
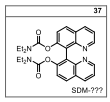
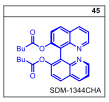
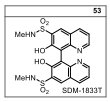
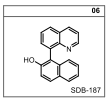
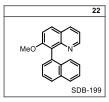
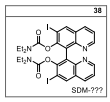
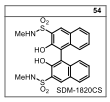
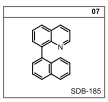
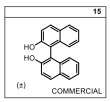
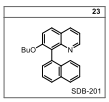
A	01  SDB-96	09  (*aR*) SDB-253	17  ZW-???	25  SDB-198	33  SDB-109	41  SDB-95	49  SDB-1771T	57 new!  $C_{23}H_{18}N_2O$ (314.4) PRB-464
B	02  SDB-94	10  (*aS*) SDB-252	18  SDM-450	26  SDB-200	34  SDM-1668CS2	42  SDB-186	50  SDM-1845H	58 new!  $C_{23}H_{18}N_2O_2$ (314.4) PRB-465
C	03  SDB-93	11 ###-###	19  SDM-1774CHA	27  CW-???	35  SDM-???	43  $C_{24}H_{23}N_3O_2$ (370.4) SDB-193P	51  SDM-???	59 new!  $C_{23}H_{19}NO$ (313.4) SDB-330P
D	04  SDB-215	12 ###-###	20  SDM-1233CHA	28 EMPTY ###-###	36  SDM-1038CHB02	44 EMPTY ###-###	52  SDM-1752CR	60 new!  $C_{23}H_{19}N_3O_2$ (370.4) SDB-329P
E	05  SDB-197	13 ###-###	21  SDM-1234CHB	29 ###-###	37  SDM-???	45  SDM-1344CHA	53  SDM-1833T	61 ###-###
F	06  SDB-187	14 ###-###	22  SDB-199	30 ###-###	38  SDM-???	46 EMPTY ###-###	54  SDM-1820CS	62 ###-###
G	07  SDB-185	15  (±) COMMERCIAL	23  SDB-201	31 ###-###	39 SDB-216	47 EMPTY ###-###	55 SDM-532	63 ###-###
H	08 (–)-(*aS*) COMMERCIAL	16 (+)-(*aR*) COMMERCIAL	24 $C_{23}H_{19}NO$ (313.4) SDB-202P	32 ###-###	40 SDB-194	48 ###-###	56 ZW-???	64 ###-###

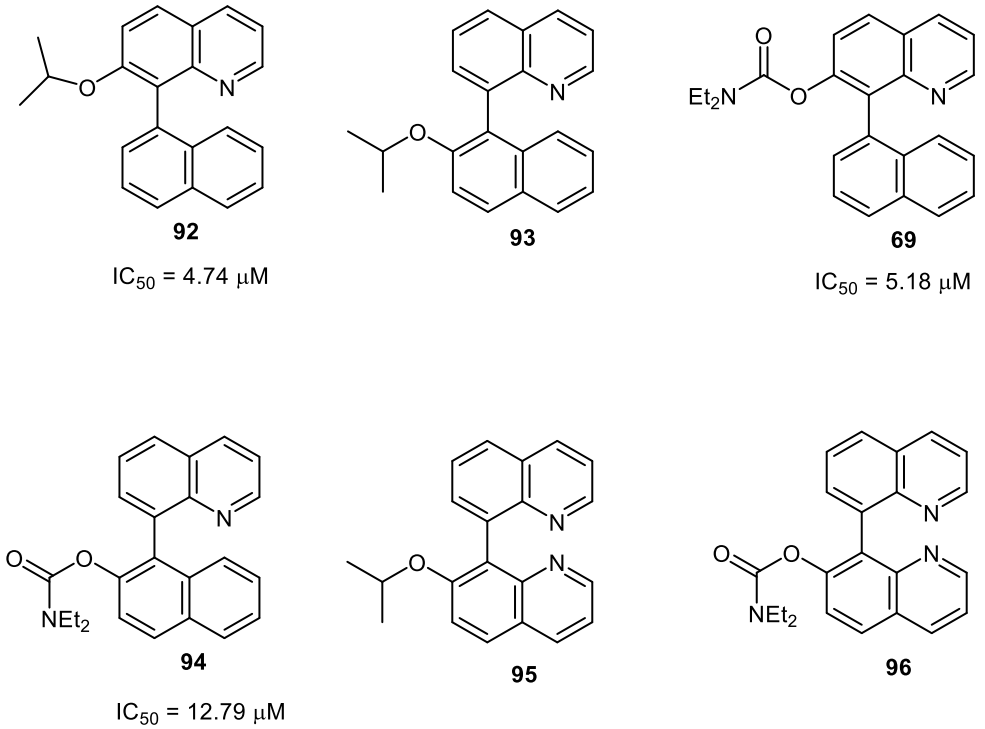


Figure 10. Compounds of interest from viral entry/cell viability assay

3. Conclusion

In summary, it has been discovered that two derivatives of a family of azaanalogs of the archetypal axially chiral biaryl ligand BINOL, inhibit the entry of HIV-1 into TZMBl cells. Furthermore, high affinity binding of these compounds, the isopropyl ether (**92**) and the *N*,*N*-diethyl carbamate (**69**) derivatives of 7-hydroxy-8-(naphth-1-yl)quinoline, to one of the specific proteins responsible for HIV-1 entry was identified. While biaryl compounds of natural origin have long been known to exhibit significant biological activity,[65, 66] this study suggests that further investigations of the bioactivity of artificial biaryls designed purely with synthetic utility in mind, are warranted.

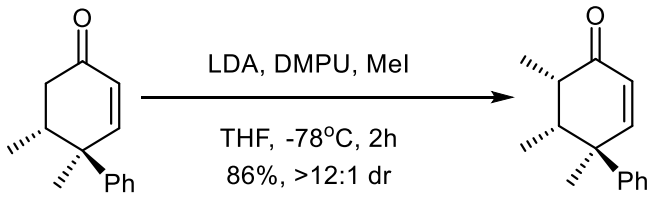
Part III. Experimental Section

1. General experimental conditions

Preparative chromatographic separations were performed on silica gel 60 (35-75 μm) and reactions followed by TLC analysis using silica gel 60 plates (2-25 μm) with fluorescent indicator (254 nm) and visualized by UV or phosphomolybdic acid (PMA). All commercially available reagents were used as received (Aldrich). Anhydrous solvents were obtained from a Pure Process Technologies solvent purification system and dispensed under Ar. Melting points were recorded on a Mel-Temp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Perkin Elmer Spectrum II FT-IR using KBr discs for solids or a thin film between NaCl plates for oils. NMR spectra were recorded on Bruker Avance spectrometers at the field strength specified from 5 mm diameter tubes. Chemical shift in ppm is quoted relative to solvent signals calibrated as follows for $CDCl_3$: δ_H ($CHCl_3$) = 7.26 ppm, δ_C ($CDCl_3$)= 77.2 ppm, and for d_6-acetone: δ_H [$D_3CC(O)CHD_2$] = 2.05 ppm, δ_C [$D_3C(CO)OCD_3$) = 29.8 ppm. Numbers in parentheses following carbon atom chemical shifts refer to the number of attached hydrogen atoms as revealed by the DEPT spectral editing technique. Low (MS) and high resolution (HRMS) mass spectra were obtained using electrospray (ES), electron impact (EI), or chemical ionization (CI) techniques. Ion mass/charge (*m/z*) ratios are reported as values in atomic mass units. Chiral stationary phase (CSP) high performance liquid chromatography (HPLC) was executed on an Agilent 1100 series modular HPLC system equipped with standard Daicel Industries chiral columns as indicated. Circular dichroism (CD) spectra were recorded on a Jasco

J-815 instrument at a scan rate of 100 nm min^{-1} from MeOH solutions in a cell with 1 mm path length.

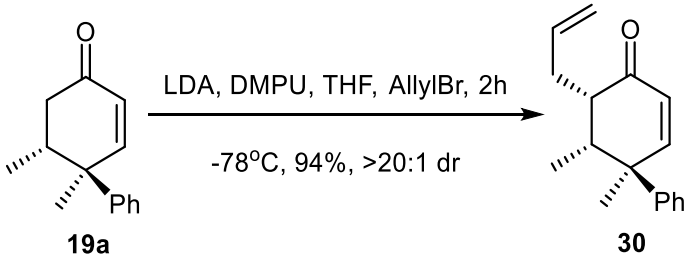
2. Experimental details for results presented in Part I



4,5,6-Trimethyl-4-phenyl-2-cyclohexen-1-one (29): To a solution of **19a** (20 mg, 0.1 mmol) in THF (0.2 mL) at −78 °C was added sequentially LDA§ (0.15 mL, 0.15 mmol, 1.0 M in THF–hexanes) and freshly distilled DMPU (0.05 mL, 0.4 mmol). The reaction was gradually warmed to 0 °C over a period of 20 min. After recooling the system to −78 °C, MeI (182.4 mg, 80 µl, 1.0 mmol) was added. After 2 h, the reaction was quenched with sat. aq. NH_4Cl (0.2 mL), warmed to rt and partitioned between Et_2O (5 mL) and water (5 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layer was dried with anhydrous $MgSO_4$, concentrated in vacuo and purified by chromatography over silica gel eluting with 1–4% of EtOAc–hexanes to give **29** (17 mg, 0.08 mmol, 86%, >20 : 1 dr) as a thick oil: $[\alpha]_D^{23} = -38.0°$; IR (neat) 2971, 2927, 2878, 1712, 1680 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.39 (m, 5H), 6.77 (d, J = 10.0 Hz, 1H), 6.08 (d, J = 10.0 Hz, 1H), 2.35–2.43 (m, 1H), 2.03–2.10 (m, 1H), 1.48 (s, 3H), 1.19 (d, J = 6.8 Hz, 3H), 0.96–1.00 (m, 1H), 0.828 (d, J = 6.8 Hz, 3H); 13C NMR (400 MHz, $CDCl_3$) δ 201.6, 158.2, 146.8, 128.4, 127.0, 126.7, 126.6,

46.5, 44.9, 44.1, 30.9, 16.1, 13.7, 12.1; HRMS (CI+) calcd for C15H18O (M+) 215.1436, found 215.1442.

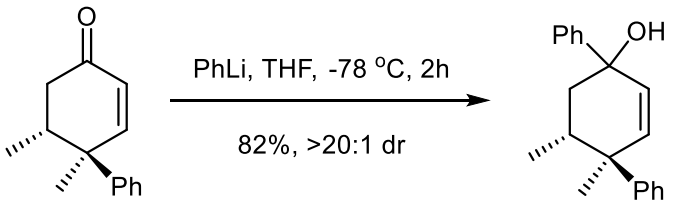
§ Preparation of LDA Solution (1 M in THF–hexanes): To a solution of diisopropylamine (0.607 g, 0.85 mL, 6.0 mmol) in THF (2.63 mL) at −78 °C, was added n-BuLi (2.52 mL, 6.3 mmol, 2.5 M in hexanes). After 5 min, the white slurry was warmed to −10 °C and stirred for 15 min prior to use.



19a **30**

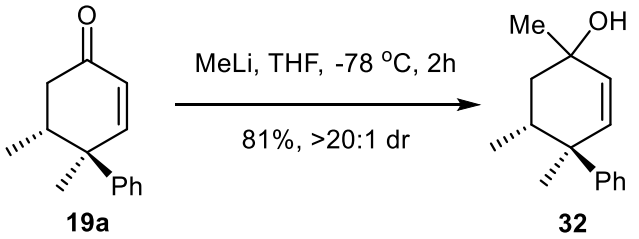
6-Allyl-4,5-dimethyl-4-phenyl-2-cyclohexen-1-one (30): To a solution of **19a** (20 mg, 0.1 mmol) in THF (0.2 mL) at −78 °C was added sequentially LDA§ (0.15 mL, 0.15 mmol, 1.0 M in THF–hexanes) and freshly distilled DMPU (0.05 mL, 0.4 mmol). The reaction was gradually warmed to 0 °C over a period of 20 min. After recooling the system to −78 °C, allyl bromide (125.1 mg, 90 μL, 1.0 mmol) and TBAI (0.37 g, 1.0 mmol) were added. After 2 h, the reaction was then with sat. aq. NH_4Cl (0.2 mL), warmed to rt and partitioned between Et_2O (5 mL) and water (5 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layer was dried with anhydrous $MgSO_4$, concentrated in vacuo and purified by chromatography over silica gel eluting with 1–4% of EtOAc– hexanes to give **30** (0.019 g, 0.08 mmol, 94%, >20 : 1 dr) as a thick oil: $[\alpha]_D^{23}$= −109.1°; IR (neat) 2973, 1675, 761, 702 cm−1; 1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.39 (m, 5H), 6.78 (d, J = 10.0 Hz, 1H), 6.09 (d, J = 10.0

Hz, 1H), 5.68–5.80 (m, 1H), 5.00–5.09 (m, 2H), 2.91–2.95 (m, 1H), 2.43–2.47 (m, 1H), 2.22–2.35 (m, 2H), 1.48 (s, 3H), 0.83 (d, J = 6.8 Hz, 3H); 13C NMR (400 MHz, $CDCl_3$) δ 200.2, 158.48, 146.7, 135.0, 128.4, 127.1, 127.1, 126.7, 117.1 48.43, 44.71, 42.6, 30.1, 16.5, 13.2; HRMS (CI+) calcd for C17H20O (M+) 241.1592, found 241.1584.

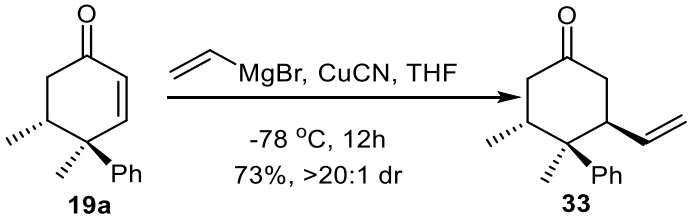


19a **31**

4,5-Dimethyl-1,4-diphenyl-2-cyclohexen-1-ol (31): To a solution of **19a** (20 mg, 0.1 mmol) in THF (0.2 mL) at −78 °C was added PhLi (0.25 mL, 0.4 mmol, 1.7 M in Bu_2O). After 2 h, the reaction was quenched with sat. aq. NH_4Cl (0.2 mL), warmed to rt and partitioned between Et_2O (5 mL) and water (5 mL). The aqueous layer was extracted with Et_2O (3× 5 mL) and the combined organic layer was dried with anhydrous $MgSO_4$, concentrated in vacuo and purified by chromatography over silica gel eluting with 1–4% of EtOAc–hexanes to give **31** (23 mg, 0.08 mmol, 82%, >20 : 1 dr) as a thick oil: $[\alpha]_D^{23}$= −13.8°; IR (neat) 3374, 3085, 3020, 2965, 2867 cm−1; 1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 1.2 Hz, 2H), 7.22–7.46 (m, 8H), 5.93 (d, J = 10.0 Hz, 1H), 5.87 (d, J = 11.2 Hz, 1H), 2.06–2.16 (m, 3H), 1.80–1.86 (m, 1H), 1.42 (s, 3H), 0.70 (d, J = 7.2 Hz, 3H); 13C NMR (400 MHz, $CDCl_3$) δ 148.2, 147.0, 140.1, 130.0, 128.3, 128.1, 127.5, 127.0, 126.3, 126.1, 44.4, 43.6, 37.1, 18.0, 15.8; HRMS (CI+) calcd for C20H22O (M+) 278.1671, found 278.1664.

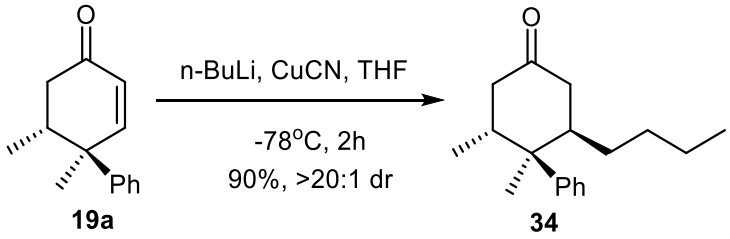


1,4,5-Trimethyl-4-phenyl-2-cyclohexen-1-ol (32): To a solution of **19a** (0.02 g, 0.1 mmol) in THF (0.2 mL) at −78 °C was added MeLi (0.25 mL, 0.4 mmol, 1.6 M in Et_2O). After 2 h, the reaction was quenched with sat. aq. NH_4Cl (0.2 mL), warmed to rt and partitioned between Et_2O (5 mL) and water (5 mL). The aqueous layer was extracted with Et_2O (3× 3.5 mL) and the combined organic layer was dried with anhydrous $MgSO_4$, concentrated in vacuo and purified by chromatography over silica gel eluting with 1–4% of EtOAc–hexanes to give **32** (17 mg, 0.08 mmol, 81%, >20 : 1 dr) as a thick oil: $[\alpha]_D^{23}$= −16.8°; IR (neat) 3281, 3058, 3009, 2971, 2867 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$) δ 7.21–7.35 (m, 5H), 5.68 (d, J = 10.0 Hz, 1H), 5.54 (d, J = 10.0 Hz, 1H), 1.93–1.97 (m, 1H), 1.75 (d, J = 8.0 Hz, 2H), 1.58 (s, 2H), 1.44 (s, 3H), 1.32 (s, 3H), 0.79 (d, J = 6.8 Hz, 3H); 13C NMR (400 MHz, CDCl3) δ 137.5, 132.4, 128.0, 127.0, 125.9, 70.7, 43.9, 43.6, 39.2, 28.8, 17.9, 16.0; HRMS (CI+) calcd for C15H20O (M+) 216.1514, found 216.1511.



3-Vinyl-4,5-dimethyl-4-phenyl-1-cyclohexanone (33): To a suspension of CuCN (18 mg, 0.2 mmol) in THF (0.2 mL) at −78 °C was added vinyl magnesium bromide (0.6

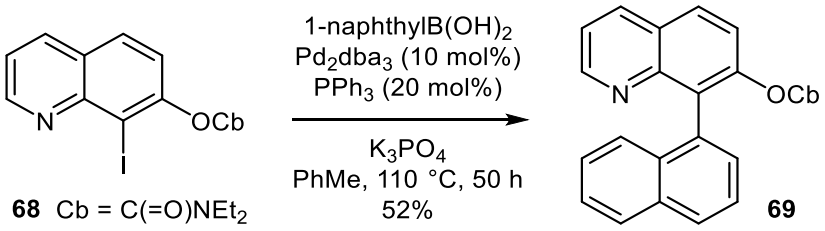
mL, 0.4 mmol, 0.7 M in THF). The reaction mixture was gradually warmed to 0 °C over a period of 30 min. After recooling the system to −78 °C, a solution of **19a** (20 mg, 0.1 mmol) in THF (0.3 mL) was added. After 12 h, the reaction was quenched with sat. aq. NH_4Cl (0.2 mL), warmed to rt and partitioned between Et_2O (5 mL) and water (5 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layer was dried with anhydrous $MgSO_4$, concentrated in vacuo and purified by chromatography over silica gel eluting with 1–4% of EtOAc– hexanes to give **33** (16 mg, 0.07 mmol, 73%, 12 : 1 dr) as a thick oil: $[\alpha]_D^{23}$= −29.5°; IR (neat) 3080, 2971, 1707 cm^{-1}; 1H NMR (400 MHz, CDCl3) δ 7.22–7.35 (m, 5H), 5.39–5.43 (m, 1H), 4.87 (d, J = 10.8 Hz, 1H), 4.72 (d, J = 14.8 Hz, 1H), 2.80–2.86 (m, 2H), 2.65–2.66 (m, 1H), 2.35–2.56 (m, 3H), 1.61 (s, 3H), 0.95 (d, J = 6.4 Hz, 3H); 13C NMR (400 MHz, CDCl3) δ 211.0, 145.6, 137.9, 128.0, 127.1, 126.0, 116.7, 52.4, 45.8, 43.3, 42.3, 32.9, 20.4, 17.0; HRMS (CI+) calcd for C16H20O (M+) 4862



3-Butyl-4,5-dimethyl-4-phenyl-1-cyclohexanone (34): To a suspension of CuCN (30 mg, 0.33 mmol) in THF (0.2 mL), cooled at −78 °C, was added n-BuLi (0.42 mL, 0.67 mmol, 1.6 M in hexanes) and the reaction mixture was gradually warmed to 0 °C. After recooling the system to −78 °C, a solution of **19a** (50 mg, 0.25 mmol) in THF (0.3 mL) was added. After 2 h, the reaction was quenched with sat. aq. NH_4Cl (0.2 mL), warmed to rt and partitioned between Et_2O (5 mL) and water (5 mL). The aqueous layer was

extracted with Et_2O (3 × 5 mL) and the combined organic layer was dried with anhydrous $MgSO_4$, concentrated in vacuo and purified by chromatography over silica gel eluting with 1–4% of EtOAc–hexanes to give 49 (0.060 g, 0.23 mmol, 90%, >20 : 1 dr) as a thick oil: $[\alpha]_D^{23} = -57.8°$; IR (neat) 3085, 3052, 2954, 2873, 1718 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.35 (m, 5H), 2.82–2.85 (m, 1H), 2.72–2.77 (m, 1H), 2.33–2.43 (m, 3H), 1.84–1.86 (m, 1H), 1.56 (s, 3H), 1.02–1.18 (m, 1H), 1.00–1.02 (m, 2H), 0.98 (d, J = 6.4 Hz, 3H), 0.86–0.94 (m, 2H), 0.78–0.86 (m, 1H), 0.66 (t, J = 7.2 Hz, 3H); 13C NMR (400 MHz, $CDCl_3$) δ 211.8, 146.3, 128.0, 127.1, 126.8, 125.8, 49.4, 45.8, 43.5, 41.5, 32.9, 29.7, 28.6, 22.2, 21.0, 17.3, 13.7; HRMS (CI+) calcd for C18H26O (M+) 259.2062, found 259.2070.

3. Experimental details for results presented in Part II



7-(Diethylaminocarbonyloxy)-8-(naphth-1-yl)quinoline (69): A 30 mL thick-walled glass reaction tube equipped with a telfon screw-fitting stopper (a 'sealed tube' apparatus) was opened and charged with a stir bar, 7-(diethylamino-carbonyloxy)-8-iodoquinoline (**68**, 1.00 g, 2.70 mmol)[5a] and anhydrous toluene (15 mL). Stirring was initiated and the suspension treated with naphthalene-1-boronic acid (645 mg, 3.75 mmol) followed by dipalladium tris(dibenzylideneacetone) (230 mg, 0.27 mmol),

triphe-nylphosphine (131 mg, 0.50 mmol), and K_3PO_4 (1.06 g, 5.00 mmol). After purging with Ar, the tube was sealed tightly with its telfon stopper and its contents then heated at 110 °C with stirring for 50 h. After this time, the tube and its contents were allowed to cool to rt and the stopper was cautiously removed. The tube contents were partitioned between EtOAc (30 mL) and H_2O (30 mL) and the aqueous phase was extracted with EtOAc (3x20 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting residue was purified by column chromatography (SiO_2, eluting with 10-30% EtOAc in hexanes) to afford the desired biaryl compound **69** (524 mg, 1.41 mmol, 52%) as a pale yellow solid: mp 103-105 °C (hexane-CH_2Cl_2).

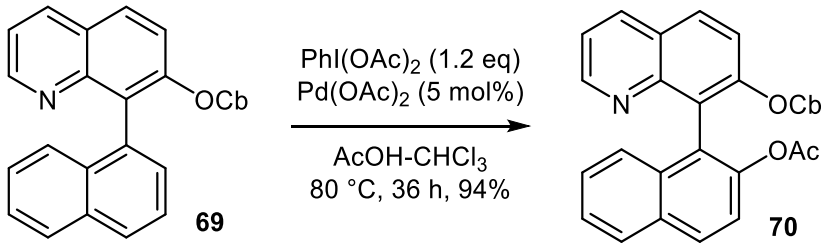
IR (KBr): 3053, 2976, 2932, 1718, 1417, 1267, 1206, 1157, 1057, 993, 783 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 8.82 (d, *J* = 4.0 Hz, 1H), 8.22 (d, *J* = 8.2 Hz, 1H), 7.97-7.89 (m, 3H), 7.67 (d, *J* = 8.9 Hz, 1H), 7.62 (t, *J* = 7.9 Hz, 1H), 7.53 (d, *J* = 7.0 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.40 (d, *J* = 9.0 Hz, 1H), 7.34 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 3.17-3.04 (m, 2H), 2.76-2.65 (m, 1H), 2.65-2.53 (m, 1H), 0.91 (t, *J* = 6.9 Hz, 3H), 0.40 (t, *J* = 6.8 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.6 (0), 150.8 (1), 150.3 (0), 148.2 (0), 136.1 (1), 133.7 (0), 133.0 (0), 132.8 (0), 130.6 (0), 128.4 (1), 128.3 (1), 128.1 (1), 128.0 (1), 126.4 (0), 126.3 (1), 125.8 (1), 125.5 (1), 125.4 (1), 123.5 (1), 120.5 (1), 41.9 (2), 41.3 (2), 13.0 (2C, 3).

MS (ES+): *m/z* (%) = 371 (100, $[M + H^+]$).

HRMS (ES+): *m/z* calcd for $C_{24}H_{23}N_2O_2$: 371.1760; found: 371.1756.



7-(Diethylaminocarbonyloxy)-8-(2-acetoxynaphth-1-yl)quinoline (70): A 5 mL RB flask was charged with a magnetic stir bar, 7-(diethylaminocarbonyloxy)-8-(naphth-1-yl)quinoline (**69**, 40 mg, 0.108 mmol), palladium diacetate (1.5 mg, 0.007 mmol), and (diacetoxyiodo)benzene (39 mg, 0.121 mmol). A blended solvent of AcOH-$CHCl_3$ (1:7, 1.0 mL) was added, a condenser fitted to the flask, and the flask contents stirred at a gentle reflux for 36 h. The solvent was then removed *in vacuo* and the residue purified by column chromatography (SiO_2, eluting with 20-40% EtOAc in hexanes) to yield the desired oxidized product **70** (44 mg, 0.103 mmol, 95%) as a yellow solid: mp 158-160 °C (hexane-CH_2Cl_2).

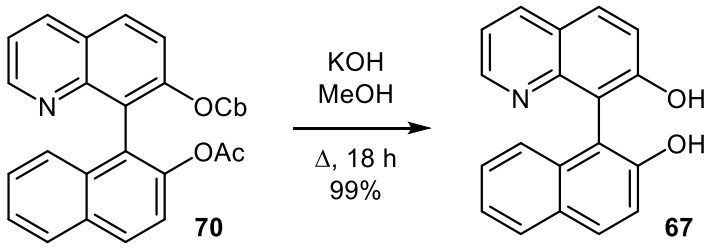
IR (KBr): 3061, 2970, 2929, 1764, 1717, 1418, 1247, 1199, 1154, 991, 757 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.83 (d, *J* = 2.9 Hz, 1H), 8.27 (d, *J* = 8.1 Hz, 1H), 7.97 (d, *J* = 9.1 Hz, 1H), 7.95 (d, *J* = 9.0 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.73 (d, *J* = 8.9 Hz, 1H), 7.45 (d, *J* = 8.9 Hz, 1H), 7.45-7.36 (m, 2H), 7.32-7.28 (m, 2H), 3.15 (dq, *J* = 13.8, 7.0 Hz, 1H), 3.05 (dq, *J* = 13.9, 7.0 Hz, 1H), 2.73-2.60 (m, 2H), 1.76 (s, 3H), 0.92 (t, *J* = 7.1 Hz, 3H), 0.37 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2 (0), 153.2 (0), 150.8 (1), 146.9 (0), 136.7 (1), 133.6 (0), 131.8 (0), 129.4 (1), 128.7 (1), 128.2 (1), 126.6 (1), 126.2 (1), 126.1 (0), 125.5 (1), 125.1 (0), 123.9 (1), 123.7 (0), 122.1 (1), 120.7 (1), 42.1 (2), 41.5 (2), 20.8 (3), 13.1 (2C, 3) [x2 quaternary carbons not distinguishable].

MS (ES+): *m/z* (%) = 429 (100, [M + H^+]).

HRMS (ES+): *m/z* calcd for $C_{26}H_{25}N_2O_4$: 429.1814; found: 429.1808.



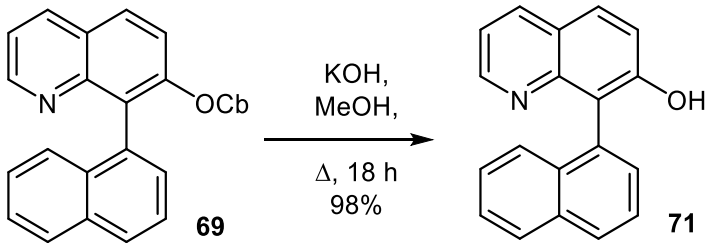
7-Hydroxy-8-(2-hydroxynaphth-1-yl)quinoline (67): A 10 mL RB flask equipped with a reflux condenser was charged with a magnetic stir bar and 7-(diethylamino-carbonyloxy)-8-(2-acetoxynaphth-1-yl)quinoline (**70**, 218 mg, 0.509 mmol). 10% w/v. KOH in MeOH (5 mL) was then added and the flask contents stirred at a gentle reflux for 18 h. After being allowed to cool, the solvent was removed *in vacuo*, the residue dissolved in H_2O (5 mL), and the pH of the solution adjusted to ca. 7.0 by careful dropwise addition of conc. aq. HCl. The neutralized aqueous phase was extracted with EtOAc (5x10 mL) and the combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluting with 40-60% EtOAc in hexanes) to afford 8-azaBINOL (**67**, 146 mg, 0.508 mmol, 99%) as a yellow solid: mp 212-214 °C (TBME).

IR (KBr): 3250 (br), 2927, 2856, 1621, 1499, 1427, 1316, 1142 748 cm^{-1}.

^{1}H NMR (700 MHz, d_6-acetone): δ = 8.54 (dd, *J* = 4.1, 1.8 Hz, 1H), 8.28 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.96 (d, *J* = 8.9 Hz, 1H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.43 (d, *J* = 8.9 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 1H), 7.28 (dd, *J* = 8.1, 4.1 Hz, 1H), 7.24 (ddd, *J* = 8.0, 6.7, 1.2 Hz, 1H), 7.18 (ddd, *J* = 8.3, 6.7, 1.3 Hz, 1H), 7.07 (d, *J* = 8.5 Hz, 1H).

^{13}C NMR (175 MHz, d_6-acetone): δ = 157.6 (0), 154.3 (0), 150.8 (1), 150.0 (0), 136.7 (1), 135.6 (0), 130.1 (1), 130.0 (1), 129.9 (0), 128.7 (1), 126.5 (1), 125.6 (1), 124.3 (0), 123.2 (1), 120.2 (1), 119.6 (1) 119.2 (1), 117.1 (0), 115.5 (0).

MS (ES+): *m/z* (%) = 288 (100, [M + H^+]). HRMS (ES+): *m/z* calcd for $C_{19}H_{14}NO_2$: 288.1025; found: 288.1017.



69 **71**

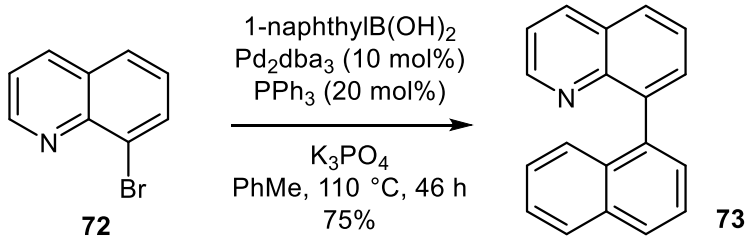
7-Hydroxy-8-(naphth-1-yl)quinoline (71): A 25 mL RB flask equipped with a reflux condenser was charged with a magnetic stir bar and 7-(diethylamino-carbonyloxy)-8-(naphth-1-yl)quinoline (**69**, 334 mg, 0.902 mmol). 10% w/v. KOH in MeOH (9 mL) was then added and the flask contents stirred at a gentle reflux for 18 h. After being allowed to cool, the solvent was removed *in vacuo*, the residue dissolved in H_2O (10 mL), and the pH of the solution adjusted to ca. 7.0 by careful dropwise addition of conc. aq. HCl. The neutralized aqueous phase was extracted with EtOAc (3x10 mL) and the combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluting with 20-40% EtOAc in hexanes) to afford the title quinol **71** (241 mg, 0.888 mmol, 98%) as a yellow solid: mp 123-125 °C (TBME).

IR (KBr): 3053, 2923, 1621, 1595, 1498, 1427, 1376, 1316, 1286, 1216, 774 cm^{-1}.

^{1}H NMR (400 MHz, d_6-acetone): δ = 8.53 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.33 (dd, *J* = 8.2, 1.8 Hz, 1H), 8.01 (d, *J* = 7.4 Hz, 1H), 7.97-7.93 (m, 2H), 7.60 (dd, *J* = 8.2, 7.1 Hz, 1H), 7.52 (d, *J* = 8.9 Hz, 1H), 7.48-7.43 (m, 2H), 7.32-7.25 (m, 3H).

^{13}C NMR (175 MHz, d_6-acetone): δ = 156.4 (0), 150.9 (1), 149.9 (0), 136.4 (1), 134.81 (0), 134.77 (0), 134.3 (0), 129.9 (1), 129.8 (1), 128.9 (1), 128.3 (1), 127.1 (1), 126.4 (1), 126.19 (1), 126.15 (1), 123.9 (0), 122.2 (0), 119.9 (1), 119.2 (1).

HRMS (ES+): *m/z* calcd for $C_{19}H_{14}NO$: 272.1075; found: 272.1088.



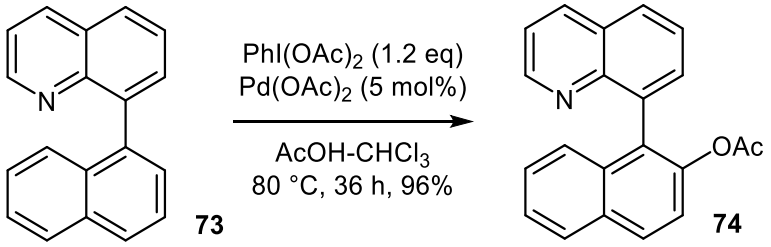
8-(Naphth-1-yl)quinoline (73): A 30 mL thick-walled glass reaction tube equipped with a telfon screw-fitting stopper (a 'sealed tube' apparatus) was opened and charged with a stir bar, 8-bromo-quinoline (853 mg, 4.09 mmol) and anhydrous toluene (18 mL). Stirring was initiated and the suspension treated with naphthalene-1-boronic acid (1.05 g, 6.11 mmol) followed by dipalladium tris(dibenzylideneacetone) (366 mg, 0.430 mmol), triphenylphosphine (210 mg, 0.802 mmol), and K_3PO_4 (1.74 g, 8.21 mmol). After purging with Ar, the tube was sealed tightly with its telfon stopper and its contents then heated at 110 °C with stirring for 46 h. After this time, the tube and its contents were allowed to cool to rt and the stopper was cautiously removed. The tube contents were partitioned between EtOAc (30 mL) and H_2O (30 mL) and the aqueous phase was extracted with EtOAc (3x20 mL). The combined organic phases were

washed with brine (20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting residue was purified by column chromatography (SiO_2, eluting with 20% EtOAc in hexanes) to afford the title biaryl compound **73** (787 mg, 3.08 mmol, 75%) as a yellow solid: mp 143-145 °C (hexane-CH_2Cl_2). ^1H and ^{13}C NMR spectral data in agreement with those reported previously.[21]

IR (KBr): 3042, 2920, 1592, 1490, 1377, 1016, 943, 838 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.84 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.26 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.98-7.92 (m, 3H), 7.76 (dd, *J* = 7.0, 1.5 Hz, 1H), 7.68 (dd, *J* = 8.0, 7.1 Hz, 1H), 7.63 (t, *J* = 8.1 Hz, 1H), 7.56 (dd, *J* = 7.0, 1.2 Hz, 1H), 7.46 (ddd, *J* = 8.0, 6.8, 1.1 Hz, 1H), 7.42-7.37 (m, 2H), 7.29 (ddd, *J* = 8.1, 6.7, 1.1 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.6 (1), 147.3 (0), 140.3 (0), 138.2 (0), 136.4 (1), 133.8 (0), 133.0 (0), 131.8 (1), 128.6 (0), 128.4 (1), 128.2 (1), 128.1 (1), 128.0 (1), 126.8 (1), 126.3 (1), 125.8 (1), 125.7 (1), 125.5 (1), 121.2 (1).



8-(2-Acetoxynaphth-1-yl)quinoline (74): A 50 mL RB flask was charged with a magnetic stir bar, 8-(naphth-1-yl)quinoline (**73**, 1.08 g, 4.23 mmol), palladium diacetate (47 mg, 0.21 mmol), and (diacetoxy-iodo)benzene (1.60 g, 4.97 mmol). A blended solvent of AcOH-$CHCl_3$ (1:7, 27 mL) was added, a condenser fitted to the flask, and the flask contents stirred at a gentle reflux for 36 h. The solvent was then removed *in vacuo* and the residue purified by column chromatography (SiO_2, eluting

with 0-30% EtOAc in hexanes) to afford the title biaryl compound **74** (1.28 g, 4.08 mmol, 96%) as a pale yellow solid: mp 154-156 °C (hexane-CH_2Cl_2).

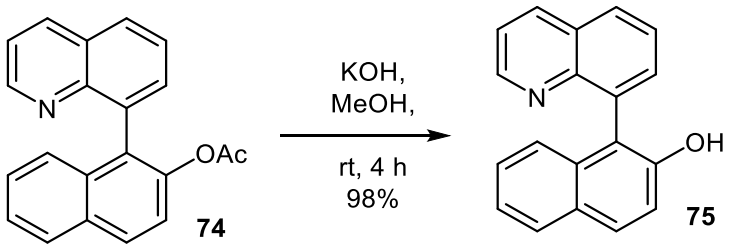
IR (KBr): 3050, 2923, 2851, 1762, 1593, 1499, 1370, 1198, 1013 cm^{-1}.

^1H NMR (700 MHz, $CDCl_3$): δ = 8.84 (br s, 1H), 8.28 (d, *J* = 7.2 Hz, 1H), 7.99 (d, *J* = 8.9 Hz, 1H), 7.97 (dd, *J* = 6.9, 2.5 Hz, 1H), 7.93 (d, *J* = 8.3 Hz, 1H), 7.70-7.66 (m, 2H), 7.45-7.41 (m, 2H), 7.40 (d, *J* = 8.9 Hz, 1H), 7.30-7.25 (m, 2H), 1.77 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$): δ = 169.9, 150.7, 146.3, 133.9, 132.1, 129.7, 128.5 (2C), 128.4, 126.6, 126.4, 125.6 (2C), 121.8, 121.4, 20.7.

MS (ES+): *m/z* (%) = 314 (100, $[M + H^+]$).

HRMS (ES+): *m/z* calcd for $C_{21}H_{16}NO_2$: 314.1181; found: 314.1166.



8-(2-Hydroxynaphth-1-yl)quinoline (75): A 50 mL RB flask was charged with a magnetic stir bar and 8-(2-acetoxynaphth-1-yl)quinoline (**74**, 1.30 g, 4.15 mmol). 10% w/v. KOH in MeOH (12 mL) was then added and the flask contents stirred at rt for 4 h. The solvent was removed *in vacuo*, the residue dissolved in H_2O (10 mL), and the pH of the solution adjusted to ca. 7.0 by careful dropwise addition of conc. aq. HCl. The neutralized aqueous phase was extracted with EtOAc (3x10 mL) and the combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluting with 40%

EtOAc in hexanes) to afford the title naphthol **75** (1.10 g, 4.05 mmol, 98%) as a yellow solid: mp 163-165 °C (TBME).

IR (KBr): 3421, 2929, 1637, 1498, 1345 cm^{-1}.

^1H NMR (700 MHz, d_6-acetone): δ = 8.70 (dd, *J* = 4.0, 1.8 Hz, 1H), 8.44 (dd, *J* = 8.3, 1.8 Hz, 1H), 8.09 (dd, *J* = 7.7, 1.9 Hz, 1H), 8.01 (br s, OH), 7.88 (d, *J* = 8.8 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.78-7.73 (m, 2H), 7.51 (dd, *J* = 8.3, 4.0 Hz, 1H), 7.32 (d, *J* = 8.7 Hz, 1H), 7.26 (ddd, *J* = 7.9, 6.7, 1.1 Hz, 1H), 3.59 (ddd, *J* = 8.1, 6.7, 1.3 Hz, 1H), 7.06 (d, *J* = 8.5 Hz, 1H).

^{13}C NMR (175 MHz, $CDCl_3$): δ = 153.1 (0), 150.9 (1), 148.5 (0), 137.2 (1), 136.7 (0), 135.7 (0), 133.7 (1), 129.7 (1), 129.6 (0), 129.1 (1), 128.6 (1), 127.3 (1), 126.5 (1), 125.8 (1), 123.3 (1), 122.1 (1), 121.1 (0), 119.4 (1) [x1 quaternary carbon not distinguishable].

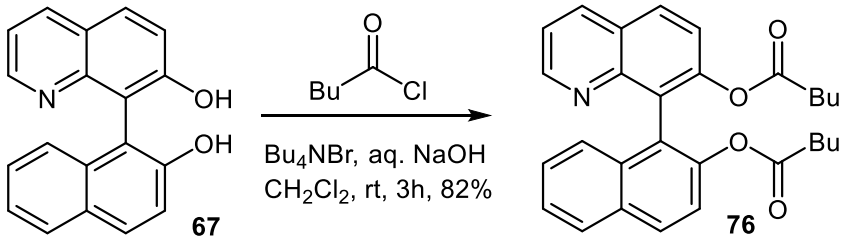
MS (ES+): *m/z* (%) = 272 (100, $[M + H^+]$).

HRMS (ES+): *m/z* calcd for $C_{19}H_{14}NO$: 272.1075; found: 272.1077.

X-ray Diffraction Analysis of (±)-75 (Figure 8): Diffraction intensities were collected at 200(2) K on an Apex 2 CCD diffractometer with MoKα radiation (λ = 0.71073 Å). Space group determination was based on intensity statistics. Absorption correction was applied by SADABS.[22a] The structure was solved by direct methods and Fourier techniques and refined on F^2 using full matrix least-squares procedures. All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were found on the residual density map and refined with isotropic thermal parameters. There are two symmetrically independent molecules in the crystal structure connected

by hydrogen-bonds. All calculations were performed with the SHELXL-2013 packages.[22b]

$C_{19}H_{13}NO$, M = 271.31, 0.27 x 0.21 x 0.14 mm, T = 200(2) K, triclinic, space group *P*-1, a = 9.3146(7) Å, b = 12.5039(10) Å, c = 13.0244(11) Å, α = 101.811(4)°, β = 107.920(4)°, γ = 90.902(3)°, V = 1407.7(2) Å^3, Z = 4, Z' = 2, D_c = 1.271 Mg/m^3, μ(Mo)= 1.526 mm^{-1}, F(000) = 404, $2\theta_{max}$ = 50°, 22359 reflections, 4954 independent reflections [R_{int} = 0.0349], R1 = 0.0408, wR2 = 0.0957 and GOF = 1.024 for 4954 reflections (483 parameters) with I>2σ(I), R1 = 0.672, wR2 = 0.1153 and GOF = 1.024 for all reflections, max/min residual electron density +0.189/-0.182 eÅ^3.



7-(Pentanoyloxy)-8-[2-(pentanoyloxy)naphth-1-yl]quinoline (76): A solution of 8-azaBINOL (**67**, 162 mg, 0.356 mmol) in aq. NaOH (7.5 mL, 3.0 M) was treated with tetra-*n*-butylammonium bromide (97 mg, 0.300 mmol) in CH_2Cl_2 (7.5 mL) followed by neat pentanoyl chloride (360 mg, 2.99 mmol). The resulting biphasic mixture was stirred vigorously for 4 h at rt. After this time, H_2O (8 mL) and CH_2Cl_2 (8 mL) were added and the layers shaken and separated. The aqueous phase was extracted with CH_2Cl_2 (2x8 mL) and the combined organic phases were washed with brine (5 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluting with 20% EtOAc in hexanes) to afford the diester **76** (210 mg, 0.462 mmol, 82%) as a colorless solid: mp 63-65 °C (EtOAc).

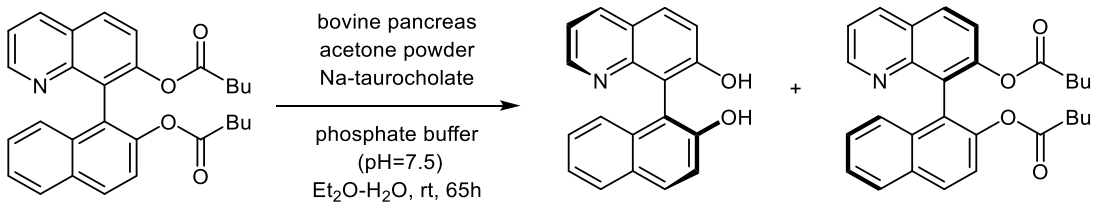
IR (KBr): 3059, 2961, 1762, 1597, 1497, 1356, 983, 834, 808 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.80 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.24 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.00-7.94 (m, 2H), 7.90 (d, *J* = 10.2 Hz, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.45 (d, *J* = 8.9 Hz, 1H), 7.41 (dm, *J* = 8.2 Hz, 1H), 7.39 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.30-7.21 (m, 2H), 2.13-2.00 (m, 4H), 1.20-0.86 (m, 8H), 0.67 (t, *J* = 7.3 Hz, 3H), 0.62 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9 (0), 171.8 (0), 151.1 (1), 150.0 (0), 148.1 (0), 146.7 (0), 136.1 (1), 133.6 (0), 131.7 (0), 129.4 (1), 128.9 (1), 128.2 (1), 126.5 (2C, 0 & 1), 126.2 (1), 126.1 (0), 125.5 (1), 123.3 (0), 123.1 (1), 122.0 (1), 121.0 (1), 34.0 (2), 33.9 (2), 26.7 (2), 26.6 (2), 22.0 (2), 21.9 (2), 13.7 (3), 13.7 (3).

MS (ES+): *m/z* (%) = 456 (100, [M + H^+]).

HRMS (ES+): *m/z* calcd for $C_{29}H_{30}NO_4$: 456.2175; found: 456.2177.



76 (–)-(*aS*)-**67**, 46%, 99% ee (+)-(*aR*)-**76**, 51%, 90% ee

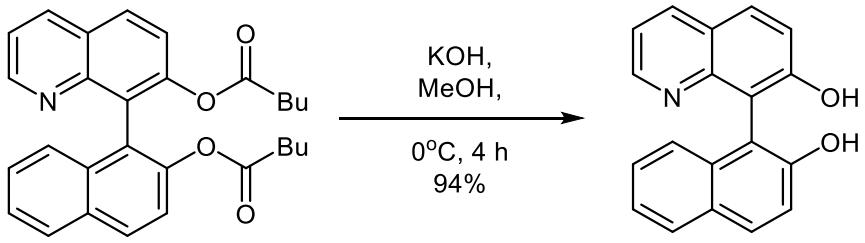
Hydrolytic enzymatic resolution of diester (±)-9; (–)-(*aS*)-7-hydroxy-8-(2-hydroxynaphth-1-yl)quinoline (2) and (+)-(*aR*)-7-(pentanoyloxy)-8-[2-(pentanoyl-oxy)naphth-1-yl]quinoline (9): Adapted from the resolution of the dipentanoate of **50**[11] and based on the procedure of Kazlauskas.[12] A 50 mL RB-flask equipped with a magnetic stir bar was charged with diester (±)-**76** (82 mg, 0.180 mmol), Et_2O (7 mL), aq. pH 7.5 phosphate buffer (7 mL, 0.1 M), and sodium taurocholate emulsifier (20

mg). Bovine pancreas acetone powder (25 mg) was added and the contents of the then sealed flask stirred vigorously for 65 h at rt. The resulting yellow mixture was de-emulsified with EtOH (1 mL), EtOAc (15 mL) added, and the layers well shaken and separated. The aqueous phase was extracted with EtOAc (3x15 mL) and the combined organic extracts washed with brine (15 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatograpy (eluting with 10-100% EtOAc in hexanes) to give (+)-(*aR*)-**76** (42 mg, 0.092 mmol, 51%, 90% ee) as a pale yellow solid followed by (–)-(*aS*)-azaBINOL (**67**, 24 mg, 0.084 mmol, 46%, 99% ee) as a pale yellow solid. Enantiomeric excess (%ee) for diester (+)-(*aR*)-**76** was determined by CSP HPLC analysis; %ee for diol (–)-(*aS*)-**67** was determined indirectly by its conversion to diester (–)-(*aS*)-**76** using the Scotten-Baum protocol shown above, followed by CSP HPLC analysis.

CSP HPLC analysis of the samples of diester **76** was performed with a Daicel Chiralcel® OD-H column (4.6 mm ID x 250 mm), eluting with 0.3% *i*-PrOH in hexanes at 0.5 mL min^{-1} and monitored by UV at 210 nm. An authentic sample of the racemic diester **76** showed resolved peaks: $t_{ret.}$ [(+)-(*aR*)] = 43.4 min, $t_{ret.}$ [(–)-(*aS*)] = 51.9 min (see Figure S6 in the Supporting Information for chromatogram).

(–)-(*aS*)-**67**: $[\alpha]_D^{24°C} = -142$ (c = 0.10, acetone, 99% ee)

(+)-(*aR*)-**76**: $[\alpha]_D^{24°C} = +173$ (c = 0.12, $CHCl_3$, 90% ee)



76 **67**

Non-racemizing saponification of diester 76: A sample of (–)-(*aS*)-diester **76** (15 mg, 0.033 mmol, 99% ee) was dissolved in 10 wt.% methanolic KOH (2 mL) and the solution stirred at 0 °C for 4 h. After this time, the resulting yellow reaction mixture was concentrated *in vacuo*. The residue was dissolved in H_2O (3 mL) and the alkaline solution neutralized by careful addition of 1.5 M aq. HCl. The neutral aqueous phase was extracted with EtOAc (4x3 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluting with 40-60% EtOAc in hexanes) to afford the pure diol (–)-(*aS*)-**67** (9 mg, 0.031 mmol, 94%) as a pale yellow solid: $[\alpha]_D^{24°C} = –139$ (c = 0.15, acetone, ≥ 97% ee).

6.3 Determination of Enantiomerization Rate Constants for 1-3 in DMSO

Derivation of first order rate law for enantiomerization: *Enantiomerization* is the conversion of a compound into its enantiomer. For a spontaneous enantiomerization process (i.e., one not mediated by a chiral reagent/catalyst), the rate constant, k, for the conversion of the (a*S*)-atropisomer into the (a*R*)-atropisomer is necessarily identical to that for the reverse reaction.

let, k = enantiomerization rate constant [S] = mole fraction of (*aS*)-isomer [R] = mole fraction of (*aR*)-isomer

then, $[S] + [R] = 1$

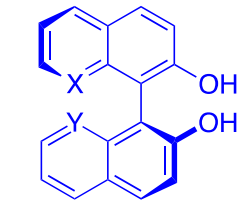
and, $$\frac{d[S]}{dt} = -k[S] + k[R] = -2k[S] + k$$

$$\Longrightarrow \int_{S_0}^{S_t} \frac{1}{-2k[S] + k}\, d[S] = \int_0^t 1\, dt$$

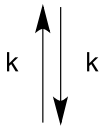
$$\Longrightarrow \left[\frac{1}{-2k} \ln\left(-2k[S] + k\right) \right]_{S_0}^{S_t} = \left[t \right]_0^t$$

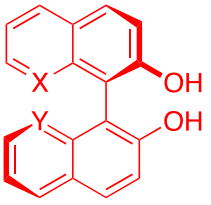
$$\Longrightarrow \ln\left(-2k[S_0] + k\right) - \ln\left(-2k[S_t] + k\right) = 2kt$$

$$\Longrightarrow \ln\left(\frac{1 - 2[S_0]}{1 - 2[S_t]}\right) = 2kt \Longrightarrow \boxed{\ln\left(\frac{\%ee_0}{\%ee_t}\right) = 2kt}$$



(*aS*)-**1** X = Y = N
(*aS*)-**2** X = N, Y = CH
(*aS*)-**3** X = Y = CH





(*aR*)-**1** X = Y = N
(*aR*)-**2** X = N, Y = CH
(*aR*)-**3** X = Y = CH

Determination of enantiomerization rate constants for 7,7′-dihydroxy-8,8′-biquinolyl (1) in DMSO: A magnetically stirred solution of enantioenriched 7, 7′-dihydroxy-8,8′- biquinolyl (**1**, 5.0 mg, 0.0174 mmol)[1] in DMSO (5 mL), residing in a 10 mL pear-shaped two-neck RB-flask equipped with thermometer and condenser, was immersed in an isothermal bath. Once the internal temperature of the solution had reached a steady value, an aliquot (0.1 mL) was removed and the diol converted to its dipentanoate ester (see below) for indirect determination of %ee: this value constituted $\%ee_0$ (i.e., %ee at time t = 0 sec). The solution was then allowed to incubate

in the isothermal bath and 0.1 mL aliquots removed at regular intervals and analyzed as before to obtain %ee as a function of time (see Figures S2-S5 below).

Aliquot processing and CSP HPLC analysis: Immediately following its removal, the sampled aliquot (0.1 mL) was injected into a vigorously stirred biphasic mixture of valeryl chloride (0.025 mL, d = 1.016, 25.4 mg, 0.211 mmol) in tetrabutylammonium bromide solution (TBAB, 0.5 mL, 0.062 M in CH_2Cl_2) and aq. NaOH (0.5 mL, 3 M) at rt. After 10 min, H_2O (4 mL) and CH_2Cl_2 (4 mL) were added and the layers well shaken and separated. The organic layer was concentrated *in vacuo* and the residue was dissolved in Et_2O (4 ml). The Et_2O layer was washed with H_2O (3x4 mL), dried (Na_2SO_4), and concentrated *in vacuo* to afford the dipentanoate ester now free from traces of DMSO (which if present leads to poor CSP HPLC resolution).

To determine %ee, chiral stationary phase (CSP) HPLC analysis of the diester sample was performed with a Daicel Chiralcel® OD column (4.6 mm ID x 250 mm), eluting with 10% *i*-PrOH in hexanes at 1.0 mL min^{-1} and monitored by UV at 210 nm. An authentic sample of the racemic diester showed resolved peaks: $t_{ret.}$ [(+)-(*R*)] = 18.5 min, $t_{ret.}$ [(–)-(*S*)] = 24.9 min (Figure S1)

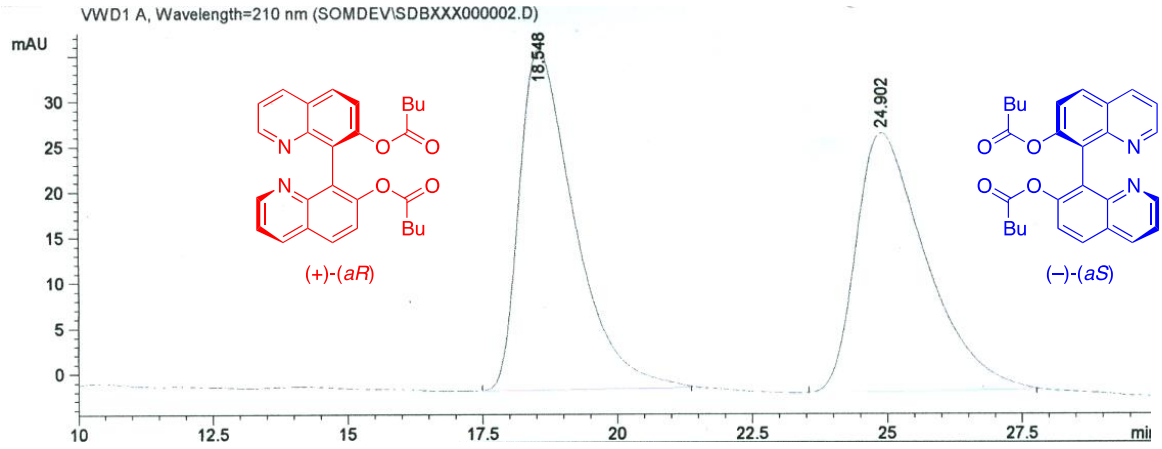


*Figure S1. Resolution of (±)-7,7′-di(pentanoyloxy)-8,8′-biquinolyl (diester of **1**) via CSP HPLC.*

t (sec)	%ee	ln (%ee$_0$ / %ee$_t$)
0	55.6	0
12840	51.6	0.07466153
38460	42.8	0.2616451
74820	35.6	0.44583756
128160	25.2	0.79133921
185520	18.6	1.09502162
245640	15.6	1.27091229

slope = 5.36755 x 10^{-6}; R^2 = 0.994

k (313 K) = 26.8378 x 10^{-7} s^{-1}

7,7′-dihydroxy-8,8′-biquinolyl (1)

T = 313 K (40 °C) in DMSO

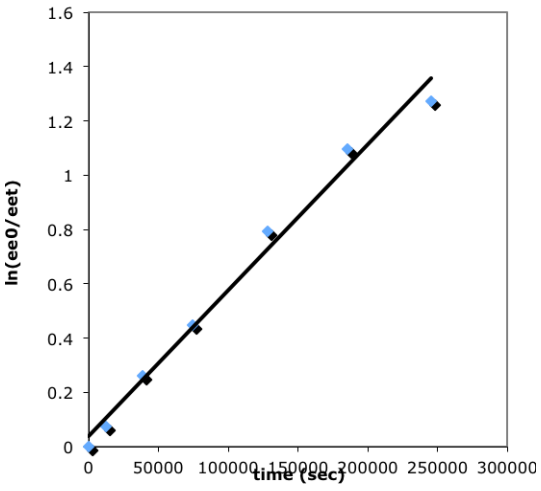


*Figure S2. Determination of enantiomerization rate constant for 7,7′-dihydroxy-8,8′-biquinolyl (**1**) at 313 K (40 °C) in DMSO.*

t (sec)	%ee	ln (%ee$_0$ / %ee$_t$)
0	59.6	0
1680	55.8	0.0658817
5880	49.2	0.19176195
9540	43.4	0.31719613
13200	38.6	0.4344033
28380	22.0	0.99661312
40860	15.2	1.36636015

slope = 3.38867 x 10^{-5}; R^2 = 0.999

k (324 K) = 169.433 x 10^{-7} s^{-1}

7,7′-dihydroxy-8,8′-biquinolyl (1)

T = 324 K (51 °C) in DMSO

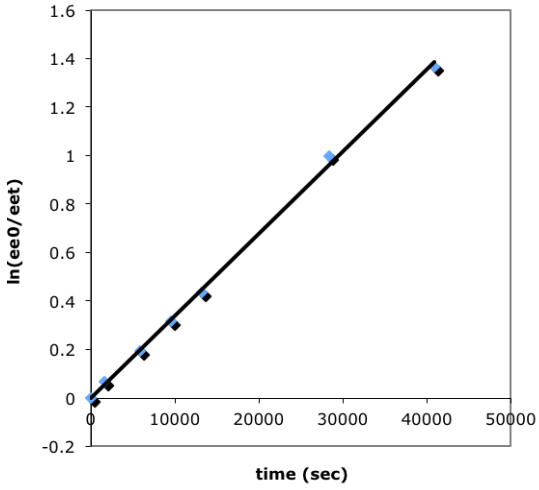


*Figure S3. Determination of enantiomerization rate constant for 7,7′-dihydroxy-8,8′-biquinolyl (**1**) at 324 K (51 °C) in DMSO.*

t (sec)	%ee	ln (%ee$_0$ / %ee$_t$)
0	49.6	0
2760	29.6	0.51621647
4680	22.8	0.7772303
6180	18.2	1.00256924
7680	16.4	1.1067095
9840	10.6	1.54313683

slope = 1.49798 x 10^{-4}; R^2 = 0.994

k (334 K) = 748.988 x 10^{-7} s^{-1}

7,7′-dihydroxy-8,8′-biquinolyl (1)

T = 334 K (61 °C) in DMSO

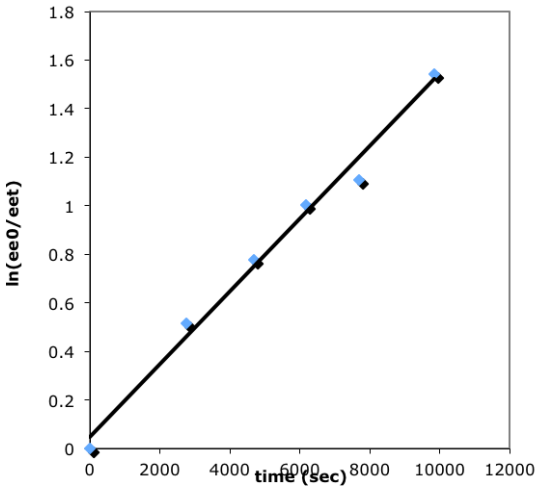


*Figure S4. Determination of enantiomerization rate constant for 7,7′-dihydroxy-8,8′-biquinolyl (**1**) at 334 K (61 °C) in DMSO.*

t (sec)	%ee	ln (%ee$_0$ / %ee$_t$)
0	58.0	0
4500	26.0	0.80234647
9300	7.4	2.05896301
10500	6.0	2.2686354
13500	3.4	2.83666758

slope = 2.17209 x 10^{-4}; R^2 = 0.997

k (342 K) = 1086.05 x 10^{-7} s^{-1}

7,7′-dihydroxy-8,8′-biquinolyl (1)

T = 342 K (69 °C) in DMSO

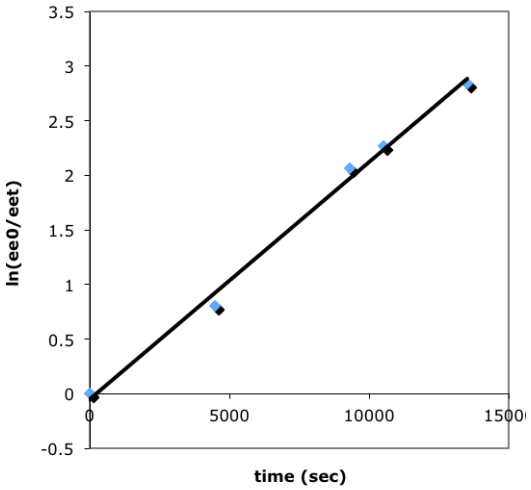


*Figure S5. Determination of enantiomerization rate constant for 7,7′-dihydroxy-8,8′-biquinolyl (**1**) at 342 K (69 °C) in DMSO.*

Determination of enantiomerization rate constants for 7-hydroxy-8-(2-hydroxynaphth-1-yl)quinoline (2) in DMSO: A magnetically stirred solution of enantioenriched 8-(2-hydroxynaphth-1-yl)quin-oline (**2**, 5.0 mg, 0.0174 mmol) in DMSO (5 mL), residing in a 10 mL pear-shaped two-neck RB-flask equipped with thermometer and condenser, was immersed in an isothermal bath. Once the internal temperature of the solution had reached a steady value, an aliquot (0.1 mL) was removed and the diol **2** converted to its dipentanoate ester **9** (see below) for indirect determination of %ee: this value constituted %ee$_0$ (i.e., %ee at time t = 0 sec). The solution was then allowed to incubate in the isothermal bath and 0.1 mL aliquots

removed at regular intervals and analyzed as before to obtain %ee as a function of time (see Figures S7-S10 below).

Aliquot processing and CSP HPLC analysis: Immediately following its removal, the sampled aliquot (0.1 mL) was injected into a vigorously stirred biphasic mixture of valeryl chloride (0.025 mL, d = 1.016, 25.4 mg, 0.211 mmol) in tetrabutylammonium bromide solution (TBAB, 0.5 mL, 0.062 M in CH_2Cl_2) and aq. NaOH (0.5 mL, 3 M) at rt. After 10 min, H_2O (4 mL) and CH_2Cl_2 (4 mL) were added and the layers well shaken and separated. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to afford a sample of diester **9** suitable for CSP HPLC.

To determine %ee, chiral stationary phase (CSP) HPLC analysis of the diester sample was performed with a Daicel Chiralcel® OD-H column (4.6 mm ID x 250 mm), eluting with 0.5% *i*-PrOH in hexanes at 0.5 mL min^{-1} and monitored by UV at 210 nm. An authentic sample of the racemic diester (±)-**9** showed resolved peaks: $t_{ret.}$ [(+)-(*R*)-**9**] = 43.4 min, $t_{ret.}$ [(–)-(*S*)-**9**] = 51.9 min (Figure S6).

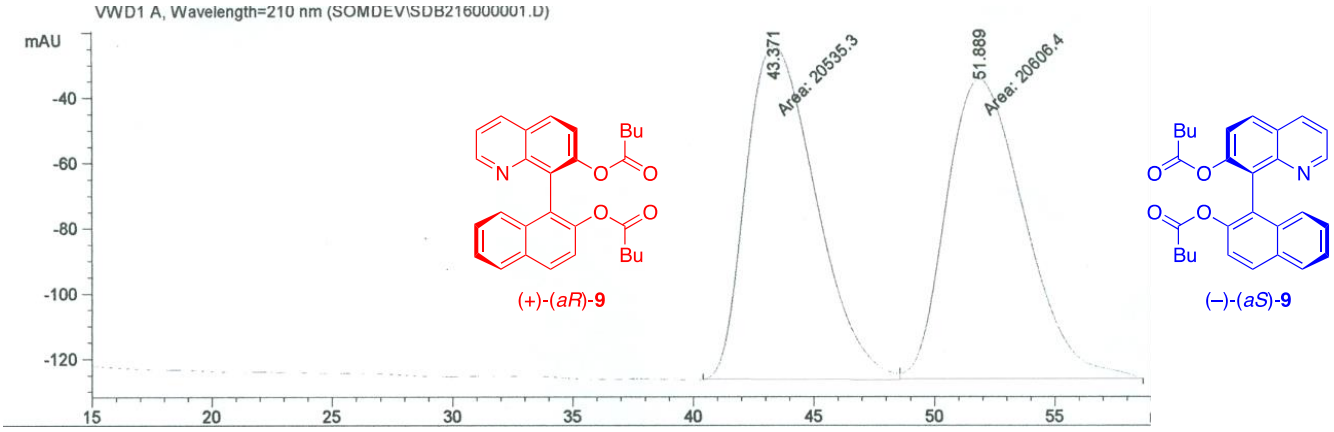


*Figure S6. Resolution of (±)-7-(pentanoyloxy)-8-[2-(pentanoyloxy)naphth-1-yl]quinoline (**9**) via CSP HPLC.*

t (sec)	%ee	ln (%ee$_0$ / %ee$_t$)
0	99.5	0
10800	98.4	0.01091913
42840	84.3	0.16491733
59940	78.6	0.23566506
82152	70.9	0.33852563
101340	70.3	0.34702546
135828	53.3	0.6246572
157716	49.7	0.69465661
215928	34.8	1.0511877
slope = 4.84491×10^{-6}; $R^2 = 0.992$		
k (353 K) = 24.2246×10^{-7} s^{-1}		

7-hydroxy-8-(2-hydroxynaphth-1-yl)quinoline (2); T = 353 K (80 °C) in DMSO

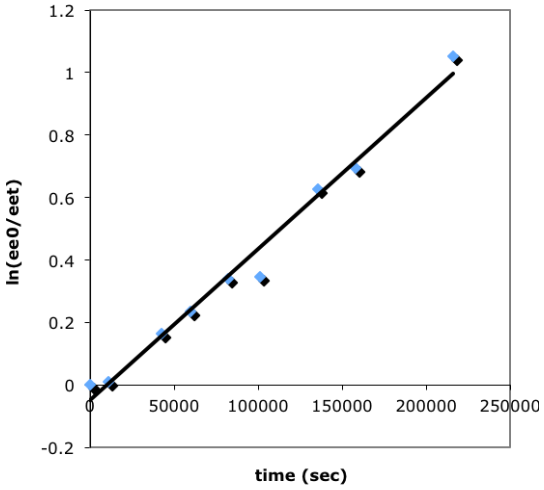


*Figure S7. Determination of enantiomerization rate constant for 7-hydroxy-8-(2-hydroxynaphth-1-yl)quinoline (**2**) at 353 K (80 °C) in DMSO.*

t (sec)	%ee	ln (%ee$_0$ / %ee$_t$)
0	43.0	0
2700	38.8	0.10264786
5400	38.0	0.1266133
10800	30.8	0.33252196
22500	23.1	0.62150358
33600	16.1	0.9843278

slope = 2.88544 x 10^{-5}; R^2 = 0.998

k (334 K) = 144.27 x 10^{-7} s^{-1}

7-hydroxy-8-(2-hydroxynaphth-1-yl)quinoline (2); T = 370 K (97 °C) in DMSO

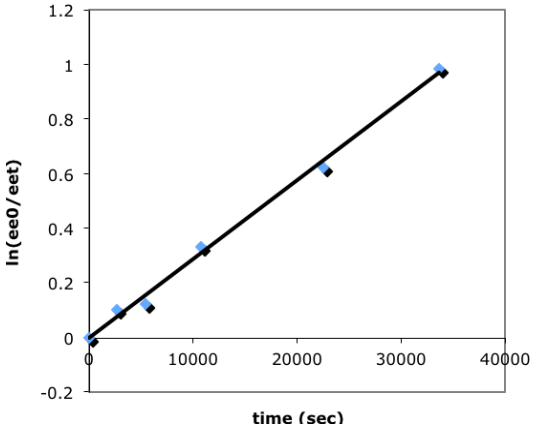


*Figure S8. Determination of enantiomerization rate constant for 7-hydroxy-8-(2-hydroxynaphth-1-yl)quinoline (**2**) at 370 K (97 °C) in DMSO.*

t (sec)	%ee	ln (%ee$_0$ / %ee$_t$)
0	99.5	0
3000	92.0	0.07743174
4500	91.1	0.08813638
6300	79.8	0.22075826
7800	73.4	0.30345863
9300	65.3	0.42035674
16500	41.0	0.8853515
24300	31.0	1.16502285
27900	28.0	1.2685225

slope = 4.97781 x 10^{-5}; R^2 = 0.992

k (381 K) = 248.89 x 10^{-7} s^{-1}

7-hydroxy-8-(2-hydroxynaphth-1-yl)quinoline (2); T = 381 K (108 °C) in DMSO

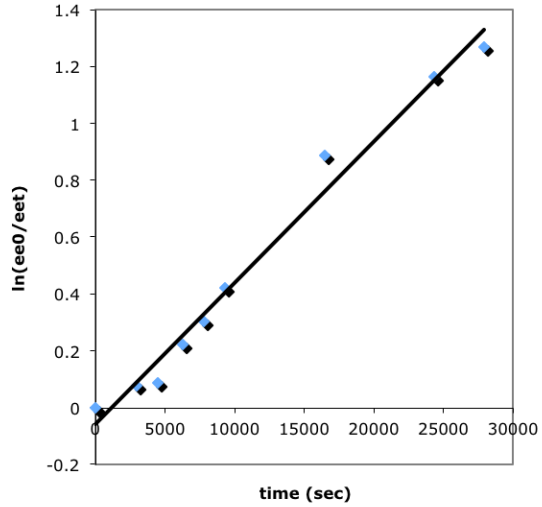


*Figure S9. Determination of enantiomerization rate constant for 7-hydroxy-8-(2-hydroxynaphth-1-yl)quinoline (**2**) at 381 K (108 °C) in DMSO.*

t (sec)	%ee	ln (%ee$_0$ / %ee$_t$)
0	87.1	0
600	84.1	0.03491918
1200	80.3	0.08175618
2400	71.6	0.19588728
4500	54.8	0.46371106
5400	47.2	0.61385518

slope = 1.14282 x 10^{-4}; R^2 = 0.992

k (395 K) = 571.41 x 10^{-7} s^{-1}

7-hydroxy-8-(2-hydroxynaphth-1-yl)quinoline (2); T = 395 K (122 °C) in DMSO

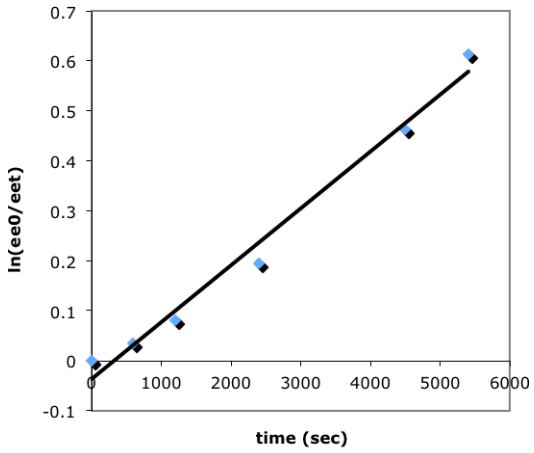


*Figure S10. Determination of enantiomerization rate constant for 7-hydroxy-8-(2-hydroxynaphth-1-yl)quinoline (**2**) at 395 K (122 °C) in DMSO.*

Determination of enantiomerization rate constants for 1,1′-bi-2-naphthol (3) in DMSO: A magnetically stirred solution of enantioenriched 1,1′-bi-2-naphthol (**3**, 10.0 mg, 0.0350 mmol) in DMSO (5 mL), residing in a 10 mL pear-shaped two-neck RB-flask equipped with thermometer and condenser, was immersed in an isothermal bath. Once the internal temperature of the solution had reached a steady value, an aliquot (0.1 mL) was removed and diluted with Et_2O (4 mL). The diluted aliquot was washed with H_2O (3x4 mL), dried (Na_2SO_4), and concentrated *in vacuo* to afford a sample of **3** free from residual DMSO and suitable for %ee determination by CSP HPLC (see below): this value constituted %ee$_0$ (i.e., %ee at time t = 0 sec). The DMSO solution was allowed to incubate in the isothermal bath and 0.1 mL aliquots removed at regular intervals and the aliquots processed and analyzed as before to obtain %ee as a function of time (see Figures S12-S15 below). To determine %ee, chiral stationary phase (CSP)

HPLC analysis of the BINOL (**3**) samples was performed with a Daicel Chiralcel® OJ column (4.6 mm ID x 250 mm), eluting with 10% *i*-PrOH in hexanes at 1.0 mL min^{-1} and monitored by UV at 210 nm. An authentic sample of non-enantiomerically pure (–)-(*aS*)-BINOL with 20%ee showed resolved peaks: $t_{ret.}$ [(+)-(*R*)-**3**] = 31.1 min, $t_{ret.}$ [(–)-(*S*)-**3**] = 41.2 min (Figure S11).

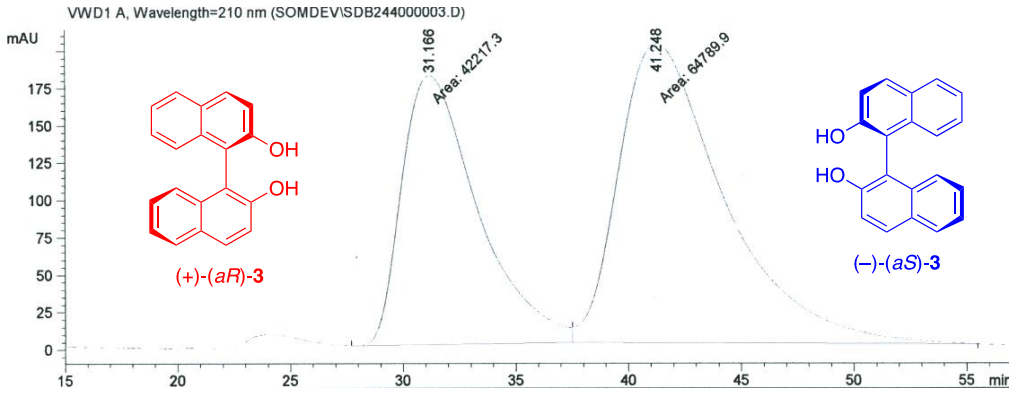


*Figure S11. Resolution of an authentic sample of 20% ee (–)-(aS)-1,1′-bi-2-naphthol (**3**) via CSP HPLC.*

t (sec)	%ee	ln (%ee$_0$ / %ee$_t$)
0	100	0
5700	97.6	0.02429269
36120	72.2	0.32573014
68820	44.6	0.80743633
80700	33.8	1.08470938
91800	29.2	1.23100148

slope = 1.36068 x 10^{-5}; R^2 = 0.992

k (403 K) = 68.0338 x 10^{-7} s^{-1}

1,1´-bi-2-naphthol (3)

T = 403 K (130 °C) in DMSO

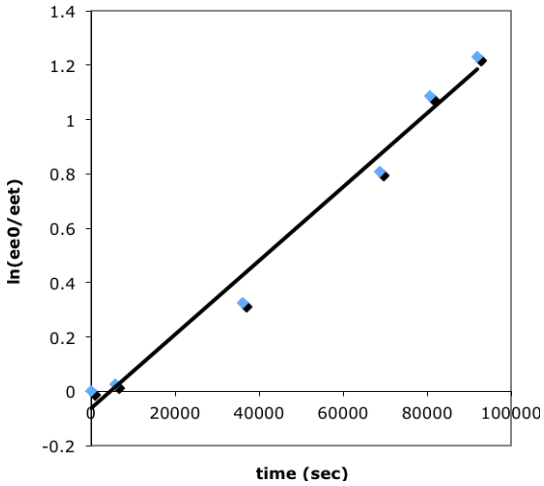


*Figure S12. Determination of enantiomerization rate constant for 1,1´-bi-2-naphthol (**3**) at 403 K (130 °C) in DMSO.*

t (sec)	%ee	ln (%ee$_0$ / %ee$_t$)
0	100	0
3060	90.6	0.09871597
6660	76.4	0.26918749
13860	56.2	0.57625343
16680	49.0	0.71334989
20280	40.0	0.91629073
23280	33.4	1.09661429

slope = 4.67519 x 10^{-5}; R^2 = 0.997

k (423 K) = 233.76 x 10^{-7} s^{-1}

1,1´-bi-2-naphthol (3)

T = 423 K (150 °C) in DMSO

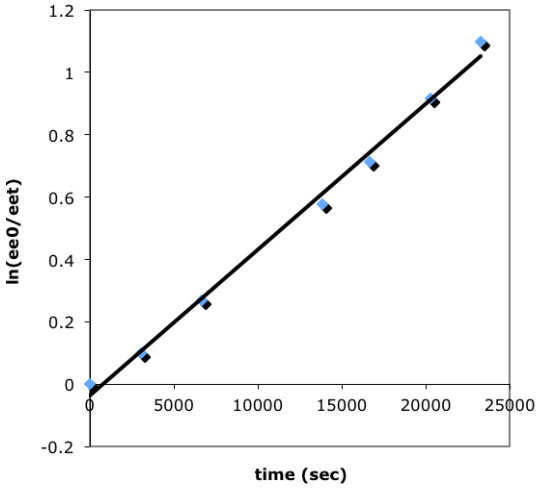


*Figure S13. Determination of enantiomerization rate constant for 1,1´-bi-2-naphthol (**3**) at 423 K (150 °C) in DMSO.*

t (sec)	%ee	ln (%ee$_0$ / %ee$_t$)
0	100	0
1200	92.6	0.07688104
2400	84.6	0.16723592
4860	68.0	0.38566248
8220	50.8	0.67727383
13620	27.8	1.28013417

slope = 9.40213 x 10^{-5}; R^2 = 0.997

k (430 K) = 470.107 x 10^{-7} s^{-1}

1,1´-bi-2-naphthol (3)

T = 430 K (157 °C) in DMSO

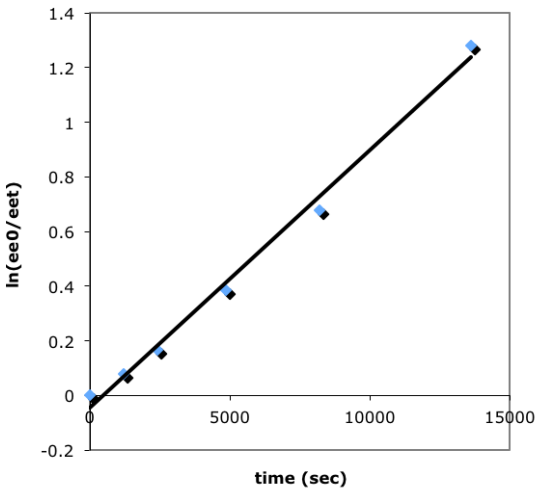


*Figure S14. Determination of enantiomerization rate constant for 1,1´-bi-2-naphthol (**3**) at 430 K (157 °C) in DMSO.*

t (sec)	%ee	ln (%ee$_0$ / %ee$_t$)
0	100	0
1140	84.2	0.17197526
1980	74.8	0.2903523
3120	69.6	0.36240562
4200	57.4	0.55512588
5400	47.8	0.73814455
6540	39.8	0.92130327

slope = 1.37302 x 10^{-4}; R^2 = 0.995

k (437 K) = 686.51 x 10^{-7} s^{-1}

1,1´-bi-2-naphthol (3)

T = 437 K (164 °C) in DMSO

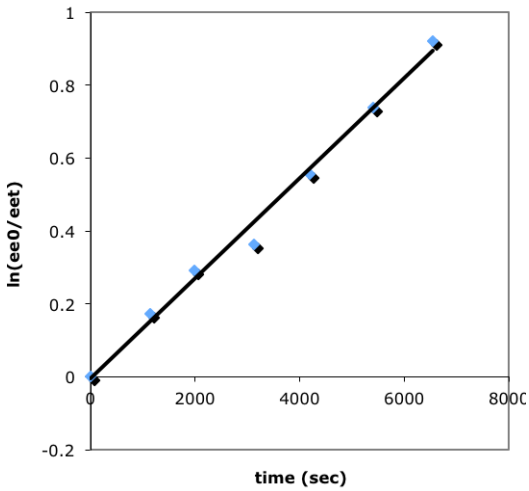
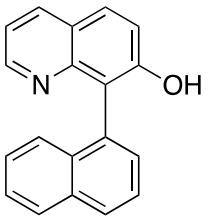
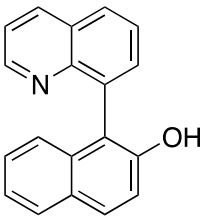


*Figure S15. Determination of enantiomerization rate constant for 1,1´-bi-2-naphthol (**3**) at 437 K (164 °C) in DMSO.*

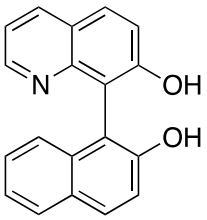
3. Determination of Racemization Half-lives for Biaryls 7, 8, and 2 in $CHCl_3$ & MeOH (Table 2)



7: $C_{19}H_{13}NO$



8: $C_{19}H_{13}NO$



2: $C_{19}H_{13}NO_2$

7-Hydroxy-8-(naphth-1-yl)quinoline (7): Small (5-10 mg) scalemic samples of quinol **7** were obtained by semi-preparative chiral stationary phase (CSP) HPLC of the racemate using an Agilent 1100 series HPLC system interfaced to a Daicel Industries, Chiralcel® OD semi-preparative column of dimensions 250 mm (length) x 10 mm (internal diameter) with a chiral stationary phase of cellulose tris(3,5-dimethylphenylcarbamate) on 10 □m SiO_2. For each run, 200 □L of a 15 mg mL^{-1} solution of the racemate in isopropanol was injected onto the above column (= 3.0 mg per run). Isocratic elution using a solvent blend of 2% *i*-PrOH in hexanes and a flow rate of 0.5 mL min^{-1} was performed with UV detection at 210 nm. The faster eluting (–)-enantiomer was collected from 145-160 min and the slower eluting (+)-isomer was collected from 175-205 min (Figure S16 shows resolution on an analytical OD column). Once in hand, the scalemic material was dissolved in either $CHCl_3$ or MeOH at a concentration of 1.5 mg mL^{-1} and the solution loaded into a polarimetry cell. Decay in the observed optical rotation value (at 24 °C) was recorded against time and the first

order enantiomerization rate constant and associated half-life for racemization extracted from the data (Figures S17 & S18).

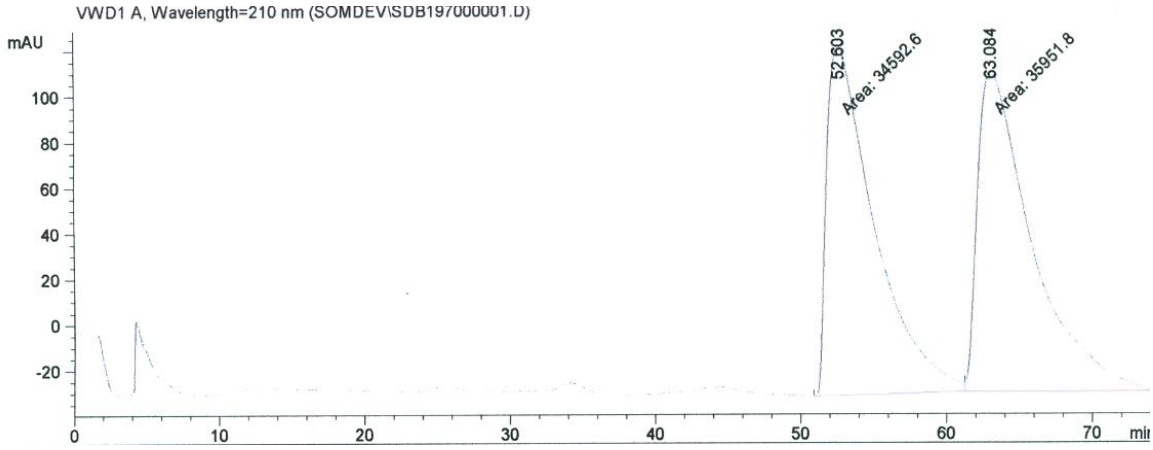


Figure S16. Resolution of (±)-7-hydroxy-8-(naphth-1-yl)quinoline (7) via CSP HPLC using a Daicel OD analytical column.

t (sec)	α_{obs}	ln (α_0 / α_t)
0	0.064	0
90000	0.057	0.115831816
165600	0.049	0.267062785
342000	0.037	0.547965171
525600	0.029	0.791587253
698400	0.017	1.325669739
864000	0.013	1.593933726
1036800	0.008	2.079441542
1209600	0.008	2.079441542
1382400	0.006	2.367123614

slope = 1.81309 x 10^{-6}; R^2 = 0.993

k (297 K) = 9.065 x 10^{-7} s^{-1}

$\tau_{1/2(rac.)}$ = 382301 s = 106 h

7-Hydroxy-8-(naphth-1-yl)quinoline (7)

T = 297 K (24 °C) in $CHCl_3$

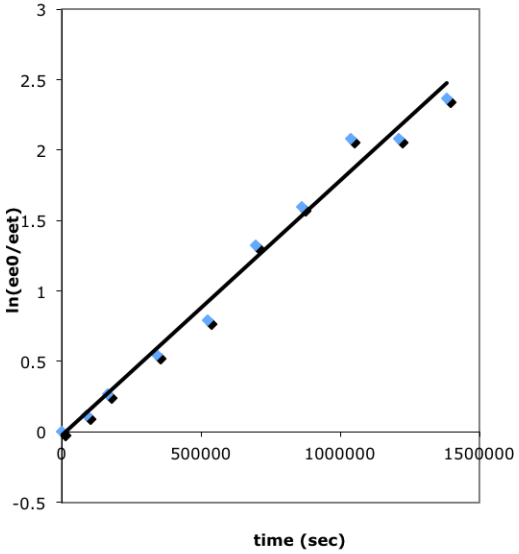


Figure S17. Determination of enantiomerization rate constant and racemization half-life for 7-hydroxy-8-(naphth-1-yl)quinoline (7) at 297 K (24 °C) in $CHCl_3$.

t (sec)	α_{obs}	ln (α_0 / α_t)
0	0.046	0
108000	0.04	0.139761942
172800	0.035	0.273293335
349200	0.032	0.362905494
504000	0.025	0.609765572
684000	0.018	0.938269639
864000	0.018	0.938269639
1080000	0.007	1.882731247
1224000	0.007	1.882731247
1386000	0.005	2.219203484

slope = 1.60873 x 10^{-6}; R^2 = 0.979

k (297 K) = 8.044 x 10^{-7} s^{-1}

$\tau_{1/2(rac.)}$ = 430866 s = 120 h

7-Hydroxy-8-(naphth-1-yl)quinoline (7)

T = 297 K (24 °C) in MeOH

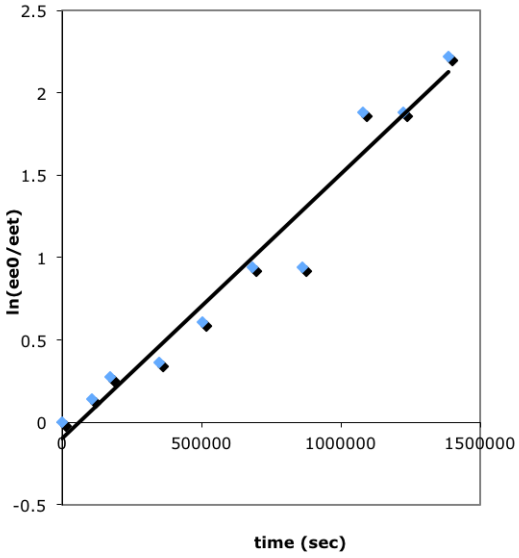


Figure S18. Determination of enantiomerization rate constant and racemization half-life for 7-hydroxy-8-(naphth-1-yl)quinoline (7) at 297 K (24 °C) in MeOH.

8-(2-Hydroxynaphth-1-yl)quinoline (8): Small (5-10 mg) scalemic samples of naphthol **8** were obtained by semi-preparative chiral stationary phase (CSP) HPLC of the racemate using an Agilent 1100 series HPLC system interfaced to a Daicel Industries, Chiralcel® OD semi-preparative column of dimensions 250 mm (length) x 10 mm (internal diameter) with a chiral stationary phase of cellulose tris(3,5-dimethylphenylcarbamate) on 10 μm SiO_2. For each run, 200 μL of a 15 mg mL^{-1} solution of the racemate in isopropanol was injected onto the above column (= 3.0 mg per run). Isocratic elution using a solvent blend of 2% *i*-PrOH in hexanes and a flow rate of 0.5 mL min^{-1} was

performed with UV detection at 210 nm. The faster eluting (–)-enantiomer was collected from 148-158 min and the slower eluting (+)-isomer was collected from 170-210 min (Figure S19 shows resolution on an analytical OD column). Once in hand, the scalemic material was dissolved in either $CHCl_3$ or MeOH at a concentration of 1.5 mg mL^{-1} and the solution loaded into a polarimetry cell. Decay in the observed optical rotation value (at 24 °C) was recorded against time and the first order enantiomerization rate constant and associated half-life for racemization extracted from the data (Figures S20 & S21).

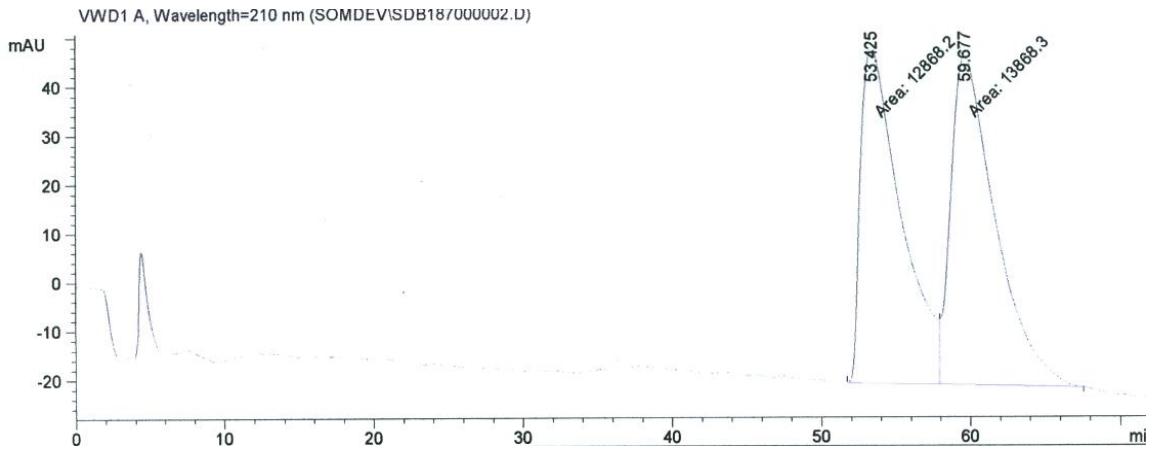


*Figure S19. Resolution of 8-(2-hydroxynaphth-1-yl)quinoline (**8**) via CSP HPLC using a Daicel OD analytical column.*

t (sec)	α_{obs}	ln (α_0 / α_t)
0	0.072	0
3600	0.055	0.269332934
7200	0.043	0.515466003
10800	0.033	0.780158558
14400	0.025	1.057790294
18000	0.018	1.386294361
21600	0.015	1.568615918
25200	0.012	1.791759469
28800	0.009	2.079441542
32400	0.007	2.33075597

slope = 7.19241 x 10^{-5}; R^2 = 0.999

k (297 K) = 3.5962 x 10^{-5} s^{-1}

$\tau_{1/2(rac.)}$ = 9637 s = 2.68 h

8-(2-Hydroxynaphth-1-yl)quinoline (8)

T = 297 K (24 °C) in $CHCl_3$

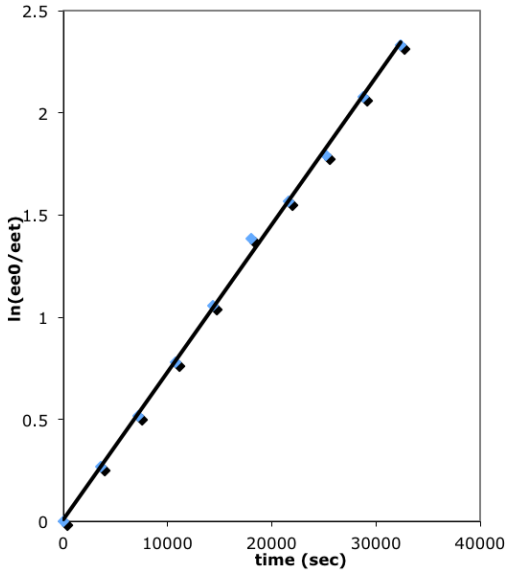


*Figure S20. Determination of enantiomerization rate constant and racemization half-life for 8-(2-hydroxynaphth-1-yl)quinoline (**8**) at 297 K (24 °C) in $CHCl_3$.*

t (sec)	α_{obs}	ln (α_0 / α_t)
0	0.056	0
93600	0.046	0.196710294
180000	0.038	0.387765531
252000	0.032	0.559615788
432000	0.022	0.934309237
594000	0.02	1.029619417
792000	0.009	1.828127113
900000	0.008	1.945910149
1036800	0.006	2.233592222

slope = 2.16318 x 10^{-6}; R^2 = 0.993

k (297 K) = 1.08159 x 10^{-6} s^{-1}

$\tau_{1/2(rac.)}$ = 320429 s = 89.0 h

8-(2-Hydroxynaphth-1-yl)quinoline (8)

T = 297 K (24 °C) in MeOH

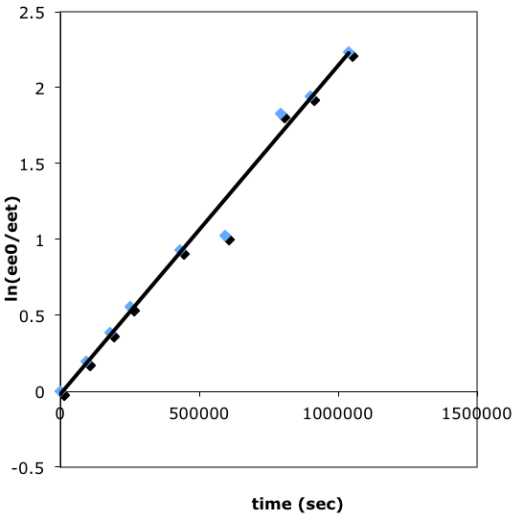


*Figure S21. Determination of enantiomerization rate constant and racemization half-life for 8-(2-hydroxynaphth-1-yl)quinoline (**8**) at 297 K (24 °C) in MeOH.*

7-Hydroxy-8-(2-hydroxynaphth-1-yl)quinoline (2): The enantiomerization kinetics of **2** in $CHCl_3$ (Figure S22) and MeOH (Figure S23) at 56 °C were followed using the same protocol as that given above for the DMSO experiments, i.e., aliquots were sampled at regular intervals and converted into diester **9** for ee determination via CSP HPLC analysis (as before, see Figure S6).

t (sec)	%ee	ln (%ee$_0$ / %ee$_t$)
0	100	0
82800	94.2	0.059750004
165600	88.6	0.121038328
414000	73.4	0.30924625

slope = 7.48783 x 10^{-7}; R^2 = 0.999

k (329 K) = 3.74391 x 10^{-7} s^{-1}

$\tau_{1/2(rac.)}$ = 925699 s = 257 h

7-Hydroxy-8-(2-hydroxynaphth-1-yl)quinoline (2), T = 329 K (56 °C) in $CHCl_3$

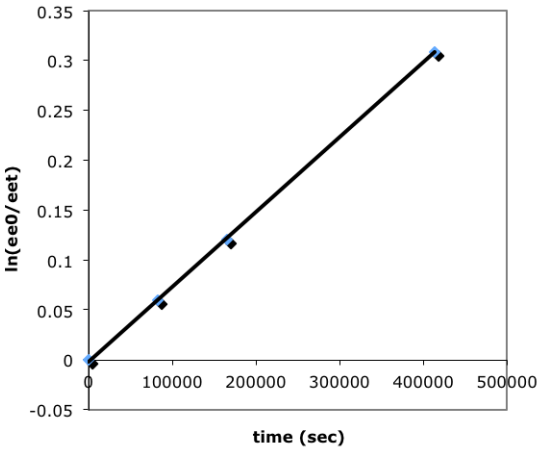


*Figure S22. Determination of enantiomerization rate constant and racemization half-life for 7-hydroxy-8-(2-hydroxynaphth-1-yl)quinoline (**2**) at 329 K (56 °C) in $CHCl_3$*

t (sec)	%ee	ln (%ee$_0$ / %ee$_t$)
0	100	0
82800	82.4	0.193584749
165600	63.8	0.449416996
414000	32.4	1.127011763

slope = 2.7497 x 10^{-6}; R^2 = 0.999

k (329 K) = 1.37485 x 10^{-6} s^{-1}

$\tau_{1/2(rac.)}$ = 252081 s = 70 h

7-Hydroxy-8-(2-hydroxynaphth-1-yl)quinoline (2), T = 329 K (56 °C) in MeOH

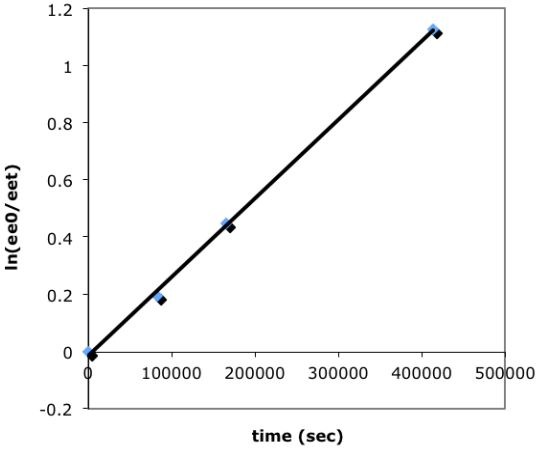


*Figure S22. Determination of enantiomerization rate constant and racemization half-life for 7-hydroxy-8-(2-hydroxynaphth-1-yl)quinoline (**2**) at 329 K (56 °C) in MeOH.*

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conformation is '*s*-(*Z*)' in character. Crystallographic data for (±)-**8** have been submitted to the Cambridge Crystallographic Data Centre with deposition number CCDC 1059679. Copies of the data may be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 33603 or e-mail: depost@ccdc.cam.ac.uk).

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