

Axially chiral phenolic derivatives of 8,8'-biquinolyl and 8-(naphth-1-yl)quinoline as platforms for discovery: The unfolding story of the 'azaBINOLs'

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Dedicated to the memory of Professor James D. White (1935-2020)

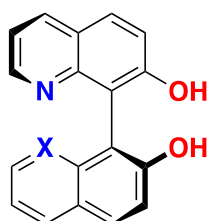
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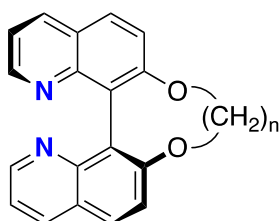
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Abstract

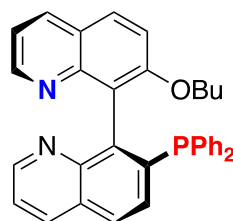
This account encapsulates the Author's interests in the chemistry of nitrogenous analogs of 1,1'-bi-2-naphthol (BINOL) in which either the 8-position ('8-azaBINOL') or both of the 8- and 8'-positions ('8,8'-diazBINOL') of the binaphthyl have been formally replaced by N-atoms. The consequences that such structural perturbations have on various kinetic (rate of enantiomerization), thermodynamic (basicity), and biological (anti-HIV activity) properties of the biaryl nucleus are elaborated and opportunities for the application of azaBINOLs in reaction catalysis are highlighted. The synthesis of parent azaBINOLs and their substituted derivatives is summarized, together with techniques to resolve these axially chiral compounds into their enantiomeric atropisomers.



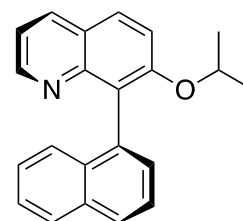
• X = CH, N: aza-analogs of BINOL



• conformation dependent pK_{aH}



• chiral ligand for enantioselective Pd catalysis



• HIV-1 neutralization agent

Keywords: Axially chiral biaryls, enantiomerization kinetics, ambifunctional catalysis, HIV-1 neutralizations

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1. Introduction

1.1. General

The introduction of subtle perturbations into a well-known molecular system may afford opportunities for the exploration of new and useful chemistry. Furthermore, such an exercise will most likely provide a context for the study of fundamental phenomena that could have impacts beyond whatever premise initially motivated an examination of the altered system in the first place. A case in point, and the subject of this account of an area of the Author's research, is the so-called 'azaBINOL' family of heterocyclic biaryl molecules; parent members of which, **2** and **3**, are shown in Figure 1. AzaBINOLs are nitrogenous analogues of the well-known axially chiral biaryl ligand BINOL (**1**),¹ in which one or two of the peri-CH moieties have been formally replaced by N-atoms to reveal quinoline ring systems in place of naphthalenes. Some of the effects of this perturbation are obvious and could be readily anticipated, but others are not, and therein lies the reward common to the study of all new things.

Herein, the history of the azaBINOL project is traced from its inception point as an essentially curiosity-driven piece of research in the realm of enantioselective catalysis, to where it lies today after some quite unexpected findings have led to useful advances across a range of different areas, including: directed metallation chemistry, anionic rearrangements, interannular proximity effects, biaryl configurational stability, and HIV-1 neutralization. The interested reader is referred to the original azaBINOL publications cited herein for a full exposition of the topics presented with more extensive background literature.²⁻¹⁰ Throughout, atom positions within azaBINOL molecules are referred to in relation to BINOL numbering (see Figure 1); however, the numbering of any quinoline precursors conforms to the usual IUPAC convention.

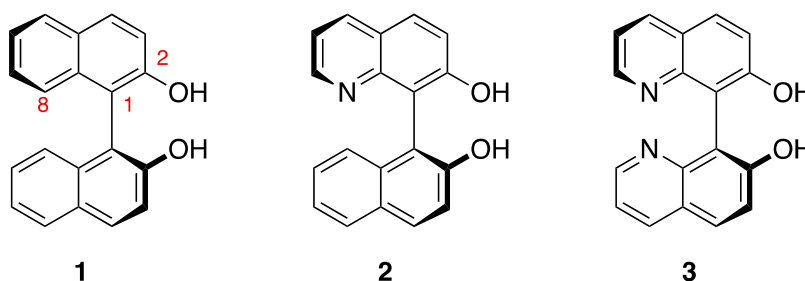


Figure 1. BINOL (**1**, 1,1'-bi-2-naphth-2-ol) and parent members of the 'azaBINOL' family, referred to herein by a colloquial replacement nomenclature as 8-azaBINOL [**2**, 7-hydroxy-8-(2-hydroxynaphth-1-yl)quinoline] and 8,8'-diazabINOL (**3**, 7,7'-dihydroxy-8,8'-biquinolyl). Molecules are depicted in (*aS*)-configuration.

1.2. Notes on the motivation for the study of azaBINOLs

Some elaboration on the motivation to study azaBINOLs is warranted. At the time the azaBINOL project began (ca. 2000), interest arose in an axially chiral biaryl motif **4** containing 'ambifunctional quadrants,' each one a zone of potential catalytic activity by virtue of being flanked by a frustrated Lewis acid (LA)-Lewis base (LB) pair (Figure 2). Frustrated LA-LB pairs are known to promote a wide variety of reactions,¹¹ and it was envisioned that the semi-rigid biaryl structure of **4** would serve the dual purpose of physically separating LA and LB sites while simultaneously offering a necessary chiral environment for enantioselective catalysis. Although several ambifunctional catalysts based on chiral biaryl frameworks were known at this time (e.g., **7** and **8**),^{12,13} none shared the topology of motif **4**, which we felt may offer unique reactivity and be worthy of further study. Conceivably, a construct such as **4** could catalyze enantioselective bond formation between pro-nucleophiles and pro-electrophiles within its ambifunctional quadrants (as generically illustrated) and perhaps also enable atom-transfer reactions from enoid species to unsaturated bonds and other moieties.

8,8'-DiazabINOLs with additional coordinating substituents at C3 and C3' to form C2/C3 and C2'/C3' chelates with suitable metal residues (e.g., MgX_2 , BX_3 , AlX_3 , TiX_4), such as bisulfonamide **5** (Figure 3), were identified to be among the simplest molecules that could lead to a physical embodiment of scaffold **4**. Speciation of metal residues by **5** in the appropriate manner would give a metal complex (**6**) containing filled (N-centered sp^2 -lone pairs) and vacant orbitals (metal centered p-orbitals) unable to directly interact with each other (at least, in an intramolecular sense) because of the skewed orthogonality of their positions in space. Adding to the allure of this plan was the structural similarity of the requisite precursor molecules involved to BINOL (**1**), and it was felt that the mass of collected knowledge on BINOL could be leveraged throughout our study. Thus, the azaBINOL project began with a focus on preparing molecules such as **5** and examining derived metal complexes as enantioselective ambifunctional catalysts. However, as documented herein, the analogy between 8,8'-diazabINOL (**3**) and BINOL (**1**) was found to extend only so far and during the

course of our investigations our attention was increasingly drawn to explore how biquinolyls, and related mixed naphthylquinoline biaryls, differ from the better known binaphthyls. Also, as is invariably the case when novel chemical entities are prepared, new possibilities for azaBINOLs became evident as the project moved forward and our thinking about them grew to be more sophisticated.

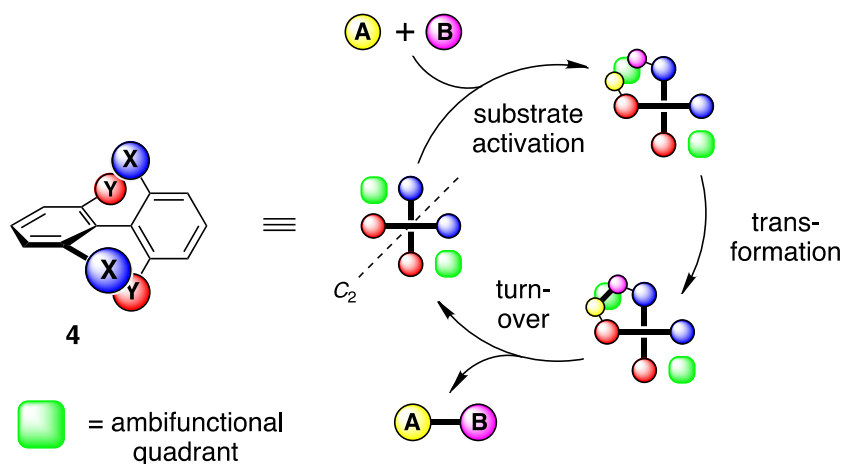


Figure 2. A notional ambifunctional catalyst system **4** based on the location of frustrated Lewis acid-Lewis base pairs within an axially chiral C_2 -symmetric biaryl template. X = Lewis base, Y = Lewis acid, A = pro-electrophile, B = pro-nucleophile.

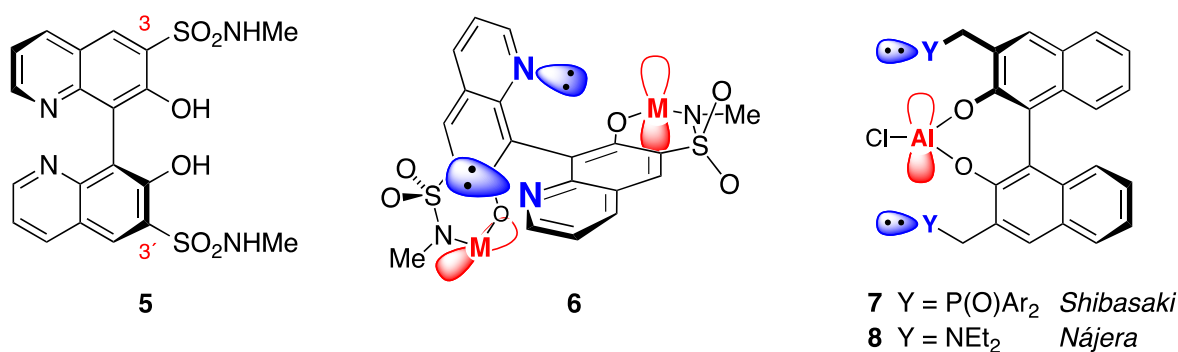
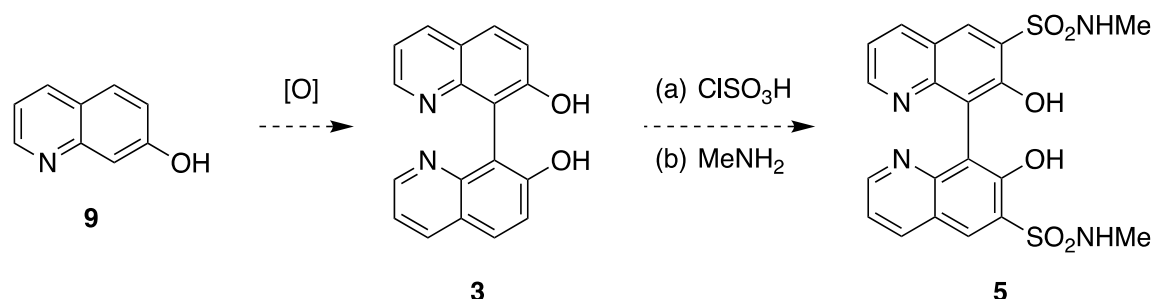


Figure 3. A 3,3'-bissulfonamidyl derivative of 8,8'-diazabinoxaline (**5**) as a putative precursor to an axially chiral ambifunctional catalyst (**6**) representing motif **4** and two previously established ambifunctional catalysts based on BINOL derivatives (**7** and **8**).^{12,13}

2. Synthesis of Parent AzaBINOLs and Their Derivatives

Synthesis of 8,8'-diazabinoxaline (**3**) in racemic form and its subsequent advancement to bissulfonamide **5** was the first objective. Our forays in this endeavor were wholly unsuccessful because they were based on flawed logic; viz, that **3** could be obtained in an analogous fashion to its all carbocyclic congener BINOL (**1**) by oxidative phenolic coupling of 7-hydroxyquinoline (**9**), and that conversion of **3** to **5** could be achieved in high yield by direct chlorosulfonation/amination (Scheme 1). A survey of many different kinds of oxidants, all of which are known to successfully convert 2-naphthol to BINOL, identified none that could transform **9** to its oxidized

dimeric form **3** (in general, no reaction was observed).² When 8,8'-diazabINOL (**3**) was later obtained by a different means, its exposure to hot excess chlorosulfonic acid followed by treatment with methylamine, gave **5** in no more than trace quantities (<5% yield). Neither result is surprising in retrospect when considering the very different character of 2-naphthol (electron-rich, non-basic) versus 7-hydroxyquinoline (**9**) (electron-poor arene containing a basic heteroatom). Although a quinoline nucleus is not as easily oxidized as a naphthalene system, nor as facile in its electrophilic substitution reactions, much other unique chemistry is possible, indeed, to such an extent as to make the azaBINOLs far more amenable to derivatization than BINOLs.

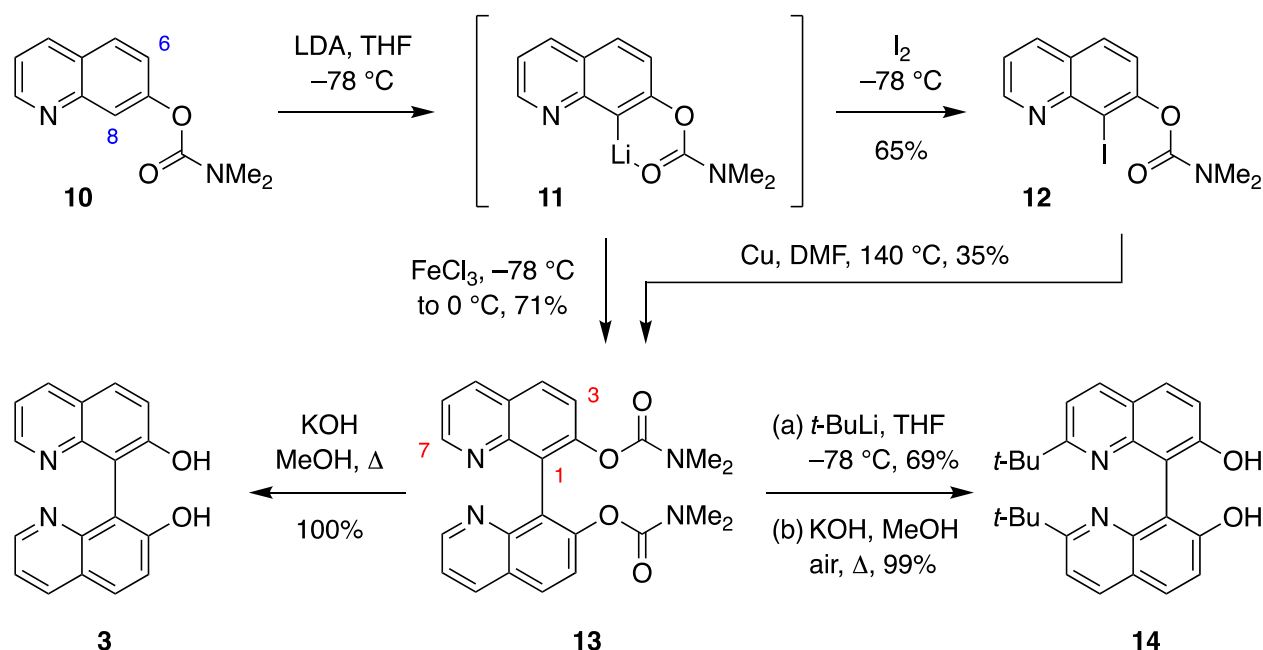


Scheme 1. An unsuccessful plan for a concise synthesis of bisulfonamide **5** from 7-hydroxyquinoline (**9**) that draws a false parallel to the reactivity of 2-naphthol and that expected for BINOL (**1**).

Two different successful approaches (described below) were developed to access 8,8'-diazabINOL (**3**), both rational in their design and the second relying on modern CH functionalization chemistry; however, the route ultimately identified to generate bisulfonamide **5** is far from obvious and it illustrates the role that reaction discovery can play in target directed synthesis efforts.

2.1. First generation synthesis of 8,8'-diazabINOL and use of discovered anionic rearrangements to access 3,3'-disubstituted derivatives

The first successful approach to 8,8'-diazabINOL (**3**)² was based on directed *ortho*-metallation chemistry and it took advantage of the known propensity of the *N,N*-dimethyl carbamate derivative of 7-hydroxyquinoline (**10**) to selectively lithiate at C8 (Scheme 2).¹⁴ With the C8-position activated as a carbanion (organolithium **11**), the desired biquinolyl **13** was generated initially by iodination followed by Ullmann-type biaryl coupling of the intermediate 8-iodoquinoline **12**. Soon after, it was discovered that a high yielding and more step efficient entry to **13** was available by direct anhydrous FeCl₃ mediated oxidative coupling of the organolithium. Simple saponification of biscarbamate **13** gave 8,8'-diazabINOL (**3**) as a pale yellow powder sparingly soluble in most common organic solvents, but with high solubility in dipolar aprotic solvents (DMSO and DMF) and in water. Recrystallization of **3** from MeOH gave a disolvate as yellow plates (mpt. 258-260 °C), X-ray diffraction (XRD) analysis of which revealed a preference for a transoid conformation in the solid state (Figure 4).² A potentially useful sterically hindered variant of **3**, 7,7'-di-*tert*-butyl-8,8'-diazabINOL (**14**), akin to an axially chiral version of 2,6-di-*tert*-butyl-4-methylpyridine, was generated from **13** by facile addition of *t*-BuLi and aerial oxidation, followed by saponification in air.⁴ By contrast to the parent diol **3**, alkylated azaBINOL **14** readily dissolves in a range of organic solvents (e.g., THF, CH₂Cl₂, MeOH) and XRD analysis of crystals obtained from MeOH showed much heightened transoid character with evidence for interannular H-bonds between the head-to-tail oriented quinol units (Figure 4).⁴



Scheme 2. First generation syntheses of 8,8'-diazBINOL (**3**) and 7,7'-di-*tert*-butyl-8,8'-diazBINOL (**14**) via directed *ortho*-metallation of a carbamate derivative of 7-hydroxyquinoline (**10**).^{2,4}

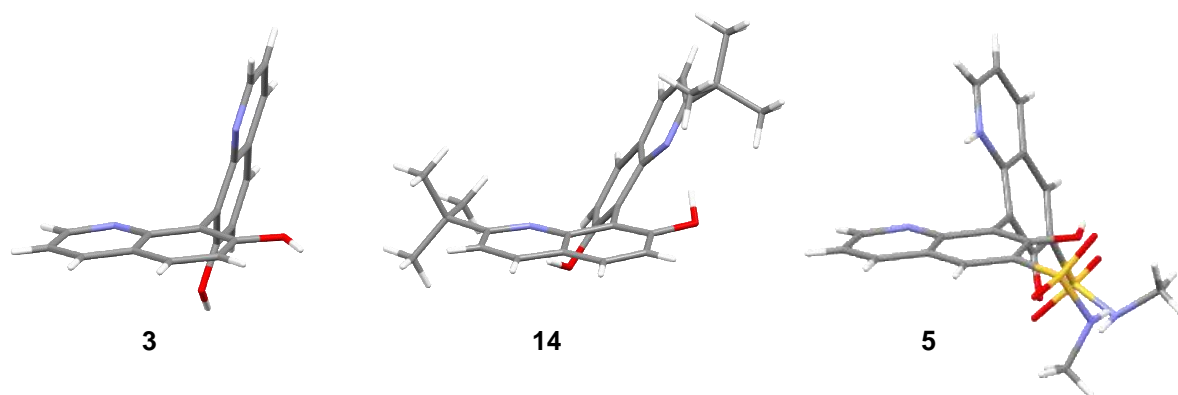
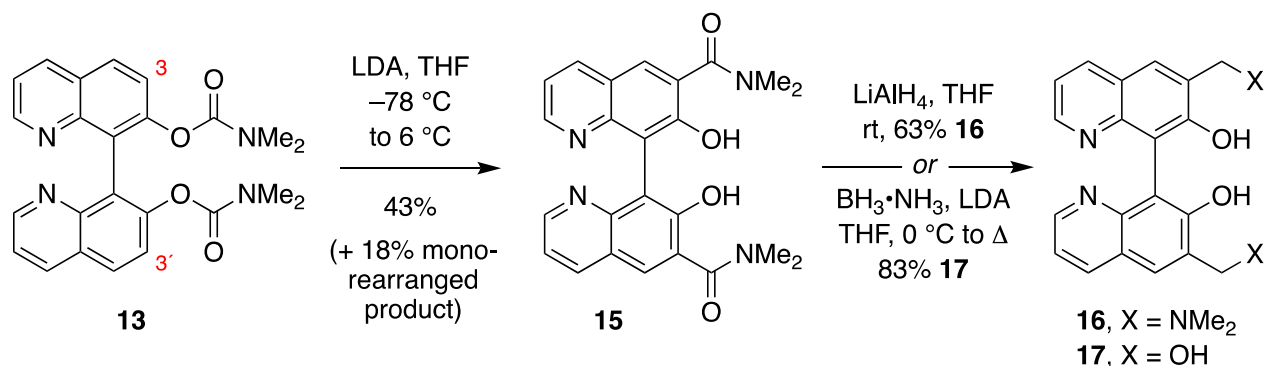


Figure 4. X-ray crystal structures for 8,8'-diazBINOL (**3**), 7,7'-di-*tert*-butyl-8,8'-diazBINOL (**14**), and 3,3'-bis(methylaminosulfonyl)-8,8'-diazBINOL (**5**). Detailed notes concerning XRD analyses and relevant CIFs are available in the original publications.^{2,4,7}

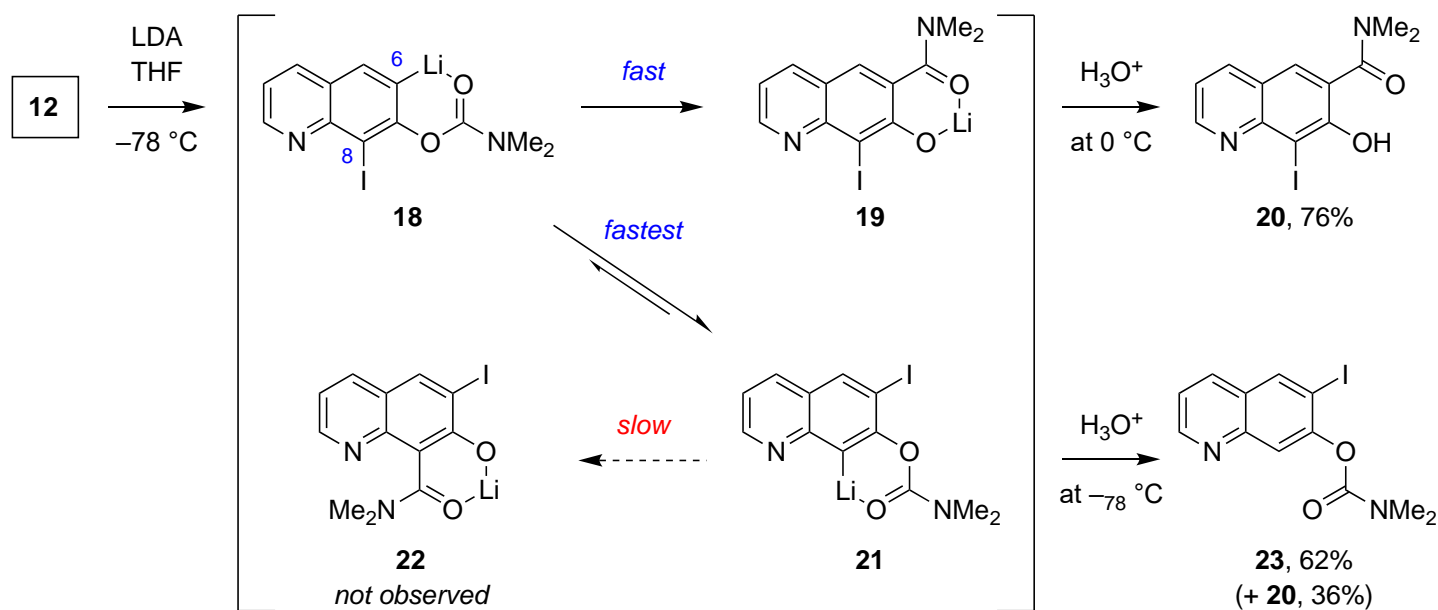
With a viable approach to the 8,8'-diazBINOL scaffold realized, attention focused on further advancement to the actual target of initial interest, bissulfonamide **5**. As mentioned above, direct chlorosulfonation of **3** was not effective; however, with *ortho*-metallation activating groups present at C2 and C2' of the azaBINOL nucleus of **13**, it was an obvious tactic to employ them again in the task of introducing substituents at C3 and C3'. In the event, treatment of **13** with LDA at $-78\text{ }^{\circ}\text{C}$ resulted in a facile anionic *ortho*-Fries rearrangement¹⁵ of one of the carbamoyl moieties, but since our goal was the installation of metal-coordinating substructure at C3 and C3' anyway, we recognized the rearrangement as fortuitous. After some optimization it proved possible to migrate both carbamoyl groups, albeit in modest yield, to arrive at bisamide **15** (Scheme 3). This compound, of interest in its own right as an appropriate ligand precursor to a motif **4**, was

advanced to other potential catalyst precursors, **16** and **17**, by the illustrated standard amide reduction protocols.



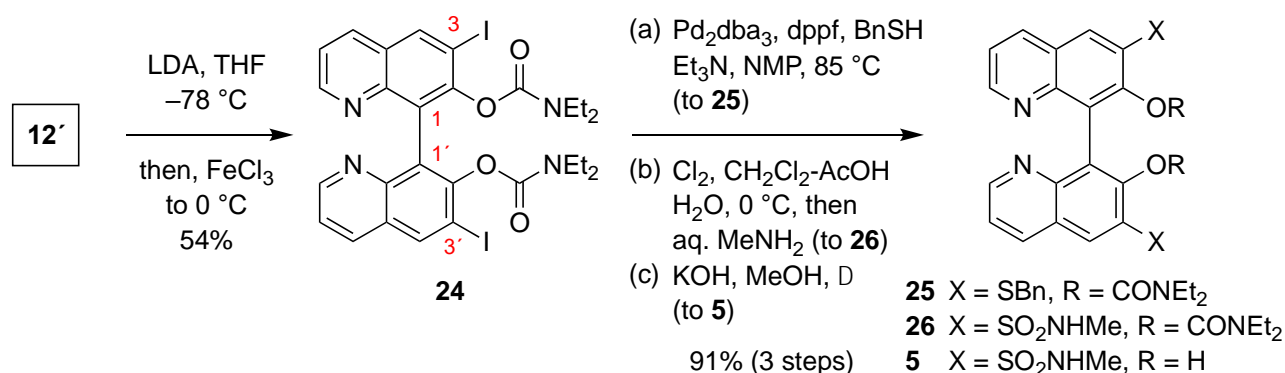
Scheme 3. Double anionic *ortho*-Fries rearrangement from biscarbamate **13** and advancement of resulting bisamide **15**.²

The modest efficiency of the second anionic Fries rearrangement involved in the conversion of **13** to **15** was attributed to the difficulty of establishing the necessary complex-induced proximity effect (CIPE)¹⁷ to achieve deprotonation at C3' following the first rearrangement because, at this stage, the emergent lithium alkoxide at C2 likely competes with LDA for coordination of the remaining carbamate at C2'. In seeking a higher yielding synthesis of **15**, it was felt that a strategic reversal in biquinolyl synthesis and carbamate rearrangement steps would pay dividends; viz, the anionic *ortho*-Fries rearrangement should be effected on 8-iodoquinoline **12** and then the resulting product converted to **15** by Ullmann coupling. In the event, the anionic Fries rearrangement from **12** gave the intended amide **20** (confirmed by XRD analysis) when the putative 6-lithio-8-iodoquinoline **18** generated from **12** with LDA at $-78\text{ }^{\circ}\text{C}$, was allowed to warm to $0\text{ }^{\circ}\text{C}$ before protonolysis (Scheme 4).²



Scheme 4. Competing anionic rearrangements of iodoquinolyl lithium **18**.²

It transpired that reductive coupling of **20** was not successful, but a closer examination of the process that generated this amide led to the development of a more efficient approach to access 3,3'-disubstituted 8,8'-diazabINOLs than any of those that we had previously designed. In a key experiment, quenching the lithiation reaction of **12** at low temperature was observed to afford 6-iodoquinoline **23**, the result of a halogen-dance rearrangement.¹⁸ The accumulated data are explicable as follows. Upon generation, **18** enters into a dynamic equilibrium with its Li/I transposed regioisomer **21**, presumably by virtue of the usual ionic chain mechanism for 1,*n* (*n* > 2) halogen-dance reactions and so involving an intermediate diiodide.¹⁸ Although 6-iodo-8-lithioquinoline **21** is the thermodynamically more stable carbanion of the pair **18** and **21**, it is a kinetically less competent organolithium than 8-iodo-6-lithioquinoline **18** for the ensuing anionic *ortho*-Fries rearrangement. Thus, as the temperature is increased, a Curtin-Hammett scenario operates wherein the thermodynamically less stable isomer of the halogen-dance equilibrium (**18**) is irreversibly siphoned-off to give alkoxide **19** but the anionic *ortho*-Fries rearrangement product from **21** (alkoxyamide **22**) is not formed. A novel tandem halogen-dance/oxidative coupling process was immediately devised to take advantage of the observations and to gain a general entry to 3,3'-disubstituted 8,8'-diazabINOLs (Scheme 5). As illustrated, low temperature lithiation of the *N,N*-diethylcarbamate congener of **12** (**12'**) followed by addition of anhydrous FeCl₃ to splice together the intermediate 6-iodo-8-lithioquinoline, delivers 3,3'-diiodo-8,8'-diazabINOL biscarbamate **24** directly. Herein, use of the *N,N*-diethyl- (**12'**) rather than the *N,N*-dimethyl- (**12**) carbamate derivative serves to suppress the now unwanted anionic *ortho*-Fries rearrangement. Given the synthetic versatility of aryl iodides, one may regard **24** as a precursor to almost any 3,3'-disubstituted 8,8'-diazabINOL of interest and its advancement to the long sought after bisulfonamide **5** was achieved without incident (see Figure 4 for X-ray structure).²

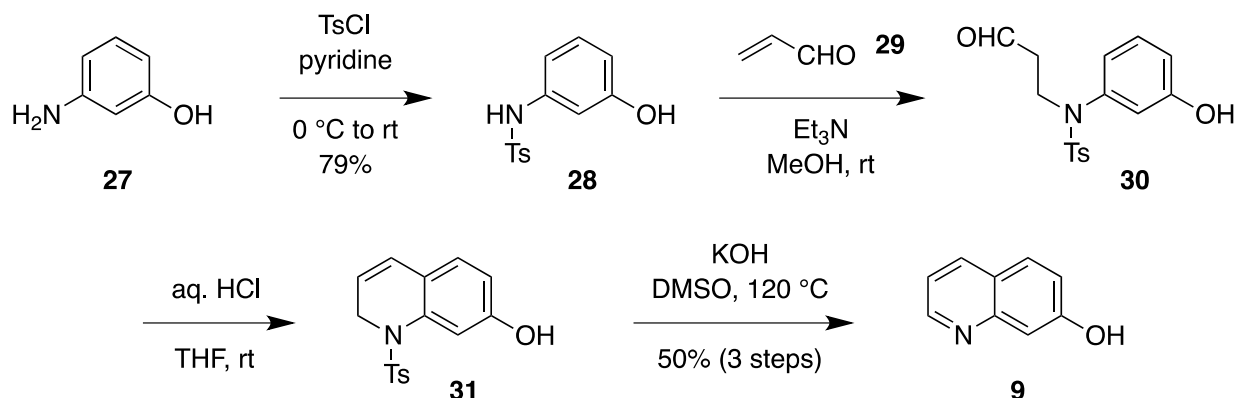


Scheme 5. Tandem halogen-dance / oxidative coupling from a 7-carbamoyloxy-8-iodoquinoline (**12'**) to realize an efficient entry to 3,3'-disubstituted 8,8'-diazabINOLs.²

2.2. Second generation synthesis of 8,8'-azaBINOL via *N*-directed CH-functionalization and its extension to 8-azaBINOL

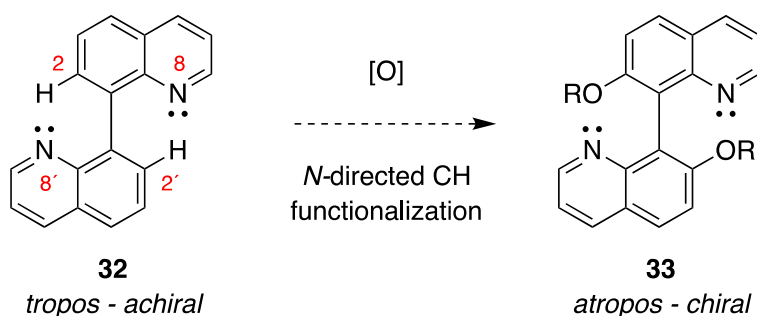
Although satisfactory in many ways, the first approach to 8,8'-diazabINOL (**3**) as described above was viewed as less than ideal because of its overall length and reliance on 7-hydroxyquinoline (**9**) as an intermediate. This simple quinol is expensive and it has limited commercial availability due to the difficulty of its preparation. For example, the direct Skraup synthesis¹⁹ from 3-aminophenol (**27**) is low yielding because it is complicated by a lack of regiocontrol (5-hydroxyquinoline is co-generated) and obtaining satisfactorily pure samples of **9** from the resinous crude material obtained is very challenging. Of the alternate possibilities, Fukuyama's ingenious synthesis of 7-hydroxyquinoline (**9**) via conjugate addition of the *N*-tosyl derivative of 3-aminophenol (**28**) to acrolein (**29**) was our preferred entry to this critical material; however, four steps are needed to access **9** using

this approach (Scheme 6).²⁰ All told, at seven steps long overall and necessitating several chromatographic purification stages, the first generation synthesis of 8,8'-diazabINOL (**3**)² via 7-hydroxy-quinoline (**9**) was regarded as too arduous to allow for unfettered development of azaBINOL chemistry and a more efficient entry to this biaryl family was sought.⁶



Scheme 6. Fukuyama's four-step synthesis of 7-hydroxyquinoline (**9**).²⁰

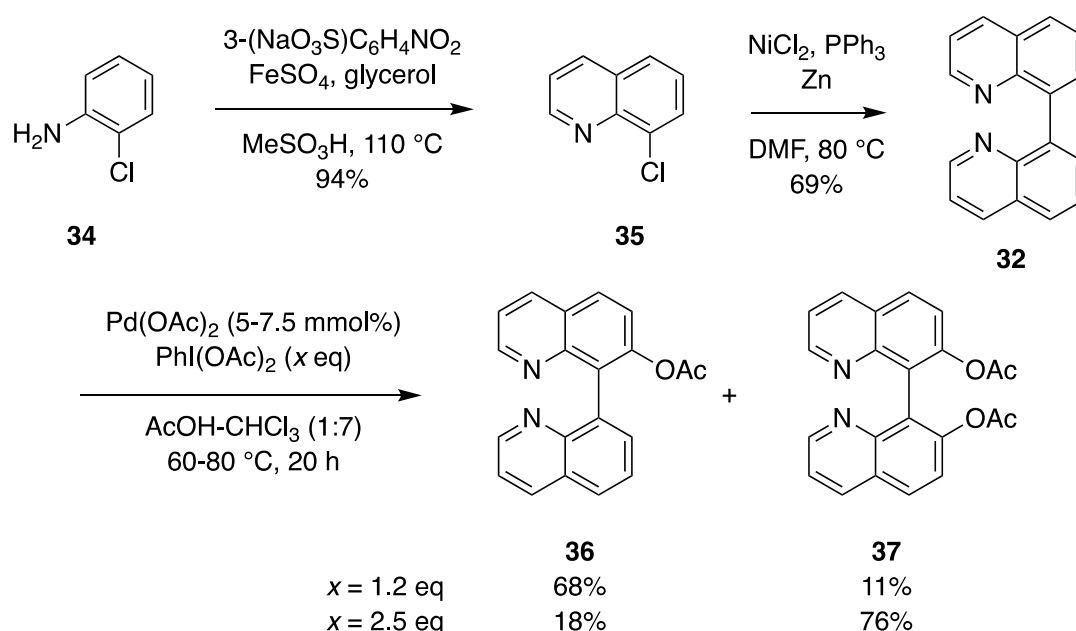
Contemporaneous advances in CH functionalization chemistry by Sanford,²¹ among others,²² predicated that an alternate route to 8,8'-diazabINOLs **33** was potentially available by *N*-directed Pd(II) mediated oxidation of biquinoyl **32** (Scheme 7). During such a transformation, in which the N8-atom of the proto-azaBINOL serves to direct oxidation of the C2' CH-bond while the N8'-atom does likewise for the CH-bond located at C2, an initially *tropos* (freely rotating) and essentially achiral biaryl **32** is converted to an *atropos* and axially chiral biaryl **33**. Given the likely ease of accessing **32**, this process was regarded as attractive; furthermore, such a reaction could conceivably be rendered enantioselective by the use of an appropriate scalemic Pd(II) complex.



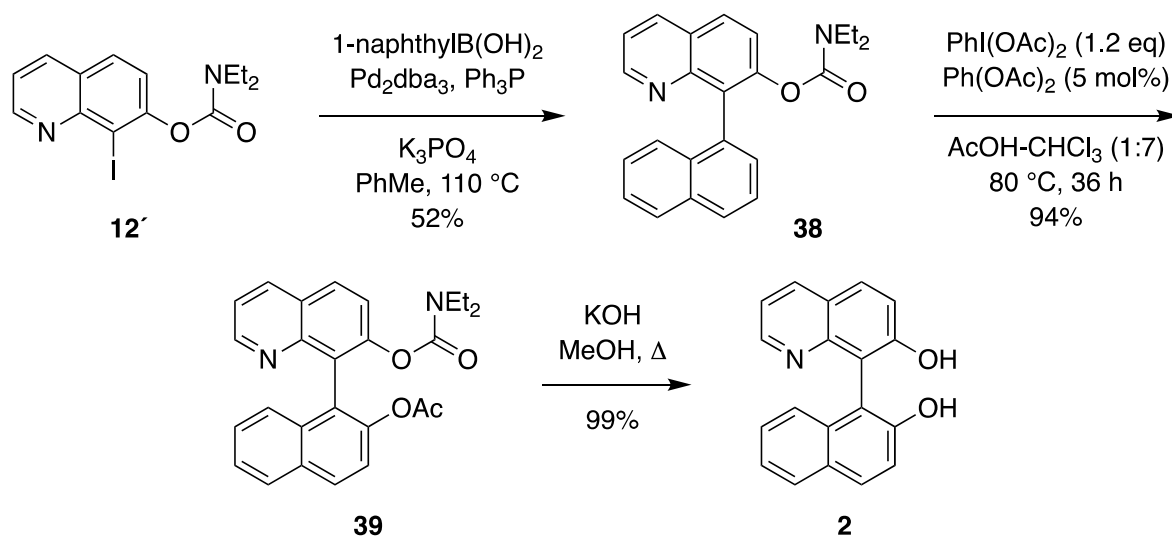
Scheme 7. A concise entry to 8,8'-diazabINOLs **33** by *N*-directed CH functionalization of biquinoyl **32**.

The plan outlined above was successfully executed (Scheme 8).⁶ Of various approaches evaluated, a practical synthesis of biquinoyl **32** was best achieved by a Ni(0)-mediated coupling of 8-chloroquinoline (**35**),²³ which was obtained by the high yielding Skraup reaction of 2-chloroaniline (**34**). After extensive optimization of reaction variables, it was discovered that the Sanford oxidation of **32** performed very well and the diacetate of 8,8'-diazabINOL (**37**) or the monoacetate of deoxy-8,8'-diazabINOL (**36**) could be produced as desired based on the stoichiometry of terminal oxidant [PhI(OAc)₂] employed. Straightforward saponification of the esters

gave the corresponding quinols in quantitative yield. Adding to the attractiveness of this now four step entry to 8,8'-diazabINOL (**3**) is the fact that the whole sequence can be successfully implemented without recourse to chromatographic purification.⁶ An enantioselective variant awaits its realization.



Scheme 8. Synthesis of biquinolyl **32** and its advancement to diacetyl 8,8'-diazabINOL (**37**) by double *N*-directed CH-functionalization using the Sanford oxidation.⁶



Scheme 9. Synthesis of 8-azaBINOL (**2**) via Sanford oxidation of 2'-deoxy-8-azaBINOL carbamate **38**.

Extension of the same approach to 8-azaBINOL (**2**) was straightforward (Scheme 9).⁹ This hybrid naphthyl-quinoline biaryl compound became of interest to us later on as a more soluble member of the azaBINOL family with superior configurational stability to **3** (see Section 3.2). To access the requisite precursor for the Sanford oxidation in this case (naphthylquinoline **38**), 8-iodoquinolinyl carbamate **12'**, used in the earlier tandem halogen-dance/oxidative dimerization, was coupled with 1-naphthylboronic acid via a Suzuki-Miyaura cross-

coupling reaction.²⁴ The desired diol **2** was obtained as a microcrystalline material in high yield from **38** by *N*-directed CH-functionalization as indicated followed by saponification. Diol **2** is indeed more soluble than its polar congener **3**, and it was found to readily dissolve in a number of common organic solvents, such as THF, toluene, and CH₂Cl₂.⁹ Samanta and coworkers recently realized an elegant alternative synthesis of **2** via Rh(III)-catalyzed C8-arylation of 7-methoxyquinoline-*N*-oxide with diazonaphthalen-2(1*H*)-one.²⁵

3. Resolution and Configurational Stability of AzaBINOLs

For a given azaBINOL derivative to have potential applications in an area such as enantioselective synthesis or chiral recognition, etc., it is important for a method to exist to obtain it in an enantioenriched form and for the configurational stability of the resulting scalemic material to be appreciated and understood. The well known 'axial chirality' of biaryl molecules like the azaBINOLs is due to restricted rotation about the interannular bond giving rise to the possibility of a meaningful separate existence for the enantiomeric atropisomers. Chirality conferred solely by virtue of atropisomerism is not the concrete property that one would like it to be; thus, rather than being able to give a simple 'Yes' or a 'No' answer to the question of "Is this molecule chiral?", one must instead refer the enquirer to the limits of the compound's configurational stability (e.g., its racemization half-life, $\tau_{1/2\text{-rac}}$) under a given set of conditions. The simplest pathways to consider for the configurational inversion of BINOL and azaBINOL derivatives are rotations about the interannular bond via either *syn*- or *anti*-type eclipsed conformational transition states **41** (Figure 5); however, in the case of free phenolic compounds,

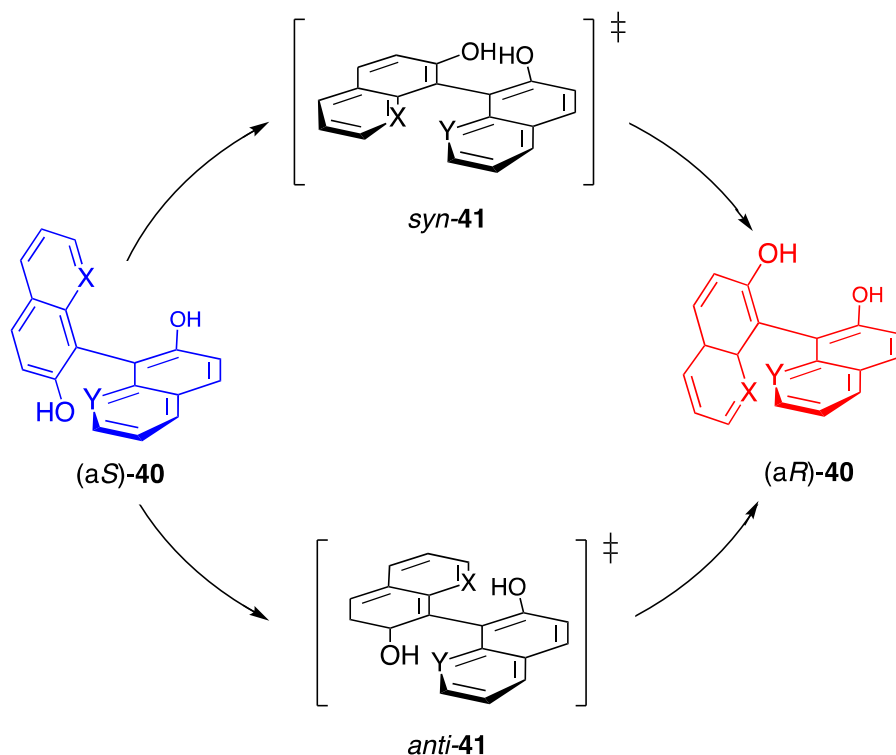
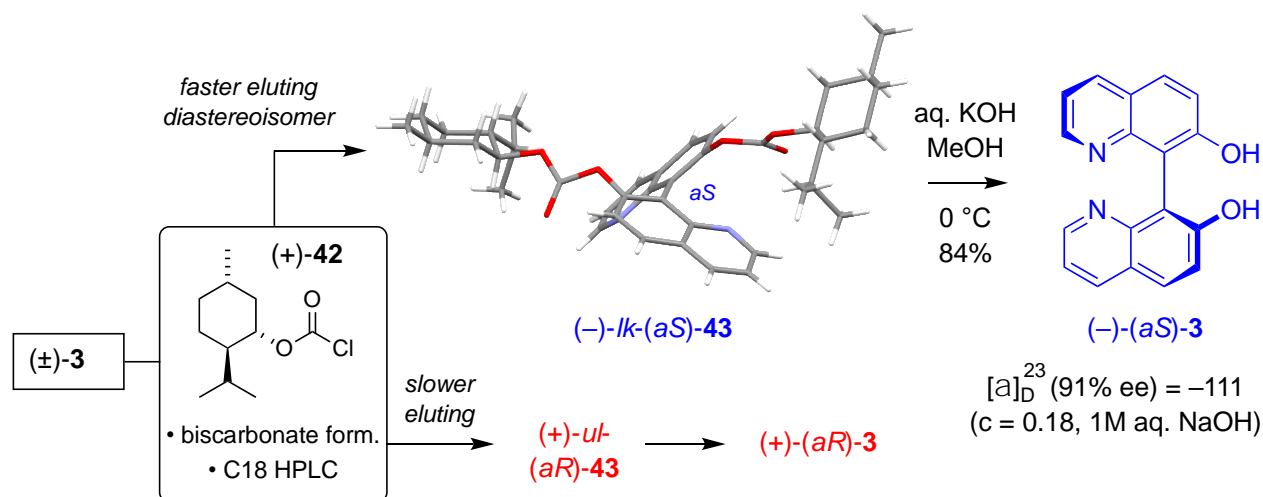


Figure 5. Simple pathways for enantiomerization of BINOL (X = Y = CH) and azaBINOLs (X = N, Y = N or CH) involving achiral *syn* or *anti* transition states (**41**) accessed by interannular bond rotation.

tautomerization to one of several possible keto forms may be implicated in the overall racemization process. In this section, strategies to achieve the resolution of azaBINOL derivatives will be presented alongside determination of the enantiomerization/racemization kinetics for a number of key compounds. Regarding the parent diol molecules, **1**, **2**, and **3**, and considering the simple enantiomerization pathways shown below, one may surmise that BINOL (**1**) is the most configurationally stable of the three compounds, and 8,8'-diaz-BINOL (**3**) the least, on the basis that a C-H bond is presumably more sterically encumbering than an N-atom lone-pair. While this reasoning does predict the correct order for configurational stability within the series (as **1** > **2** > **3**), enantiomerization kinetic experiments suggest that it is likely for the wrong reason (*vide infra*).

3.1. Resolution of azaBINOLs and their chiroptical properties

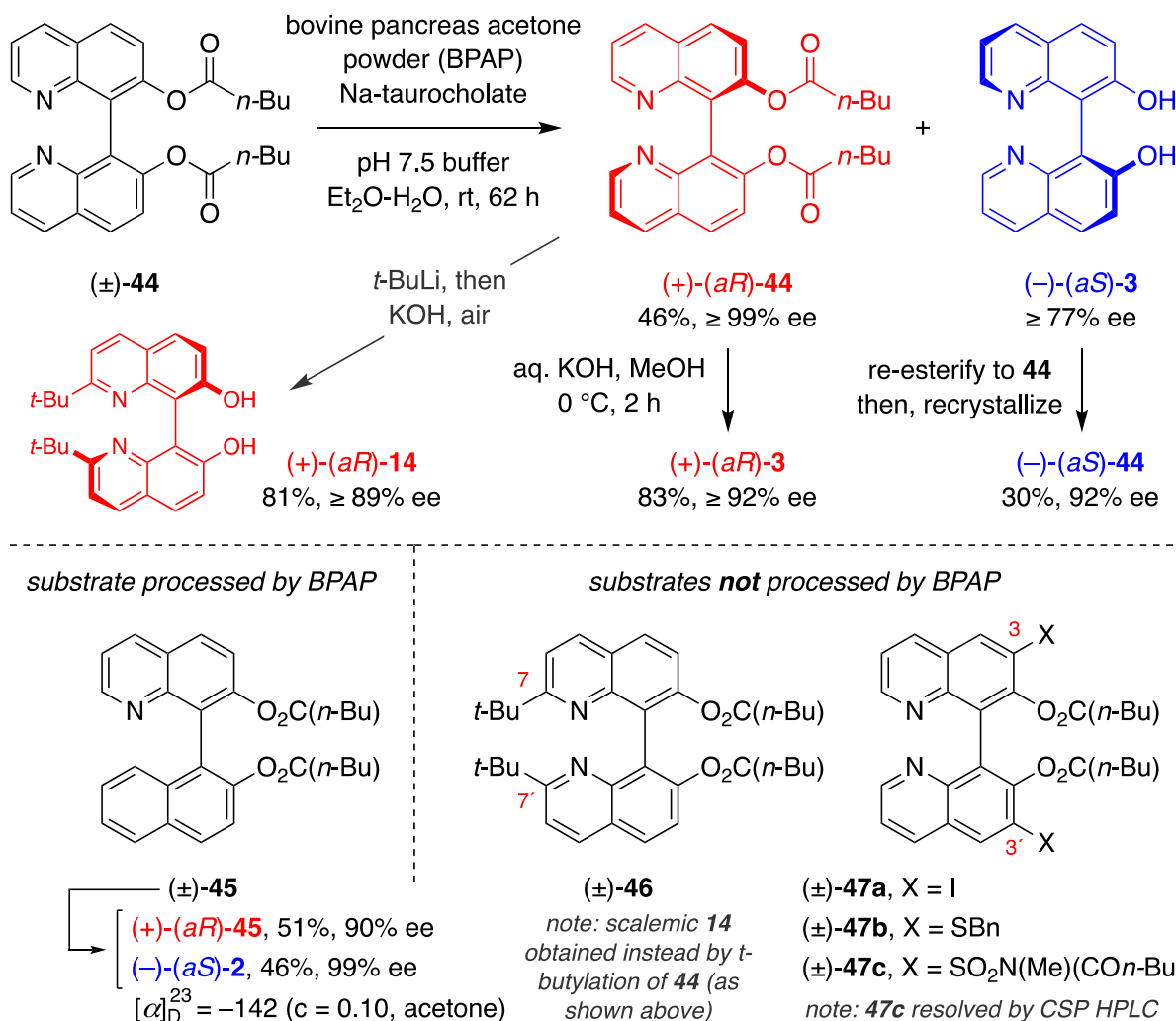
It has generally been found that methods developed for the resolution of BINOL (**1**) are also effective when applied to the resolution of the isostructural azaBINOLs. Drawing a parallel to an approach successfully used for the resolution of various BINOLs²⁶ enantioenriched samples of 8,8'-diazBINOL (**3**) were first obtained by chromatographic separation of the diastereomeric biscarbonates (**43**) formed by acylation with (+)-menthyl chloroformate (**42**), followed by saponification (Scheme 10). An XRD analysis of the biscarbonate antecedent $[(-)-lk-(aS)-43]$ of levorotatory 8,8'-diazBINOL enabled unambiguous assignment of absolute configurations to the enantiomeric atropisomers of this parent azaBINOL as $(-)-(aS)-3$ and $(+)-(aR)-3$.³



Scheme 10. Resolution of 8,8'-diazBINOL (**3**) by chromatographic separation of diastereomeric bismenthyl carbonate derivatives (**43**) and assignment of absolute configuration as $(-)-(aS)-3$ and $(+)-(aR)-3$ by virtue of an XRD analysis of intermediate biscarbonate $(-)-lk-(aS)-43$.³

The biscarbonate resolution method was significant for providing absolute stereochemical assignments, but it is impractical to apply above a 500 mg scale and so a superior method was sought to obtain scalemic azaBINOLs. Here again, the isostructural relationship between azaBINOLs and BINOL proved useful. Thus, Kazlauskas had reported the curious discovery that cholesterol esterase (a digestive enzyme found in mammalian pancreas) is an effective catalyst for the hydrolytic kinetic resolution of (\pm)-BINOL diesters despite their lack of any obvious similarity with the natural substrate of the enzyme, cholesterol acetate.²⁷ Adding to the utility of the method, it was found that the resolution does not require purified enzyme and that inexpensive bovine pancreas acetone powder (BPAP) will suffice. As anticipated, Kazlauskas' method proved

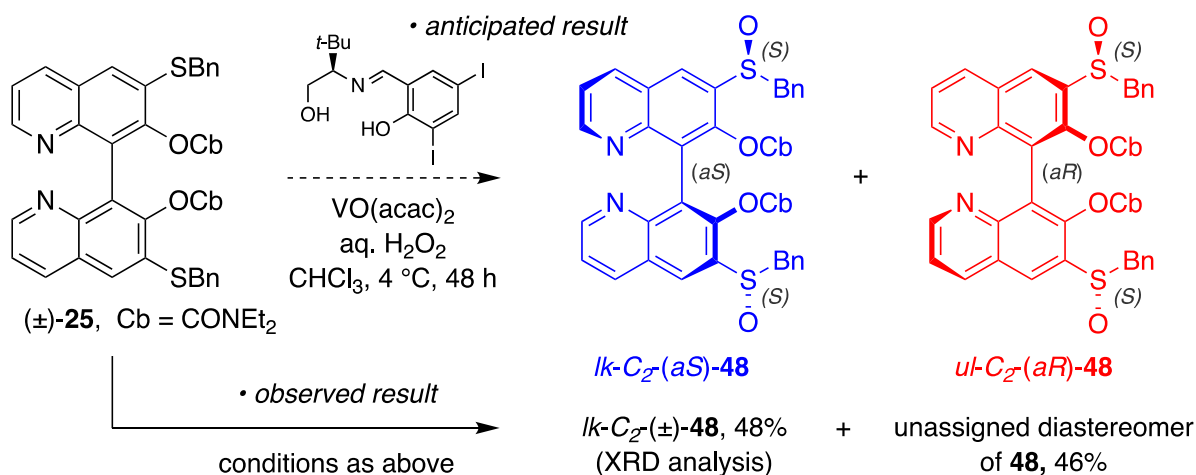
highly effective for the resolution of the racemic dipentanoates of 8,8'-diazabINOL (**44**) and 8-azaBINOL (**45**); also, and as for the dipentanoate of (\pm)-BINOL, it was found that (*aS*)-configured diesters of the azaBINOLs were hydrolyzed while their (*aR*)-antipodes were not (Scheme 11).^{4,9} 8,8'-DiazabINOL (**3**) has limited configurational stability (see Section 3.2) and so it is best to immediately reconvert the product of esterase digestion, (*-*)-(*aS*)-**3**, back into (*-*)-(*aS*)-**44**, which has high configurational stability (e.g., no change in %ee after 7 d at 110 °C in toluene), for storage. When needed, scalemic samples of **3** are conveniently obtained by a mild and fast saponification procedure at 0 °C.⁴ The heightened configurational stability of 8-azaBINOL (**2**) means that there is no need to store scalemic material in diester form; however, to safeguard against loss in %ee over time, it should be kept in a refrigerator.⁹



Scheme 11. Resolutions and attempted resolutions of azaBINOL diester derivatives using bovine pancreas acetone powder (BPAP). Resolution yields are given as the quotient of moles received to total moles of racemate input (i.e., 50% yield with 100% ee is a perfect resolution).^{4,9}

Additional substituents, either at C7/C7' or C3/C3' on the azaBINOL scaffold, are not tolerated by the esterase; thus, neither (\pm)-**46** nor any of a family of potential precursors to bissulfonamide **5** [(\pm)-**47abc**] were processed by BPAP. The need to resolve (\pm)-**46** was obviated with the finding that addition of *t*-butyllithium to (+)-(*aR*)-**44** followed by oxidative saponification of the intermediate double *tert*-butylated bisdihydroquinoline

diester, gave the desired enantioenriched azaBINOL (+)-(*aR*)-**14**.⁴ Identification of a method to obtain bissulfonamide **5** in enantioenriched form was not easy and the prosaic solution ultimately identified to solve this problem, HPLC based separation of the atropisomers of tetrapentanoyl derivative (\pm)-**47c** using a chiral stationary phase (CSP),⁷ belies the many alternative approaches that were investigated for this purpose.²⁸ Of the unsuccessful resolution strategies that were evaluated, one of them gave a curious result that warrants comment here because it likely informs on the coordinating ability of azaBINOLs. Thus, it was anticipated that catalytic enantioselective sulfoxidation of racemic bissulfide **25** using the efficient method of Jackson *et al.*²⁰ (as illustrated) would result in bifurcation of the starting material into a pair of enantioenriched bissulfoxide products, each of C_2 -symmetry, one of 'like' relative configuration, *lk*- C_2 -(*S,S,aS*)-**48**, and the other of 'unlike' relative configuration, *ul*- C_2 -(*S,S,aR*)-**48** (Scheme 12). The expectation here is of course that sulfoxide formation is reagent controlled and that the first oxidation event does not affect the second. In this scenario, the third possible diastereoisomer of **48**, a non-symmetric pseudo-*meso*-type isomer, should not be formed. In the event, we were initially delighted when the experiment afforded two, and not three, diastereoisomers of **48**, and each of those in an essentially equal quantity. The isomers were separable by standard silica gel column chromatography and the faster eluting one was discovered to possess *lk*- C_2 -type stereochemistry by a single-crystal XRD analysis. However, conversion of the *lk*- C_2 -**48** so obtained to the biscarbamate precursor of bissulfonamide **5** (**26**) using the conditions shown in Scheme 5 (step b), gave optically inactive material. Furthermore, it was discovered that running the oxidation of **25** in the absence of a chiral ligand gave the same product diastereomer ratio. On the basis of the observed results, it is evident that sulfoxidation in this case is substrate-, and not reagent-, controlled; thus, it is not possible to escape the racemic starting state of (\pm)-**25** with this particular implementation of the resolution concept envisioned. Nonetheless, it is likely that the general strategy embodied here could be effective for the resolution of racemic azaBINOLs using other types of enantioselective chemistry.



Scheme 12. An envisioned oxidative resolution of **25** by conversion of each atropisomer to a different diastereomer of **48** using an enantiopure chiral metal-complex (top) and the observed result (bottom).²⁸

Perhaps as may be expected, BINOL and azaBINOL compounds share closely related chiroptical properties and they display the bisignate exciton Cotton effect features typical for biaryls in their electronic circular dichroism (eCD) spectra.³⁰ For a given absolute configuration, the parent compounds **1**, **2**, and **3** share the same eCD exciton chirality phase with (*aS*)-isomers showing a positive exciton chirality phase (Figure 6).^{3,9} The

exciton feature becomes weaker and it is red-shifted as the series is traversed from **1** to **2** to **3**. In the absence of more definitive techniques to determine absolute configuration, exciton chirality phase may be used to make a tentative assignment of configuration for a given new scalemic azaBINOL derivative; however, it should be noted that biaryls of the same absolute configuration but with distinctly different preferred interannular dihedral angles (i.e., conformer distributions) need not share a common exciton chirality phase.³⁰

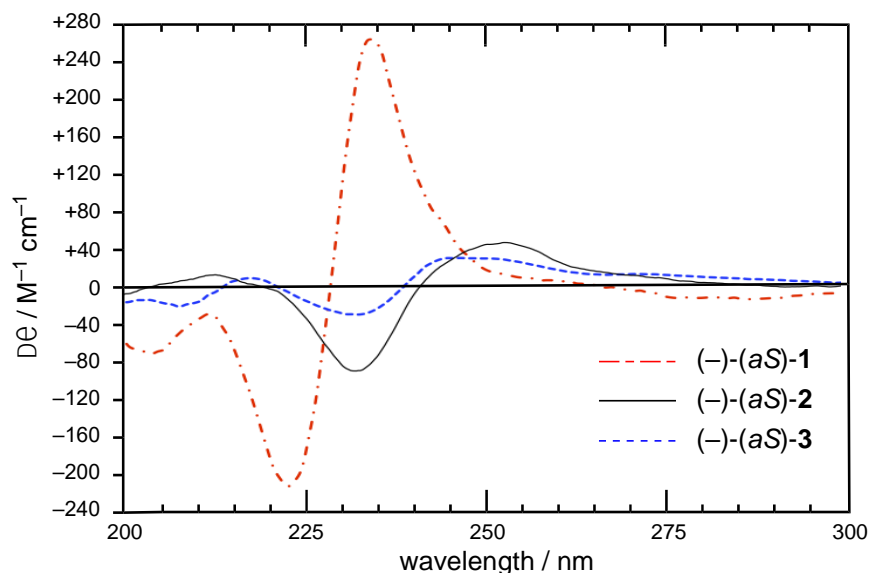


Figure 6. Electronic circular dichroism (ECD) spectra of levorotatory (*aS*)-configured azaBINOLs (**2**, **3**) and BINOL (**1**) each showing a positive exciton chirality phase. Spectra for (*−*)-(*aS*)-**1** and (*−*)-(*aS*)-**2** collected from MeOH solution and that for (*−*)-(*aS*)-**3** from H₂O. All plots are corrected to 100% ee.^{3,9}

3.2. Enantiomerization and racemization kinetics of azaBINOLs

Within this section, the enantiomerization and racemization behaviors of azaBINOL compounds and BINOL are considered. Some confusion exists in the literature as to the subtle distinction between the formal processes of *racemization* and *enantiomerization*, and so a brief digression will be taken here to define each of these 'reactions'. An excellent tutorial on this topic was recently provided by Mayor *et al.*³¹

- *Racemization* is a macroscopic process describing an ensemble of enantiomers attaining a net racemic state and it can be formalized for kinetic purposes as a first-order reaction involving a homochiral complex of a pair of chiral molecules, (+)-**A**•(+)-**A**, that becomes a heterochiral pair, (+)-**A**•(−)-**A** (Figure 7). This treatment enables progression from an enantiopure (or enantioenriched) starting state toward a racemic final state to be mapped. As so defined, racemization has a conclusion and it is complete when all (+)-**A** molecules are equally paired with an (−)-**A** molecule partner such that there is no more free (+)-**A**•(+)-**A** 'starting material' (i.e., *er* = 50:50). The *rate* of racemization is highest at the start of the reaction and it decays over time exponentially to become effectively zero after multiple half-lives of racemization have been endured.

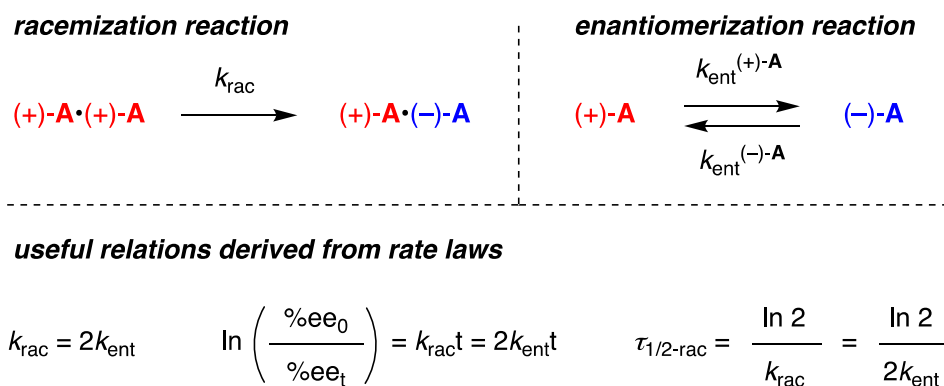
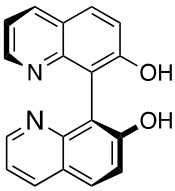
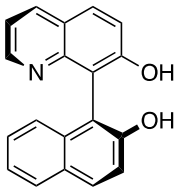
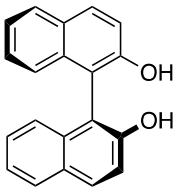


Figure 7. The formalized processes of racemization and enantiomerization and some useful relations derived from the rate laws for each. %ee₀ = %ee at time t = 0; %ee_t = %ee at time t; τ_{1/2-rac} = half-life of racemization.

• *Enantiomerization* is a microscopic process describing the reaction of one molecule of (+)-A becoming one molecule of (–)-A (Figure 7). In a spontaneous setting, this process cannot be separated from the reverse process, (–)-A to (+)-A, and the rate constants for forward and reverse reactions are necessarily equal [$k_{\text{ent}}^{(+)\text{-A}} = k_{\text{ent}}^{(-)\text{-A}}$]. By contrast to racemization, enantiomerization is a reaction without end that continues indefinitely. In the ensemble, forward and reverse reactions will have different rates at a non-racemic state, but over time the two rates will equalize as entropy is maximized en route to thermodynamic equilibrium and arrival at the racemate (i.e., er = 50:50).

Enantiomerization is a more natural and a less contrived process to consider than racemization; furthermore, the activation parameters of interest for probing mechanism of biaryl configurational inversion are necessarily those for the microscopic process of enantiomerization, ΔG[‡]_{ent}, ΔH[‡]_{ent}, and ΔS[‡]_{ent}.³¹ Nonetheless, arguably the most intuitively accessible metric regarding configurational stability for a given molecule is its racemization half-life at a given temperature; thus, it should be noted that the rate constant for racemization is equal to twice that of enantiomerization, $k_{\text{rac}} = 2k_{\text{ent}}$, and so, $\tau_{1/2\text{-rac}} = (\ln 2)/(2k_{\text{ent}})$.³¹ Eyring plot analyses, which allow for extraction of the critical activation parameters, ΔH[‡]_{ent} and ΔS[‡]_{ent}, by measurement of the dependence of rate constants on temperature,³² were conducted for the enantiomerization reactions of parent azaBINOLs (**2**, **3**) and BINOL (**1**).^{3,9} Initial kinetic experiments concerning just 8,8'-diazabINOL (**3**) were performed in water,³ and follow-up studies were later extended to all three compounds in DMSO, a mutually compatible solvent.⁹ A 2012 study by Davoren *et al.* provides additional data for BINOL (**1**) in diglyme.³³ Data are collated together in Table 1 together with racemization half-lives obtained by substituting experimentally determined parameters ΔH[‡]_{ent} and ΔS[‡]_{ent} back into the Eyring equation at a given temperature of interest.

Table 1. Activation parameters for enantiomerization of parent azaBINOLs (**3**, **2**) and BINOL (**1**)

					
	----- 3 -----		2	----- 1 -----	
parameter / solvent	H ₂ O ³	DMSO ⁹	DMSO ⁹	DMSO ⁹	diglyme ³³
$\Delta H_{\text{ent}}^{\ddagger}$ (kcal mol ⁻¹)	+34.0	+27.4	+19.9	+23.2	+32.2
$\Delta S_{\text{ent}}^{\ddagger}$ (cal mol ⁻¹ K ⁻¹)	+18.7	+3.8	-27.9	-25.3	-15.6
temp. (°C)	$\tau_{1/2\text{-rac}}$	$\tau_{1/2\text{-rac}}$	$\tau_{1/2\text{-rac}}$	$\tau_{1/2\text{-rac}}$	$\tau_{1/2\text{-rac}}$
25	1.2 y	12 d	0.87 y	62 y ^a	1.9 x10 ⁶ y
50	4.9 d	7.2 h	22 d	2.8 y ^a	26 x10 ³ y
100	5.1 min	73 s	7.1 h	6.8 d ^a	27 y
200	15 ms	23 ms	69 s	10 min	19 h

Activation parameters for enantiomerization of parent azaBINOLs (**3**, **2**) and BINOL (**1**) as determined by Eyring plot analyses of kinetic experiments and calculated racemization half-lives ($\tau_{1/2\text{-rac}}$) at given temperatures obtained from the Eyring equation using the experimentally determined values for $\Delta H_{\text{ent}}^{\ddagger}$ and $\Delta S_{\text{ent}}^{\ddagger}$. Eyring equation, $k = (k_B/h) \cdot T \cdot \exp[(-\Delta H^{\ddagger} + T\Delta S^{\ddagger})/RT]$.

^aIndicated $\tau_{1/2\text{-rac}}$ values were erroneously listed as twice the illustrated magnitudes (i.e., 120 y, 5.5 y, and 14 d) in the original paper (ref. 9).^{3,9,33}

Regarding the directly comparable data in common DMSO solvent, and as highlighted above, configurational stability within the series of three analogous biaryls conforms with the order (**1** > **2** > **3**) expected based on simple heuristic grounds (Figure 5). However, the individual enantiomerization activation parameters for **3** are starkly different in their character to those for the naphthalene containing compounds **2** and **1**. Thus, the factor responsible for the lower configurational stability of **3** is not a low $\Delta H_{\text{ent}}^{\ddagger}$ value, which in fact is by far the highest within the series, but rather the finding that the entropy of activation for enantiomerization in this case is positive and not negative as for **2** and **1**.^{3,9} One plausible explanation is that an ordered solvation sphere of solvent molecules in the ground state is disrupted on the journey to the transition state; in accord with such a hypothesis, both $\Delta H_{\text{ent}}^{\ddagger}$ and $\Delta S_{\text{ent}}^{\ddagger}$ values for **3** are heightened in water, where solvation effects would be much stronger than in DMSO (i.e., in the case of H₂O and **3**, both substrate and solvent are H-bond donors and acceptors). The presence of a hydrophobic naphthyl unit in the chimeric azaBINOL **2** is perhaps enough to disrupt strong solvation effects and render it more akin to BINOL (**1**) than 8,8'-diazabino[1,2-b:1',2'-d']binaphthalen-2,2'-diol (**3**), and, since **2** possesses only one and not two peri CH bonds, an attendant drop in $\Delta H_{\text{ent}}^{\ddagger}$ occurs that accounts for the lower configurational stability of **2** vs. **1**. Before moving on, it is fascinating to note the enormous solvent dependence of enantiomerization rate for BINOL in DMSO vs. diglyme which at 25 °C is ca. 30,000 times faster in the dipolar aprotic solvent as compared to the polyether.

Returning to the bond rotation view of enantiomerization (Figure 5), it is of interest which of the two simple pathways, *syn* or *anti*, is preferred for a given biaryl system to achieve its configurational inversion. In

the case of BINOL (**1**), DFT calculations performed at the B3LYP/6-31G(d,p) level indicate that the *anti*-pathway (via an out-of-plane distorted structure similar to *anti*-**41**) is ca. 9 kcal mol⁻¹ lower in energy than the comparable *syn*-pathway.³⁴ We performed molecular mechanics calculations at the AM1 level for the enantiomerization of 8,8'-diazabINOL (**3**) and located similarly bond distorted *syn* and *anti* transition structures but in this case the *syn* structure (*syn*-**50**) was found to be preferred by ca. 6 kcal mol⁻¹ (Figure 7).³ A *syn* transition structure for the enantiomerization of **3** is expected to be particularly sensitive to low (<2) or high (>12) pH extremes because its dicationic [2(+)-*syn*-**49**] or dianionic [2(-)-*syn*-**51**] forms encounter greater electrostatic destabilization than one would anticipate for the analogous *anti* transition structure. Lending some credence to the result of the calculation, it was found experimentally that **3** is indeed more configurationally stable at extremes of the pH scale as compared to pH 7. Thus, strongly alkaline (1.0 M aq. NaOH) and strongly acidic (1.0 M aq. HCl) solutions of optically active **3** showed no deterioration in %ee during 20 h at 75 °C. The racemization half-life for **3** at the same temperature in neutral aqueous media is only ca. 2.5 h. Interestingly, and by contrast to **3**, BINOL (**1**) becomes less configurationally stable at pH extremes.³⁵

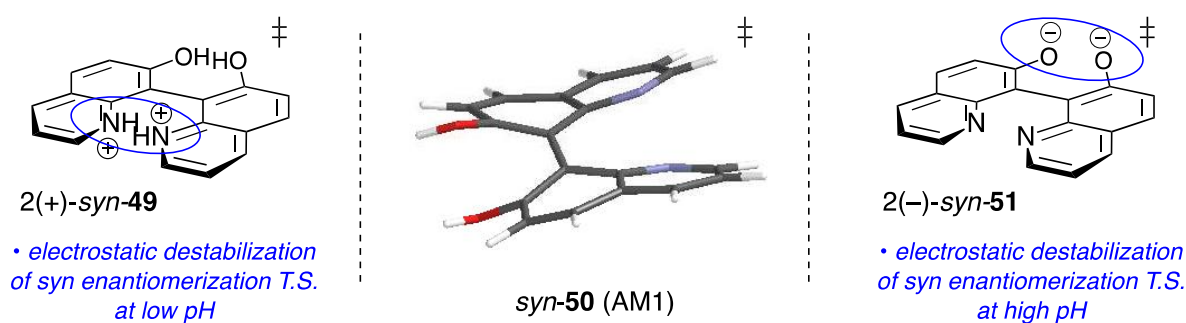


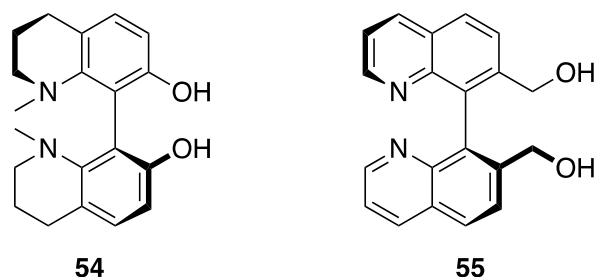
Figure 8. Lowest energy computed transition state for the enantiomerization of 8,8'-diazabINOL (**3**) via AM1 molecular mechanics simulation and anticipated electrostatic destabilization of dicationic and dianionic forms.

Significant solvent dependent trends for configurational stability have been observed for a number of more soluble azaBINOLs (Table 2).^{4,9} For example, 7,7'-di-*tert*-butyl-8,8'-diazabINOL (**14**), a compound that is far less configurationally stable than 8,8'-diazabINOL (**3**) despite possessing bulky substituents, racemizes 16 times faster in chloroform as compared to methanol. The solid-state (XRD analysis) structure of **14** exhibits interannular H-bonds (N...HO) between opposing quinol units (Figure 4) and disruption of these interactions, which presumably lower the barrier to configurational inversion, by a H-bond donating/accepting solvent such as methanol, results in increased configurational stability.⁴ Consistent with this finding are the facts that 2-deoxy-8-azaBINOL (**52**), which is also capable of supporting an interannular H-bond, is likewise less (33 times) configurationally stable in chloroform vs. methanol, while the racemization half-life for its regioisomer 2'-deoxy-8-azaBINOL (**53**), which cannot form such a H-bond, does not show a strong solvent dependency.⁹ An unexpected exception to this behavior was observed for 8-azaBINOL (**2**) which, although embedding the same motif found within **52**, actually exhibits greater configurational stability in chloroform than methanol.⁹

Table 2. Effect of solvent on racemization half-life for selection azaBINOL derivatives^{4,9}

	14	52	53	2
solvent	$\tau_{1/2\text{-rac}}$ (23 °C)	$\tau_{1/2\text{-rac}}$ (24 °C)	$\tau_{1/2\text{-rac}}$ (24 °C)	$\tau_{1/2\text{-rac}}$ (56 °C)
CHCl ₃	1.9 h	2.7 h	106 h	257 h
MeOH	30.5 h	89 h	120 h	70 h

Finally, it is noteworthy that two analogs of 8,8'-diazabino[1,1'-b]fluorene-2,2'-diol (**3**) have been introduced by others that nicely retain the C₂-symmetry and polyfunctionality inherent in the design of **3** while overcoming its poor solubility and modest configurational stability (Figure 9).^{36,37} Xiao and Loh prepared the bis(tetrahydroquinolyl) analog **54** by transfer hydrogenation of **13** followed by double *N*-methylation and saponification, and noted that the resolved enantiomers (obtained by chromatographic separation of diastereoisomeric menthyl carbonates, cf. Scheme 10) retained their enantiomeric excess for 'several months' upon storage at rt.³⁶ Kitamura *et al.* increased configurational stability of the biquinoyl system of **3** by formally exchanging phenolic OH groups for bulkier hydroxymethyl moieties, as in **55**. Interestingly, it was demonstrated that **55** can be accessed by analogy to the second generation synthesis of 8,8'-diazabino[1,1'-b]fluorene-2,2'-diol (see Section 2.2) by a Pd(II)-mediated directed CH functionalization of 7,7'-dimethyl-8,8'-biquinol.³⁷ Scalemic samples of **55**, obtained by preparative chiral stationary phase HPLC based resolution of the racemate, or by application of the Pd(II) oxidation chemistry to enantioenriched 7,7'-dimethyl-8,8'-biquinol, exhibited no loss in optical activity after storage for two months at rt or after being refluxed in toluene solution. Applications for these potentially useful materials have yet to be reported.

**Figure 9.** Two analogues of 8,8'-diazabino[1,1'-b]fluorene-2,2'-diol (**3**) with heightened configurational stability and solubility.^{36,37}

4. Physical and Thermodynamic Properties of AzaBINOLs

Some of the physical properties of azaBINOL compounds have been commented on above, for example, it is generally found that 8,8'-diazabino[1,1'-b]fluorene-2,2'-diol derivatives are crystalline solids and the parent compound (**3**) is a high melting solid soluble only in dipolar and/or protic solvents (e.g., H₂O, DMSO, DMF). Masking of the phenolic

OH groups as ethers or esters dramatically improves solubility, as does the addition of alkyl groups elsewhere (e.g., **14**). By contrast to their symmetrical diaza counterparts, 8-azaBINOL derivatives of all kinds are generally soluble in common organic solvents but such compounds are less likely to be crystalline solids. The amphoteric nature of azaBINOLs is a key feature of these molecules and an attribute that may provide for applications in materials chemistry and reaction catalysis. The thermodynamic basicity of 8,8'-diazabINOL ethers has been studied in detail and it is addressed within this section.⁵

4.1. Dependence of basicity on conformation and response of interannular dihedral angle to pH

Polyfunctional biaryl compounds, like the azaBINOLs, provide a convenient platform for the study of proximity effects because opposing aromatic rings can be decorated with functional groups that must face one another across the biaryl axis. Interaction between the functional groups can be expected to modulate their reactivity and properties. In the case of 8,8'-diazabINOL, in which weakly basic quinoline units are linked together by a single rotatable bond, we became intrigued by the possibility of inducing a 'proton sponge' type effect by forcing the quinolyl *N*-atom lone-pairs into close proximity through the agency of a diether tether between the two phenolic *O*-atoms, as in **58** (Figure 10). Here, a dependency of pK_{aH} (i.e., the pK_a of the conjugate acid of the given base) on diether tether length was anticipated with an expectation that basicity would *increase* as *n* is decreased. The original proton sponge, 1,8-bis(dimethylamino)naphthalene (**56**), was discovered by Alder to possess a remarkably high basicity ($pK_{aH} = 12.3$),³⁸ some seven orders of magnitude higher than comparable simple anilines (i.e., pK_{aH} of *N,N*-dimethylaniline is 5.2), because of the relief of lone-pair/lone-pair repulsion induced strain upon protonation.³⁹ Heightened basicity due to the same kind of free base destabilization was found by Staab and coworkers for the benzannulated diquinoline **57**, a compound topologically related to 8,8'-diazabINOL, which is over five orders of magnitude more basic than quinoline ($pK_{aH} 4.9$).⁴⁰ Notwithstanding the structural resemblance of **58** (small *n*) to **57**, it was found that the basicity of cyclic diethers **58** actually *decreases* significantly as *n* decreases. During the course of this work we also discovered that the interannular dihedral angle within diazaBINOLs is responsive to pH.⁵

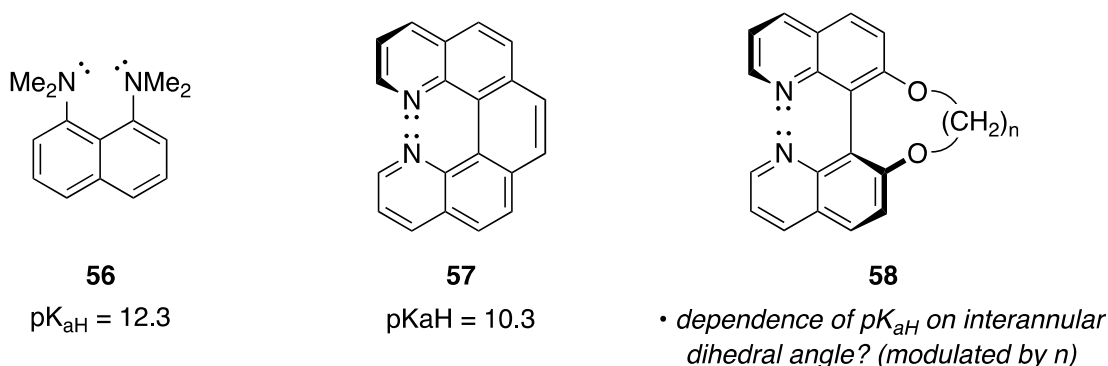
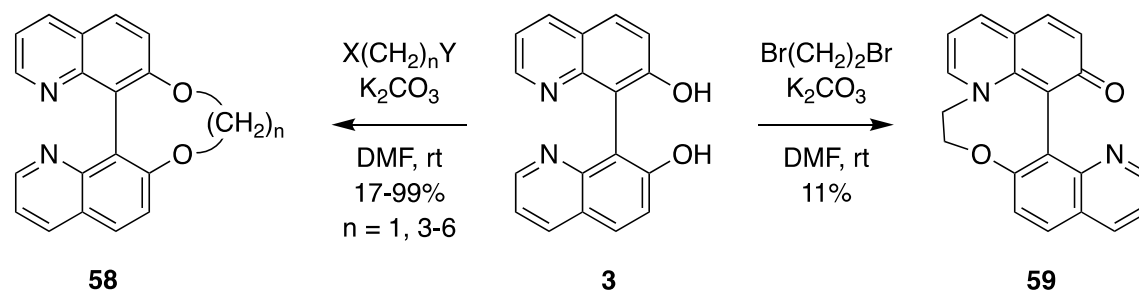


Figure 10. Two compounds with strain induced heightened thermodynamic basicity, Alder's original proton sponge, 1,8-bis(dimethylamino)naphthalene (**56**),³⁸ and Staab's diaza[5]helicene (**57**),⁴⁰ and cyclic diether derivatives of 8,8'-diazabINOL (**58**) with tunable interannular dihedral angles (IDA).⁵

Cyclic diethers **58** (*n* = 1, 3-6) were prepared in a straightforward manner from 8,8'-diazabINOL (**3**) via the Williamson ether synthesis (Scheme 13). Attempts to access **58** (*n* = 2) using the same approach led instead only to the *N,O*-linked quinolinyquinolone **59**.⁵ All of the cyclic diethers were crystalline materials and each was subjected to XRD analysis, as was the dimethyl ether derivative of 8,8'-diazabINOL (**60**) for comparative

purposes (Figure 11; data for $n = 4$ and 6 can be found in the original paper).⁵ The diether linkage fulfilled its desired function and interannular dihedral angle (IDA) was found to smoothly decrease as the alkylidene chain length was shortened; each cyclic diether was cisoid (i.e., acute IDA) while the non-constrained diether **60** exhibited a transoid (obtuse IDA) conformation. The observation of associated variations in λ_{\max} for the ${}^1A \rightarrow {}^1B_b$ quinoline electronic transition,⁴¹ which has a long-axis aligned transition moment and so sensitive to IDA in 8,8'-diazabINOLs, as the series of cyclic diethers **58** is traversed gave confidence that similar conformational changes are most likely also manifested in a solution phase. Acidity constants for the compounds of interest were determined by potentiometric titration in aqueous methanol. As noted above, the opposite trend to that expected for pK_{aH1} vs. n was observed, with the biquinolyls actually becoming less basic as IDA narrows and the N-atom/N-atom contact distance lessens, to the extent that **58** ($n = 1$) is over two orders of magnitude less basic than its unconstrained congener **60**. It is likely that the biquinolyl lone-pairs within **58** ($n = 1$) remain too far apart for strain-induced basicity effects to operate. Instead, as IDA tightens, the ease of solvation of the biquinolium monocationic conjugate acid form is presumably lessened due to steric effects and so there is an attenuation in basicity (solvation effects are well appreciated to be an important factor in determining pK_{aH} for alkylamines).⁴²



Scheme 13. Synthesis of cyclic diethers **58** ($n = 1, 3-6$) and unexpected generation of quinolylquinolone **59**. X, Y = Cl, Br, or I.⁵

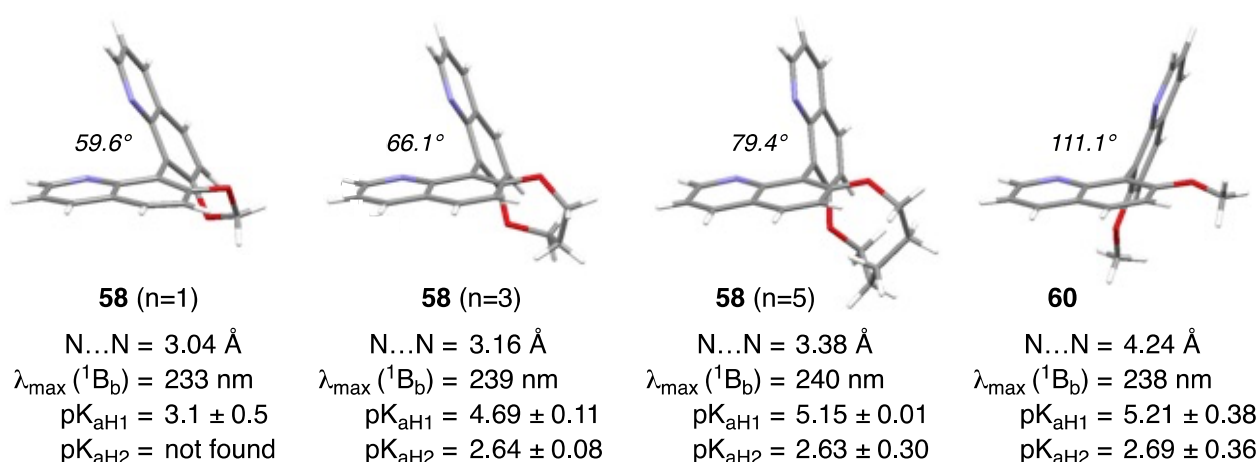


Figure 11. Solid state structures for cyclic diethers **58** ($n = 1, 3, 5$) and dimethyl ether **60** obtained from single crystal X-ray diffraction analyses, structural and spectroscopic parameters of interest, and acidity constants determined by potentiometric titration experiments in MeOH/H₂O.⁵

A corollary to the fact that basicity of 8,8'-diazabINOLs is dependent on IDA was established with the finding that the preferred IDA of unconstrained examples is influenced by their protonation state. Thus, in the solid state (XRD analyses, see Figure 12), the IDA for dimethyl ether **60** was found to transition from obtuse to acute upon monoprotection with perchloric acid (**60** to **60**•HClO₄) and then to return to an obtuse state upon addition of a second proton (**60**•HClO₄ to **60**•2HClO₄). The cisoid nature of **60**•HClO₄ was attributed to Coulombic attraction between the cationic quinolinium ring and the opposing electron-rich/basic quinoline ring that still possesses its N-atom lone-pair. By contrast, electrostatic repulsion between the cationic sites within **60**•2HClO₄ may account for its transoid conformation. Lending some credence to this argument, it was found that **58** (n = 1) could not be converted beyond its monoprotected state [**58**•HClO₄ (n = 1)] to the putative double salt **58**•2HClO₄ (n = 1). In this case, repulsion within such a dication cannot be relieved by a widening in IDA because the short cyclic diether tether does not allow for such conformational flexibility (note: the solid state IDA for **58**•HClO₄ (n = 1) was found to lie between 50.8-53.6° by XRD analysis).⁵

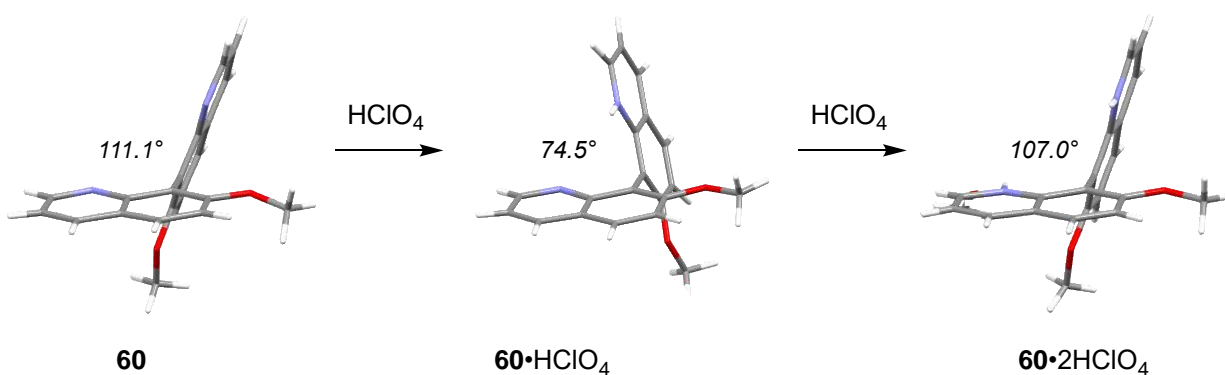


Figure 12. Solid state structures for dimethyl ether **60** and its single (**60**•HClO₄) and double perchlorate salts (**60**•2HClO₄) obtained from single crystal X-ray diffraction analyses. Perchlorate counter anions and solvent molecules are omitted for clarity.⁵

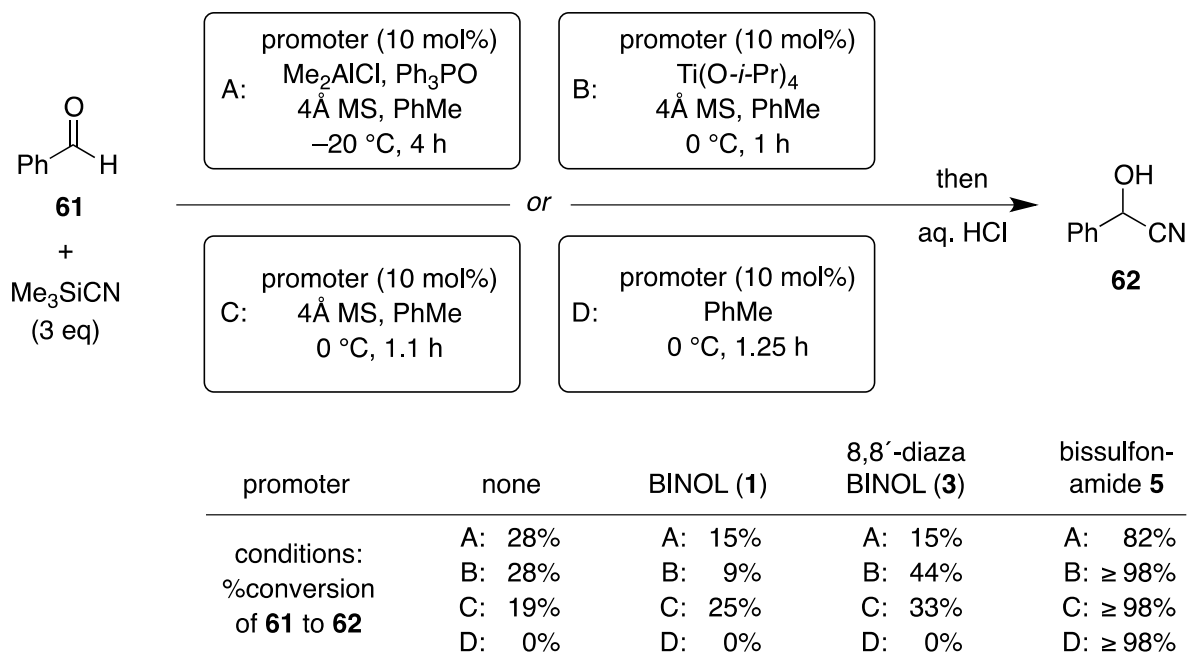
5. Promotion and Stereocontrol of Reaction Chemistry by AzaBINOLs

The polyfunctional nature of azaBINOLs, the ease with which such structures can be decorated with additional ancillary moieties, and their inherent axially chirality, offer numerous opportunities for utilization of these biaryl molecules as catalysts, reagents, and/or metal ligands in enantioselective synthesis. Of primary interest are reaction types that may benefit specifically from the presence of the quinoline N-atoms and that could not necessarily be replicated by simpler carbocyclic BINOL-based compounds. Documented in this section are our explorations of various azaBINOL derivatives as reaction promoters and stereocontrolling elements in a range of processes of contemporary interest.

5.1. Silylcyanation of C=X bonds catalyzed by a bisulfonamidyl 8,8'-diazabINOL derivative

As related above (Section 1.1), the original motivation for studying azaBINOLs was to realize an ambifunctional catalyst of type **4**, conceivably embodied by a notional metal complex (**6**) of sulfonamide **5**. Silylcyanation of carbonyl compounds and imines was selected as a suitable benchmark process to explore the effectiveness, or otherwise, of such a construct since it is known that the addition of TMSCN across C=X bonds benefits from

dual activation of the pro-nucleophile and the electrophile.⁴³ Shibasaki's complex **7** and Najera's complex **8** are examples of BINOL-based ambifunctional silylcyanation catalysts that were known at the time of our work to promote highly enantioselective cyanohydrin formation;^{12,13} however, the orientation of Lewis acid and Lewis basic sites in each of them is fundamentally different from that envisioned in **6**. Unfortunately, experiments to elucidate the speciation of metal ions by bissulfonamide **5** following its incubation with various metal sources (e.g., $\text{BH}_3\cdot\text{thf}$, $\text{MeB}(\text{OH})_2$, Me_2AlCl) were inconclusive;²⁸ nonetheless, we moved forward with an examination of TMSCN addition to benzaldehyde with and without Al(III) and Ti(IV) metal additives and in the presence or absence of BINOL (**1**), 8,8'-diazabINOL (**3**), and bissulfonamide **5** (Scheme 14).⁷



Scheme 14. Silylcyanation of benzaldehyde with and without metal additives in the presence or absence of BINOL (**1**), 8,8'-diazabINOL (**3**), and bissulfonamide 8,8'-diazabINOL derivative **5**.⁷

The surprising outcome of this study was the finding that bissulfonamide **5** itself, in the absence of any other components save for TMSCN and the aldehyde (Conditions D), was uniquely effective in promoting formation of the cyanohydrin, essentially as an organocatalyst. The silylcyanation reaction was extended to other aldehydes [RCHO : e.g., R (%yield) = BnCH_2 (89%), $c\text{-C}_6\text{H}_{11}$ (86%), $(E)\text{-PhCH=CH}$ (90%), 1-naphthyl (92%), 3-pyridyl (42%)] and a limited number of ketones [RCOME : R (%yield) = Ph (22%), $n\text{-C}_6\text{H}_{13}$ (82%)] and aldimines [RCH=NBn : R (% yield) = 3- ClC_6H_4 (72%), 3-pyridyl (14%)].⁷ Although it is a highly effective chemical promoter of silylcyanation, when bissulfonamide **5** was re-evaluated in scalemic form (>80% ee) it was revealed to be an inefficient stereoinductive element and cyanohydrin products were generated from aldehydes with uniformly low enantioselectivities [$< 10\%$ ee, $(-)\text{-(aR)-5}$ gives cyanohydrins with (S) -configuration].⁷

To identify which structural features are responsible for the organocatalytic activity of **5**, a series of related sulfonamides were prepared and likewise evaluated as promoters for the conversion of benzaldehyde (**61**) to mandelonitrile (**62**) (Figure 13). Aside from additional methylation of the sulfonamidyl NHMe group (**63**), all other structural changes investigated significantly lowered catalytic activity or eliminated it altogether. Thus, loss of free phenolic OH groups (**26** and **66**) or quinoline N-atoms (**65**) resulted in catalytically incompetent molecules while a monomeric quinoline analog of **5** (**64**) was barely active, revealing that the

proximity of contrasting functional groups on opposite sides of the biaryl axis is important for effective silylcyanation.⁷

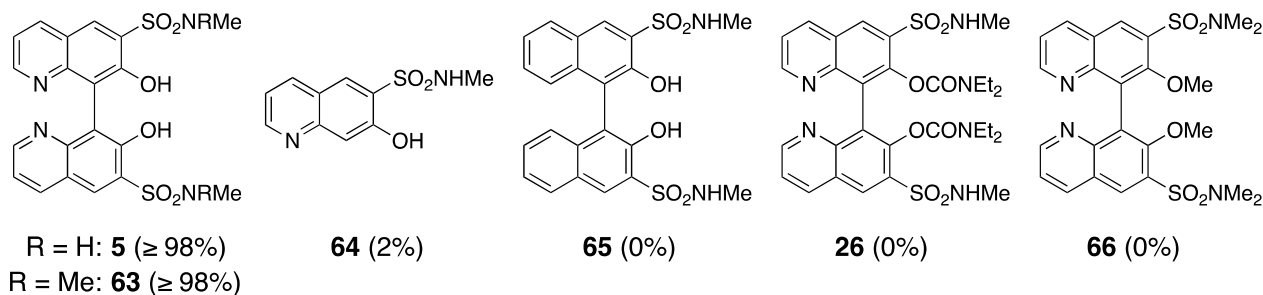
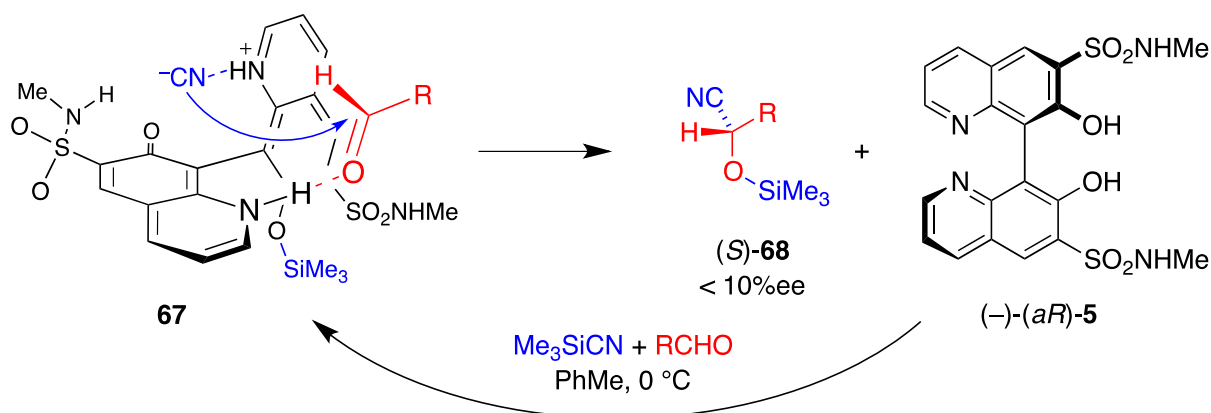


Figure 13. Evaluation of sulfonamides related to **5** as organocatalysts for the addition of TMSCN to PhCHO (**61**). Numbers in parentheses are the conversion of **61** to **62** using the indicated promoter and reaction conditions D (as shown in Scheme 14).

The above findings suggest that bisulfonamide **5** exerts its catalytic action through a combination of H-bond /Brønsted acid effects⁴⁴ (need for phenolic OH groups with vinylogous sulfamic acid character) aided by a general base capability (need for quinoline N-atoms) with close proximity (need for biaryl). On the basis of this analysis, and conforming to validated models proposed for other organocatalytic platforms for silylcyanation,⁴⁵ the mode of action of **5** is proposed to involve initial silylation of an acidic phenol by TMSCN then transfer of the resulting biquinolyl associated HCN to the aldehyde, itself activated by H-bond donation from an NH or OH moiety (Scheme 15).⁷ Consistent with a process that benefits from a bifunctional catalyst but with a rate-determining step requiring electrophilic activation of the aldehyde,⁴⁶ a modestly positive reaction constant ($\rho = +1.52$) was measured by a Hammett analysis of silylcyanation of a series of 4-substituted benzaldehydes.⁷ The low enantioselectivity realized by this chemically efficient mode of organocatalysis is not surprising when given the expectation of weakly directional interactions within the putative transition state assembly **67** and the fairly open space occupied by the aldehyde substrate. Conceivably, structural variations to bisulfonamide **5** could result in a more enantioselective catalyst.



Scheme 15. A mechanistic proposal and stereocontrol model for the addition of TMSCN to aldehydes as catalyzed by bisulfonamide **5**.⁷

5.2. Enantioselective Suzuki-Miyaura reactions mediated by a phosphanyl 8,8'-diazabINOL derivative

Axially chiral molecules, such as BINOL (**1**),¹ its related bisphosphine analog BINAP (**69**),⁴⁷ and the isoquinolyl substituted naphthalene biaryl system QUINAP (**70**),⁴⁸ are most commonly applied as chiral ligands to enable enantioselective metal-catalyzed processes (Figure 14). An obvious question to ask is whether members of the azaBINOL family could be similarly useful as simple ligands in metal-based asymmetric catalysis? The presence of multiple hard (phenoxide) and soft (quinoline N-atoms, arene) coordination sites within 8,8'-diazabINOL (**3**) complicates how a given metal center may be ligated; thus, for initial work, we elected to study a somewhat less complicated azaBINOL derived system, monophosphine **72**.⁸ Phosphine **72** is a nitrogenous analog of the well-studied monophosphine ligand MOP (**71**)⁴⁹ with the possibility of engaging a metal through interactions with both N- and P-atoms but in a manner quite distinct to the N/P ligand QUINAP (**70**).

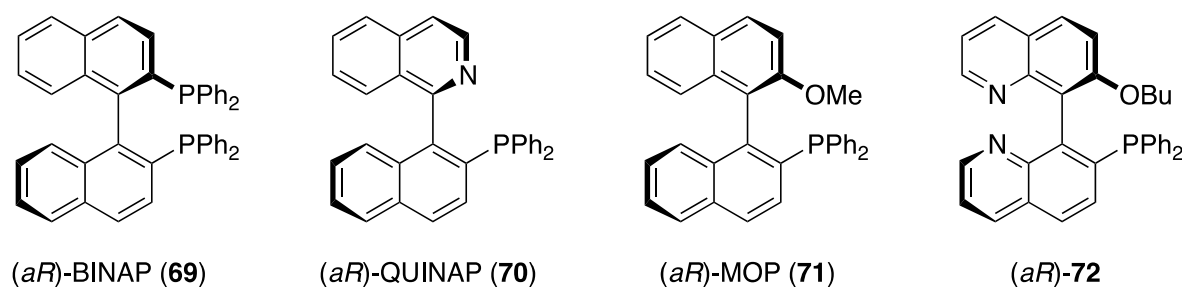
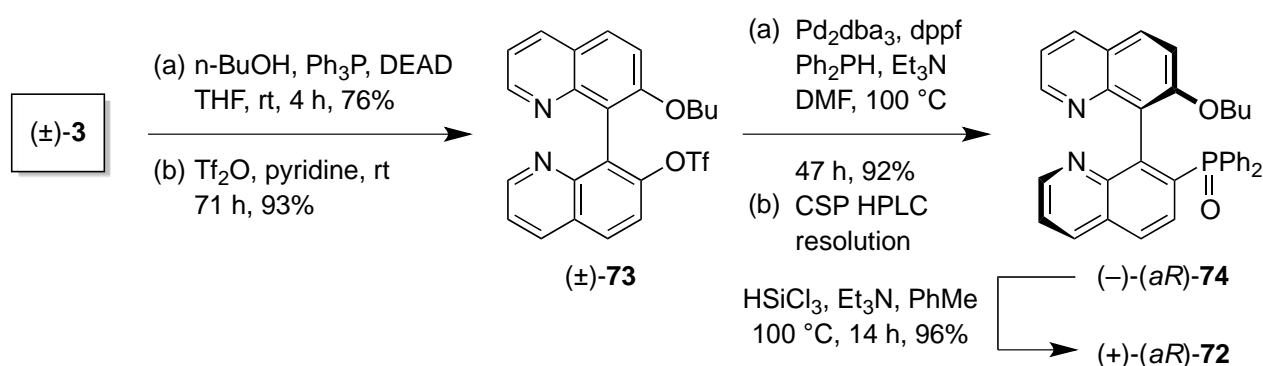


Figure 14. Three well-known axially chiral biaryl phosphine ligands (**69–71**) and an 8,8'-diazabINOL analog of MOP (**72**).

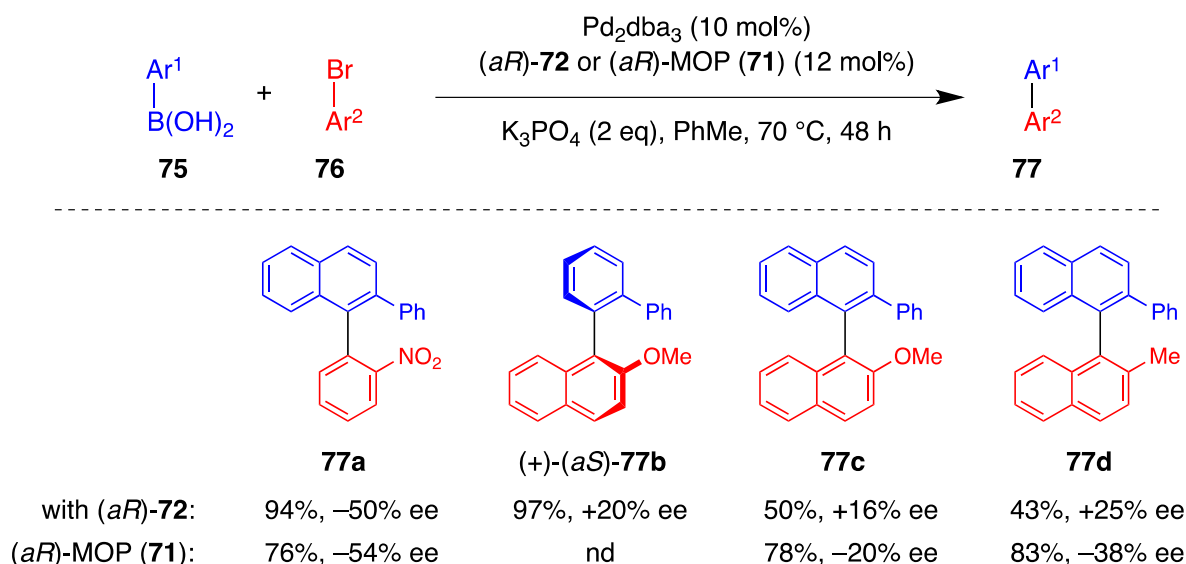
Phosphanylbiquinolyl **72** was accessed in a scalemic form from racemic 8,8'-diazabINOL (**3**) via Pd-catalyzed nucleophilic substitution of triflate **73** with diphenylphosphine in the presence of air, followed by resolution of the resulting phosphine oxide (**74**) by chiral stationary phase (CSP) HPLC and then reduction (Scheme 16). The absolute configuration of the enantiomeric atropisomers of **74** were assigned by comparison of eCD spectra with that obtained from the phosphine oxide derivative of (*aR*)-MOP. Phosphine **72** is configurationally stable beyond 100 °C in toluene, but it is chemically labile toward oxidative conversion back to its phosphine oxide **74** in solution in the presence of air (and indeed, much more so than MOP).⁸



Scheme 16. Synthesis of phosphine ligand **72** from 8,8'-diazabINOL (**3**).⁸

The efficacy of (*ar*)-**72** as a stereocontrolling chiral ligand for metal catalyzed enantioselective synthesis was evaluated in the context of the Suzuki-Miyaura cross-coupling approach to axially chiral biaryl molecules⁵⁰

and results were compared to its carbocyclic ligand congener (*ar*)-MOP (**71**) (Scheme 17).⁸ AzaBINOL phosphine **72** was found to be more efficient than MOP for the generation of modestly hindered biaryls (**77a,b**) but it was inferior in terms of both yield and enantioselectivity for the preparation of tetra-*ortho*-substituted biaryls (**77c,d**). Significantly, that 8,8'-diazabINOL derivative **72** is not simply an isostere for MOP (**71**) was revealed by the fact that the (*ar*)-enantiomer of each of these ligands produced hindered biaryls (**77c** and **77d**) with the opposite absolute configuration. Also of note, the excellent stereoselectivity provided by the commercially available MOP ligand for enantioselective Suzuki-Miyaura reactions was unknown prior to this study.⁸



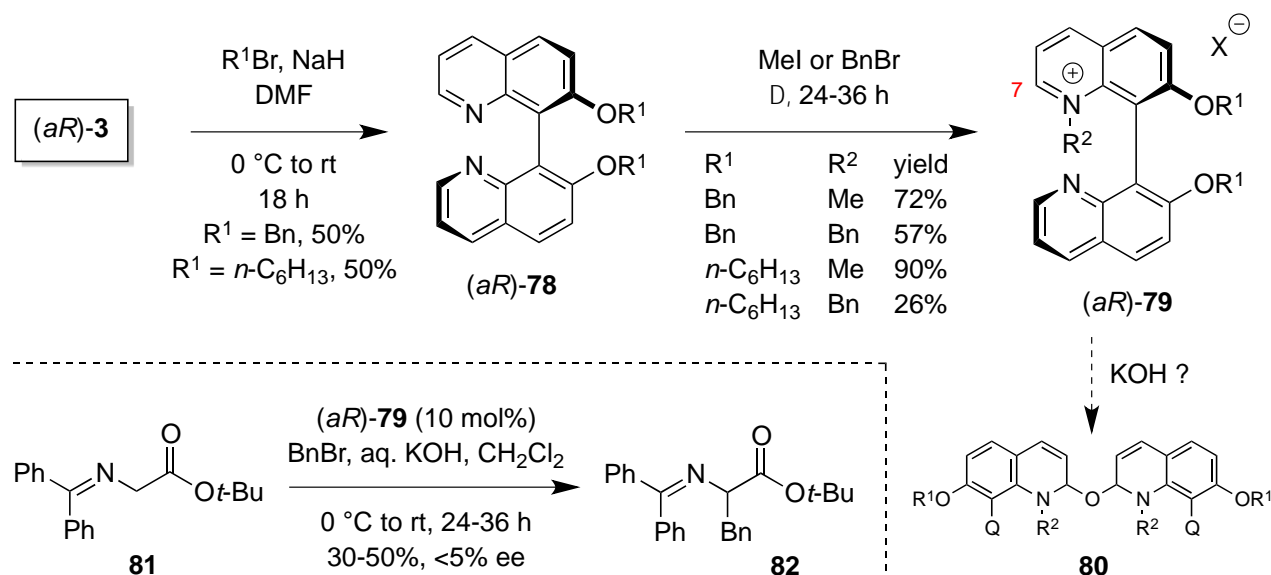
Scheme 17. Enantioselective formation of biaryls by Suzuki-Miyaura cross-coupling catalyzed by Pd(0) complexes of biquinolyl phosphine (*aR*)-**72** or (*aR*)-MOP (**71**). The sign associated with a given ee value is the sign of the optical rotation value for the biaryl product **77** obtained.⁸

5.3. Miscellaneous processes mediated by azaBINOL derivatives

Two applications of azaBINOL derivatives that have been explored in a more preliminary fashion are presented in this section: phase-transfer catalysis (PTC) using biquinolium salts and direct amidation using an azaBINOL derived boronic acid.^{28,51} Although in each case only limited success was realized, new chemotypes that can be accessed from the basic 8,8'-diazabINOL scaffold are revealed and it is hoped that the disclosure of this data here will provide a stimulus for further azaBINOL research.

5.3.1. Phase transfer catalysis with biquinolium cations derived from 8,8'-diazabINOL diethers. Enantioselective PTC using chiral organocations is a powerful means to effect a wide variety of reactions.⁵² O'Donnell and co-workers described the first genuinely useful such method; a synthesis of α -amino acids via alkylation of glycinate imine **81** in a two-phase solvent system promoted by quaternized ammonium salts prepared from cinchona alkaloids.⁵³ There are obvious limitations on the kind of organocationic structural motifs that can be accessed from alkaloid based templates and so, in a departure from tradition, Maruoka *et al.* introduced a novel class of organocations for enantioselective PTC based on axially chiral spiroammonium salts.⁵⁴ Further new types of chiral cations for PTC have been introduced more recently, including quaternary phosphonium salts derived from BINAP.⁵⁵ A vast majority of known chiral PTC's contain sp³-hybridized cationic atoms (N or P)

and although achiral pyridinium cations have been previously employed in PTC applications,⁵⁶ extensions to chiral analogs have not been reported. To explore the possibility of enantioselective PTC based on non-sp³-hybridized cationic centers, a small collection of biquinolinium salts **79** were prepared from 8,8'-diazabINOL diesters **78** and evaluated in the O'Donnell reaction (Scheme 18).⁵¹

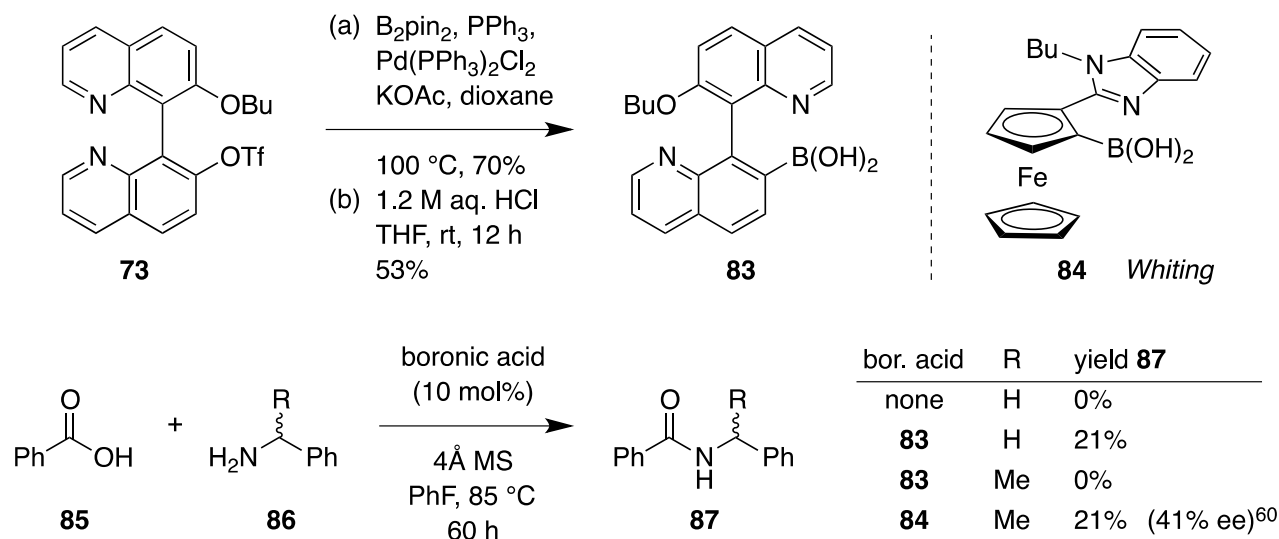


Scheme 18. Synthesis of quinolinium salts of 8,8'-diazabINOL diethers (**79**) and their evaluation as chiral phase transfer catalysts in the O'Donnell reaction of **81** to **82**.⁵¹

Diester **78** ($R^1 = \text{Bn}$, $n\text{-C}_6\text{H}_{13}$), accessed as illustrated via Williamson ether synthesis from enantioenriched 8,8'-diazabINOL (**3**), exhibit excellent solubility and were found to be configurationally stable (i.e., no change in optical rotation upon reflux in toluene for > 12 h). Conversion to the requisite monocationic biquinolinium salts **79** was achieved by simple heating in neat excess organohalide (MeI or BnBr); further alkylation to give dicationic species was observed upon protracted exposure to the alkylating agent. Biquinolinium salts **79** promoted the desired alkylation of glycine derived Schiff base **81** to give phenylalanine derivative **82**; however, a detectable level of enantiomeric excess was not discerned in **82** and progression of the reactions stalled after attainment of only modest yields due to catalyst decomposition. It is likely that irreversible conversion of *N*-alkyl biquinolinium salts **79** to the so-called 'pseudo-base diethers' **80**⁵⁷ is responsible for their limited turnover numbers. The addition of blocking groups at C7/(C7') is likely to improve the stability of **79** to nucleophilic attack of hydroxide, albeit the added steric hindrance will make quaternization of the biquinolyl more difficult. Other structural changes to this novel class of PTC's, most easily achieved by variations to R^1 and R^2 , could presumably positively impact stereoselectivity. *A propos* to this last point, the enantioselectivity offered by cinchonidium salt based PTC's is very sensitive to the alkyl group introduced to quaternize the 3° amine.⁵³

5.3.2. Direct amidation catalyzed by a boronic acid derivative of 8,8'-diazabINOL. Direct amide formation, i.e., the formation of amides from amines and carboxylic acids without stoichiometric activation of either coupling partner, is recognized as a significant and important challenge for contemporary organic synthesis.⁵⁸ Some of the most successful catalysts for achieving this aim are based on boronic acids, even quite simple examples, which readily generate competent acylating agents upon a facile dehydration reaction with carboxylic acids.⁵⁹ In a remarkable report, Whiting *et al.* disclosed that the planar chiral imidazolyl boronic acid

84 is capable of enantioselective amidation via kinetic resolution of racemic chain-branched 1° amines upon their acylation.⁶⁰ Inspired by this work, an axially chiral analog of **84** (**83**) was prepared from the 8,8'-diazBINOL-derived triflate (**73**) previously used as an intermediate *en route* to phosphine ligand **72** (Scheme 19). The azaBINOL based boronic acid **83** was found to be only a weakly active catalyst for direct amidation; thus, **83** is capable of promoting the formation of *N*-benzylbenzamide (**87**, R = H) from benzoic acid and benzylamine but not the comparable benzamide (**87**, R = Me) from α -methylbenzylamine. A more active catalyst would be necessary before an assessment of the potential enantioselectivity for this kind of system can be made.



Scheme 19. Synthesis of an 8,8'-diazBINOL boronic acid derivative (**83**) and its application as a catalyst for a direct amidation reaction with comparative data for Whiting's catalyst **84**.^{51,60}

6. Emerging Biological Activity of AzaBINOLs

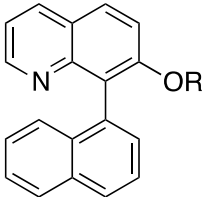
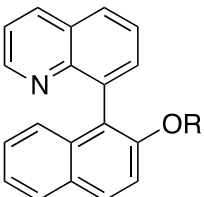
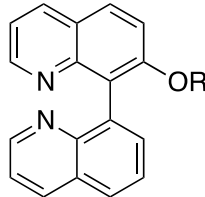
6.1. Prefatory remarks

Libraries of compounds designed to be used primarily as chiral ligands and/or organocatalysts for the purpose of enantioselective synthesis are seldom systematically screened for biological activity. This fact is regrettable when given that sources of novel structures are constantly needed by drug discovery efforts and that features present in organocatalysts and ligands that are necessary for their intended function (e.g., chiral scaffolds with few rotatable bonds, metal ion binding sites, H-bond acceptors and donors, sites of high charge density and/or ionization, and zones of steric encumbrance, etc.), could allow for them to engage in meaningful and selective interactions with proteinogenic targets implicated in disease amelioration. The polyfunctionality of azaBINOL derivatives, and the ease with which diverse sets of such compounds can be generated, means that this family of compounds is, in principle, particularly well-suited for biological screening efforts. Indeed, many better known biaryl molecules, and especially examples of natural origin,⁶¹ have shown useful biological activities, including selective anti-HIV activity.⁶² Accordingly, in a collaborative effort, we elected to screen a collection of azaBINOL derivatives against HIV relevant bioassays and in doing so, and as summarized below, a promising lead compound for HIV-1 neutralization that acts against a little explored molecular target was identified.¹⁰

6.2. Inhibition of HIV-1 RNase H activity by an ether derivative of 2'-deoxy-8-azaBINOL

HIV/AIDS remains a global health epidemic and although modern drug regimens are able to keep viral loads low in infected patients, these treatments are far from ideal, being at once expensive, subject to side-effects, limited in their geographical and socioeconomic group availability, and increasingly threatened by emergence of drug resistance.⁶³ Thus, novel therapeutics that act on previously untargeted steps of the viral life-cycle are of great interest. In a triage screen, three 8-azaBINOL derivatives were identified from a modestly sized library of azaBINOL compounds to possess promising activity in a pseudo-typed viral particle single-round infectivity assay (HIVpp) at single-dose concentrations: **88**, **89**, and **91**.¹⁰ These compounds, in addition to a set of three close-structural analogs including comparable 8,8'-diazBINOLs (**92** and **93**), were further evaluated for their IC₅₀ values against HIV-1 particles pseudo-typed with HIV-1 envelope proteins originating from three different HIV-1 strains in TZM-bl cells (the data illustrated for the HXB2 isolate are representative), and then in fully-infectious, replication competent HIV-1_{LAI} in LC5-RIC cells using the 'EASY-HIT' full viral infection assay system (Table 3).⁶⁴ Of the six compounds studied at this level of detail, only the isopropyl ether of 2'-deoxy-8-azaBINOL (**88**) showed consistent low micromolar IC₅₀ values against HIV-1 while exhibiting a cytotoxicity to efficacy selectivity index (CC₅₀/IC₅₀) in the employed cell types of over 10.¹⁰ It is noteworthy that isosteric changes to the structure of **88**, including formally relocating the isopropoxy substituent to the naphthyl-ring (**90**) and introduction of an additional aromatic-ring bound N-atom (**92**), result in loss of anti-viral activity.

Table 3. IC₅₀ and CC₅₀ values for the indicated ether (in black) or carbamate (in blue) azaBINOL

	 (±)- 88 (R = <i>i</i> -Pr) (±)- 89 (R = CONEt ₂)		 (±)- 90 (R = <i>i</i> -Pr) (±)- 91 (R = CONEt ₂)		 (±)- 92 (R = <i>i</i> -Pr) (±)- 93 (R = CONEt ₂)	
IC ₅₀ (HXB2)	6.7 ± 0.9	61.4 ± 3.3	> 100	12.6 ± 1.6	no effect	no effect
CC ₅₀ (TZM-bl)	68.5 ± 17.1	95.0 ± 13.1	> 100	69.3 ± 4.9	no effect	no effect
IC ₅₀ (HIV-1 _{LAI})	6.7 ± 1.4	24.1 ± 0.7	39.5 ± 1.7	50.1 ± 3.7	no effect	no effect
CC ₅₀ (LC5-RIC)	86.5 ± 3.7	51.9 ± 1.2	144.7 ± 7.7	71.4 ± 2.8	no effect	382.8 ± 166.2

IC₅₀ and CC₅₀ values for the indicated ether (in black) or carbamate (in blue) azaBINOL derivatives are in μM units. Details of appropriate control studies are described in the original publication.¹⁰

Given the promising *in vitro* anti-HIV activity discovered for **88**, which it was found extended to a multi-drug resistant isolate (HIV-1_{V13-03413B})⁶⁵ extensive mode-of-action studies were undertaken to identify its molecular target. These experiments, which included enzyme inhibition assays for HIV-1 integrase and HIV-1 reverse transcriptase (RT) dual functions (DNA polymerase and RNase H activity),¹⁰ revealed that **88** is likely to exert its anti-HIV-1 effect by specific inhibition of RT RNase H activity via a binding site distinct from that engaged by typical non-nucleoside RT inhibitors (NNRTIs).⁶⁶ Thus, the NNRTI efavirenz and **88** were shown not

to compete in their HIV-1 neutralization effects in an HIVpp assay.¹⁰ Few potential therapeutic agents for the treatment of HIV/AIDS have been identified to date that act by inhibition only of the RNase H function of the RT enzyme (and including: acyl hydrazones,⁶⁷ vinylogous ureas,⁶⁸ and cHTCs⁶⁹) and so the discovery of **88** is significant. It is speculated that the naphthyl moiety of **88** binds to a hydrophobic surface present on the RNase H domain of HIV-1 RT⁷⁰ leaving the polar substituted quinoline unit to further interact with interior aspects of the protein. The 8,8'-diazabINOL analog of **88** (**92**) lacks the requisite hydrophobic ring-system for effective binding, while the bulkier and more polar naphthyl ring of its regioisomer (**90**) likely also fails to properly engage with the hydrophobic surface.¹⁰ In ongoing work, it has been established that **88** is configurationally stable at rt and that its dextrorotary enantiomeric atropisomer has 3-6 times greater potency for HIV-1 neutralization than the levorotary antipode.⁷¹ In closing, it should be borne in mind that **88** is an unoptimized lead compound and that structural modifications are anticipated to result in improved binding affinity for the RNase H domain of the RT enzyme and an overall enhanced HIV-1 neutralization capability.

7. Conclusion and Outlook

This account on the chemistry and biology of the azaBINOL-family of compounds illustrates that fundamental research on novel chemical entities, even if initiated for esoteric purposes, will be likely to lead to useful discoveries if the molecular system in question offers something significantly new to be explored. For example, herein, in seeking to access 3,3'-disubstituted 8,8'-diazabINOL derivatives, the fascinating anionic rearrangements of 6-lithio-8-iodoquinoline **18** were uncovered (Section 2).² Elsewhere, in assessing the configurational stability of azaBINOLs, the fact that the enantiomerization pathway for 8,8'-diazabINOL (**3**) is wholly distinct from those of 8-azaBINOL (**2**) and BINOL (**1**) was unexpectedly revealed (Section 3).^{3,9} In other work, curiosity about strain-induced basicity led us to discover that the interannular dihedral angles within 8,8'-diazabINOL derivatives are dependent on pH (Section 4),⁵ a finding that could have implications for the creation of stimulus responsive extended materials (e.g., MOFs) that incorporate biquinolyls. In the latest research described (Section 6),¹⁰ a novel HIV-1 neutralization agent that inhibits RNase H activity of the dual function reverse transcriptase (RT) enzyme, *O*-isopropyl-2'-deoxy-8-azaBINOL (**88**), was identified from a library of azaBINOLs. Isosteres of ether **88** lack anti-viral activity and its bioactivity is dependent on absolute configuration; taken together, these facts indicate that the promising lead compound **88** engages in specific/directional interactions with its biological target and therefore meaningful optimization of the structure for better efficacy should be possible.

It is fair to acknowledge that the azaBINOL derivatives examined so far for reaction catalysis (all based on 8,8'-diazabINOL) have not delivered an acceptable level of enantioselectivity (Section 5). However, given that non-canonical reactivity modes for biaryl catalysts were studied, and that structural optimization efforts were not pursued, the poor stereocontrol encountered is perhaps not surprising and certainly it does not preclude more effective azaBINOL based catalysts being identified in future. Accordingly, further investigations of azaBINOL derivatives in reaction catalysis are warranted, including research on as yet unexplored azaBINOL chemotypes (e.g., *N*-oxides, 5-dialkylamino substituted etc.) and incorporating molecules based on 8-azaBINOL (**2**), which will offer solubility and configurational stability advantages over 8,8'-diazabINOL (**3**) derivatives. A powerful new method for the resolution of axially chiral azacyclic biaryls by enantioselective transfer hydrogenation, already successfully demonstrated for 8-azaBINOL derivatives in the first report of this process by Zhou *et al.*,⁷² complements existing approaches to access non-racemic azaBINOLS and will help to facilitate future studies.

Finally, notwithstanding the welcome discovery of an interesting organocatalysis mode for the silylcyanation of C=X bonds by bissulfonamide **5** (Section 5.1),⁷ it will not have escaped the notice of an attentive reader, that the validity of the original premise that motivated instigation of the azaBINOL project, namely bond formation catalyzed via the agency of a frustrated LA/LB pair manifested across a biaryl cleft (Figure 2), has yet to be tested. Before such a plan is revisited and truly evaluated, now with the benefit of hindsight, the speciation of metal residues by azaBINOL derivatives needs to be properly understood, beginning with experiments to probe the basic coordination chemistry of 8-azaBINOL (**2**), and then progressing to 8,8'-diazabINOL (**3**) before more elaborate ligand systems, such as bissulfonamide **5**, are tackled.

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Author's Biography



Paul R. Blakemore was born in East London in 1973. He obtained B.Sc. degrees in Chemistry and Mathematics from the University of Southampton (1995) and earned a Ph.D. degree from the University of Glasgow (1999) for research on sulfone-based olefination methods with Professor Philip J. Kocienski. Following post-doctoral work on the target-directed synthesis of complex natural product molecules with Professor James D. White at Oregon State University (USA), he began his independent career as a Royal Society University Research Fellow at the University of Leeds (UK) in 2001. Since returning to Oregon in 2005, Dr. Blakemore has been a faculty member of the Department of Chemistry at OSU where he is currently Professor of Chemistry. In addition to azaBINOL chemistry, his research is focused on the development of new methods for the absolute control of

molecular constitution and stereochemistry by using enantioenriched main-group chiral carbenoids as generic synthons for the synthesis of polysubstituted alkyl domains and carbon-carbon double bonds. Dr. Blakemore is the author of numerous research/review articles and book chapters and he currently serves on the editorial board of Organic Reactions (since 2018).

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