EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201200333

Silylcyanation of Aldehydes, Ketones, and Imines Catalyzed by a 6,6′-Bis-sulfonamide Derivative of 7,7′-Dihydroxy-8,8′-biquinolyl (azaBINOL)

Selena Milicevic Sephton,[a] Chao Wang,[a] Lev N. Zakharov,[a] and Paul R. Blakemore*[a]

Keywords: Organocatalysis / Biaryls / Nitrogen heterocycles / Cyanohydrins / Strecker reaction

6,6′-Bis(methylaminosulfonyl)-7,7′-dihydroxy-8,8′-biquinolyl (**3**) catalyzes (5–10 mol-%) the addition of trimethylsilyl cyanide to aldehydes (aryl, alkyl, and α,β-unsaturated; 42–92 % yields), ketones (aryl alkyl, dialkyl; 22–82 % yields), and *N*-benzylaldimines (14–78 % yields) in toluene (0 °C or room temp.) to give the expected cyanohydrin and Strecker adducts following desilylation. Among a series of closely related compounds lacking any one of their defining structural features, bis-sulfonamide **3** and its *N*,*N*′-dimethyl derivative are exceptional in catalyzing the silylcyanation of benzaldehyde in the absence of all other additives. Hammett analysis of the competitive silylcyanation of *para*-substituted benzaldehydes catalyzed by **3** showed a linear free-energy relationship (R^2 = 0.928) with a modest positive reaction constant (ρ = +1.52). X-ray diffraction analysis of (±)-**3** indicated a *cisoid* biaryl conformation and the existence of an intramolecular hydrogen bond between C7′–OH and C7–O. Resolution of (±)-**3** was achieved by HPLC separation of its tetravalerate derivative on a chiral stationary phase. The absolute configurations of the optical isomers of **3** were assigned by correlation of the ECD spectra with those of related biquinolyls of known configuration. The silylcyanation of aldehydes catalyzed by (–)-(*aR*)-**3** leads to cyanohydrins with a preference for the (*S*)-configured product with an *ee* of <10 %. The organocatalytic action of **3** is ascribed to hydrogen bonding and Brønsted acid catalysis effects that are dependent on its acidifying sulfonamide groups, general base capability, and interannular proximity effects made possible by the biaryl structure.

Introduction

Given the enormous structural diversity of aromatic heterocycles, their capacity to directly catalyze certain chemical transformations, and the ease with which many such ring systems can be synthetically modified, placement of heterocycles within chiral scaffolds can provide fertile ground for the discovery of new and potentially enantioselective processes. Configurationally stable, axially chiral, heteroaromatic biaryl molecules offer ample opportunities for such developments[1,2] and yet few reactions utilizing this class of compounds have emerged.[3] In contrast, the proliferation of methods based on functionally limited carbacyclic biaryl systems, particularly 1,1′-bi-2-naphthol (BINOL) derivatives,[4,5] continues apace.[6] 2,2′-Bipyridyls are the best studied group of heterocyclic biaryl molecules,[7] however, the interannular axes of these versatile metal ligands are configurationally labile unless at least one of the pyridyl N atoms is quaternized, for instance, as an *N*-alkylpyridinium salt or an *N*-oxide. Examples of *atropos* 2,2′-bipyridyls used in enantioselective synthesis are therefore largely limited to *N*,*N*′-dioxide derivatives which have been employed as chiral Lewis base promoters.[8] Related *N*,*N*′-dioxides of 2,2′-biquinolyls and 1,1′-biisoquinolyls have been similarly used.[9] Other axially chiral aromatic heterocycles that have found utility in catalysis include non-C_2-symmetric atropisomeric mixed carba/azacyclic biaryl systems such as the P,N ligand QUINAP[10] and an axially chiral DMAP analogue introduced by Spivey et al.[11] It is evident that the exploration of a greater array of heterocyclic biaryl types could lead to the discovery of significant new metal ligand families and the identification of new viable modes for organocatalysis.

In the search for a readily manipulated axially chiral heterocyclic biaryl template with a wide range of potential applications and yet topologically distinct from well-studied 2,2′-bipyridyl systems, 7,7′-disubstituted 8,8′-biquinolyls (e.g., **1**–**5**) were targeted (Figure 1).[12] In earlier work we developed synthetic approaches to 7,7′-dioxygenated 8,8′-biquinolyls,[12a,12c,12e] introduced methods to resolve these compounds into their enantiomeric atropisomers,[12b,12c] and determined many of the physical properties of such "azaBINOL" molecules,[13] including enantiomerization kinetics,[12b,12c] chiroptical behavior,[12b,12c] and the dependence of basicity on conformation.[12d] Polyfunctionalized azaBINOLs provide a platform for the interrogation of inherently chiral interannular proximity effects that may form the basis of significant new catalysis modes. In this regard,

[a] Department of Chemistry, Oregon State University, 153 Gilbert Hall, Corvallis, OR 97331-4003, USA
Fax: +1-541-737-2062
E-mail: paul.blakemore@science.oregonstate.edu

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201200333.

azaBINOLs with a ligating substructure at C6 and C6′ (e.g., **3**–**5**) were of initial interest as likely precursors to novel dinuclear metal complexes possessing pairs of biaryl quadrants flanked by filled (N atom lone pair) and vacant (metal) orbitals. The topology of notional complexes of this nature (e.g., **6**) contrasts with that of known ambiphilic catalysts derived from the modified BINOLs **7** and **8**[14] and we wished to explore what benefits their unique attributes could offer a suitable comparative benchmark process, in this case, the silylcyanation of carbonyl derivatives. Herein, we report our findings and the unexpected discovery that the bis-sulfonamide "ligand" **3** is itself an effective catalyst for the synthesis of cyanohydrin TMS ethers from aldehydes (and related adducts from ketones and imines), but that similar compounds lacking any one of its defining structural features are not. Despite the fact that the organocatalytic action identified depended critically on the chiral axis of **3**, the specific mechanism controlling silylcyanation was found to be only barely enantioselective in the reactions examined.

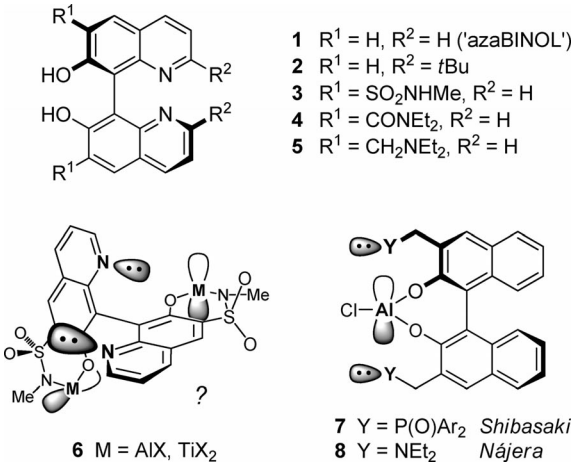


Figure 1. AzaBINOL derivatives **1**–**5**, notional dinuclear ambiphilic metal complex **6** derived from bis-sulfonamide **3**, and the known 1,1′-bi-2-naphthol (BINOL)-derived ambiphilic Al complexes **7** and **8**.

Results and Discussion

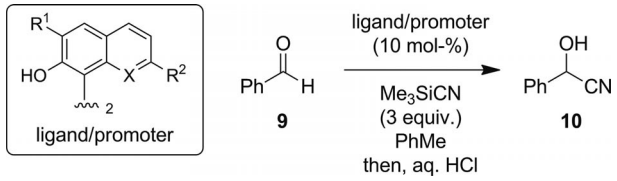
Cyanohydrins are synthetically useful[15] and intense efforts have been directed at the development of efficient enantioselective methods to target these carbinols and their derivatives by cyanide addition to carbonyl derivatives.[16] A majority of the approaches to stereocontrolled cyanohydrin synthesis rely on metal catalysis,[17] although promoters based on small organic molecules are being increasingly used for their synthesis.[18] The silylcyanation of carbonyls offers a convenient access to cyanohydrins (by hydrolysis of the resulting silyl ethers) and this process invites numerous modes for catalysis because cyanosilanes are intrinsically poor nucleophiles that cannot add across a C=O bond without activation. Significant recent developments in ambiphilic (bifunctional) catalysis[19] have seen silylcyanation reactions effected by discrete chiral metal complexes that contain both Lewis acid (LA) and Lewis base (LB) sites.[20] Such complexes (e.g., **7** and **8**)[14] offer simultaneous activation of the carbonyl electrophile and cyanosilane nucleophile (typically TMSCN) through the corresponding interactions with the LA and LB functionalities.[21] Given that carbonyl silylcyanation provides a platform for the study of new ambiphilic catalysts, we elected to focus on this process initially to evaluate the metal complexes derived from chelating azaBINOLs **3**–**5** (e.g., **6**). However, it became apparent that compound **3** was capable of directly catalyzing silylcyanation by a novel organocatalytic mechanism and this became the major focus of the work now detailed.

Silylcyanation of Aldehydes, Ketones, and Imines

At the outset, to establish the catalytic activity of putative ambiphilic biquinolyl–metal complexes, the silylcyanation of benzaldehyde in the presence of racemic azaBINOLs **1**–**5** (prepared as before)[12a,12c,12e] and various metal and other additives was investigated (Table 1). Nájera and co-workers previously identified that silylcyanation catalyzed by BINOLAM-AlCl (**8**)[14d] was optimal when conducted in the presence of Ph_3PO and 4 Å molecular sieves (MS). The phosphane oxide ostensibly prevents oligomerization of the catalyst by binding to Al while enabling the metal center to adopt a more reactive bipyramidal pentavalent coordination sphere during the reaction.[22] The role played by zeolites is less clear and their beneficial action was attributed to the possibility of molecular sieves actually contributing a trace of water to the reaction.[23] We began by adopting the protocol of Nájera and co-workers[14d] and incubated the biaryl diols of interest with Ph_3PO, molecular sieves (4 Å), and Me_2AlCl in toluene (1 h, 30 °C) to form uncharacterized Al complexes before cooling (to –20 °C) and the addition of benzaldehyde and TMSCN (entries 1–7). Conversion to mandelonitrile (**10**) was dependent on the exact provenance of the zeolite additive used, making early experiments difficult to reproduce.[24] Nonetheless, azaBINOL derivatives with a ligating substructure at C6 and C6′ gave consistently superior results (cf. entries 5–7 with 3 and 4). AzaBINOL diamine **5**, strictly analogous to Nájera's BINOLAM ligand system performed best under these conditions (entry 7). Ti^{IV} complexes generated from biaryl diols and $Ti(OiPr)_4$ in the presence of molecular sieves (4 Å), a protocol also demonstrated previously for the silylcyanation with modified BINOLs,[14b,14d] were next evaluated (entries 8–11). Again, the nature of the metal complexes formed was not established. However, the conversion of **9** into **10** was best effected in the presence of bis-sulfonamide **3** rather than the other ligands.[25]

At this stage we sought to better define the expectation of "blank" reactions conducted in the absence of Lewis acidic metal additives and discovered a modest promotion of the reaction by using molecular sieves (4 Å) alone (cf. entries 12 and 16). The efficacy improved a little by the

Table 1. Synthesis of mandelonitrile (**10**) by silylcyanation of benzaldehyde (**9**) with TMSCN in the presence of biaryl promoters.



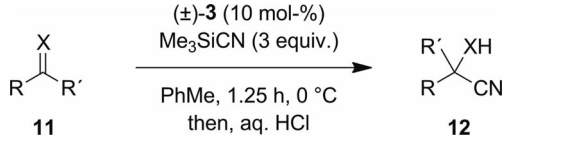
Entry	Ligand/Promoter[a]	Additives	Conditions	Conv.[b] [%]
1	none		–20 °C, 4 h	28
2	BINOL (X = CH)	↑	–20 °C, 4 h	15
3	**1**	Me_2AlCl,	–20 °C, 4 h	15
4	**2** (R^2 = *t*Bu)	Ph_3PO,	–20 °C, 4 h	13
5	**3** (R^1 = SO_2NHMe)	MS (4 Å)[c]	–20 °C, 4 h	82
6	**4** (R^1 = $CONEt_2$)	↓	–20 °C, 4 h	71
7	**5** (R^1 = CH_2NEt_2)		–20 °C, 4 h	92
8	none	↑	0 °C, 1 h	28
9	BINOL (X = CH)	$Ti(OiPr)_4$,	0 °C, 1 h	9
10	**1**	MS (4 Å)[d]	0 °C, 1 h	44
11	**3** (R^1 = SO_2NHMe)	↓	0 °C, 1 h	≥98
12	none	↑	0 °C, 1.1 h	19
13	BINOL (X = CH)	MS (4 Å)	0 °C, 1.1 h	25
14	**1**		0 °C, 1.1 h	33
15	**3** (R^1 = SO_2NHMe)	↓	0 °C, 1.1 h	≥98
16	none	↑	0 °C, 1.25 h	0
17	BINOL (X = CH)	none	0 °C, 1.25 h	0
18	**1**		0 °C, 1.25 h	0
19	**3** (R^1 = SO_2NHMe)	↓	0 °C, 1.25 h	≥98

[a] Unless otherwise indicated, X = N, R^1 = R^2 = H, BINOL = 1,1′-bi-2-naphthol. [b] The conversion of **9** into **10** was determined by ^1H NMR spectroscopy. [c] Me_2AlCl (10 mol-%), Ph_3PO (40 mol-%). [d] $Ti(OiPr)_4$ (10 mol-%).

combined action of molecular sieves (4 Å) and either BINOL or azaBINOL (**1**), but a dramatic increase in conversion was noted when bis-sulfonamide **3** was used instead (entries 13–15). Further simplification of the reaction manifold indicated that biquinolyl **3** was unique among the compounds initially evaluated in catalyzing the reaction in the absence of all other additives (entries 16–19). Structure probing control experiments later revealed just how critical the juxtaposition of functional groups within **3** is for effective catalysis of this simple reaction (see below).

Intrigued by the fact that we had uncovered a novel metal-free silylcyanation process, the scope of the reaction was then assessed by gauging the ability of bis-sulfonamide **3** to catalyze cyanide transfer to a range of other carbonyl compounds and imines (Table 2). Cyanohydrins **12** (X = O) were obtained in good-to-excellent yields from all but one of the aromatic aldehydes examined (entries 1–7). Similar results were also found with α,β-unsaturated and enolizable aliphatic aldehydes (entries 8–10). The reactions of ketones were less consistent (entries 11 and 12), but it was notable that simple *N*-benzylaldimines yielded Strecker adducts **12** (X = NBn) under the same conditions (entries 13 and 15).[26] In all of the reactions examined, sulfonamide catalyst **3** could be recovered chemically unaltered from the acidic aqueous phase following hydrolytic workup.[27]

Table 2. Silylcyanation of carbonyl compounds and imines catalyzed by bis-sulfonamide (±)-**3**.



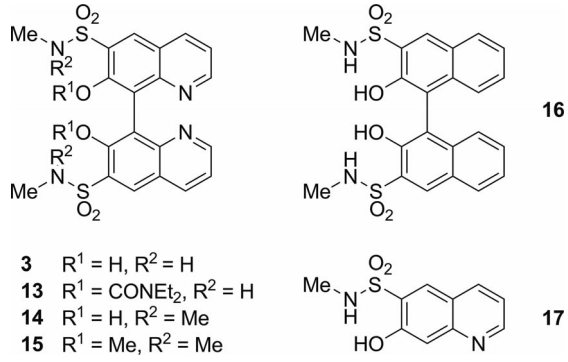
Entry	R	R′	X	Yield[a] [%]	Ref.[b]
1	Ph	H	O	88	[14d]
2	4-$MeOC_6H_4$	H	O	75	[14d]
3	4-$NO_2C_6H_4$	H	O	86	[44a]
4	3-ClC_6H_4	H	O	76	[44b]
5	2,6-$Cl_2C_6H_3$	H	O	92	[44b]
6	1-naphthyl	H	O	92	[18d]
7	3-pyridyl	H	O	42	[44c]
8	(*E*)-PhCH=CH	H	O	90	[14d]
9	$PhCH_2CH_2$	H	O	89	[14d]
10	*c*-C_6H_{11}	H	O	86	[14d]
11	Ph	Me	O	22	[44d]
12	*n*-C_6H_{13}	Me	O	82	[44b]
13[c]	Ph	H	NBn	72	[26a]
14[c]	3-ClC_6H_4	H	NBn	78	[26c]
15[c]	3-pyridyl	H	NBn	14	[26c]

[a] Isolated yield after SiO_2 chromatography. [b] All products **12** exhibited spectroscopic data (IR and NMR) in agreement with those previously reported. [c] Silylcyanation reactions of imines performed for 9 h at room temp.

Mechanistic Studies

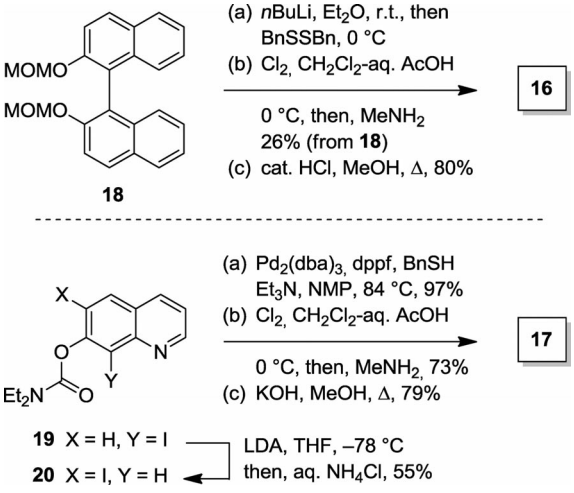
Five varied analogues of bis-sulfonamide **3** presenting unique functional group deletions and/or masking were targeted to identify which structural features were implicated in the organocatalysis (Scheme 1). In the first series of analogues (**13–15**), the hydrogen-bond-donating OH and NH groups were systematically masked. Bis-carbamate **13** containing free sulfonamide NH but capped OH is the immediate synthetic precursor to bis-sulfonamide **3** and was prepared as described previously.[12a] Tertiary sulfonamide **14** containing free OH but capped NH was prepared in an analogous fashion to secondary sulfonamide **3** by substituting Me_2NH for $MeNH_2$ during aminolysis of a bis-sulfonyl chloride intermediate. Straightforward base-mediated tetramethylation of bis-sulfonamide **3** with MeI led to the targeted analogue **15** lacking all protic/hydrogen-bond donor sites.

In the second series of analogues (**16** and **17**), changes of a more fundamental nature were envisioned. A 1,1′-binaphthyl-based carbacyclic analogue of **3** (**16**) was prepared from the known bis-MOM ether of BINOL (**18**)[28] by using the double-directed *ortho*-metalation strategy of Snieckus and co-workers[29] (Scheme 2). Thus, 3,3′-dilithiation of **18** with *n*BuLi followed by electrophilic sulfenation with BnSSBn led to a bis-sulfide that was oxidized to the corresponding bis-sulfonyl chloride. Aminolysis and MOM ether removal then gave the desired 3,3′-bis-sulfonamidyl BINOL derivative **16**. A monoquinoline analogue of **3** (**17**) was prepared along similar lines to the bis-sulfonamide itself by omitting oxidative aryllithium dimerization following halo-



Scheme 1. Bis-sulfonamide **3** and five structurally varied analogues **13**–**17**.

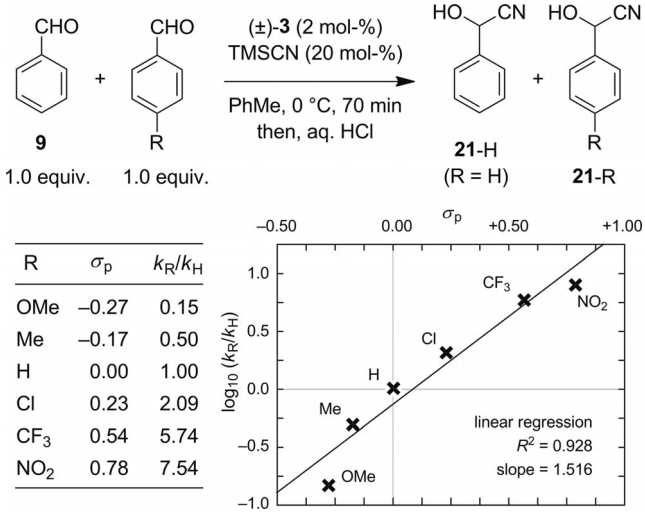
gen-dance rearrangement from the known 8-iodoquinolyl carbamate **19**.[12a] Thus, the net transposition of the corresponding hydrogen and iodine atoms at C6 and C8 in **19** by treatment with LDA followed by proton quenching gave 6-iodoquinoline **20** that evolved to **17** in good overall yield in a three-step sequence of Pd^0-catalyzed thioether formation, oxidative sulfonamide generation, and saponification.



Scheme 2. Synthesis of binaphthyl and monoquinoline analogues of bis-sulfonamide **3**.

With the five sulfonamidyl analogues of **3** in hand, each was evaluated as a potential organocatalyst for the silylcyanation of benzaldehyde according to the protocol previously developed (cf. Table 2, i.e., 10 mol-% catalyst, 3.0 equiv. TMSCN, 1.0 equiv. PhCHO, PhMe, 1.25 h, 0 °C, then, aq. HCl). Remarkably, with the notable exception of **14**, which gave full conversion, none of the new compounds tested promoted the addition reaction to any appreciable extent. Sulfonamides lacking free phenolic OH groups (**13** and **15**) or without embedded quinoline moieties (**16**) failed to catalyze the reaction at all whereas the monoquinoline congener of **3** (**17**) elicited only a 2% conversion of benzaldehyde to mandelonitrile. The fact that **17** is almost devoid of catalytic activity despite possessing all three distinct types of functional groups found in **3** is striking and suggests that the spatial relationship between these moieties, as defined by the intervening biquinolyl motif, is critical for reactivity.[30] Significantly, an X-ray crystallographic analysis of bis-sulfonamide **3** revealed an intramolecular hydrogen bond between neighboring polyfunctionalized quinoline rings (see below). The impact of such an interannular proximity effect will extend beyond influencing the solid-state structure of **3** and may distinguish its chemical behavior from that of monoquinoline **17** during the silylcyanation reaction. Given the catalytic activity of analogue **14** (a tertiary bis-sulfonamide), it is evident that free sulfonamide NH groups are not essential elements for catalysis. However, sulfonamidyl substituents of some kind are important because azaBINOL (**1**) itself is not an organocatalyst for silylcyanation. In addition to providing further sites for potentially significant dipolar interactions, the requirement for sulfonamides is undoubtedly associated with the effect that these strongly electron-withdrawing functional groups will have on modulating the acid–base properties of azaBINOLs (raising phenol acidity and lowering quinoline basicity).

To shed further light on the nature of the catalytic effect elicited by bis-sulfonamide **3**, a kinetic study was conducted to establish the relative rates for the silylcyanation of benzaldehyde compared with some *para*-substituted derivatives (Figure 2). Hammett analysis[31] of the resulting data by using appropriate literature σ_p values[32] for the substituents revealed a good linear free-energy relationship ($R^2 = 0.928$) with a reaction constant of $\rho = +1.52$. The modestly positive ρ value observed is consistent with a reaction that benefits from a catalyst with bifunctional character but with a rate-determining step dominated by a requirement for electrophilic activation of the aldehyde.[33]



R	σ_p	k_R/k_H
OMe	–0.27	0.15
Me	–0.17	0.50
H	0.00	1.00
Cl	0.23	2.09
CF_3	0.54	5.74
NO_2	0.78	7.54

Figure 2. Hammett analysis of the competitive silylcyanation of 4-substituted benzaldehydes as compared with benzaldehyde. k_R/k_H is equal to the ratio of **21**-R/**21**-H and was determined by integration of the ^1H NMR spectrum of the crude product mixture.

X-ray Diffraction Analysis of 3

Determination of the solid-state structure of racemic bis-sulfonamide **3** revealed tautomerism and conformational issues that could influence its chemical reactivity. Single crys-

tals of (±)-**3** suitable for X-ray diffraction analysis were obtained by recrystallization from ethanol to produce a solvate of composition (±)-**3**·0.5EtOH. Two symmetrically independent molecules of **3** were identified within the unit cell of the racemate and each showed numerous interesting structural features (Figure 3). In contrast to other unconstrained azaBINOLs previously studied by X-ray diffraction analysis,[12a–c] both forms of bis-sulfonamide **3** were found to be *cisoid* rather than *transoid* in their biaryl conformational preference. Also hitherto unknown for azaBINOLs, in each case here the two hydroxyquinoline units defining the biquinolyl are distinct tautomers, one phenolic and the other of quinolone (vinylogous amide) type. Although similar in these two regards, a closer examination of the data revealed some significant differences between the independent forms of **3**. In addition to exhibiting different biquinolyl ring-plane dihedral angles, by virtue of the presence of pyramidalized sulfonamide nitrogen atoms, each molecule is seen to be a distinct diastereoisomer (presumably an artifact of crystal-packing forces rather than true intrinsic configurational differences).[34] The more *cisoid* form of **3** has a formal (*R*,*aR*,*S*)* relative configuration and displays an interannular hydrogen bond between C7′–OH and C7–O (Figure 3, A). Conversely, the less *cisoid* form of **3** has a formal (*S*,*aR*,*S*)* relative configuration and lacks any semblance of the interannular hydrogen bond found in its unit cell partner (Figure 3, B). In this case, it can also be seen that both sulfonamide methyl groups are directed inwards towards the biaryl quadrant flanked by C7 and C7′ (i.e., NW quadrant in the right-hand side-view of **3** in Figure 3, B) whereas for the more *cisoid* molecule one methyl group is directed inwards and the other outwards in the same quadrant (Figure 3, A).

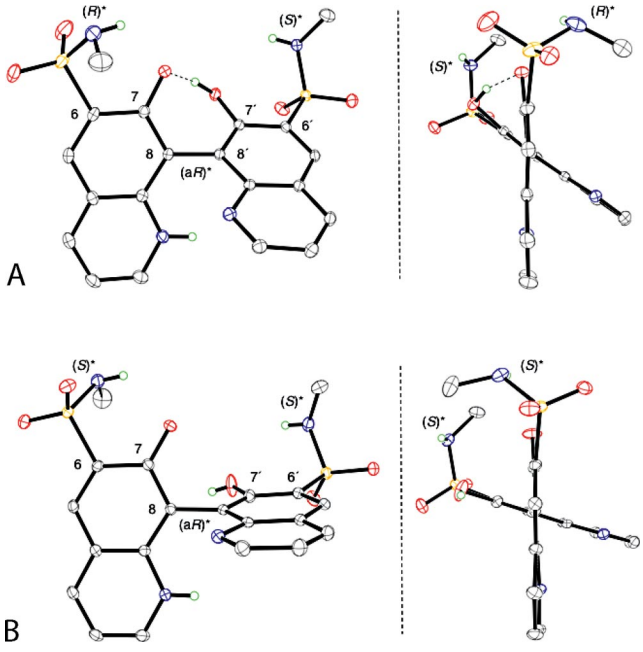
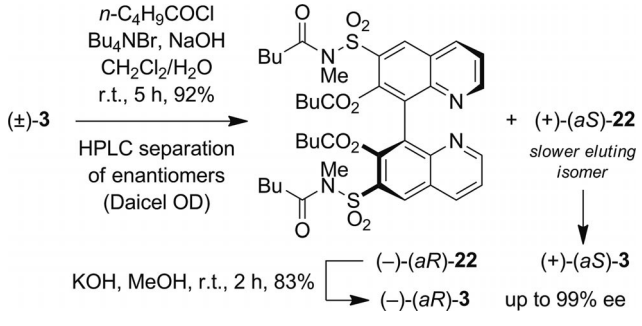


Figure 3. A: Two mutually orthogonal views of the ORTEP diagram for the more *cisoid* symmetrically independent form of bis-sulfonamide **3** present in the unit cell of (±)-**3**·0.5EtOH with relative stereochemical descriptors. The angle between the least-squares fitted quinoline ring planes is 54.21(5)°. Parameters associated with the indicated interannular hydrogen bond, C7′–OH···O–C7, are: *d*(O′–H) = 0.94(4) Å, *d*(H···O) = 1.62(4) Å, *d*(O···O′) = 2.526(3) Å, ∠(O′–H···O) = 162(4)°. Angle sums for bonds surrounding sulfonamide nitrogen atoms are 336° for C6–SO_2NHMe and 352° for C6′–SO_2NHMe. B: Two mutually orthogonal views of the ORTEP diagram for the less *cisoid* symmetrically independent form of bis-sulfonamide **3** present in the unit cell of (±)-**3**·0.5EtOH with relative stereochemical descriptors. The angle between least-squares fitted quinoline ring planes is 72.33(4)°. Angle sums for bonds surrounding sulfonamide nitrogen atoms are C6–SO_2NHMe = 338° and C6′–SO_2NHMe = 343°. Ellipsoids are plotted at the 30% probability level for non-hydrogen atoms and all hydrogen atoms bonded to carbon atoms have been omitted for clarity.

Resolution of (±)-3 and Evaluation of Enantioselectivity

Enantioenriched samples of **3** were obtained by preparative HPLC separation of the enantiomorphic atropisomers of its tetravalerate derivative **22** by using a standard chiral stationary phase (Scheme 3). Saponification of the resulting enantioenriched pervalerates gave scalemic material in up to 99% *ee*.[35] However, in common with other azaBINOL derivatives with free OH groups,[12b,12c] it was noted that **3** possesses limited configurational stability. For example, a 15% drop in optical activity was noted for a solution of (–)-(*aR*)-**3** after around 1 d at 28–32 °C (0.2 mM in MeOH). In contrast, a sample of (+)-(*aS*)-**3** (82% *ee*) stored at 5 °C in the solid state for 16 d was then later converted into (+)-(*aS*)-**22** with 80% *ee* (by HPLC analysis). The absolute configurations of the optical isomers of **3**, as (–)-(*aR*) and (+)-(*aS*),[36] were assigned on the basis of a comparison of the electronic circular dichroism (ECD) spectra with those previously recorded for scalemic samples of **1** and **2** of known configuration (Figure 4).[37] Thus, biquinolyl (–)-(*aR*)-**3** exhibited the same negative exciton chirality phase in its long-axes polarized ^1B_b Platt transition band (λ_{max} = 240 nm)[38] as that previously observed for both (+)-(*aR*)-**1** and (+)-(*aR*)-**2**.[12b,12c]



Scheme 3. Chromatographic resolution of bis-sulfonamide **3** through its tetravalerate derivative **22**.

With access to scalemic samples of **3** secured, the enantioselectivity in the silylcyanation of a limited number of aldehydes was examined but found to be uniformly low (cf. Table 2, entries 1–3, 8, and 9, *ee* < 10%).[39] Recovery of the catalyst **3** from the acidic aqueous phase of the reaction mixture after workup and subsequent assay for *ee* (by

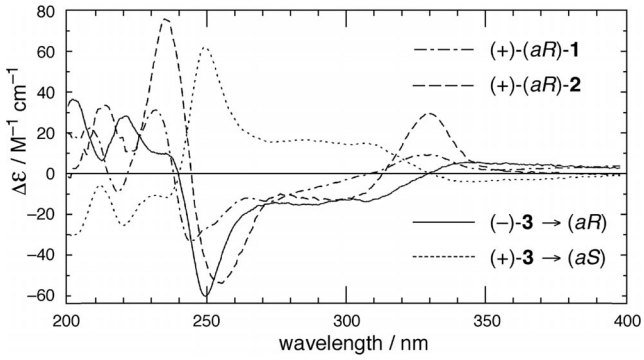


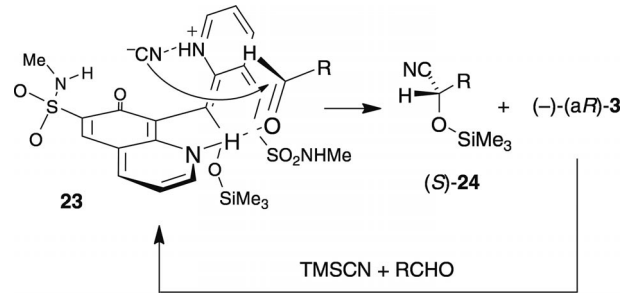
Figure 4. Comparison of the electronic circular dichroism (ECD) spectra of bis-sulfonamides (–)-**3** and (+)-**3** with biquinolyls (+)-(*aR*)-**1** and (+)-(*aR*)-**2** of known configuration.[12b,12c] Collection parameters (including cell pathlength): **1**: 2.4 mM, H_2O, 50% *ee*, 0.01 cm); **2**: 1.9 mM, MeOH, 40% *ee*, 0.01 cm; (–)-**3**: 0.19 mM, MeOH, 90% *ee*, 0.1 cm; (+)-**3**: 0.19 mM, MeOH, 82% *ee*, 0.1 cm. All curves are corrected to 100% *ee*.

derivatization to **22** followed by HPLC analysis) revealed a negligible loss in the enantiomeric purity of the sulfonamide. It was also established that the cyanohydrin products maintained configurational integrity during the hydrolytic workup. Thus, the origin of the low *ee* was associated with ineffectual stereoinduction during the enantiodetermining step of the silylcyanation. Correlation of the chiral HPLC chromatograms of mandelonitrile (**10**) obtained in this manner with literature reports[14d] revealed that sulfonamide catalyst (–)-(*aR*)-**3** favored the formation of the (*S*)-configured cyanohydrin product.

Mechanistic Conjecture

From the results of the structure versus catalytic activity relationship study, it is evident that bis-sulfonamide **3** acts through a combination of hydrogen bond and Brønsted acid catalysis effects[40] possibly aided by a cooperative general base capability. Apropos to these findings, Fuerst and Jacobsen discovered that a small peptide-like thiourea molecule failed to catalyze the silylcyanation of ketones unless equipped with a free basic amine within its substructure and also if no means of generating HCN in situ from TMSCN were available.[18b] Thus, it is speculated that the mode of action of **3** involves the initial silylation of a phenol group by TMSCN, then transfer of the resulting biquinolyl associated HCN to the aldehyde, itself activated by hydrogen-bond donation from either an NH or OH moiety.[41] Breakage of the Si–C bond of TMSCN in the first stage of this sequence would be facilitated by the heightened acidity of bis-sulfonamide **3** resulting from its unique vinylogous sulfamic acid character.

Ternary complex **23** represents a plausible scenario for cyanide anion delivery that is consistent with the fact that most of the analogues of **3**, including monoquinoline **17**, failed to catalyze the same process (Scheme 4). Following cyanide addition, recapture of the phenolic TMS group by the incipient alkoxide would lead to the silylcyanated product **24** and return **3** to the catalytic cycle. Considering the low level of enantioselectivity observed, advance of a rigorous stereocontrol model is moot. Nonetheless, given the openness of the biaryl quadrant occupied by the aldehyde in the proposed assembly, there is little reason to expect a significant energetic bias between the presentation of either a *Re* (illustrated) or *Si* face of the carbonyl component towards the core of a given enantiomer of the TMS-biquinolyl·HCN adduct **23** [(a*R*) isomer is shown].



Scheme 4. Mechanistic proposal for the silylcyanation of aldehydes as catalyzed by bis-sulfonamide **3**.

Conclusions

The study of azaBINOL derivatives equipped with a metal-ligating substructure at C6 and C6′ (e.g., **3**–**5**) was motivated by a desire to develop ambiphilic catalysts based on frustrated Lewis acid/Lewis base pairs. During the course of this work, which remains an active area of investigation, bis-sulfonamide **3** was discovered to directly catalyze the addition of TMSCN to aldehydes, ketones, and imines. The organocatalysis was dependent on multivalent expression of basic and hydrogen-bond-donating functional groups juxtaposed across a chiral biaryl axis. Although in this case the effect did not give rise to a synthetically useful level of enantioselectivity, the findings further strengthen the view that the catalytic efficiency of functional group clusters within small molecule activators is determined by a delicate balance of factors and that subtle structural variations can profoundly affect reactivity. A parallel can be drawn with the interactions found within the ternary complex of the substrate, co-factor, and enzyme in the vicinity of a proteinogenic active site, albeit, in its role as a simple "chemzyme",[42] the superstructure of **3** evidently does a poor job in orienting the reacting partners for effective stereoinduction. Systematic variations in the structure of **3** are reasonably expected to improve its ability to function as a general platform for enantioselective hydrogen bond and Brønsted acid catalysis in a broad array of different reaction types.

Finally, this work validates the proposition that investigations of heteroaromatic biaryl molecules can lead to the discovery of new and useful modes of reactivity. The 8,8′-biquinolyl scaffold, suitably constrained by 7,7′-disubstitution to confer the attribute of atropisomerism, is an ideal vehicle for such endeavors in many respects, for example, it

can be readily decorated with additional substituents at any position desired,[12e] the quinoline units have the capacity to act as general bases or ligating sites and may engage in nucleophilic catalysis, and the fundamental physical properties of the entire system can be fine-tuned by substituent and media effects. Accordingly, further applications of aza-BINOL-derived molecules in organocatalysis, metal-mediated synthesis, and materials chemistry are anticipated.

Experimental Section

General: All reactions requiring anhydrous conditions were conducted in flame-dried glass apparatus under Ar. THF and PhMe were obtained from a solvent purification system (SPS) employing activated Al_2O_3 drying columns.[43] 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 with UV or phosphomolybdic acid. All commercially available reagents were used as received unless otherwise noted. Melting points were determined in open capillary tubes with a melting-point apparatus. IR spectra were recorded in Fourier transform mode using KBr disks for solids whereas oils were supported between NaCl plates ("neat"). ^1H and ^{13}C NMR spectra were recorded at the field strength specified and in the indicated deuteriated solvents in standard 5 mm diameter tubes. Chemical shifts are quoted in ppm relative to residual solvent signals: $CDCl_3$: δ_H ($CHCl_3$) = 7.26 ppm, δ_C = 77.2 ppm; $(CD_3)_2SO$ δ_H (CD_3SOCHD_2) = 2.50 ppm, δ_C = 39.5 ppm. The 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 recorded by using either electron impact (EI), chemical ionization (CI), or electrospray (ES) ionization techniques. Ion mass/charge (m/z) ratios are reported as atomic mass units. Electronic circular dichroism (ECD) spectra were collected at 1 nm per step scan with an integration time of 1–2 s over the range 200–400 nm.

Silylcyanation with Ligand/Promoter, Me_2AlCl, Ph_3PO, and MS (4 Å): See Table 1, entries 1–7. Based on the protocol of Nájera and coworkers,[14d] a flame-dried 10 mL round-bottomed flask was charged with the indicated ligand (25 μmol, 10 mol-%) and freshly recrystallized Ph_3PO (28 mg, 100 μmol, 40 mol-%) and purged with Ar. Anhydrous PhMe (1.0 mL) was then added followed by dried molecular sieves (4 Å) (6 beads, ca. 45 mg, supplied by J. T. Baker and oven-dried for 24 h at 220 °C before use). A solution of Me_2AlCl (25 μL, 1.0 M in hexanes, 25 μmol, 10 mol-%) was added dropwise and the resulting mixture was stirred at 30 °C (bath temp.) for 1 h. After this time, the preformed Al complex was cooled to –20 °C and treated simultaneously with neat PhCHO (25 μL, d = 1.045, 26 mg, 250 μmol) and TMSCN (100 μL, d = 0.744, 74.4 mg, 750 μmol, 3.0 equiv.). The reaction mixture was stirred for 4 h at –20 °C and then quenched by the addition of EtOAc (2 mL) and aq. HCl (2.0 mL, 2.0 M) and then stirred for 1.25 h at room temp. The biphasic mixture was filtered through a short pad of Celite, which was washed with EtOAc (4 mL) and H_2O (4 mL). The filtrate and combined washings were separated and the organic phase dried (Na_2SO_4). The organic phase was concentrated on a rotary evaporator (with a water bath set at 30 °C) to remove the majority of the solvent with care taken not to distil out any unreacted PhCHO. The ^1H NMR spectral signature (300 MHz, $CDCl_3$) of the residue was consistent with a mixture of benzaldehyde (**9**) and mandelonitrile (**10**) and conversion was determined by comparison of the integrals for PhC*H*(CN)OH (δ = 5.53 ppm) and PhC*H*O (δ = 10.00 ppm).

Silylcyanation with Ligand/Promoter, Ti(O*i*Pr)$_4$, and MS (4 Å): See Table 1, entries 8–11. A flame-dried 10 mL round-bottomed flask was charged with the indicated ligand (50 μmol, 10 mol-%) and purged with Ar. Anhydrous PhMe (2.0 mL) was then added followed by dried molecular sieves (4 Å) (12 beads, ca. 90 mg, dried as above). Neat Ti(O*i*Pr)$_4$ (15 μL, d = 0.97, 14.6 mg, 50 μmol, 10 mol-%) was added dropwise and the resulting mixture was stirred at 30 °C (bath temp.) for 1 h. After this time, the preformed Ti complex was cooled to 0 °C and treated simultaneously with neat PhCHO (51 μL, d = 1.045, 53.3 mg, 500 μmol) and TMSCN (200 μL, d = 0.744, 149 mg, 1.50 mmol, 3.0 equiv.). The reaction mixture was stirred for 1 h at 0 °C and then quenched by the addition of EtOAc (4 mL) and aq. HCl (4.0 mL, 2.0 M) and then stirred for 1.25 h at room temp. Subsequent workup and analysis were then conducted as described above for Table 1, entries 1–7.

Silylcyanation with Ligand/Promoter and MS (4 Å): See Table 1, entries 12–15. A flame-dried 10 mL round-bottomed flask was charged with the indicated ligand (25 μmol, 10 mol-%) and purged with Ar. Anhydrous PhMe (1.0 mL) was then added followed by dried molecular sieves (4 Å) (6 beads, ca. 45 mg, dried as above). The mixture was cooled to 0 °C, treated simultaneously with neat PhCHO (25 μL, d = 1.045, 26 mg, 250 μmol) and TMSCN (100 μL, d = 0.744, 74.4 mg, 750 μmol, 3.0 equiv.), and stirred for 1.1 h. Quenching, workup, and analysis were performed as indicated above for Table 1, entries 1–7.

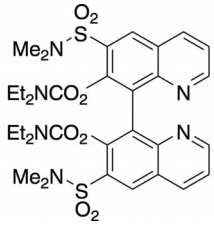
Silylcyanation with Only Ligand/Promoter: See Table 1, entries 16–19. As indicated above without addition of molecular sieves (4 Å). A detailed protocol for the use of bis-sulfonamide **3** as catalyst follows in the description of reaction conditions associated with Table 2.

Silylcyanation of Aldehydes and Ketones Catalyzed by Bis-sulfonamide 3: See Table 2, entries 1–12. As a representative procedure (entry 1), a flame-dried 10 mL round-bottomed flask was charged with bis-sulfonamide **3** (6.0 mg, 12.5 μmol, 10 mol-%) and purged with Ar. Anhydrous PhMe (0.5 mL) was then added and the resulting orange suspension stirred for 5 min at room temp. and then cooled to 0 °C. Neat PhCHO (12.5 μL, d = 1.045, 13 mg, 123 μmol) and TMSCN (50 μL, d = 0.744, 37 mg, 375 μmol, 3.0 equiv.) were added simultaneously and the mixture was stirred for 1.25 h at 0 °C. After this time, EtOAc (1 mL) and aq. HCl (1.0 mL, 2.0 M) were added and stirring was continued for 1.5 h at room temp. The mixture was then filtered through a short pad of Celite, which was washed with EtOAc (5 mL) and H_2O (5 mL). The combined filtrate and washings were separated and the organic phase dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, eluting with 10–20% EtOAc in hexanes) to afford mandelonitrile (14.5 mg, 109 μmol, 88%) as a colorless oil. The spectral data (IR, ^1H and ^{13}C NMR) for all the cyanohydrins prepared in this manner were in agreement with those previously reported.[14d,18d,44]

Silylcyanation of *N*-Benzylaldimines: See Table 2, Entries 13–15. As a representative procedure (entry 13), a flame-dried 10 mL round-bottomed flask was charged with bis-sulfonamide **3** (6.0 mg, 12.5 μmol, 10 mol-%) and purged with Ar. Anhydrous PhMe (0.5 mL) was added and the resulting orange suspension stirred for 5 min at room temp. and then cooled to 0 °C. PhCHNBn (24.5 mg, 125 μmol) and TMSCN (50 μL, d = 0.744, 37 mg, 375 μmol, 3.0 equiv.) were added simultaneously and the mixture stirred for 9 h at room temp. After this time, EtOAc (1 mL) and 2.0 M aq. HCl (1.0 mL) were added and stirring was continued for 2 h at room

temp. The pH of the aq. layer was adjusted to 7.0 by addition of 15% aq. NaOH and, after further dilution with EtOAc (5 mL), the layers were shaken and separated. The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The resulting residue was purified by column chromatography (SiO_2, eluting with 5–10% EtOAc in hexanes) to afford PhCH(CN)NHBn (20 mg, 90.5 μmol, 72%) as a colorless oil. The spectral data (IR, ^1H and ^{13}C NMR) for all the Strecker adducts prepared in this manner agreed with those previously reported.[26]

7,7′-Bis(diethylaminocarbonyloxy)-6,6′-bis(dimethylaminosulfonyl)-8,8′-biquinolyl (25). En Route to 14: A steady stream of Cl_2 gas (generated by the dropwise addition of concd. aq. HCl to $KMnO_4$) was bubbled through a biphasic mixture of 6,6′-bis-(benzylthio)-7,7′-(diethylaminocarbonyloxy)-8,8′-biquinolyl (247 mg, 0.338 mmol, prepared as described in ref.[12a]) in CH_2Cl_2/AcOH/H_2O (4:2:1 mL, resp.) at 0 °C for 5 min. The reaction mixture turned a bright-yellow color and excess dissolved Cl_2 was dissipated by sparging with Ar gas for 5 min. The resulting bis-sulfonyl chloride was then treated with excess 40 wt.-% aq. Me_2NH until the pH of the aqueous phase was 9–10 (***caution!***), warmed to room temp., and stirred for 3 h to allow for complete conversion to the bis-sulfonamide. The mixture was treated with CH_2Cl_2 (50 mL) and H_2O (50 mL) and the aqueous phase neutralized by addition of 6 M aq. HCl. The layers were shaken and separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were washed with brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, eluting with 4% MeOH in CH_2Cl_2) to afford the title compound (**25**; 156 mg, 0.223 mmol, 66%) as a colorless solid; m.p. 270 °C (dec.). IR ($CDCl_3$): $\tilde{\nu}$ = 2965, 1725, 1607, 1344, 1162, 1067, 964, 794, 739 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.83 (d, J = 2.8 Hz, 2 H), 8.67 (s, 2 H), 8.26 (d, J = 8.0 Hz, 2 H), 7.42 (dd, J = 8.0, 4.0 Hz, 2 H), 3.67 (dq, J = 14.4, 7.1 Hz, 2 H), 3.02–2.90 (m, 4 H), 2.85 (s, 12 H), 2.54 (dq, J = 13.7, 6.9 Hz, 2 H), 1.22 (t, J = 6.9 Hz, 6 H), 0.26 (t, J = 6.7 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, all signals × 2): δ = 152.9 (1), 152.0 (0), 149.8 (0), 146.3 (0), 136.7 (1), 133.7 (1), 131.4 (0), 129.2 (0), 125.2 (0), 121.9 (1), 42.4 (2), 41.9 (2), 36.9 (2 C, 3), 13.8 (3), 12.3 (3) ppm. MS (ES+): m/z = 723 $[M + Na]^+$, 701 $[M + H]^+$. HRMS (ES+): calcd. for $C_{32}H_{40}N_6NaO_8S_2$ 723.2247; found 723.2238.



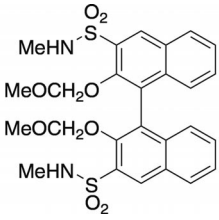
25

6,6′-Bis(dimethylaminosulfonyl)-7,7′-dihydroxy-8,8′-biquinolyl (14): A suspension of finely powdered NaOH (200 mg, 5.00 mmol) in DMSO (0.70 mL) was stirred for 30 s at 108 °C (bath temp.) and then treated with MeOH (0.05 mL) followed by bis-carbamate **25** (4.0 mg, 5.7 μmol). The resulting yellow solution was stirred at 108 °C for 24 h and then allowed to cool to room temp. and H_2O (1 mL) was added. The pH of the aqueous phase was adjusted to 7.0 by careful addition of 1.5 M aq. HCl and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with H_2O (3 × 5 mL) and brine (5 mL), then dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 1–3% MeOH in CH_2Cl_2) to afford the desired diphenol **14** (1.0 mg, 2.0 μmol, 35%) as a yellow solid. IR (CH_2Cl_2): $\tilde{\nu}$ = 3344, 2924, 1614, 1459, 1329, 1151, 965, 909, 731, 706 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$): δ = 8.78 (dd, J = 4.1, 1.7 Hz, 2 H), 8.37 (s, 2 H), 8.25 (dd, J = 8.3, 1.5 Hz, 2 H), 7.34 (dd, J = 8.3, 4.1 Hz, 2 H), 2.86 (s, 12 H) ppm. ^{13}C NMR (175 MHz, $CDCl_3$, all signals × 2): δ = 153.5 (1), 152.0 (0), 150.1 (0), 137.7 (1), 131.1 (1), 122.5 (0), 122.3 (0), 120.8 (0), 120.3 (1), 38.1 (2 C, 3) ppm. MS (CI+): m/z = 503 $[M + H]^+$. HRMS (CI+): calcd. for $C_{22}H_{23}N_4O_6S_2$ 503.1059; found 503.1049.

6,6′-Bis(dimethylaminosulfonyl)-7,7′-dimethoxy-8,8′-biquinolyl (15): A stirred solution of bis-sulfonamide **3** (10 mg, 21.1 μmol) in anhydrous DMF (0.50 mL) at room temp. under Ar was treated with NaH (6.0 mg, 60 wt.-% disp. in oil, 0.150 mmol). After 15 min, the suspension was treated with neat MeI (9.0 μL, d = 2.28, 20.5 mg, 145 μmol) and the resulting yellow solution was stirred for a further 18 h at room temp. The mixture was then partitioned between H_2O (10 mL) and EtOAc (10 mL) and the pH of the aq. phase adjusted to 7.0 by addition of 2.0 M aq. HCl. The layers were shaken and separated and the aq. phase extracted with EtOAc (2 × 10 mL). The combined organic phases were then washed with H_2O (10 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, eluting with EtOAc) to afford the desired methylated compound **15** (8.0 mg, 15.1 μmol, 71%) as a colorless solid. IR (KBr): $\tilde{\nu}$ = 2924, 1606, 1478, 1340, 1152, 971, 788, 746 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.78 (dd, J = 4.2, 1.8 Hz, 2 H), 8.66 (s, 2 H), 8.31 (dd, J = 8.3, 1.8 Hz, 2 H), 7.42 (dd, J = 8.3, 4.2 Hz, 2 H), 3.42 (s, 6 H), 2.87 (s, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, all signals × 2): δ = 155.6 (0), 153.0 (1), 150.5 (0), 137.5 (1), 133.6 (1), 131.8 (0), 128.9 (0), 124.5 (0), 121.5 (1), 62.0 (3), 38.0 (3) ppm. MS (CI+): m/z = 531 $[M + H]^+$. HRMS (CI+): calcd. for $C_{24}H_{27}N_4O_6S_2$ 531.1372; found 531.1363.

2,2′-Bis(methoxymethyloxy)-3,3′-bis(methylaminosulfonyl)-1,1′-binaphthyl (26). En Route to 16: See Scheme 2, steps (a) and (b). A stirred solution of **18** (214 mg, 0.572 mmol)[28] in anhydrous Et_2O (10 mL) at room temp. under Ar was treated with nBuLi (1.12 mL, 1.53 M in hexanes, 1.71 mmol) added dropwise over 2 min. The resulting brown suspension was stirred for 3 h at room temp. and then cooled to 0 °C and treated over 6 min with a solution of freshly prepared BnSSBn (491 mg, 2.00 mmol)[45] in anhydrous Et_2O (10 mL). The resulting yellow mixture was warmed to room temp. and stirred for a further 5 h during which time it became an homogeneous solution. After this time, satd. aq. NH_4Cl (10 mL) was added and the layers shaken and separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to afford 236 mg of 2,2′-bis(methoxymethyloxy)-3,3′-bis(benzylthio)-1,1′-binaphthyl. A portion of the crude dithioether (176 mg, 75% of total, ≤0.284 mmol) was dissolved in CH_2Cl_2/AcOH/H_2O (8:4:2 mL, respectively) and the biphasic mixture cooled to 0 °C. A steady stream of Cl_2 gas (generated by dropwise addition of concd. aq. HCl to $KMnO_4$) was bubbled through the solution for 2 min causing the mixture to first turn brown and then to bright yellow. Excess dissolved Cl_2 was dissipated by sparging the reaction mixture with Ar gas for 15 min and the solution of bis-sulfonyl chloride was then treated with excess aq. $MeNH_2$ (60 mL, 40 wt.-%) and warmed to room temp. (***caution!*** vigorous reaction). Following a period of 6 h at room temp., CH_2Cl_2 (50 mL) was added and the layers separated. The pH of the aqueous layer was carefully adjusted to 7 (by addition of 6 M aq. HCl) and then it was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The resulting crude residue was purified by column chromatography (SiO_2, eluting with 20–100% EtOAc in hexanes) to afford the title bis-sulfonamide **26**

(63 mg, 0.112 mmol, 26% from **18**) as a colorless solid; m.p. 182–184 °C (TBME). IR (KBr): $\tilde{\nu}$ = 3319, 3074, 2976, 2894, 1625, 1587, 1500, 1337, 1174, 912, 749 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.71 (s, 2 H), 8.06 (d, J = 8.1 Hz, 2 H), 7.58 (tm, J = 7.2 Hz, 2 H), 7.47 (tm, J = 7.5 Hz, 2 H), 7.20 (d, J = 8.5 Hz, 2 H), 5.30 (q, J = 5.2 Hz, 2 H), 4.79 (d, J = 5.2 Hz, 2 H), 4.51 (d, J = 5.2 Hz, 2 H), 2.82 (s, 6 H), 2.70 (d, J = 5.3 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, all signals ×2): δ = 149.7 (0), 136.0 (0), 133.3 (1), 131.5 (0), 129.9 (1), 129.8 (1), 129.5 (0), 127.0 (1), 126.8 (0), 125.9 (1), 100.8 (2), 57.1 (2), 29.8 (3) ppm. MS (ES+): m/z = 583 [M + Na]$^+$. HRMS (ES+): calcd. for $C_{26}H_{28}N_2O_8S_2Na$ 583.1185; found 583.1165.

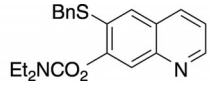


26

3,3′-Bis(methylaminosulfonyl)-1,1′-bi-2-naphthol (16): See Scheme 2. A stirred solution of the MOM diether **26** (34 mg, 0.061 mmol) in MeOH (4 mL) was treated with concd. aq. HCl (5 drops, 12 M) and the resulting yellow mixture was heated at a gentle reflux for 85 min. After this time, the mixture was allowed to cool to room temp. and concentrated in vacuo to give an amorphous solid which was triturated with Et_2O to afford pure diol **16** as a colorless solid (11 mg). The triturate residue was purified by column chromatography (SiO_2, eluting with 40% EtOAc in hexanes) to afford an additional 12 mg of diol **16** (total yield 23 mg, 0.049 mmol, 80%); m.p. >260 °C (dec., MeOH). IR (KBr): $\tilde{\nu}$ = 3357, 1620, 1593, 1326, 1299, 1124, 847, 749 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.43 (s, 2 H), 8.54 (s, 2 H), 8.12 (dd, J = 7.0, 1.9 Hz, 2 H), 7.41–7.35 (m, 4 H), 7.02 (q, J = 4.9 Hz, 2 H), 6.87 (dd, J = 7.4, 1.6 Hz, 2 H), 2.56 (d, J = 4.7 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, all signals ×2): δ = 150.1 (0), 136.0 (0), 131.8 (1), 129.6 (1), 128.9 (1), 127.5 (0), 126.9 (0), 124.0 (1), 123.7 (1), 115.7 (0), 28.8 (3) ppm. MS (EI+): m/z = 472 [M]$^{+\cdot}$. HRMS (EI+): calcd. for $C_{22}H_{20}N_2O_6S_2$ 472.07629; found 472.07535.

***O*-(6-Iodoquinol-7-yl) *N*,*N*-Diethylcarbamate (20):** See Scheme 2. A stirred solution of iPr$_2$NH (1.15 mL, d = 0.722, 830 mg, 8.22 mmol) in anhydrous THF (20 mL) at –20 °C under Ar was treated with nBuLi (5.00 mL, 1.48 M in hexanes, 7.40 mmol). The resulting solution of LDA was stirred for 20 min, further cooled to –78 °C, and then *O*-(8-iodoquinol-7-yl) *N*,*N*-diethylcarbamate (**19**; 2.30 g, 6.21 mmol)[12a] in anhydrous THF (25 mL) was added over 5 min down the side-wall of the cold flask. The resulting dark-brown mixture was stirred for 10 min at –78 °C and then satd. aq. NH_4Cl (40 mL) was added and the mixture warmed to room temp. The biphasic system was further diluted with EtOAc (100 mL) and H_2O (60 mL) and the layers shaken and separated. The aqueous phase was extracted with EtOAc (2 × 100 mL) and the combined organic phases dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, eluting with 80% EtOAc in hexanes) to afford, in order of elution, recovered starting material **19** (969 mg, 2.62 mmol, 42%) and the desired halogen-dance rearrangement product **20** (1.27 g, 3.43 mmol, 55%) as a colorless solid; m.p. 73–75 °C (THF). IR (KBr): $\tilde{\nu}$ = 2930, 1615, 1477, 1314, 1282, 1206, 1161, 952, 881, 754 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.91 (dd, J = 4.3, 1.7 Hz, 1 H), 8.34 (s, 1 H), 8.04 (dd, J = 8.4, 1.7 Hz, 1 H), 7.89 (s, 1 H), 7.37 (dd, J = 8.3, 4.3 Hz, 1 H), 3.59 (q, J = 7.1 Hz, 2 H), 3.45 (q, J = 7.1 Hz, 2 H), 1.37 (t, J = 7.1 Hz, 3 H), 1.26 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.0 (0), 151.5 (0), 151.5 (1), 148.6 (0), 138.5 (1), 134.7 (1), 127.6 (0), 122.1 (1), 121.3 (1), 91.7 (0), 42.6 (2), 42.3 (2), 14.5 (3), 13.5 (3) ppm. MS (ES+): m/z = 371 [M + H]$^+$. HRMS (ES+): calcd. for $C_{14}H_{16}{}^{127}IN_2O_2$ 371.0257; found 371.0242.

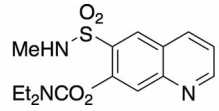
***O*-[6-(Benzylthio)quinol-7-yl] *N*,*N*-Diethylcarbamate (27). En Route to 17:** See Scheme 2, step (a). A stirred solution of iodide **20** (1.20 g, 3.24 mmol) in NMP (10 mL) at room temp. under Ar was treated with Et_3N (1.80 mL, d = 0.726, 1.31 g, 13.0 mmol) followed by tris-(dibenzylideneacetone)dipalladium (89 mg, 97.4 μmol) and then 1,1′-bis(diphenylphosphanyl)ferrocene (dppf; 215 mg, 388 μmol). The resulting mixture was sparged with Ar for 25 min before BnSH (1.50 mL, d = 1.06, 1.59 g, 12.8 mmol) was added and then the vessel was heated at 84 °C (bath temperature) for 14 h. After this time, the mixture was allowed to cool to room temp. and then partitioned between H_2O (100 mL) and EtOAc (100 mL). The layers were separated and the aqueous phase extracted with EtOAc (2 × 100 mL). The combined organic phases were washed with H_2O (2 × 100 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, eluting with EtOAc) to afford the title thioether **27** (1.15 g, 3.14 mmol, 97%) as a yellow solid; m.p. 110–112 °C (THF, yellow prisms). IR (KBr): $\tilde{\nu}$ = 2973, 1718, 1417, 1273, 1159 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.85 (dd, J = 4.2, 1.5 Hz, 1 H), 7.98 (d, J = 8.1 Hz, 1 H), 7.87 (s, 1 H), 7.59 (s, 1 H), 7.39–7.26 (m, 6 H), 4.21 (s, 2 H), 3.55 (q, J = 7.0 Hz, 2 H), 3.45 (q, J = 7.1 Hz, 2 H), 1.35 (t, J = 7.0 Hz, 3 H), 1.26 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.5 (0), 150.5 (1), 147.6 (0), 136.59 (0), 134.9 (1), 131.7 (0), 129.2 (2 C, 1), 128.7 (2 C, 1), 127.8 (1), 127.6 (1), 126.6 (0), 121.7 (1), 121.1 (1), 42.6 (2), 42.3 (2), 38.1 (2), 14.5 (3), 13.5 (3) ppm (one quat. carbon signal obscured). MS (CI+): m/z = 367 [M + H]$^+$. HRMS (CI+): calcd. for $C_{21}H_{23}N_2O_2S$ 367.14803; found 367.14762.



27

***O*-[6-(Methylaminosulfonyl)quinol-7-yl] *N*,*N*-Diethylcarbamate (28). En Route to 17:** See Scheme 2, step (b). A steady stream of Cl_2 gas (generated by dropwise addition of concd. aq. HCl to $KMnO_4$) was bubbled through a biphasic mixture of thioether **27** (924 mg, 2.52 mmol) in CH_2Cl_2/AcOH/H_2O (16:8:4 mL, respectively) at 0 °C for 7 min. The color of the mixture turned to yellow-green and excess dissolved Cl_2 was dissipated by sparging the reaction mixture with Ar gas for 5 min. The sulfonyl chloride thus produced was then treated with a large excess of aq. $MeNH_2$ (50 mL, 40 wt.-%), warmed to room temp., and stirred for 4 h. The mixture of crude sulfonamide was diluted with H_2O (100 mL) and the pH of the aqueous phase adjusted to 7 by careful addition of aq. HCl (4.0 M). Further CH_2Cl_2 (100 mL) was then added and the layers shaken and separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were washed with brine (2 × 100 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, eluting with 50% EtOAc in hexanes) to afford the title sulfonamide **28** (622 mg, 1.84 mmol, 73%) as a colorless oil. IR (neat): $\tilde{\nu}$ = 3303, 2973, 2932, 1729, 1619, 1413, 1160 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.01 (dd, J = 4.2, 1.7 Hz, 1 H), 8.45 (s, 1 H), 8.27 (ddm, J = 8.4, 1.6 Hz, 1 H), 7.90 (s, 1 H), 7.49 (dd, J = 8.3, 4.3 Hz, 1 H), 5.41 (q, J = 5.2 Hz, 1 H), 3.54 (q, J = 7.1 Hz, 2 H), 3.41 (q, J = 7.1 Hz, 2 H), 2.66 (d, J = 5.3 Hz, 3 H), 1.33 (t, J = 7.1 Hz, 3

H), 1.23 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.2 (0), 153.6 (1), 150.2 (0), 147.8 (0), 137.1 (1), 132.1 (1), 130.5 (0), 125.2 (0), 124.1 (1), 122.2 (1), 42.8 (2), 42.6 (2), 30.1 (3), 14.1 (3), 13.4 (3) ppm. MS (CI+): m/z = 338 $[M + H]^+$, 307, 265. HRMS (CI+): calcd. for $C_{15}H_{20}N_3O_4S$ 338.11745; found 338.11769.



28

7-Hydroxy-6-(methylaminosulfonyl)quinoline (17): See Scheme 2. A stirred solution of carbamate **28** (438 mg, 1.30 mmol) in methanolic KOH (10 wt.-%, 20 mL) was heated at a gentle reflux for 16 h. The mixture was then allowed to cool and concentrated in vacuo. The resulting yellow residue was dissolved in H_2O (20 mL) and the pH adjusted to 7 by careful addition of aq. HCl (4.0 M). The neutral aqueous phase was then extracted with EtOAc (5 × 40 mL) and the combined organic extracts dried (Na_2SO_4) and concentrated in vacuo to afford the pure hydroxysulfonamide **17** (243 mg, 1.02 mmol, 79%) as a yellow solid; m.p. 251–253 °C (dec., MeOH, yellow prisms). IR (KBr): $\tilde{\nu}$ = 3311 (sharp), 1621, 1456, 1310, 1151, 1071 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.25 (s, 1 H), 8.86 (dd, J = 4.2, 1.7 Hz, 1 H), 8.45 (dd, J = 8.3, 1.4 Hz, 1 H), 8.42 (s, 1 H), 7.44 (s, 1 H), 7.39 (dd, J = 8.2, 4.2 Hz, 1 H), 7.09 (s, 1 H), 2.45 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 154.7 (0), 153.0 (1), 150.6 (0), 137.2 (1), 131.4 (1), 127.9 (0), 121.1 (0), 119.7 (1), 112.0 (1), 28.8 (3) ppm. MS (CI+): m/z = 239 $[M + H]^+$. HRMS (CI+): calcd. for $C_{10}H_{11}N_2O_3S$ 239.04905; found 239.04808.

X-ray Crystallographic Analysis of (±)-3·0.5EtOH: Crystals of bis-sulfonamide (±)-**3** suitable for X-ray diffraction analysis were obtained by recrystallization from EtOH. Diffraction intensities were collected at 100 K with a Bruker Apex diffractometer by using Mo-K_α radiation (λ = 0.710 73 Å). Space groups were determined based on intensity statistics. Absorption corrections were made by using SADABS.[46] Structures were solved by direct methods using standard Fourier techniques and refined on F^2 using full-matrix least-squares procedures. Non-hydrogen atoms were refined with anisotropic thermal parameters except for the carbon and oxygen atoms in the disordered solvent EtOH molecule, which were refined with isotropic thermal parameters. Hydrogen atoms were found on the Fourier map and refined with isotropic thermal parameters except those in the disordered solvent EtOH molecule, which were refined in calculated positions in a rigid group model. The solvent EtOH molecule is disordered over two positions (in a ratio of 3:2) corresponding to two possible hydrogen bonds between the main and solvent molecules. The hydrogen atom in the OH group of the disordered solvent molecule (EtOH) was not found and was not taken into consideration. All calculations were performed by using the Bruker SHELXTL software package.[47]

CCDC-871198 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Tetravalerate 22: See Scheme 3. A solution of bis-sulfonamide (±)-**3** (21 mg, 44.3 μmol)[12a] in aq. NaOH (0.90 mL, 1.5 M) at room temp. was treated with nBu$_4$NBr (6 mg, 18.6 μmol) in CH_2Cl_2 (0.90 mL) and then pentanoyl chloride (53 μL, d = 1.02, 54.1 mg, 451 μmol) was added dropwise. The biphasic reaction mixture was vigorously stirred for 1.1 h at room temp. and then partitioned between H_2O (3 mL) and CH_2Cl_2 (3 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 3 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, eluting with 20–100% EtOAc in hexanes) to afford the title compound as a colorless solid (33 mg, 40.7 μmol, 92%); m.p. 170–171 °C (EtOAc). IR (KBr): $\tilde{\nu}$ = 2962, 1778, 1707, 1361, 1161, 1086 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.81 (dd, J = 4.1, 1.6 Hz, 2 H), 8.76 (s, 2 H), 8.34 (dd, J = 8.3, 1.5 Hz, 2 H), 7.48 (dd, J = 8.3, 4.2 Hz, 2 H), 3.36 (s, 6 H), 2.70–2.55 (m, 4 H), 2.17 (ddd, J = 15.2, 8.2, 6.5 Hz, 2 H), 1.99 (ddd, J = 15.4, 8.1, 7.0 Hz, 2 H), 1.60–1.52 (m, 4 H), 1.36–1.24 (m, 4 H), 1.07–1.00 (m, 4 H), 0.92–0.77 (m, 4 H), 0.86 (t, J = 7.3 Hz, 6 H), 0.64 (t, J = 7.2 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3 (0), 170.1 (0), 153.8 (1), 149.6 (0), 145.4 (0), 137.3 (1), 134.1 (1), 131.4 (0), 129.1 (0), 125.4 (0), 122.6 (1), 36.5 (2), 33.6 (2), 33.4 (3), 26.7 (2), 26.2 (2), 22.3 (2), 21.8 (2), 14.0 (2), 13.7 (2) ppm. MS (ES+): m/z = 811 $[M + H]^+$. HRMS (ES+): calcd. for $C_{40}H_{51}N_4O_{10}S_2$ 811.3047; found 811.3061.

HPLC Resolution of (±)-22: The racemate of tetrapentanoyl adduct **22** was resolved by using an Agilent 1100 series HPLC system interfaced with a Daicel Industries Chiralcel® OD semipreparative column (250 mm × 10 mm) with a chiral stationary phase of cellulose tris(3,5-dimethylphenylcarbamate) on 10 μm SiO_2. Multiple chromatographic runs were performed; for each run, 60 μL of a 92.5 mg mL^{-1} solution of the racemate in MeCN/EtOH (1:1) was injected onto the above column (5.6 mg per run). Isocratic elution using a solvent blend of 10% iPrOH in hexanes and a flow rate of 5.0 mL min^{-1} was performed with UV detection at 210 nm. The faster eluting enantiomer, (–)-(*aR*)-**22**, was collected from 22–46 min and the slower eluting isomer, (+)-(*aS*)-**22**, was collected from 47–85 min. Baseline separation was typically achieved by this protocol and both enantiomorphic atropisomers were routinely obtained with >96% *ee*. An enantiopure sample of (–)-(*aR*)-**22** exhibited $[\alpha]_D^{23}$ = –24.3 (c = 1.75, $CHCl_3$). Enantiomeric purity for batches of scalemic **22** obtained by the above method was determined by analytical HPLC analysis using a smaller OD column (250 mm × 4.6 mm I.D.), eluting with 10% iPrOH in hexanes at 1.5 mL min^{-1} and monitored by UV at 210 nm. Resolved peaks appeared at the following retention times: $t_{ret.}$ [(–)-(*aR*)-**22**] = 22.9 min, $t_{ret.}$ [(+)-(*aS*)-**22**] = 42.8 min.

(–)-(*aR*)-6,6′-Bis(methylaminosulfonyl)-7,7′-dihydroxy-8,8′-biquinolyl (3): See Scheme 3. Tetravalerate (–)-(*aR*)-**22** (35 mg, 43.2 μmol, ≥99% *ee*) was treated with methanolic KOH (8.0 mL, 10 wt.-%) and stirred at room temp. for 2 h. After this time, the resulting bright-yellow solution was concentrated in vacuo. The residue was dissolved in aq. HCl (3.0 mL, 6 M) and the valeric acid byproduct was removed by washing with EtOAc (3 × 5 mL). The pH of the aqueous phase, which at this stage contained the water-soluble cationic form of the protonated biquinolyl (**3**·2H$^+$), was then adjusted first to 13 by the addition of aq. NaOH (15 wt.-%) and then brought back carefully to 7 by subsequent addition of aq. HCl (6 M). The now pH-neutral aqueous phase was extracted with EtOAc (8 × 8 mL) and the combined organic extracts concentrated in vacuo. The residue was triturated with MeOH (1–2 mL) to afford the desired catalytically active bis-sulfonamide (–)-(*aR*)-**3** (17 mg, 35.8 μmol, 83%) as a yellow solid. $[\alpha]_D^{23}$ = –163 (c = 0.10, MeOH). Dextrorotatory material (+)-(*aS*)-**3** was similarly obtained from scalemic samples of (+)-(*aS*)-**22** and gave $[\alpha]_D^{23}$ = +170 (c = 0.36, MeOH). Other characterization data for bis-sulfonamide **3** were identical to those previously reported for the racemate.[12a]

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for all compounds.

Acknowledgments

Prof. Karl Scheidt (Northwestern University) is thanked for helpful discussions and Drs. Walter A. Baase and Brandon Green (University of Oregon) are acknowledged for technical assistance in obtaining ECD spectra from scalemic samples of bis-sulfonamide **3**. Financial support by the National Science Foundation (grant numbers CHE-0722319; CHE-0906409, partial support) is gratefully acknowledged. The Murdock Charitable Trust (2005265) is thanked for support of the OSU NMR spectroscopy facility.

[1] G. Chelucci, R. P. Thummel, *Chem. Rev.* **2002**, *102*, 3129–3170.
[2] For work highlighting the diversity in heterocyclic biaryls, see: a) S. K. Dey, D. A. Lightner, *J. Org. Chem.* **2007**, *72*, 9395–9397; b) M. S. Mudadu, R. P. Thummel, *J. Org. Chem.* **2006**, *71*, 7611–7617; c) D. Garciá-Cuadrado, A. M. Cuadro, J. Alvarez-Builla, U. Sancho, O. Castaño, J. J. Vaquero, *Org. Lett.* **2006**, *8*, 5955–5958.
[3] For selected recent examples, see: a) T. Seki, S. Tanaka, M. Kitamura, *Org. Lett.* **2012**, *14*, 608–611; b) A. Bouet, B. Heller, C. Papamicaël, G. Dupas, S. Oudeyer, F. Marsais, V. Levacher, *Org. Biomol. Chem.* **2007**, *5*, 1397–1404; c) M. P. A. Lyle, N. D. Draper, P. D. Wilson, *Org. Biomol. Chem.* **2006**, *4*, 877–885; d) P. Aschwanden, C. R. J. Stephenson, E. M. Carreira, *Org. Lett.* **2006**, *8*, 2437–2440.
[4] For reviews of 1,1′-bi-2-naphthol (BINOL) chemistry and a general discourse on 1,1′-binaphthyls, see: a) J. M. Brunel, *Chem. Rev.* **2005**, *105*, 857–897; b) Y. Chen, S. Yekta, A. K. Yudin, *Chem. Rev.* **2003**, *103*, 3155–3211; c) L. Pu, *Chem. Rev.* **1998**, *98*, 2405–2494.
[5] For reviews of 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl (BINAP), see: a) M. Berthod, G. Mignani, G. Woodward, M. Lemaire, *Chem. Rev.* **2005**, *105*, 1801–1836; b) R. Noyori, H. Takaya, *Acc. Chem. Res.* **1990**, *23*, 345–350.
[6] For selected recent highlights, see: a) Z. Zhang, P. Jain, J. C. Antilla, *Angew. Chem. Int. Ed.* **2011**, *50*, 10961–10964; b) S. Shirakawa, K. Liu, K. Maruoka, *J. Am. Chem. Soc.* **2012**, *134*, 916–919; c) I. Coric, S. Vellalath, B. List, *J. Am. Chem. Soc.* **2010**, *132*, 8536–8537; d) G. Hou, W. Li, M. Ma, X. Zhang, X. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 12844–12846; e) M. Turlington, Y. Du, S. G. Ostrum, V. Santosh, K. Wren, T. Lin, M. Sabat, L. Pu, *J. Am. Chem. Soc.* **2011**, *133*, 11780–11794; f) S. Yu, L. Pu, *J. Am. Chem. Soc.* **2010**, *132*, 17698–17700.
[7] N. C. Fletcher, *J. Chem. Soc., Perkin Trans. 1* **2002**, 1831–1842.
[8] S. E. Denmark, Y. Fan, M. D. Eastgate, *J. Org. Chem.* **2005**, *70*, 5235–5248.
[9] M. Nakajima, M. Saito, M. Shiro, S.-i. Hashimoto, *J. Am. Chem. Soc.* **1998**, *120*, 6419–6420.
[10] C. W. Lim, O. Tissot, A. Mattison, M. W. Hooper, J. M. Brown, A. R. Cowley, D. I. Hulmes, A. J. Blacker, *Org. Process Res. Dev.* **2003**, *7*, 379–384.
[11] A. C. Spivey, S. Arseniyadis, T. Fekner, A. Maddaford, D. Leese, *Tetrahedron* **2006**, *62*, 295–301.
[12] a) P. R. Blakemore, C. Kilner, S. D. Milicevic, *J. Org. Chem.* **2005**, *70*, 373–376; b) P. R. Blakemore, C. Kilner, S. D. Milicevic, *J. Org. Chem.* **2006**, *71*, 8212–8218; c) P. R. Blakemore, S. D. Milicevic, L. N. Zakharov, *J. Org. Chem.* **2007**, *72*, 9368–9371; d) P. R. Blakemore, S. D. Milicevic, H. Perera, A. Shvarev, L. N. Zakharov, *Synthesis* **2008**, 2271–2277; e) C. Wang, D. M. Flanigan, L. N. Zakharov, P. R. Blakemore, *Org. Lett.* **2011**, *13*, 4024–4027; for the synthesis of tetrahydroquinoline analogues of azaBINOL, see: f) J. Xiao, T.-P. Loh, *Org. Lett.* **2009**, *11*, 2876–2879.
[13] The parent member of this group, 7,7′-dihydroxy-8,8′-biquinolyl (azaBINOL, **1**) is a diaza-analogue of 1,1′-bi-2-naphthol (BINOL) in which two peri CH units have been formally replaced by nitrogen atoms, see: P. R. Blakemore, S. D. Milicevic, *7,7′-Dihydroxy-8,8′-biquinolyl*, in: *Encyclopedia of Reagents for Organic Synthesis*, Wiley, Chichester, **2009**; DOI: 10.1002/047084289X.rn00939.
[14] a) Y. Hamashima, D. Sawada, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **1999**, *121*, 2641–2642; b) Y. Hamashima, D. Sawada, H. Nogami, M. Kanai, M. Shibasaki, *Tetrahedron* **2001**, *57*, 805–814; c) J. Casas, C. Nájera, J. M. Sansano, J. M. Saá, *Org. Lett.* **2002**, *4*, 2589–2592; d) J. Casas, C. Nájera, J. M. Sansano, J. M. Saá, *Tetrahedron* **2004**, *60*, 10487–10496.
[15] R. J. H. Gregory, *Chem. Rev.* **1999**, *99*, 3649–3682.
[16] For reviews, see: a) J.-M. Brunel, I. P. Holmes, *Angew. Chem.* **2004**, *116*, 2810; *Angew. Chem. Int. Ed.* **2004**, *43*, 2752–2778; b) F.-X. Chen, X. Feng, *Curr. Org. Synth.* **2006**, *3*, 77–97; c) A. Baeza, J. M. Sansano, J. M. Saá, C. Nájera, *Pure Appl. Chem.* **2007**, *79*, 213–221; d) M. North, *Synlett* **1993**, 807–820.
[17] For selected recent work, see: a) D. H. Ryu, E. J. Corey, *J. Am. Chem. Soc.* **2005**, *127*, 5384–5387; b) S. Lundgren, E. Wingstrand, C. Moberg, *Adv. Synth. Catal.* **2007**, *349*, 364–372; c) N. H. Khan, S. Agrawal, R. I. Kureshy, S. H. R. Abdi, K. J. Prathap, R. V. Jasra, *Eur. J. Org. Chem.* **2008**, 4511–4515; d) J. Takaki, H. Egami, K. Matsumoto, B. Saito, T. Katsuki, *Chem. Lett.* **2008**, *37*, 502–503; e) Y. N. Belokon, W. Clegg, R. W. Harrington, V. I. Maleev, M. North, M. Omedes Pujol, D. L. Usanov, C. Young, *Chem. Eur. J.* **2009**, *15*, 2148–2165.
[18] a) S.-K. Tian, L. Deng, *J. Am. Chem. Soc.* **2001**, *123*, 6195–6196; b) D. E. Fuerst, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 8964–8965; c) X. Liu, B. Qin, X. Zhou, B. He, X. Feng, *J. Am. Chem. Soc.* **2005**, *127*, 12224–12225; d) Y. Suzuki, M. D. Abu-Baker, K. Muramatsu, M. Sato, *Tetrahedron* **2006**, *62*, 4227–4231; e) T. Kano, K. Sasaki, T. Konishi, H. Mii, K. Maruoka, *Tetrahedron Lett.* **2006**, *47*, 4615–4618; f) R. Chinchilla, C. Nájera, F. J. Ortega, *Tetrahedron: Asymmetry* **2008**, *19*, 265–268.
[19] For reviews, see: a) P. Li, H. Yamamoto, *Top. Organomet. Chem.* **2011**, *37*, 161–183; b) M. Kanai, N. Kato, E. Ichikawa, M. Shibasaki, *Synlett* **2005**, 1491–1508; c) J.-A. Ma, D. Cahard, *Angew. Chem.* **2004**, *116*, 4666; *Angew. Chem. Int. Ed.* **2004**, *43*, 4566–4583; d) G. J. Rowlands, *Tetrahedron* **2001**, *57*, 1865–1882.
[20] For examples based on Al^{III} or Ti^{IV}, see ref.[14] and: a) Y. Hamashima, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 7412–7413; b) J.-M. Brunel, O. Legrand, G. Buono, *Tetrahedron: Asymmetry* **1999**, *10*, 1979–1984; c) G. J. Rowlands, *Synlett* **2003**, 236–240; d) B. Zeng, X. Zhou, X. Liu, X. Feng, *Tetrahedron* **2007**, *63*, 5129–5136.
[21] H. Gröger, *Chem. Eur. J.* **2001**, *40*, 5246–5251.
[22] For insightful commentary on the role that Lewis base association can have on enhancing the Lewis acidity of metal centers by valence shell expansion, see: S. E. Denmark, G. L. Beutner, *Angew. Chem.* **2008**, *120*, 1584; *Angew. Chem. Int. Ed.* **2008**, *47*, 1560–1638.
[23] See ref.[14d] For discussion on the beneficial effects that trace additives, including H_2O and phosphane oxides, can have on catalysis, see: a) S. Ribe, P. Wipf, *Chem. Commun.* **2001**, 299–307; b) M. Vogl, H. Gröger, M. Shibasaki, *Angew. Chem.* **1999**, *111*, 1672; *Angew. Chem. Int. Ed.* **1999**, *38*, 1570–1577.
[24] A significant variation in yield was found when using molecular sieves (4 Å) obtained from different manufacturers and also when zeolites were dried according to slightly different protocols. The loading of molecular sieves (4 Å) also had a dramatic effect on conversion efficiency.
[25] The use of Ti^{IV}–sulfonamide complexes for the silylcyanation of aldehydes has previously been examined, see: J.-S. You, H.-M. Gau, M. C. K. Choi, *Chem. Commun.* **2000**, 1963–1964.
[26] For selected examples of the silylcyanation of imines, see: a) N. H. Khan, S. Saravanan, R. I. Kureshy, S. H. R. Abdi, H. C. Bajaj, *Tetrahedron: Asymmetry* **2010**, *21*, 2076–2080; b) A. M. Seayad, B. Ramalingam, K. Yoshinaga, T. Nagata, C. L. L. Chai, *Org. Lett.* **2010**, *12*, 264–267; c) J. Jarusiewicz, Y. Choe, K. S. Yoo, C. P. Park, K. W. Jung, *J. Org. Chem.* **2009**, *74*, 2873–2876; d) I. V. P. Raj, G. Suryavanshi, A. Sudalai, *Tetrahe-*

dron Lett. **2007**, *48*, 7211–7214; e) M. Chavarot, J. J. Byrne, P. Y. Chavant, Y. Vallée, *Tetrahedron: Asymmetry* **2001**, *12*, 1147–1150.

[27] Cyanide anion addition to C2 and/or C2′ of the biquinolyl nucleus is therefore discounted. For Reissert-type reactions of quinolines in the presence of a bifunctional catalyst, TMSCN, and acyl halides, see: M. Takamura, K. Funabashi, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 6327–6328.

[28] a) S. Matsunagam, J. Das, J. Roels, E. M. Vogl, N. Yamamoto, T. Lida, K. Yamaguchi, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 2252–2260; b) M. Shi, C.-J. Wang, *Tetrahedron: Asymmetry* **2002**, *13*, 2161–2166.

[29] P. J. Cox, W. Wang, V. Snieckus, *Tetrahedron Lett.* **1992**, *33*, 2253–2256.

[30] Bis-sulfonamide **3** contains twice as many functional groups as its "monomeric" congener **17** and it could therefore derive a reactivity advantage in any equal loading comparison experiment due to a higher effective molarity of the activating moieties. Ruling out this possibility, it was found that the silylcyanation of PhCHO by using just 5 mol-% of **3** under otherwise identical reaction conditions still resulted in ≥95% conversion. As noted above, 10 mol-% of **17** gave only 2% conversion.

[31] a) L. P. Hammett, *Chem. Rev.* **1935**, *17*, 125–136; b) L. P. Hammett, *J. Am. Chem. Soc.* **1937**, *59*, 96–103; c) A. Williams, *Free Energy Relationships in Organic and Bio-organic Chemistry*, The Royal Society of Chemistry, Cambridge, **2003**.

[32] C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165–195.

[33] North et al. found ρ = +2.37 (R^2 = 0.943) in their Hammett analysis of the silylcyanation of benzaldehydes as catalyzed by a strongly Lewis acidic Ti^{IV}–salen complex. Use of a less Lewis acidic V^{V}-based salen complex that was potentially capable of synergistic Lewis base activation gave ρ = +1.57 (R^2 = 0.851), see: M. North, M. Omedes-Pujol, C. Williamson, *Chem. Eur. J.* **2010**, *16*, 11367–11375.

[34] The barrier to pyramidal inversion at sulfonamide nitrogen atoms is calculated to be less than 1 kcal mol^{-1}, see: P. V. Bharatam, Amita, A. Gupta, D. Kaur, *Tetrahedron* **2002**, *58*, 1759–1764.

[35] Immediate re-conversion of a scalemic sample of **3** back into **22** (for the purpose of indirect *ee* determination by HPLC analysis) revealed that transformation cycles **22**→**3**→**22** occur without measurable loss in *ee*.

[36] Defined for polarimeter readings in MeOH: (–)-(*aR*)-**3** $[a]_D^{23}$ = –163 (*c* = 0.10, MeOH); (+)-(*aS*)-**3** $[a]_D^{23}$ = +170 (*c* = 0.36, MeOH).

[37] As a caveat, it is noted that the X-ray crystallographic analysis of (±)-**3** (Figure 3) revealed that this biaryl does not share the same solid-state *transoid* conformational preference common to both (±)-**1** and (±)-**2** [from the XRD data the interannular dihedral angles are 104.5° for **1** (ref.[12a]) and 123.5° for **2** (ref.[12c])]. If the solution conformational properties of **3** differ significantly to those of **1** and **2** (unlikely in MeOH), then a simple comparison of the exciton chirality phase is not sufficient to assign the absolute configuration with confidence, see ref.[38]

[38] a) S. F. Mason, R. H. Seal, D. R. Roberts, *Tetrahedron* **1974**, *30*, 1671–1682; b) A. Rodger, B. Nordén, *Circular Dichroism and Linear Dichroism*, Oxford University Press, New York, **1997**; c) N. Berova, K. Nakanishi, in: *Circular Dichroism: Principles and Applications* (Eds.: N. Berova, K. Nakanishi, R. W. Woody), Wiley-VCH, New York, **2000**.

[39] Higher enantioselectivities in the silylcyanation of benzaldehyde (16% *ee* at 0 °C; 20% *ee* at –20 °C) were observed by using an aged sample of TMSCN, but these results could not be reproduced with fresh batches of purer TMSCN. Attempts to duplicate the aging effect, which included doping pure TMSCN with traces of acids, were unsuccessful.

[40] For reviews of hydrogen bond and Brønsted acid catalysis, see: a) C. H. Cheon, H. Yamamoto, *Chem. Commun.* **2011**, *47*, 3043–3056; b) P. H.-Y. Cheong, C. Y. Legault, J. M. Um, N. Celebi-Olcum, K. N. Houk, *Chem. Rev.* **2011**, *111*, 5042–5137; c) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713–5743; d) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999–1010; for selected recent work, see: e) J. Saadi, M. Akakura, H. Yamamoto, *J. Am. Chem. Soc.* **2011**, *133*, 14248–14251; f) G. K. Ingle, M. G. Mormino, L. Wojitas, J. C. Antilla, *Org. Lett.* **2011**, *13*, 4822–4825; g) Y. Qian, G. Ma, A. Lv, H.-L. Zhu, J. Zhao, V. H. Rawal, *Chem. Commun.* **2010**, *46*, 3004–3006; h) A. A. Rodriguez, H. Yoo, J. W. Ziller, K. J. Shea, *Tetrahedron Lett.* **2009**, *50*, 6830–6833.

[41] Jacobsen's detailed mechanistic studies of tertiary amino-thiourea catalysis and Houk's more recent theoretical treatments of the Inoue cyclic peptide [*cyclo*-(L-His-L-Phe)] catalyzed addition of HCN to aldehydes lend credence to this kind of mechanistic hypothesis, see: a) S. J. Zuend, E. N. Jacobsen, *J. Am. Chem. Soc.* **2007**, *129*, 15872–15883; b) F. Schnoenebeck, K. N. Houk, *J. Org. Chem.* **2009**, *74*, 1464–1472; c) J.-I. Oku, S. Inoue, *J. Chem. Soc., Chem. Commun.* **1981**, 229–230.

[42] For reviews concerning the concept of artificial molecules as enzyme mimics ("chemzymes"), see: a) J. Bjerre, C. Rousseau, L. Marinescu, M. Bols, *Appl. Microbiol. Biotechnol.* **2008**, *81*, 1–11; b) R. Breslow (Ed.), *Artificial Enzymes*, 1st ed., Wiley-VCH, New York, **2005**; for selected recent work with leading references, see: c) Y. Li, S. J. Miller, *J. Org. Chem.* **2011**, *76*, 9785–9791; d) G. Hu, A. K. Gupta, R. H. Huang, M. Mukherjee, W. D. Wulff, *J. Am. Chem. Soc.* **2010**, *132*, 14669–13675; e) J. Xiao, F.-X. Xu, Y.-P. Lu, T.-P. Loh, *Org. Lett.* **2010**, *12*, 1220–1223; f) R. Skouta, S. Wei, R. Breslow, *J. Am. Chem. Soc.* **2009**, *131*, 15604–15605.

[43] A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, *Organometallics* **1996**, *15*, 1518–1520.

[44] a) Y. Belokon, F. Massimilano, N. Ikonnikov, M. Moscalenko, M. North, C. Orizu, V. Tararov, M. Tasinazzo, *J. Chem. Soc. Perkin Trans. 1* **1997**, 1293–1295; b) S. Nanda, Y. Kato, Y. Asano, *Tetrahedron* **2005**, *61*, 10908–10916; c) B. E. Kane, M. K. O. Grant, E. E. El-Fakahany, D. M. Ferguson, *Bioorg. Med. Chem.* **2008**, *16*, 1376–1392; d) A. Aramini, M. R. Sablone, G. Bianchini, A. Amore, M. Fani, P. Perrone, A. Dolce, M. Allegretti, *Tetrahedron* **2009**, *65*, 2015–2021.

[45] R. Leino, J. E. Lönnqvist, *Tetrahedron Lett.* **2004**, *45*, 8489–8491.

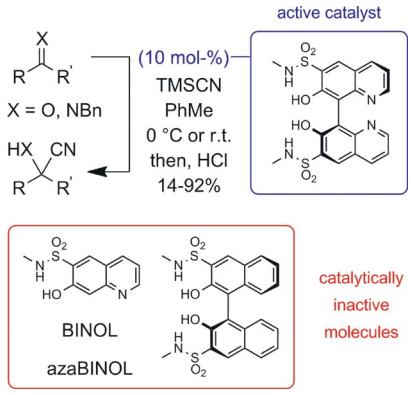
[46] G. M. Sheldrick, *SADABS*, University of Göttingen, Germany, **1995**.

[47] Bruker, *SHELXTL*, version 6.10, Bruker AXS Inc., Madison, Wisconsin, USA, **2000**.

Received: March 16, 2012
Published Online: ■

EurJOC European Journal of Organic Chemistry

6,6′-Bis(methylaminosulfonyl)-7,7′-dihydroxy-8,8′-biquinolyl catalyzes the addition of trimethylsilyl cyanide to aldehydes, ketones, and *N*-benzylaldimines to give the expected cyanohydrin and Strecker adducts following desilylation. Related compounds lacking any one of the defining structural features of the biquinolyl failed to promote the same reaction in the absence of additives.



Keywords: Organocatalysis / Biaryls / Nitrogen heterocycles / Cyanohydrins / Strecker reaction

