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Enantioselective Synthesis of Biaryl Atropisomers via the Addition of Thiophenols into Aryl-Naphthoquinones

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Supporting Information Placeholder

ABSTRACT: We report a cinchona alkaloid catalyzed addition of thiophenol into rapidly interconverting aryl-naphthoquinones, resulting in stable biaryl atropisomers upon reductive methylation. An array of thiophenols and naphthoquinone substrates were evaluated and we observed selectivities up to 98.5:1.5 e.r. Control of the quinone redox properties allowed us to study the stereochemical stabilities of each oxidation state of the substrates. The resulting enantioenriched products can also be moved on via an S_NAr-like reaction sequence to arrive at stable derivatives with excellent enantioselectivity. **Keywords:** atroposelective, thiophenol, aryl-naphthoquinone, cinchona alkaloid, biaryl atropisomers

Introduction

Atropisomerism is a hallmark of many bioactive small molecules^{1,2} and privileged catalyst scaffolds.³ As such, there has been significant effort towards developing atroposelective methodology⁴⁻⁶ over the past decade. Seminal examples include strategies where the enantioselectivity is induced during formation of the chiral axis,⁷⁻⁹ via cyclization^{10,11} and via point-to-axial chirality transfer.¹² Recently, Miller¹³⁻¹⁵ and others¹⁶⁻¹⁸ have studied atropisomer selective dynamic kinetic resolutions (DKR), wherein a configurationally unstable atropisomer is rendered stereochemically stable through various means.

Quinones are common pharmacophores in small molecules and natural products, that can often covalently target nucleophilic protein residues.¹⁹ As redox-active moieties, quinones and hydroquinones can also play distinct roles in redox cycling and cytotoxicity.^{20,21} Many bioactive quinones and hydroquinones are atropisomeric (Figure 1A). Starting in 2015, Tan²² and others²³⁻²⁵ reported the atroposelective addition of 2-naphthols into quinones using a chiral

catalyst (Figure 1B). Inspired by this seminal work, we posited that an enantioselective synthesis of atropisomers could be achieved by the addition of a nucleophile into a quinone, adjacent to a rapidly interconverting atropisomeric axis (Figure 1C). We felt this strategy, which is analogous to vicarious nucleophilic substitution, could potentially afford both biaryl and non-biaryl atropisomers with unparalleled diversity due to the plethora of nucleophiles that are amenable to catalytic activation coupled with the myriad atropisomeric scaffolds that quinones can be embedded in.

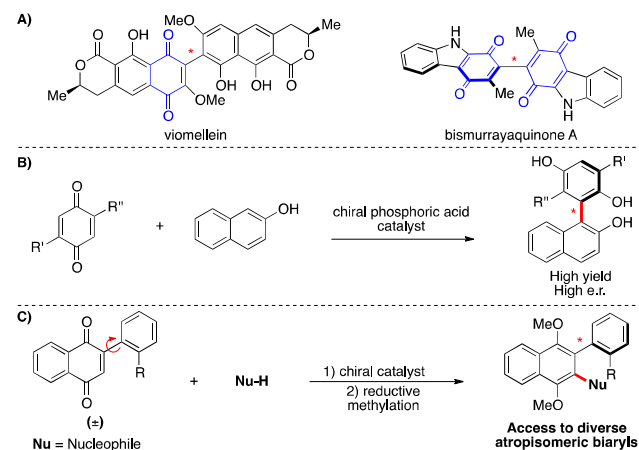
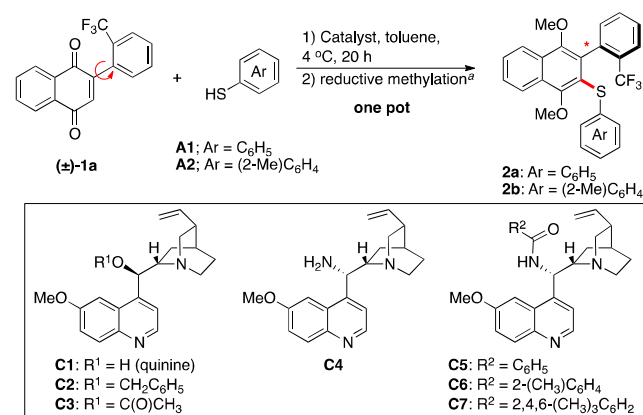


Figure 1. The Quinone Scaffold in Atropisomerism. A) Examples of axially chiral quinones in natural products. B) Previous work: Chiral biaryl-diols from 2-naphthols and quinones. C) This work: Enantioselective synthesis of stable atropisomers from aryl-naphthoquinones.

To test this approach, we chose to study the addition of thiophenols into naphthoquinones (as in Figure 1C). The addition of thiophenols proximal to an 'atropisomerically labile' aryl-naphthoquinone axis would be expected to yield stable biaryl atropisomers, and thus this approach would be amenable to a catalytic atroposelective variant. Such an approach could hold utility for diverse applications. For example, atropiso-

mers with sulfur functionality are known to be effective chiral ligands²⁶ and recent work has demonstrated that C-S bonds can be functionalized in a manner comparable to halogens, suggesting that the enantio-enriched products from such a reaction could be further elaborated to diverse chiral scaffolds.^{27,28} In support of the feasibility of an atroposelective addition, the nucleophilic addition of thiophenols is a well-studied topic in enantioselective catalysis,²⁹ exemplified by work by Wynberg.^{30,31} Furthermore, work from Smith,³² as well as a recent kinetic resolution from our group³³ have shown that chiral quaternary ammonium salts can effect atroposelective thiophenol addition via S_NAr.

Table 1. Reaction Optimization



Entry	Cat. (mol%)	Conc. [M]	Yield ^b	e.r. ^b
1	None	.025	<5%	n/a
2	C1 (10)	.025	49%	57:43
3	C2 (10)	.025	48%	50:50
4	C3 (10)	.025	17%	46:54
5	C4 (10)	.025	79%	75:25
6	C5 (10)	.025	70%	78:22
7	C6 (10)	.025	65%	87:13
8	C7 (10)	.025	69%	93:7
9	C7 (10)	.05	84%	93:7
10 ^c	C7 (10)	.05	75%	87:13
11 ^d	C7 (10)	.05	67%	86:14
12	C7 (2.5)	.1	80%	88:12
13	C7 (2.5)	.05	73%	93:7
14	C7 (5)	.05	89%	93:7
15 ^e	C7 (5)	.05	68%	96:4
16 ^{e,f}	C7 (5)	.05	82%	96:4

^aNa₂S₂O_{4(aq)}, THF, MeOH, TBAB at 0 °C then KOH_(aq), Me₂SO₄. ^bIsolated yields and enantiomeric ratios (e.r.) are reported as an average of two trials with **A1** used as the nucleophile. ^cReaction was run at room temperature. ^dReaction was placed in -18 °C freezer for 20 hours with-

out stirring. ^e**A2** was used as the nucleophile. ^fReaction was let stir for 44 hours before reductive quench.

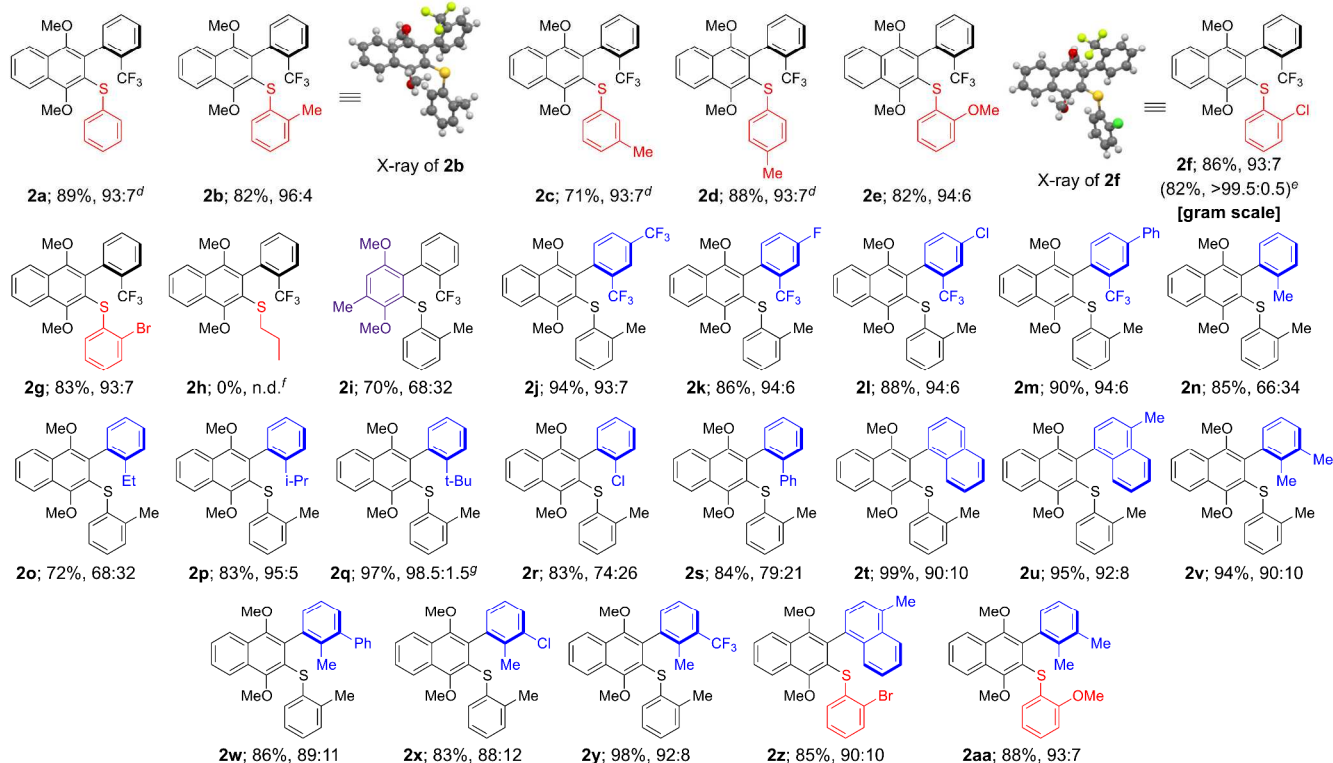
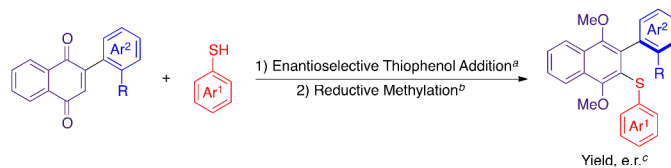
To begin our studies, we evaluated different quinine derived catalysts for the addition of thiophenol into quinone biaryl **1a**. To remove any complexities caused by the quinone oxidation state (*vide infra*), we quenched each reaction by reductive methylation using Na₂S₂O₄ and dimethyl sulfate. The reaction of **1a** with thiophenol in the absence of catalyst proceeded with minimal conversion (Table 1, entry 1). Quinine (**C1**) did catalyze the addition of thiophenol, yielding 49% **2a** with preliminary levels of enantioselectivity (57:43 e.r.; Table 1, entry 2). Benzyl quinine (**C2**) and acetylated quinine (**C3**) proved ineffective catalysts (Table 1, entries 3 and 4), however 9-amino-epi-cinchona alkaloid analogs proved promising, with primary amine **C4** yielding 79% of **2a** in 75:25 e.r. and benzoylated analog **C5** yielding similar results (Table 1, entries 5 and 6).

Methodical elaboration of **C4** to diverse ureas, carbamates, and amides were met with little improvement in enantioselectivity. These results, however, proved informative and suggested a reliance on steric bulk distal to the “active site” of the catalyst (see Supporting Information). Based on these results, we hypothesized an *ortho*-substituted benzamide might improve selectivity due to catalyst conformational changes related to the “magic methyl effect.”³⁴ For example, adding a methyl group to the 2-position of the benzamide, as in **C6**, would be expected to bias the arene-carbonyl bond towards a pseudo-perpendicular conformation, thereby increasing the effective radius of the benzamide. This hypothesis proved fruitful, as **C6** yielded a notable increase in enantioselectivity (87:13 e.r., Table 1, entry 7). The addition of a second *ortho*-methyl group led to our best catalyst, **C7**, which yielded 69% of **2a** in 93:7 e.r. (Table 1, entry 8). Further modification of reaction conditions led to 89% yield of **2a** with retained 93:7 e.r. (Table 1, entries 9–14). Finally, using *o*-toluenethiol as the nucleophile afforded **2b** with an improved e.r. of 96:4 (Table 1, entries 15 and 16).

With an optimized atroposelective synthesis in hand, we set out to gain a better understanding of the effect of the thiophenol structure (Scheme 1). Moving the methyl group on the thiophenol away from the *ortho*-position (**2c** and **2d**) resulted in decreased e.r.s. Replacing the *o*-methyl group with methoxy, chlorine, or bromine also led to slight decreases in e.r. (94:6, 93:7, 93:7; respectively). We were able to recrystallize **2f** on the gram scale in 82% overall yield as a near enantiopure atropisomer (>99.5:0.5 e.r.). We obtained the crystal structures of **2b** and **2f**, revealing the major enantiomer from this reaction to be the (*R_a*) atropisomer. Due to structural similarity, the stereochemistry of all other substrates were assigned by analogy. Reacting **1a**

with 1-propane thiol, rather than thiophenol, resulted in no observable reaction. Lastly, performing this DKR

Scheme 1. Substrate Scope



^aAryl-naphthoquinone (0.1mmol), toluene (2mL), **C7** (0.005mmol), thiophenol (0.2mmol) was stirred at 4 °C for 44 hours.

^bNa₂S₂O_{4(aq)}, toluene, THF, MeOH, TBAB at 0 °C, then KOH_(aq), Me₂SO₄. ^cIsolated yields are reported, and e.r. was determined by HPLC using a chiral stationary phase (average of three trials). ^dEnantioselective Thiophenol Addition ran for 20 hours. ^eAfter recrystallization. ^fNo reaction was observed by TLC after 20 hours. ^gEnantioselective Thiophenol Addition ran for 68 hours.

e.r., suggesting this chemistry could be applicable to quinone scaffolds upon further optimization.

Continuing with the naphthoquinone scaffold, we sought out to explore a range of substitutions on the non-quinone aryl ring (Scheme 1). In general, adding substitution at the *para*- position had little effect on enantioselectivity, giving **2j-2m** in high yields with 93:7 e.r. or better. However, replacing the -CF₃ group with methyl (**2n**) resulted in a drop in e.r. to 66:34. Enantioselectivity was improved as we increased the steric bulk of the alkyl substituent, with *i*-Pr (**2p**) resulting in 95:5 e.r. and *t*-Bu (**2q**) resulting in 98.5:1.5 e.r. Moreover, replacing -CF₃ with -Cl (**2r**) resulted in a drop in e.r. to 74:26, and a similar result was observed with a phenyl group *ortho*- to the atropisomeric axis (**2s**, 79:21 e.r.). The [1,2'-binaphthalene] atropisomer (**2t**) was isolated in 99% yield and 90:10 e.r., and the structurally analogous 4-methyl-[1,2'-

on a quinone-based scaffold gave **2i** in 70% yield and 68:32

binaphthalene], **2u**, was isolated in 95% yield and 92:8 e.r.. These results encouraged us to probe the effect of *meta*-substitution on the non-quinone aryl, finding that adding adjacent *meta*-substituents to poor substrates such as **2n**, (**2v-2y**), afforded significantly improved enantioselectivities ranging from 88:12 to 92:8 e.r., all in high yields. Notably, these selectivities were conserved when different thiophenols were used, as exemplified by **2z** and **2aa**. Overall, this methodology proved amenable to a diversity of substitution patterns within the confines of atropisomer stability.

When we did not quench the reaction via reductive methylation, we observed spontaneous oxidation of the dihydroquinone to the naphthoquinone product (i.e. **3a**), resulting in lower yields and enantioselectivities. The lower selectivity in the absence of reductant is likely due to racemization of the quinone as the reaction warms to room temperature. We experimentally

determined the barrier to rotation of **3a** to be 25.6 kcal/mol in toluene at 50 °C, which translates to an undesirable stereochemical

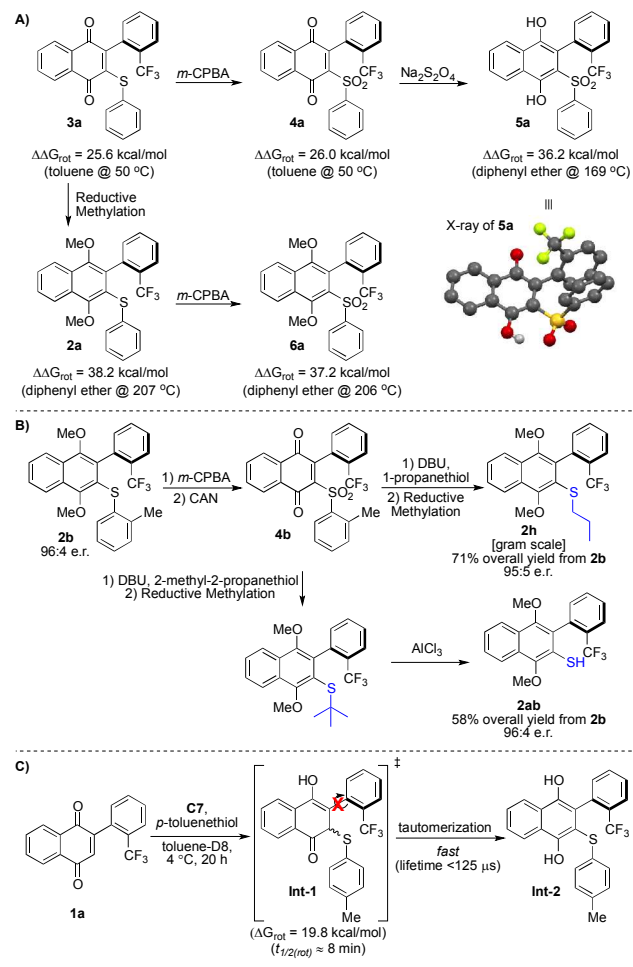


Figure 2. Stereochemical Stability and Discussion of Stereoinduction. A) The effect of quinone oxidation state on conformational stability. B) Enantioretention in gram-scale nucleophilic substitution. C) Tautomerism is likely much faster than atropisomer bond rotation.

stability at room temperature (Figure 2A). Upon oxidizing **3a** to sulfone **4a**, we observed a small increase in stereochemical stability to 26.0 kcal/mol, also in toluene at 50 °C. Moreover, this quinone could now be reduced to **5a**, which does not spontaneously oxidize due to the electron withdrawing sulfone. This allowed us to obtain a crystal structure (enantiomer was R_a) and determine its stereochemical stability, observing a barrier to rotation of 36.2 kcal/mol for **5a** in diphenyl ether at 169 °C. Thus, the observed barrier to rotation should preclude any observable racemization at room temperature. This drastic increase in stereochemical stability compared to **4a** is likely due to the longer C-O bond length in hydroquinones. Furthermore, analysis of aryl-quinone crystal structures reveal an out-of-plane distortion across the atropisomeric axis, which could also account for the lower observed barriers to rotation in aryl-quinones.³⁵ The methylated dihydro-

quinones proved even more stable, as **2a** exhibits an experimentally determined barrier to rotation of 38.2 kcal/mol in diphenyl ether at 207 °C. Next, we performed an $\text{S}_{\text{N}}\text{Ar}$ -like reaction sequence on **2b** to arrive at **2h** in 71% overall yield on the gram scale with nearly complete enantioretention (Figure 2B), despite proceeding thru the low-barrier quinone oxidation state. Moreover, when 2-methyl-2-propanethiol is used instead of 1-propanethiol, the *tert*-butyl group could be removed from the resulting *tert*-butyl sulfane with AlCl_3 to furnish the corresponding atropisomeric biaryl thiol with complete enantioretention. This result suggests that enantioretentive substitutions with other nucleophiles are possible, however that is perhaps beyond the scope of this work. Furthermore, having alkylsulfide substitution also provides a starting point for atropisomer diversification as there are several recent methodologies concerning C-S bond activation.^{36–39}

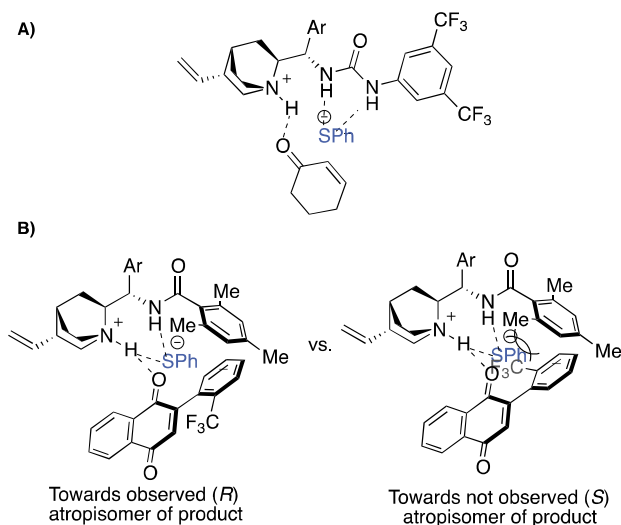


Figure 3. Mechanistic model. A) Houk's Brønsted Acid-Hydrogen Bonding Model. B) Plausible model for stereochemical induction.

Houk has recently reported a Brønsted acid-hydrogen bonding model (Figure 3A)^{40,41} for cinchona alkaloid-catalyzed sulfa-michael reactions, based on Wynberg's work.^{30,31} We postulate this transformation likely parallels Houk's model, as we found that **C7** can effect the addition of thiophenol into cyclohexanone with moderate levels of enantioselectivity (see Supporting Information). This result opens the possibility that the stereoselectivity of this transformation is induced via a 'point-to-axial' chirality transfer mechanism in which the thiophenol adds enantioselectively into the quinone to give diastereomeric **Int-1**, followed by the equilibration of the atropisomeric axis to the more stable diastereomer and tautomerization of **Int-1** to the corresponding hydroquinone **Int-2**. To probe this, we monitored the reaction of **1a** with *p*-toluenethiol in the presence of **C7** by ^1H NMR, observing no evidence of the point chiral addition adduct

Int-1, meaning tautomerization of **Int-1** to the corresponding hydroquinone (**Int-2**) likely occurs on the hundred-millisecond time scale or faster (Figure 2C, refer to discussion of NMR kinetics study in Supporting Information for more details). We next computationally determined the barrier to rotation of **Int-1** to be approximately 19.8 kcal/mol in the gas phase, which roughly translates to a $t_{1/2}$ to atropisomer bond rotation of about 8 minutes at 4 °C. While the error to the calculated barriers to rotation may not be accurate enough to draw an absolute conclusion, these experiments do suggest that tautomerization of **Int-1** to **Int-2** likely occurs faster than rotation of the atropisomeric bond, offering evidence against point-to-axial chirality, and perhaps in favor of a mechanism in which the axis is set prior to thiophenol addition.

One possible model, for stereochemical induction, largely inspired by Houk's model, is proposed in Figure 3B. Thiophenol is deprotonated by the quinuclidine base and oriented via H-bonding with the C-9 benzamide. The quinone is activated by an H-bond with the quinuclidinium ion, orienting the atropisomer axis in a way such that the *ortho*-substitution of the aryl group avoids steric interaction with the catalyst. More detailed studies are underway, including those aimed to better understand the atropisomer differentiation by **C7** to further probe the likelihood of potential modes of stereoinduction.

In conclusion, we have developed a novel atroposelective addition of thiophenol into rapidly interconverting aryl-naphthoquinones to afford stereochemically stable enantioenriched biaryl sulfides. This report lends itself as a proof-of-concept towards a general strategy towards the enantioselective synthesis of diverse biaryl and non-biaryl atropisomers. With proper control of the redox properties of the quinone moiety, we showed that we can modulate the atropisomer's stereochemical stability, as well as its reactivity. Furthermore, the resulting biaryl sulfide was moved on in an S_NAr -like reaction sequence with near complete enantioretention. Finally, an argument was made for the mode of asymmetric induction, as point-to-axial chirality transfer may not be the likely driving force for stereoinduction.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website.

Crystallographic data (CIF)

Experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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