Communication

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Catalytic Atroposelective Synthesis of *N*-Aryl Quinoid Compounds

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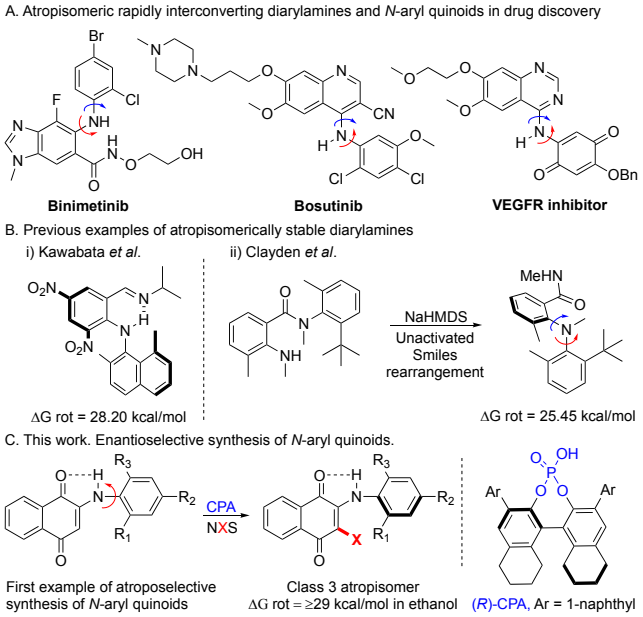
Supporting Information Placeholder

ABSTRACT: Diarylamines and related scaffolds are among the most common chemotypes in modern drug discovery. While they can potentially possess two chiral axes, there are no studies on their enantioselective synthesis as these axes typically possess lower stereochemical stabilities. Herein we report a chiral phosphoric acid catalyzed atroposelective electrophilic halogenation of *N*-aryl quinoids, a class of compounds that are analogous to diarylamines. This chemistry yields a large range of stereochemically stable *N*-aryl quinoids in excellent yields and atroposelectivity. This work represents the first example of the atroposelective synthesis of a diarylamine-like scaffold and will serve as a gateway to fundamental and applied studies on the scarcely studied chirality of these ubiquitous chiral scaffolds.

Atropisomerism, or axial chirality, is ubiquitous throughout modern drug discovery[1–4] and natural products chemistry.[5,6] While most chemists recognize atropisomeric axes pertaining to biaryls,[7] benzamides,[8] and anilides,[9] axial chirality in diarylamines and related scaffolds such as *N*-aryl quinoids are largely overlooked. Nonetheless, these structural motifs are among the most common potentially atropisomeric chemotypes in medicinal chemistry, with the FDA-approved drugs binimetinib and bosutinib representing examples of diarylamines that exist as rapidly interconverting atropisomers, and a VEGFR inhibitor from Wyeth representing a potentially atropisomeric *N*-aryl quinoid (Scheme 1A).[10–12] Indeed, a cursory search in the PDB will reveal thousands of co-crystal structures of diarylamine and related scaffolds bound to proteins in an atroposelective manner. With the rapid advancement of synthetic methodologies to form C(sp^2)-N bonds,[13,14] the ubiquitous nature of diarylamines and related scaffolds in drug discovery will likely continue to grow. These structural motifs are also interesting from a stereochemical perspective as they possess two contiguous atropisomeric axes which leads to a complex conformational profile as well as a potential gearing mechanism that can lead to lower than expected barriers to racemization.[15,16]

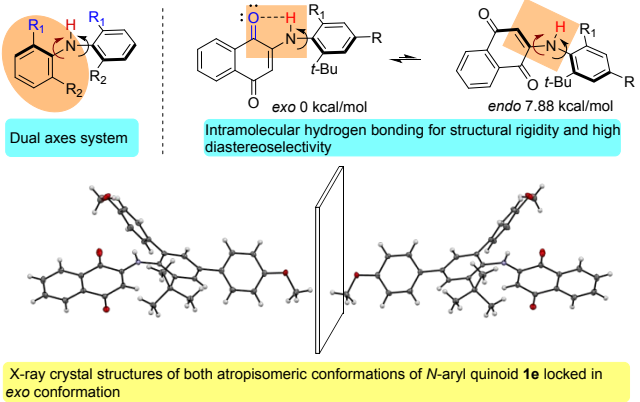
Kawabata[17,18] has resolved the atropisomers of a series of diarylamines that possessed an intramolecular N-H-N hydrogen bond that preorganized one of the axes into a planar conformation (Scheme 1B), simplifying diarylamines to a single axis system and resulting in compounds that possessed barriers to racemization of up to ~28 kcal/mol, existing as class 2 atropisomers according to LaPlante's[19] atropisomer stability classification system ($t_{1/2}$ to racemization on the day to month timescale at 37 °C). Kawabata's system proved sensitive to the strength of the intramolecular hydrogen bond, and the stereochemical stabilities quickly decreased upon removal of electron withdrawing groups. More recently, Clayden[15] resolved the atropisomers for diarylamines without an internal H-bond, finding them to only have stereochemical stabilities on the hour time scale at room temperature.

Scheme 1. Atropisomerism in Diarylamines and related scaffolds



As instances of stereochemically stable diarylamines and related scaffolds have been scarce, there are no published examples of their enantioselective synthesis. Herein we describe studies that have led to the first catalytic atroposelective synthesis of a diarylamine-like scaffold, finding *N*-aryl quinoids that possess a 5-membered intramolecular N-H-O hydrogen bond to exist as stereochemically stable class 3 atropisomers with barriers to racemization approaching and exceeding 30 kcal/mol ($t_{1/2\ (37°\ C)}$ > 4.5 years) in both protic and aprotic solvents, a classification that is considered sufficiently stereochemically stable for drug development.

Scheme 2. *N*-Aryl quinoids as a diarylamine surrogate with one chiral axis.



Inspired by Kawabata's work, as well as a series of *N*-aryl quinoid-based kinase inhibitors (also in Scheme 1A),[20] we synthesized *N*-aryl naphthoquinoide **1a** which exists as a stereochemically unstable class 1 atropisomer. Computational studies and X-ray crystallographic analysis (Scheme 2) suggested that the quinoid-nitrogen axis exists in a planar 'exo' conformation due to a strong intramolecular N-H-O hydrogen bond, simplifying the 2-axis system into a single axis system in a manner analogous to that of Kawabata. We hypothesized that functionalization of the quinoid C-H could lead to stable atropisomerism. Indeed, Tan and others have pioneered atroposelective synthesis via the addition of aryl nucleophiles into quinones,[21–25] and we have studied other nucleophiles in the context of the atroposelective synthesis.[16,26] Unfortunately, **1a** proved unreactive under these conditions.

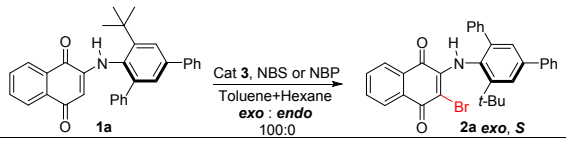
As the amino naphthoquinone moiety could be considered 'enamine-like' we next evaluated electrophilic functionalization of **1a**, observing facile electrophilic halogenation using achiral Lewis basic catalysts and *N*-halosuccinimides.[27,28] Excitingly, these halogenated products proved quite stereochemically stable (*vida infra*), confirming that this system may be amenable to atropisomer selective catalysis in which a stereochemical labile axis is rigidified via a 'net C-H functionalization', as exemplified in work by Miller and colleagues.[7,8,19,29–32]

The evaluation of chiral Lewis basic catalysts yielded little to no enantioselectivity (See SI). Inspired by the seminal work of Akiyama[33–38] on the atroposelective bromination of biaryl systems, we next evaluated several chiral phosphoric acids (CPA) with *N*-Bromosuccinimide (NBS) for the bromination of **1a** (Table 1, entries 1-4). While many of these catalysts yielded poor selectivity, the venerable CPA (*R*)-TRIPS **3d** effected this reaction to near quantitative conversions with promising enantioselectivity (77:23 e.r.). We next evaluated the less acidic octahydro-BINOL (H8-BINOL) scaffold, finding H8-BINOL (*R*)-TRIPS (**3e**, Table 1, entry 5) resulted in a slight increase in enantioselectivity (80:20 e.r.). This result encouraged us to try other H8-BINOL based catalysts (Table 1, entries 6-9). While modifying the 3,3' positions largely led to minor changes in selectivity, we found that CPA **3j**, which possesses 1-naphthyl substitution at the 3,3' position, to be an effective catalyst yielding brominated product **2a** in 94% yield and an e.r. of 91:9 (Table 1, entry 10). We next evaluated other reaction parameters such as temperature, solvent, reaction concentration, catalyst loading and bromination reagent (Table 1, entries 11-13), arriving to conditions that yielded **2a** in greater than 96:4 e.r. We finally evaluated **3k**, the BINOL based analog of our optimal catalyst, observing a slight loss in enantioselectivity (entry 14).

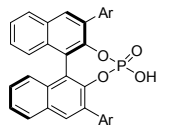
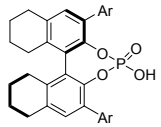
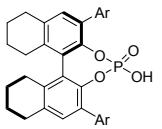
With optimal conditions in hand we next sought to define reaction scope. The chemistry proved to be tolerant of diverse aryl substitutions of the 2,4-positions of the aniline. Electron rich aryl substitutions yielding e.r.s above 95:5 (Scheme 3, **2b**-**2e**, **2i**, **2j**, **2n**, **2o**) and electron poor aryl substitutions yielding e.r.s around 90:10 (**2f**-**2h**, **2k**). Notably, aryls groups with ortho fluorine substitutions (**2l**, **2m**) yielded selectivities greater than 95:5 e.r. We were able to obtain a crystal structure of **2l**, confirming the stereochemical induction of this reaction to be the (*S*)-atropisomer in the *exo* conformation.

This chemistry also proved tolerant of fused ring systems including naphthyl (2p, 91% yield with 95:5 e.r.), benzofuran (2q, 89% yield with 85:15 e.r.) and benzothiophene (2r in 93% yield with 95:5 e.r.). We next evaluated substrates that possess 2-aryl-4-chloro substitution, obtaining 2s and 2t in excellent yield and enantioselectivity. We find these results significant, as the ability to transform aryl chlorides into diverse functionalities in a manner orthogonal to bromides[23] will allow for significant synthetic utility to obtain diverse analogs. Unfortunately, the synthesis of substrates with halogen substitution at the *ortho* position of the arene using literature methodologies failed due to

Table 1. Condition Optimization[a]



Entry	Catalyst	Br Source	Concentration	Time	Temp. (°C)	Yield (**2a**%)[b]	*e.r.* (**2a**)[c]
1	**3a** 5%	NBS	0.025M	**6 h**	24	94	45:55
2	**3b** 5%	NBS	0.025M	**6 h**	24	94	51:49
3	**3c** 5%	NBS	0.025M	**6 h**	24	94	56:44
4	**3d** 5%	NBS	0.025M	**6 h**	24	95	77:23
5	**3e** 5%	NBS	0.025M	**12 h**	24	94	80:20
6	**3f** 5%	NBS	0.025M	**12 h**	24	94	82:18
7	**3g** 5%	NBS	0.025M	**12 h**	24	95	74:26
8	**3h** 5%	NBS	0.025M	**12 h**	24	95	75:25
9	**3i** 5%	NBS	0.025M	**12 h**	24	94	50:50
10	**3j** 5%	NBS	0.025M	**12 h**	24	94	91:9
11	**3j** 10%	NBP	0.025M	**12 h**	24	94	92:8
12	**3j** 10%	NBP	0.0055M	**12 h**	24	95	95:5
13	**3j** 10%	NBP	0.0055M	**12 h**	24	95	96:4[d]
14	3k 10%	NBP	0.0055M	**6 h**	24	91	90:10[d]

3a) (*S*)-Ar = 9-antracenyl
3b) (*R*)-Ar = 9-phenanthrenyl
3c) (*R*)-Ar = 3,5-$(CF_3)_2$-C_6H_3
3d) (*R*)-Ar = 2,4,6-(*i*-Pr)$_3$-C_6H_2
3k) (*R*)-Ar = 1-naphthyl
3e) (*R*)-Ar = 2,4,6-(*i*-Pr)$_3$-C_6H_2
3f) (*R*)-Ar = *o*-tolyl
3g) (*R*)-Ar = phenyl
3h) (*R*)-Ar = 2,4,6-(Me)$_3$-C_6H_2
3i) (*R*)-Ar = 9-phenanthrene
3j) (*R*)-Ar = 1-naphthyl

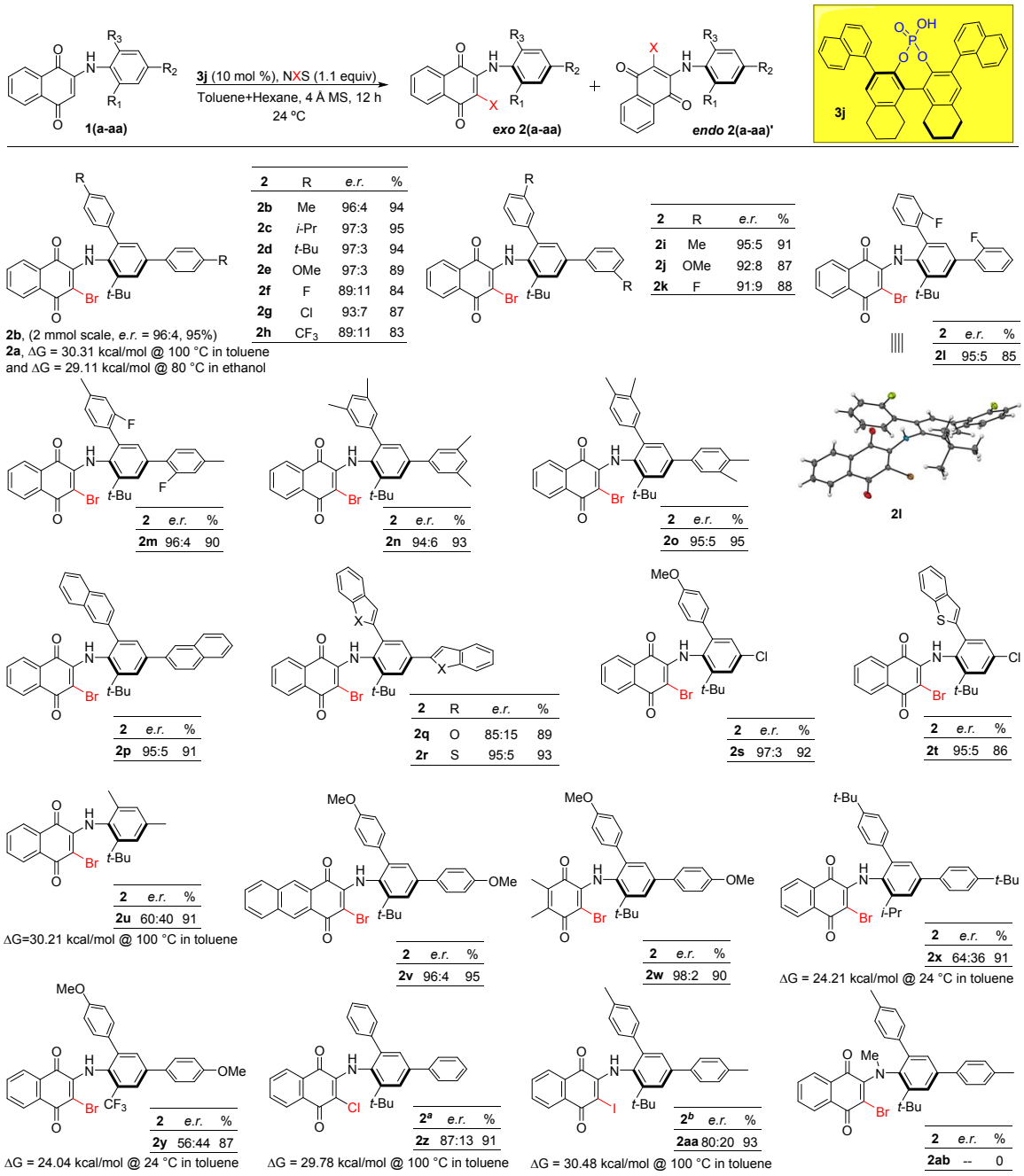
[a]Reaction conditions: Starting material **1a** (0.055 mmol), Catalyst (10%), Toluene:Hexane (1:1) 10 mL then bromine source (0.06 mmol) at 24 °C for 12 h. [b]isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase. [d] 2 fold 4Å MS. NBP = *N*-Bromophthalimide

an unexpected cyclization (see SI). Replacing the aryl substitution at both positions with methyl groups resulted in a large drop in e.r to 60:40 (**2u**, 91%), suggesting the *ortho*- aryl group partakes in an interaction with the catalyst that is crucial for enantiomer discrimination. We next evaluated different quinone fragments, finding an anthraquinone based substrate to give excellent yields and selectivities (**2v**, 95% yield with 96:4 e.r). A substituted benzoquinone-based substrate also reacted cleanly to give **2w** in 90% yield and 98:2 e.r.

We next evaluated anilines that did not possess a *t*-Bu group at the 6-position, observing that replacing the tert-butyl by isopropyl as in **2x** and trifluoromethyl as in **2y** resulted in good yield but drastic decreases in e.r. to 63:37 and 56:44 respectively, likely due to a low barrier to racemization (measured to be~24 kcal/mol) for these substrates leading to racemization during the course of the reaction. Finally, we observed that this chemistry was amenable to chlorination in the presence of a Lewis basic catalyst and NCS (**2z**, 91% yield with 87:13 e.r.) and iodination using NIS (**2aa**, 93% yield 80:20 e.r.), albeit with somewhat attenuated selectivities.

Racemization studies were also carried out to investigate the stereochemical stability of representative products. Product **2a** was found to have a barrier to rotation of 30.31 kcal/mol at 100 °C in toluene, which would be considered a stable class 3 atropisomer. Notably, when the barrier was measured in ethanol at 80 °C the barrier was only slightly lower (29.1 kcal/mol). Furthermore, the stereochemical stability was minimally affected under strongly acidic conditions (28.92 kcal/mol in a 4:1 mixture of EtOH and 0.5M HCl), and was largely unchanged from toluene under

Scheme 3. Substrate Scope



2	R	e.r.	%
2b	Me	96:4	94
2c	*i*-Pr	97:3	95
2d	*t*-Bu	97:3	94
2e	OMe	97:3	89
2f	F	89:11	84
2g	Cl	93:7	87
2h	CF_3	89:11	83

2	R	e.r.	%
2i	Me	95:5	91
2j	OMe	92:8	87
2k	F	91:9	88

2	e.r.	%
2l	95:5	85

2	e.r.	%
2m	96:4	90

2	e.r.	%
2n	94:6	93

2	e.r.	%
2o	95:5	95

2l

2	e.r.	%
2p	95:5	91

2	R	e.r.	%
2q	O	85:15	89
2r	S	95:5	93

2	e.r.	%
2s	97:3	92

2	e.r.	%
2t	95:5	86

2	e.r.	%
2u	60:40	91

2	e.r.	%
2v	96:4	95

2	e.r.	%
2w	98:2	90

2	e.r.	%
2x	64:36	91

2	e.r.	%
2y	56:44	87

2[a]	e.r.	%
2z	87:13	91

2[b]	e.r.	%
2aa	80:20	93

2	e.r.	%
2ab	--	0

[a]Reaction conditions: Starting material **1a** (0.054 mmol), Cat.3**e** (2.5%), Me_3PS (2.5%) Toluene:Hexane (1:1) 10 mL and 2 fold 4 Å MS then NCS (0.06 mmol) 24 °C for 12 h .
[b]Starting material **1a** (0.054 mmol), Cat. **3j** (10%) Toluene:Hexane (1:1) 10 mL and 2 fold 4 Å MS then NIS (0.06 mmol) 24 °C for 24 h .

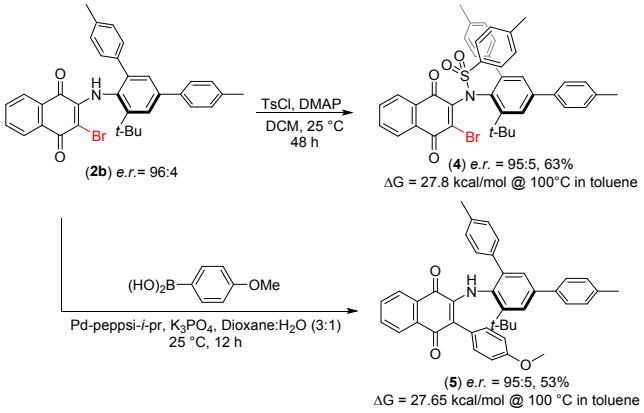
buffered aqueous conditions (30.56 kcal/mol at pH 7.5 in 1 M tris buffer). We also measured the barriers for products **2b**, **2u**, **2z** which possess varying substituent sizes about the chiral axis, finding the barrier to rotation tracked well with what is expected with other atropisomeric systems.[39] These observed trends are also in line with what Kawabata observed.

Taken together, this data is significant as it suggests that these compounds would be stereochemically stable under biological environments; thus, this work could be a gateway towards the development of atropisomerically stable analogs for the myriad diarylamines in medicinal chemistry. Moreover, these scaffolds would be stable under routine reaction conditions, thus it is possible to embed this scaffold into catalysts to give never before explored chiral environments.

We next studied the ability to modify these products to evaluate their synthetic utility (Scheme 4). We first found that the anilide functionality in **2b** could be tosylated to give sulfonamide **4** in 63% yield with no observed racemization. Compound **4**, which now lacks the internal H-bond, proved to exist as a class-2 atropiosmer with a barrier to rotation of 27.8 kcal/mol, in line with other literature precedence concerning anilide atropisomers. We also found that the bromide could be modified via Suzuki cross-coupling at room temperature using Organ's PEPPSI-*i*-Pr catalyst to afford **5** in 53% yield, also with complete retention of e.r. 95:5. As aryl substitution is significantly smaller than bromide

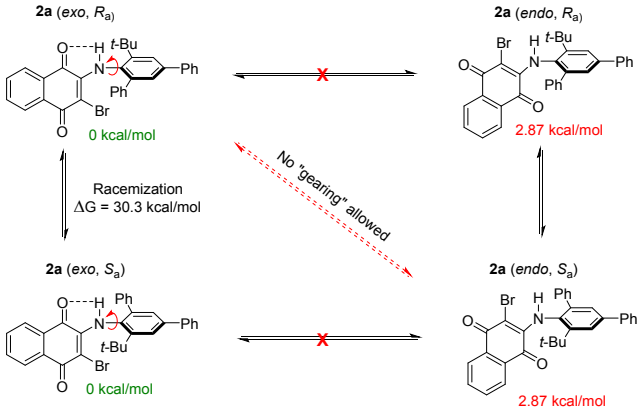
substitution[39], **5** also existed as a class-2 atropisomer. While **4** and **5** are less stable, they still possess t $_{(1/2)}$ of racemization at 37 °C on the multi-month timescale. It should be noted that this scaffold proved recalcitrant to reduction to the hydroquinone (see SI).

Scheme 4. Derivatization of Enantioenriched Products



We next sought out to better understand the unexpected stereochemical stability that was observed. In the X-ray crystal structure of **2l**, the naphthoquinone-N axis is locked into a planar *exo* orientation due to the aforementioned intramolecular hydrogen bonding.

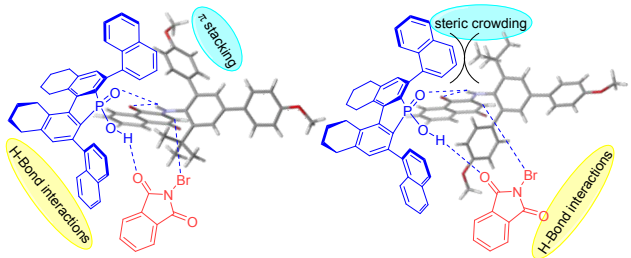
Scheme 5. Mechanism of Racemization



We further explored this by computationally evaluating the relative energy values of other conformations (Scheme 5). Both *exo*, (R_a) and *exo,* (S_a) conformations (0 kcal/mol) were significantly lower in energy than their respective *endo* conformations that possessed no intramolecular hydrogen bonding (+2.87 kcal/mol). Previously reported 2 axes systems are able to undergo concerted "gearing" to racemize, allowing for a lower energy pathway to racemization (barrier to rotations of 25-27 kcal/mol with similar sized substituents). The strong intramolecular hydrogen bonding likely precludes the gearing mechanism for racemization, requiring a more rigid pathway to racemization that is more analogous to biaryl and benzamide systems. Indeed, computational studies predicted barrier to rotations that agreed with our experimentally determined values when freezing the naphthoquinone-N axis; when the system was allowed to rotate both axes, predicted barriers to rotations were significantly lower than the experimental values (See SI).

Based on our data thus far, we propose the mechanism for stereochemical induction depicted in Scheme 6. We postulate the CPA **3j** engages in hydrogen bonding with the substrates O-H-N network with the substrate locked in the *exo* conformation. This H-bonding interaction would be expected to increase the energy level of the HOMO of the enamine-like amino naphthoquinone. The *N*-aryl axis would then be expected to rotate as to orientate the *t*-Bu group away from the catalyst, which would result in this axis being organized into the (S_a) conformation. Notably, the (S_a) conformation would also have the potential for the *ortho* aryl group to participate in pi-stacking with the catalyst naphthyl group, whereas the enantiomeric conformation would not. Finally, the acidic proton from CPA can activate the electrophilic halogenation reagent via H-bonding which will also allow for direction of bromination towards the naphthoquinone site. Upon electrophilic bromination, the axis will be rigidified selectively into the (S_a) configuration. In support of the importance of the H-bond, a *N*-methylated substrate analog (**1ab**) proved unreactive under our optimal conditions (scheme 3).

Scheme 6. Proposed transition state with substrate, catalyst and *N*-bromophthalimide



We have described the first catalytic atropisomer selective synthesis of a diarylamine-like scaffold. This chemistry proceeds via phosphoric acid catalyzed halogenation of *N*-aryl quinoids and yields products in upwards of 95:5 e.r. and 90% yield. Surprisingly, we found these products existed as stereochemically stable class-3 atropisomers in protic and aprotic conditions due to a strong intramolecular H-bond that locks one of the axes into a planar conformation. As diarylamines and related scaffolds are among the most ubiquitous scaffolds in drug discovery, the chemistry, concepts and principles put forward can extend far beyond this work and be of use for the design and enantioselective synthesis of diarylamine surrogates with applications in drug discovery and asymmetric synthesis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, and characterization data for all new compounds including ^{1}H- and ^{13}C-NMR spectra, Single-crystal X-ray diffraction, and HPLC traces (PDF).

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Notes

The authors declare no competing financial interest.

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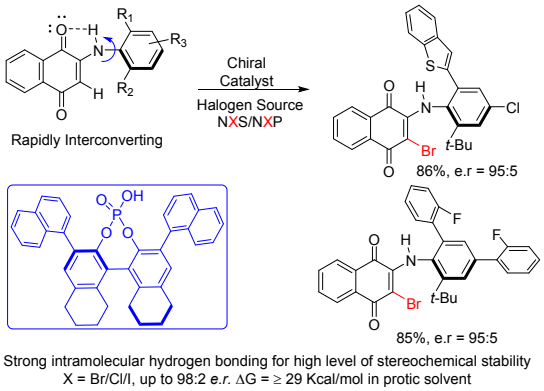

Strong intramolecular hydrogen bonding for high level of stereochemical stability
X = Br/Cl/I, up to 98:2 *e.r.* ΔG = ≥ 29 Kcal/mol in protic solvent