STRUCTURE−ENANTIOSELECTIVITY RELATIONSHIP (SER) STUDY OF CINCHONA ALKALOID CHLOROCYCLIZATION CATALYSTS

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ABSTRACT

Various structural elements of the cinchona alkaloid dimers are interrogated to establish a structure-enantioselectivity relationship (SER) in three different halocyclization reactions. SER for chlorocyclizations of a 1,1-disubstituted alkenoic acid, a 1,1-disubstituted alkeneamide, and a *trans*-1,2-disubstituted alkeneamide showed variable sensitivities to linker rigidity and polarity, aspects of the alkaloid structure, and the presence of two or only one alkaloid side group defining the catalyst pocket. The conformational rigidity of the linker−ether connections was probed via DFT calculations on the methoxylated models, uncovering especially high barriers to ether rotation out of plane in the arene systems that include the pyridazine ring. These linkers are also found in the catalysts with the highest enantioinduction. The diversity of the SER results suggested that the three apparently analogous test reactions may proceed by significantly different mechanisms. Based on these findings, a stripped-down analogue of $(DHQD)_2PYDZ$, termed "$(trunc)_2PYDZ$", was designed, synthesized, and evaluated, showing modest but considerable asymmetric induction in the three test reactions, with the best performance on the 1,1-disubstituted alkeneamide cyclization. This first effort to map out the factors essential to effective stereocontrol and reaction promotion offers guidance for the simplified design and systematic refinement of new, selective organocatalysts.

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LIST OF ABBREVIATIONS

Å	angstrom
[α]	specific rotation
δ	chemical shift
Ac	acetyl
Alk	alkyl
AQN	anthraquinone
Ar	aryl
benzoPHAL	benzophthalazine
br	broad (spectral peak)
CD	cinchonidine
CN	cinchonine
DCC	*N,N'*-Dicyclohexylcarbodiimide
DCDMH	1,3-Dichloro-5,5-dimethylhydantoin
DCDPH	1,3-Dichloro-5,5-diphenylhydantoin
DCM	dichloromethane
DHQ	dihydroquinine
DHQD	dihydroquinidine
(DHQ)2AQN	Dihydroquinine (anthraquinone-1,4-diyl) diether
DHQD-MEQ	Dihydroquinidine 4-methyl-2-quinolyl etherxvii
(DHQ)2PHAL	Dihydroquinine 1,4-phthalazinediyl diether
(DHQD)2PHAL	Dihydroquinidine 1,4-phthalazinediyl diether
DHQD-PHN	Dihydroquinidine 9-phenanthryl ether
(DHQ)2PYR	Dihydroquinine-2,5-diphenyl-4,6-pyrimidinediyl diether
DHQD-CLB	Dihydroquinidine 4-chlorobenzoate
DMA	*N*,*N*-dimethylacetamide

DMAP	4-Dimethylaminopyridine
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrmidinone
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
ee	enantioselectivity
ESI	electrospray ionization
Et	ethyl
EtOAc	Ethyl Acetate
(Et)2O	Diethyl ether
h	hour
HMPA	hexamethylphosphoramide
ISOPHTHAL	isopthaloyl
KHMDS	Potassium bis(trimethylsilyl)amide
LiHMDS	Lithium bis(trimethylsilyl)amide
Me	methyl
MHz	megahertz
Min	minues
mp	melting point
MS	mass spectrometry
Ms	mesyl
*n*Bu	*n*-butyl
NAPH	naphthalene
NAPY	naphthyridine
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance

NMP	*N*-methyl 2-pyrrolidone
Ph	phenyl
PHAL	phthalazine
PHTHAL	phthaloyl
PHN	phenanthroline
Ppm	parts per million
PYDZ	pyridazine
QD	quinidine
QN	quinidine
R	substituent
Rt	room temperature
SER	structure enantioselectivity relationship
TEA	triethylamine
Tf	triflyl
(Tf)2O	triflic anhydride
THF	tetrahydrofuran
*t*Bu	*tert*-butyl
TBAB	tetrabutylammonium bromide
TEREPHTHAL	terephthaloyl
TFE	2,2,2-trifluoroethanol
TLC	thin layer chromatograph

INTRODUCTION

The last decade has seen the emergence of powerful tools for asymmetric halofunctionalization of alkenes. These reactions can rapidly transform relatively simple olefinic substrates into complex scaffolds with multiple stereogenic centers.[1−9] Our first studies uncovered highly stereocontrolled chlorocyclizations of unsaturated carboxylic acids and amides catalyzed by $(DHQD)_2PHAL$, the same organocatalyst used in the venerable Sharpless asymmetric dihydroxylation reaction.[10,11] Mechanistic studies then demonstrated that this catalyst controls the stereochemistry of both halenium ion and nucleophile delivery.[12−15] However, despite the many literature reports on $(DHQD)_2PHAL$-catalyzed halofunctionalization,[3,11,16−20] little is known about the specific structural features of the catalyst that are responsible for asymmetric induction. This report examines the various components of $(DHQD)_2PHAL$ to develop structure−enantioselectivity relationships (SERs) for some of the asymmetric halocyclizations we have developed in recent years. As illustrated in Figure 1, the subunits that comprise the catalyst are varied to probe their influence on asymmetric selectivity. This leads to the design of a new potential catalyst that incorporates the minimum required elements.

Using $(DHQD)_2PHAL$ as the organocatalyst, our labs have explored stereocontrolled halofunctionalizations with various alkene substrates, chlorenium sources, and nucleophiles. These reactions include chlorocyclizations of alkenoic acids,[10] alkeneamides,[11,21] and alkene carbamates,[19] where the nucleophilic moiety is intramolecular, as well as reactions like chloro-etherification/amidation and dichlorination where nucleophilic attack is intermolecular.[17,22,23] Nicolaou, Hennecke, and other groups have also reported the use of $(DHQD)_2PHAL$-type catalysts for asymmetric halofunctionalizations.[16,18] The sheer numbers of successful applications speak to the robustness and versatility of these cinchona alkaloid catalysts in asymmetric halofunctionalization methodologies.

The structure of (DHQD)$_2$PHAL (Figure 1) consists of two dihydroquinidine (DHQD) alkaloid units linked by phthalazine (PHAL). The alkaloid unit is composed of quinuclidine and methoxyquinoline moieties both connected to a carbinol carbon. In the following sections, any such catalyst with two alkaloid subunits bridged by a linker is denoted as follows: *(alkaloid)$_2$linker* (Figure 1). Variation of these substructures generates catalyst candidates with a range of functional groups and conformational possibilities. Structure−enantioselectivity relationships (SER) are mapped using three asymmetric halofunctionalization reactions *R1*−*R3* (Scheme 1) in which (DHQD)$_2$PHAL is effective. These studies reveal key aspects of catalyst structure, ideally opening the door to optimization of both enantioselectivity and rate, while offering valuable insights into the mechanisms of the probe reactions.

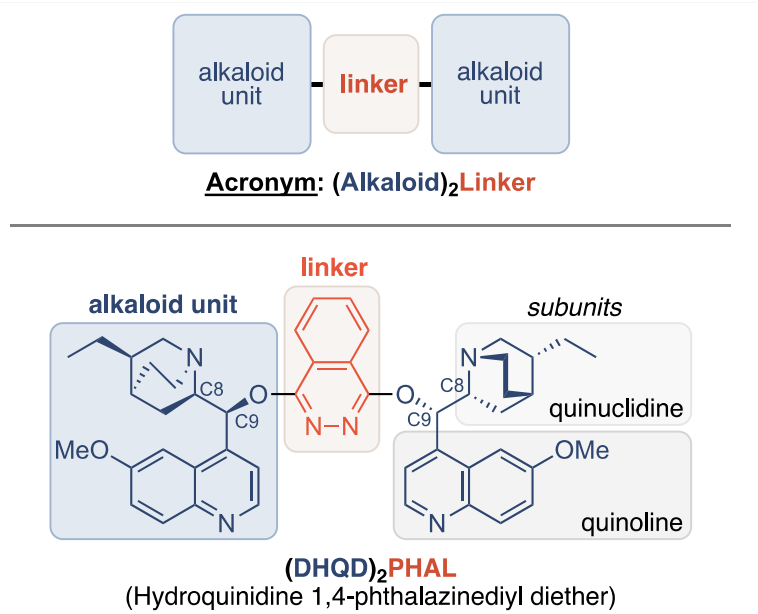


Figure 1 *General structure of cinchona alkaloid dimer catalysts as exemplified with (DHQD)2PHAL structures.*

RESULTS AND DISCUSSION

SER STUDIES

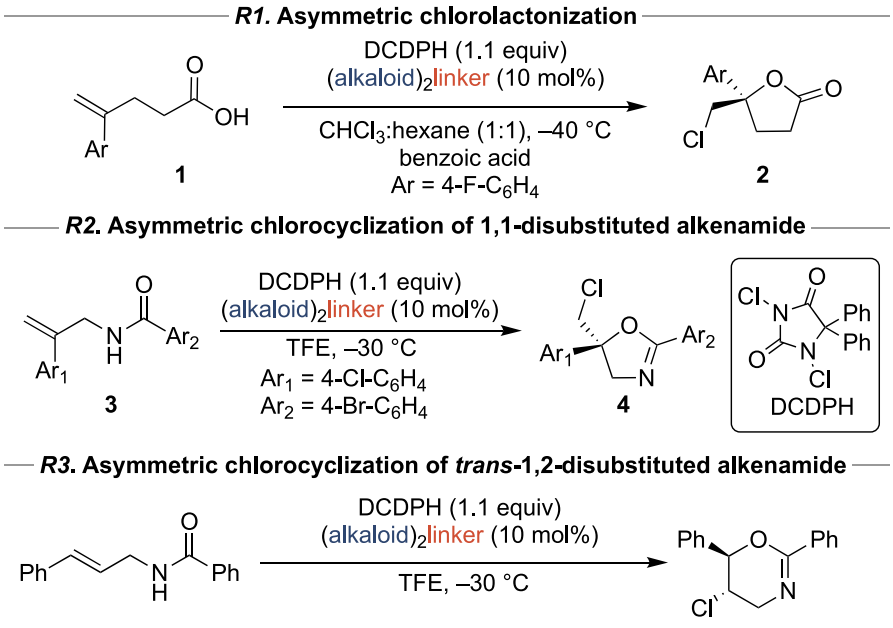
Chlorolactonization[10] and chlorocyclization of amides[11,21] represent some of the earliest reports of catalytic asymmetric chlorofunctionalizations. Here, the product enantioselectivities of these reactions are used in a structure−enantioselectivity relationship (SER) study to explore the effects of catalyst structural variations. The three chosen reactions are *R1*: chlorolactonization of a 1,1- disubstituted alkene-carboxylic acid; *R*2: chlorocyclization of a 1,1-disubstituted alkeneamide; and *R3*: chlorocyclization of a 1,2-disubstituted alkeneamide (Scheme 1). All three occur via asymmetric delivery of the chlorenium ion to one enantiotopic face of the alkene, which we have suggested is activated by the alkene's proximity to the internal nucleophile (carbonyl oxygen).[12,24] For this SER study, the original conditions for *R1*, *R2*, and *R3* were modified slightly to establish identical initial concentrations of catalysts and reactants across the different reactions. Under these new standard conditions, and with $(DHQD)_2PHAL$ as catalyst, reactions *R1*, *R2*, and *R3* yielded asymmetric products with 84, 90, and 99% *ee*, respectively (Table 1).

Cinchona alkaloid dimers, and in particular $(DHQD)_2PHAL$, were among the first organocatalysts to successfully catalyze asymmetric halofunctionalization chemistry. To establish SERs for the halocyclizations *R1*−*R3*, various structural elements of the catalysts were interrogated. Inspired by the classic $(DHQD)_2PHAL$, the catalysts in this work were built on the motif of a central linker (like PHAL) flanked by a pair of chiral moieties (like DHQD), attached via ether linkages. Structural components and aspects investigated were the linker (addressing size and the presence of aromatic sp^2 nitrogen atoms), the quinuclidine (substituents, sp^3 nitrogen atoms, chiral centers C8 and C9, see Figure 1), and the quinoline (substituent steric and electronic effects).

SER for *R1*−*R3* showed variable sensitivities to linker rigidity and polarity, aspects of the alkaloid structure, and the presence of two or only one alkaloid side group defining the catalytic site. The conformational rigidity of the linker−ether connections was probed via DFT calculations on methoxylated linker models, uncovering especially high barriers to ether rotation out of plane in the arene systems that include the

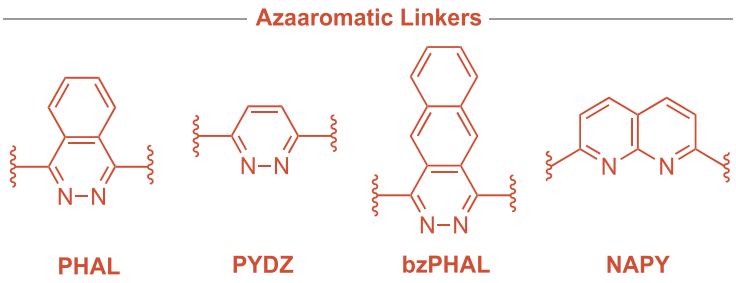
pyridazine ring. These linkers are also found in the catalysts with the highest enantioinduction. Based on these findings, a stripped-down analogue of (DHQD)$_2$PYDZ, termed "(trunc)$_2$PYDZ", was designed, synthesized, and evaluated, showing modest but substantial asymmetric induction in the three test reactions, with the best performance on the 1,1- disubstituted alkeneamide cyclization.

Importantly, this work is the first analysis of its kind *as applied to stereocontrolled halof unctionalizations*.



Scheme 1 *Test Reactions Used for the SER Study of (DHQD)$_2$PHAL-Catalyzed Chlorocyclization. Reaction 1 (R1) is an example of chlorolactonization. Reaction 2 (R2) is an example of chlorocyclization of a 1,1-disubstituted alkeneamide. Reaction 3 (R3) is an example of chlorocyclization of a 1,2-disubstituted alkeneamide. DCDPH = 1,3-dichloro-5,5-diphenylhydantoin, TFE = 2,2,2-trifluoroethanol.*

Though these reactions have catalysts in common with the long-studied (and mechanistically challenging) Sharpless asymmetric alkene dihydroxylation, they differ in essentially all other aspects. Indeed, the diversity of the SER results among *R1*–*R3* suggests that even these three apparently analogous test reactions proceed by significantly different mechanisms. By mapping out the factors essential to effective stereocontrol and reaction promotion, the results offer guidance for the simplified design and systematic refinement of new, selective organocatalysts.



	$(DHQD)_2$ PHAL	$(DHQD)_2$ PYDZ	$(DHQD)_2$ bzPHAL	$(DHQD)_2$ NAPY
R1	84	80	85	-59
R2	90	93	86	12
R3	99	98	99	4

Table 1 *Effect of Azaaromatic Linker Size on Enantioselectivity. Cinchona alkaloid units and azaaromatic linkers. Enantioselectivity of various linkers on reactions R1−R3 is presented as numbers in the table. DHQD = dihydroquinidine; PHAL = 1,4-linked phthalazine; PYDZ = 3,6-linked pyridazine; bzPHAL = 1,4-linked benzophthalazine; NAPY = 2,7- linked 1,8-naphthyridine.*

SIZE OF THE LINKER

At the center of the catalyst, the linker holds the two cinchona alkaloid units together in the required geometry. Therefore, we began our study with a structural investigation of the linker size. Two new catalysts, $(DHQD)_2$PYDZ and $(DHQD)_2$bzPHAL, were synthesized, where the linker size was varied while retaining the dihydroquinidine (DHQD) moiety. The two linkers consisted of a pyridazine (PYDZ) and a benzophthalazine (bzPHAL), smaller and larger analogues of the original phthalazine (PHAL) linker. As shown in Table 1, compared to reactions catalyzed by $(DHQD)_2$PHAL, *R1* suffered a small but measurable erosion of the enantioselectivity with the smaller linker, giving 80% *ee* with $(DHQD)_2$PYDZ, whereas $(DHQD)_2$bzPHAL with the larger linker gave 85% *ee*, a slight improvement. *R2* displayed the reverse trend, showing improvement with the smaller linker and erosion with the larger one. *R3* showed no measurable dependency on linker size.

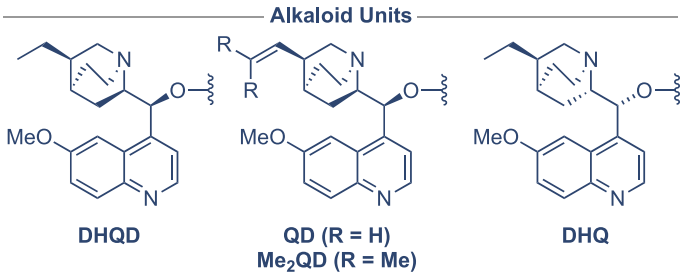
Having found only modest effects upon elongating or shortening the diazaaromatic linker “floor” of the catalytic binding pocket, we next considered the consequences of widening it by introducing a 1,8-naphthyridine (NAPY) linker. The resulting catalyst, $(DHQD)_2$NAPY (Table 1) retains the two sp^2

nitrogen atoms embedded in the bicyclic naphthalene framework of the linker, but in positions different from those in PHAL (2,3-diazanaphthalene). The linker holds the two alkaloid units further apart and at a different angle. This modification flipped the enantioselectivity for *R1* from 84% *ee* (with $(DHQD)_2PHAL$) to a nontrivial −59% *ee*. Reactions *R2* and *R3*, however, completely lost selectivity, giving nearly racemic product. Viewed in the best light, these findings offer a simple way of switching the enantioselectivity of the product without resorting to switching the chirality of the $(DHQD)_2PHAL$ catalyst itself. They also point to substantial differences between the stereochemical control elements of *R1* vs *R2* and *R3*. Specifically, they support the idea that π–π stacking[25] may play a more significant role in substrate orientation in the catalyst cleft for *R1* than for *R2* and *R3*.

ROLE OF THE PHTHALAZINE NITROGEN ATOM

To uncover the essential aspects of the linker and the role of the phthalazine nitrogen atoms, we synthesized and tested several $(alkaloid)_2$linker systems with nitrogen-free linkers. As summarized in Table 2, when attached to the phthalazine linker, the alkaloid subunits DHQD, QD, and DHQ notably all gave similar (~80%) absolute enantioselectivities in *R1*, enabling fair comparisons across $(DHQD)_2PHAL$, $(QD)_2PHAL$, and $(DHQ)_2PHAL$, the "pseudoenantiomer" of $(DHQD)_2PHAL$. Replacement of the phthalazine in $(DHQD)_2PHAL$ with a simple naphthalene linker formed the deaza analogue, $(DHQD)_2NAPH$ (see Table 2 for structures). This catalyst led to low selectivities in *R1*, *R2*, and *R3*. Somewhat surprising, however, was the inversion of selectivity of *R2*. The even simpler 1,4-benzene bridged $(QD)_2C_6H_4$ was essentially catalytically incompetent for stereoinduction, showing only slight positive selectivity in *R2*. Speculating that fluorination might introduce additional hydrogen bonding interactions or mimic the electron-withdrawing effect of the nitrogen atoms, we also explored the tetrafluorinated analogue $(QD)_2C_6F_4$, again finding low, but now inverted, selectivities for all three reactions (Table 2). Similarly, replacement of the phthalazine linker of $(DHQ)_2PHAL$ with anthraquinone (AQN) led to a near-complete loss in selectivity for *R1* and *R2*, from −77 to −12% *ee* and from −95 to −5% *ee*, respectively. Interestingly, for *R3*, enantioselectivity was inverted from −99 to 35% *ee.* Studying

asymmetric dichlorination of allylic alcohols, the Nicolaou group noted losses like those above in switching from $(DHQ)_2PHAL$ to $(DHQ)_2AQN$.[16] They proposed that the nitrogen atoms in the linker were involved in hydrogen bonding with the allylic alcohol in the transition state, while the quinuclidine moiety of the catalyst delivered the chlorenium source to the more accessible face of the alkene. Analogous interactions could be envisioned between the substrates for reactions *R1*−*R3* and the PHAL linker nitrogen atom in the catalyst; this binding mode would be lost upon replacement of PHAL with AQN. It is worth mentioning that for the Sharpless asymmetric dihydroxylation, the commercially available $(DHQ)_2AQN$ gives superior results with alkyl-substituted olefins with comparable results to $(DHQD)_2PHAL$, but is less effective for aryl olefins.[26]



	$(DHQD)_2PHAL$	$(QD)_2PHAL$	$(Me_2QD)_2PHAL$	$(DHQ)_2PHAL$
R1	84	81	85	−77
R2	90	86	81[b]	−95
R3	99	99	99[b]	−99
	$(DHQD)_2NAPH$	$(QD)_2C_6H_4$	$(QD)_2C_6F_4$	$(DHQ)_2AQN$
R1	7	0	−18	−12
R2	−14	12	−9	−5
R3	15	0	−5	35

Table 2 *Enantioselectivity Using Linkers without Aromatic Nitrogen. Deazaaromatic linkers. NAPH = 1,4-linked naphthalene; C_6H_4 = 1,4- linked benzene; C_6F_4 = 1,4-linked tetrafluorobenzene; AQN = 1,4- linked anthraquinone; DHQD = dihydroquinidine; QD = quinidine; Me_2QD = dimethylquinidine; DHQ = dihydroquinine; PHAL = 1,4- linked phthalazine.* [b]*These values were obtained with the closely analogous $(Me_2QD)_2PYDZ$ catalyst.*

The above findings confirm that the nitrogen atoms in the PHAL or PYDZ linker are important structural components of the catalyst for asymmetric chlorofunctionalizations. Though they may participate in hydrogen bonding, another important function is to rigidify the catalyst. The two ether oxygens that connect the PHAL or PYDZ linker to the alkaloid unit prefer a geometry coplanar to the PHAL ring due presumably to delocalization of the oxygen 2p lone pair electrons into the C− N π* orbital in the ring. Meanwhile, as in carboxylic esters, the stereoelectronic preference of oxygen's sp^2 (in-plane) lone pair is to lie *anti* to the C−N bond. These effects strongly favor a parallel and coplanar arrangement of the linker−O−$C_{alkaloid}$ ether moieties. To explore this issue further, we resorted to computational modeling at the B3LYP-D3/6-31+G* level of theory. Figure 2 shows calculated potential energy functions for rotation of a single methoxy group in the dimethoxylated analogues (e.g., 1,4-dimethoxyphthalazine) for seven of the linkers that are 1,4-disubstituted with alkaloid groups. Upon rotation out of the plane, the diaza linkers all show a much steeper rise in energy than the carbocyclic linkers, reflecting their stronger preference for the in-plane geometry. The latter trend holds true across analogues of the same ring size (PYDZ vs C_6H_4 and C_6F_4, PHAL vs NAPH, and bzPHAL vs AQN). Similar observations from the literature[27] support the hypothesis that a key role of the linker nitrogen atom is to rigidify the structures, holding the two cinchona alkaloid fragments via ether linkages that lie in the plane of the linker arene. This structural element defines the chiral pocket. Linkers without the nitrogen atoms lack this rigidity, and thus the structural definition, needed for catalytic stereodifferentiation. Though the low (≤3 kcal/mol) variations in energy across the methoxy rotations in 1,4-dimethoxybenzene (C_6H_4 linker) and 1,2,4,5-tetrafluoro-3,6-dimethoxybenzene (C_6F_4 linker) were unsurprising, the similarly low (≤4 kcal/mol) variations in the 1,4-dimethoxyanthracene-9,10-dione (AQN linker) case were striking. A complete conformational analysis (see the SI) of this compound found at least nine symmetry unique (i.e., not counting enantiomeric pairs) conformational minima, all

within ≤2.5 kcal/mol of the lowest energy! The reader is referred to the SI for a proposed stereoelectronic explanation of the latter observation.

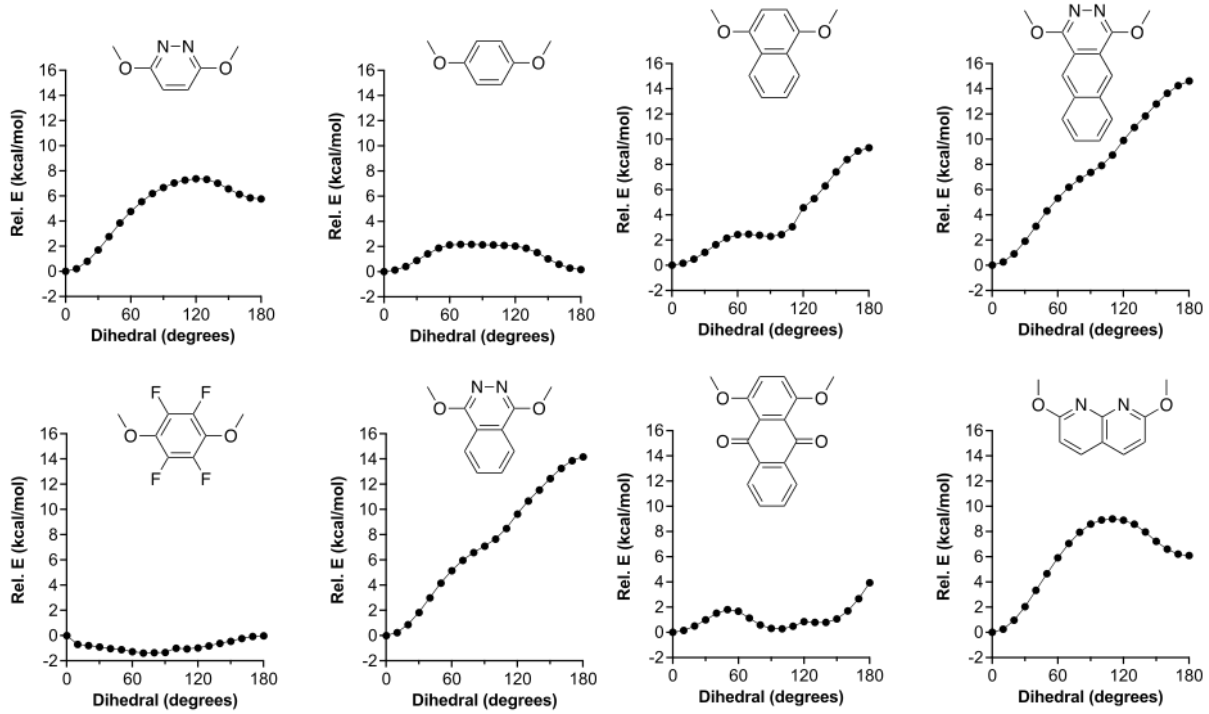


Figure 2 *B3LYP-D3/6-31+G* energy profiles for C−O bond rotations of one of the methoxy groups in each of the dimethoxylated linkers shown. Vertical axes are in kcal/mol, and horizontal axes represent N=C−O−C(H3) or analogous dihedral angles such that 0° corresponds to the methoxy carbon lying coplanar to the ring as depicted. Except for the C−O torsion angle of the methoxy group being constrained, structures were fully relaxed at each step. Particularly surprising was the 1,4-dimethoxy-9,10-anthroquinone linker (bottom left); in a more comprehensive search, between competing resonance, dipole−dipole, and steric interactions, this compound shows no less than nine symmetry-distinct conformational minima, all within ≤2.5 kcal/mol.*

ROLE OF THE QUINUCLIDINE NITROGEN ATOM

The quinuclidine moiety itself includes several chiral centers along with a basic, sp^3 nitrogen atom, which may play an important role in substrate orientation and alkene activation. Previous reports on Sharpless asymmetric dihydroxylation have shown that this quinuclidine moiety coordinates to the osmium metal center.[28]

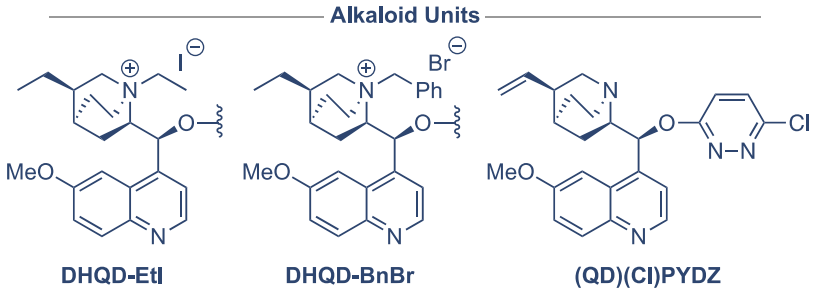
For the present chlorocyclizations, it has been suggested that the quinuclidine nitrogen atom may coordinate to the electrophilic chlorine source or even abstract the chlorenium ion itself before delivering it to the alkene. Nonetheless, based on our previously reported NMR and stereochemical results[14] the alkene-carboxylic acid substrate in *R1* binds more tightly to the strongly basic quinuclidine site than DCDMH (1,3-dichloro-5,5-dimethylhydantoin), the chlorenium ion donor. Thus, the quinuclidine nitrogen atom on the catalyst likely plays a key substrate recognition role via hydrogen bonding.

To probe the importance of the quinuclidine nitrogen atoms in the catalytic function of $(DHQD)_2PHAL$, two derivatives in which one of the two quinuclidine sites was alkylated were prepared. These mono *N*-alkylammonium salts, (DHQD)(DHQD-EtI)PHAL and (DHQD)(DHQD-BnBr)PHAL, displayed significant reductions in enantioselectivity for *R1*, giving 57% *ee* for the *N*-ethylated and 51% *ee* for the *N*-benzylated catalysts (Table 3). Nonetheless, the significant residual enantioselectivity suggested that the remaining unmodified dihydroquinidine moiety was still able to achieve some stereoselective catalytic function. Meanwhile, *R2* and *R3* showed minimal loss of enantioselectivity with the quaternized catalysts. These findings suggest that only one quinuclidine nitrogen atom is involved in the catalytic processes of *R2* and *R3*, whereas *R1* is more sensitive. More broadly, they hint that the catalytic pathways for *R2* and *R3* may differ from what has been proposed for *R1*.[14] Potential roles for the alkylated quinuclidine moieties could not be probed, as a synthesis of catalysts where both quinuclidine nitrogen atoms were alkylated led to unstable products that could not be purified to homogeneity.

IS THE SECOND ALKALOID UNIT NECESSARY?

The quinuclidine quaternization results suggested that the second quinuclidine nitrogen atom might not be needed for catalytic efficacy. To explore this issue, the "half" catalyst (QD)(Cl)PYDZ was synthesized and tested. This catalyst lacked one of the alkaloid (QD) units, which was replaced simply with a chlorine atom. As seen in Table 3, with (QD)(Cl)PYDZ as catalyst, *R1* lost all selectivity, while *R2* and *R3* retained modest and low stereoselectivities, respectively. Evidently, the second alkaloid unit, while not essential for reaction, does play a role in controlling the asymmetric induction, perhaps by placing steric boundaries on

the chiral pocket of the catalyst. It should be noted, however, that Hennecke and co-workers have had success with similar catalysts for the dichlorination of styrenyl systems.[29]



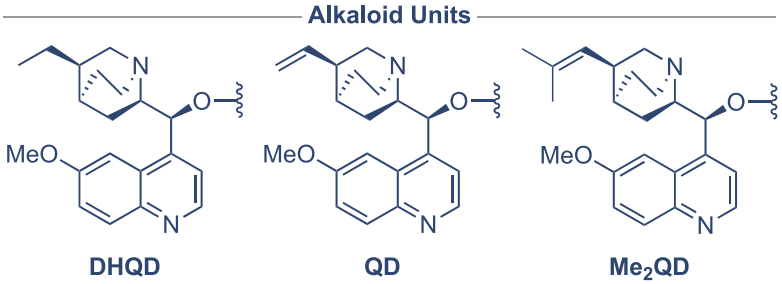
	(DHQD)(DHQD-EtI)PHAL	(DHQD)(DHQD-BnBr)PHAL	(QD)(Cl)PYDZ
R1	57	51	1
R2	80	87	51
R3	98	83	24

Table 3 *Effect of Quinuclidine Nitrogen Atoms on Enantioselectivity . DHQD = dihydroquinidine; QD = quinidine; PYDZ = 3,6-linked pyridazine; PHAL = 1,4-linked phthalazine.*

ROLE OF THE QUINUCLIDINE SUBSTITUENT

The quinuclidine moiety in the dihydroquinidine alkaloid fragment (DHQD) includes an unfunctionalized ethyl substituent at C3 (Figure 1). To test the effect of this ethyl fragment on stereoselectivity, the entire (DHQD) fragment was replaced with commercially available quinidine (QD). Replacing DHQD with QD resulted in the catalysts $(QD)_2$PHAL or $(QD)_2$PYDZ. For *R1*, this modification led to 3 and 4% drops in enantioselectivity for the PHAL and PYDZ linkers, respectively. Similar results were seen for *R2* and *R3* with negligible effects on stereoinduction (Tables 2 and 4). These small changes in selectivity are not surprising given that ethyl and vinyl groups are not drastically different in steric size. However, the low sensitivity of product enantioselectivity toward linker and alkaloid substitution does have some practical implications: (1) various quinidine alkaloids and linkers are commercially available, offering opportunities to create new potential catalysts, and (2) compared to $(DHQD)_2$PHAL, alkaloid dimers like $(QD)_2$PYDZ are structurally somewhat simpler, easier to prepare, and more readily functionalized on both the quinuclidine substituent and the linker ring to generate novel catalytic systems. Such elaboration is demonstrated in the $(Me_2QD)_2$PYDZ catalyst, a modified derivative of the $(QD)_2$PYDZ system, which

was easily synthesized using Grubbs metathesis.[30] Corey et al. had also exploited this ease of functionalization, synthesizing a cyclic derivative of the $(QD)_2PYDZ$ system[31] with a long-chain bridge joining the quinuclidine substituent sites. Despite the smaller PYDZ linker, for *R1*, the (Me QD) PYDZ catalyst showed the same selectivity as the parent $(DHQD)_2PHAL$. Overall, $(Me_2QD)_2PYDZ$ was found to have comparable selectivity to $(QD)_2PYDZ$, further confirming that the C3 substituent (e.g., the ethyl group in $(DHQD)_2PHAL$) has only a small impact on stereoselectivity (Table 4). These findings are also consistent with the relatively small differences in absolute selectivity between $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$, "pseudoenantiomer" catalysts whose only deviation from a true enantiomeric relationship is in the configuration of the ethyl attachments on the quinuclidine moieties.



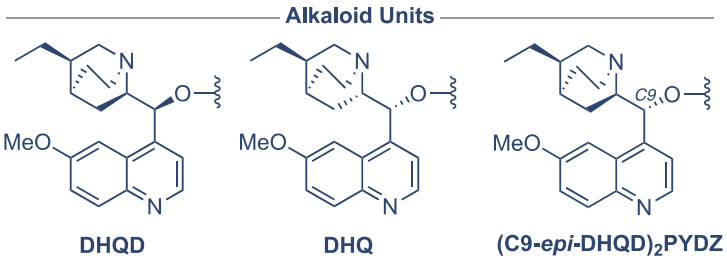
	$(QD)_2PHAL$	$(QD)_2PYDZ$	$(QD)_2bzPHAL$	$(Me_2QD)_2PYDZ$
R1	81	76	80	84
R2	86	88	86	71
R3	99	99	99	99

Table 4 *Effect of Substituent Size at C3 Position of Quinuclidine. DHQD = dihydroquinidine; QD = quinidine; Me_2QD = dimethylquinidine; PHAL = 1,4-linked phthalazine; PYDZ = 3,6-linked pyridazine; bzPHAL = 1,4-linked benzophthalazine.*

ROLE OF THE C8/C9 RELATIVE STEREOCHEMISTRY

$(DHQD)_2PHAL$ and $(DHQ)_2PHAL$ exhibit nearly complete reversal in their selectivity toward *R1*, *R2*, *andR3* (Table 2). As noted above, these two catalysts have opposite configurations at the C8 and C9 alkaloid stereocenters but the same configurations at the ethyl connection to the quinuclidine. Thus, the C8 and C9 stereocenters appear to be the most important for shaping the chiral pocket leading to enantioselectivity. To explore this hypothesis, the (C9-*epi*- $(DHQD)_2PYDZ$ was synthesized and tested on all three reactions

(Table 5). Compared to the respectable enantioselectivity obtained with $(DHQD)_2PYDZ$ (Table 5; 80, 93, and 98% *ee* for *R1*−*R3*, respectively), *R1* and *R3* lost nearly all selectivity, but *R2* retained more than half (57 vs 93%) when catalyzed with the $(C9\text{-}epi\text{-}DHQD)_2PYDZ$. This trend appears similar to the results seen with (QD)(Cl)PYDZ, where removal of one of the alkaloid units led to drastic selectivity losses for *R1* and *R3*, but less for *R2* (see Table 3). Since this catalyst was expected to have a significantly redefined chiral pocket, these results may suggest that the selectivity in *R2* is dominated by more localized substrate−catalyst interactions than in *R1* and *R3*, and further supports the hypothesis that the second alkaloid unit (DHQD or QD) simply shapes the chiral cavity. Modification of the C9 stereocenters presumably reorients the quinuclidines, moving the locus of the reaction out from binding in the chiral pocket.



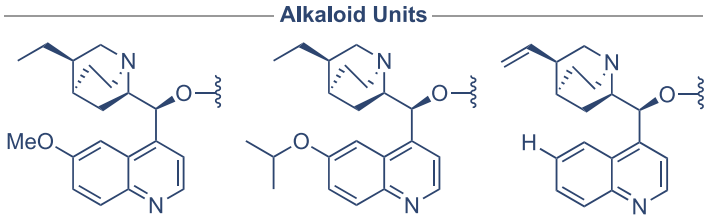
	$(DHQD)_2PYDZ$	$(DHQ)_2PHAL$	$(C9\text{-}epi\text{-}DHQD)_2PYDZ$
R1	80	−77	11
R2	93	−95	57
R3	98	−99	17

Table 5 *Effect of the C8/C9 Relative Stereochemistry on Enantioselectivity. DHQD = dihydroquinidine; DHQ = dihydroquinine; PYDZ = 3,6- linked pyridazine; PHAL = 1,4-linked phthalazine; epi-DHQD = C9- epimer of dihydroquinidine.*

STERIC EFFECTS OF QUINOLINE RING SUBSTITUENTS

The mechanistic picture proposed for the Sharpless asymmetric dihydroxylation of styrenyl substrates invokes a π–π stacking interaction between the quinoline moiety of $(DHQD)_2PHAL$ and an aromatic ring of the substrates.[25] These π–π- or CH–π-type weak interactions could be present in the asymmetric chlorofunctionalization processes as well. In fact, most of the reported alkene substrates have a neighboring aromatic moiety,[32] suggesting that the catalyst could benefit from such interactions. To test this idea, we

synthesized two new catalysts $(CN)_2$PYDZ and (iPr-DHQD)$_2$PYDZ, where the methoxy groups of the original DHQD moieties had been replaced by H and by isopropoxy groups, respectively, thus modifying the steric and electronic environment of the catalyst binding pocket. Surprisingly, both catalysts displayed lower selectivity than (DHQD)$_2$PYDZ for *R1* (Table 6). This can be rationalized in the following way: due to its increased bulk, (iPr-DHQD)$_2$PYDZ disrupts any π–π or CH–π interactions needed for optimum selectivity. $(CN)_2$PYDZ does not suffer from such steric hindrance, but removal of the electron-rich alkoxy group may change the electronics of the quinoline ring enough for it to weaken π–π interactions with the substrate due to its less polar and polarizable π-system. Neither *R2* nor *R3* showed any significant change in selectivity in either case, suggesting that such catalyst–substrate interactions are absent or at least unaffected by the changes in the catalyst. These data are in accordance with our earlier reports where the substrates with cyclohexyl instead of aryl groups gave poor enantiose lectivity for *R1* but high enantioselectivity for *R3*, implying different roles for π–π stacking in *R1* versus *R3*.[10,11]



	(DHQD)$_2$PYDZ	(iPr-DHQD)$_2$PYDZ	$(CN)_2$PYDZ
R1	80	58	65
R2	93	97	91
R3	98	99	98

Table 6 *Effect of Quinoline Size and Electronics on Enantioselectivity; Alkaloids with Modified Quinoline. DHQD = dihydroquinidine; CN = chinconine; PYDZ = 3,6-linked pyridazine.*

SUMMARY OF STRUCTURAL VARIATIONS

Variations of the substituent on the quinuclidine or the configuration of its attachment make only modest changes to the catalyst's enantioselectivities. *R2* and *R3* (but not *R1*) are also relatively insensitive to steric or electronic changes on the quinoline ring. Likewise, varying the length of the PHAL analogue linkers (PYDZ and BzPHAL) retains the selectivities seen with PHAL. These findings broaden the catalyst design

palette to include various alternative, commercially available, or laboratory- modified catalysts for these halofunctionalization reactions without sacrificing catalyst efficacy. On the other hand, the presence of aromatic nitrogen atoms in a linker of appropriate width is essential for effective stereoselectivity. The other influential elements are the relative configurations of the C8 and C9 stereocenters adjacent to the linker. Catalysts diastereomeric at C8/C9 show greatly eroded selectivity. Notably, for *R1*, modification of the catalyst geometry by use of the NAPY linker reverses the enantioselectivity despite the alkaloid subunits' chirality being unchanged. Given the C_2-symmetric structure of the $(DHQD)_2PHAL$ parent catalyst, we envision that one of the two quinuclidine moieties might create a wall that defines the substrate binding pocket, without being involved in direct coordination or activation processes during the catalysis. Therefore, both alkaloid units are necessary to retain proper catalyst functioning, as removing one unit can render the catalyst unselective. Considering the test reactions, *R1* appears to be the most sensitive to catalyst structural modifications, whereas *R2* and *R3* are more robust, likely occurring via more localized interactions with the catalyst structure (see Figure 3 for a pictorial summary).

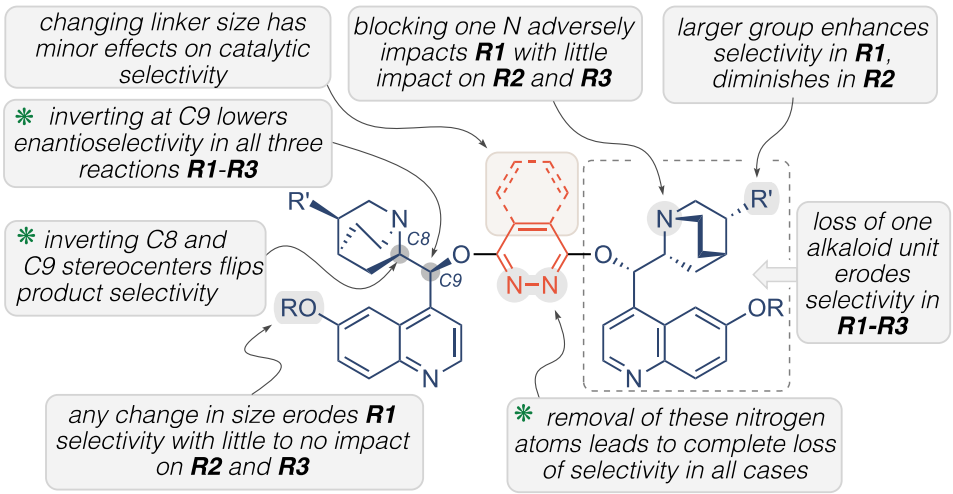
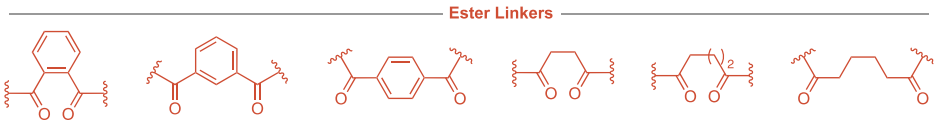


Figure 3 *Summary of SER studies on cinchona alkaloid catalyst (* denotes the critical features that affect stereoinduction).*

APPLICATION TO CATALYST DESIGN

To build on the results from the SER studies, we pursued several structural modifications on $(QD)_2$PHAL in search of a simpler, functional catalyst structure. We began by replacing the PHAL linker unit. Having noted the structural rigidification due to electron delocalization to the nitrogen atoms of the phthalazine linker (PHAL), we explored its oxygen analogue, the phthalate (benzene *ortho*-dicarboxylate) diester $(QD)_2$PHTHAL where the linking oxygen atoms are no longer attached directly to the ring (see Table 7 for structures). The two ester carbonyl groups would therefore likely lie out of the arene plane due to steric and dipole−dipole interactions; nonetheless, their structural relationship should be fairly rigid. Nearly all selectivity was lost for *R1*, presumably due to the loss of structural definition, as was found with the NAPH, C_6H_4, C_6F_4, and AQN linkers. Reactions *R2* and *R3* did retain moderate selectivity, albeit far less than with the best catalysts. Here again, the linker's poor conformational definition was likely enough to disrupt the chiral pocket created by the two alkaloid units, affecting *R1* more severely than *R2* and *R3*. Similar trends in reaction performance were found with the phthalate isomer diester linkers *iso*PHTHAL and TERE, and with aliphatic backbones in the succinate (SUCC), glutarate (GLUT), and adipate diesters (ADI), with none surpassing the original catalyst efficacy.



	$(QD)_2$PHTHAL	$(QD)_2$*iso*PHTHAL	$(QD)_2$TERE	$(QD)_2$SUCC	$(QD)_2$GLUT	$(QD)_2$ADI
R1	3	38	2	1	2	1
R2	48	15	47	75	46	57
R3	44	48	51	60	48	43

Table 7 *Effect of Ester-Based Linkers on Enantioselectivity. PHTHAL = phthaloyl linked; isoPHTHAL = i-phthaloyl linked; TERE = terephthaloyl linked; SUCC = succinyl linked; GLUT = glutaroyl linked; ADI = adipoyl linked; QD = quinidine.*

MINIMALIST APPROACH TO CATALYST DESIGN

Highlighted in Figure 3 are the components of (DHQD)$_2$PHAL with variable influence on the catalytic efficiency for the transformations investigated. Extracting the most influential components i.e., the linker, the rigidity of the 1,4-substitutions afforded by the diaza aryl group, and the relative configurations at C8 and C9, a trimmed-down version of (DHQD)$_2$PYDZ was explored (see (trunc)$_2$PYDZ structure in Figure 4). This structure contains the most basic elements deemed necessary for imparting stereoselectivity, representing a minimalist approach to the design of a new catalyst framework. The complex quinoline and quinuclidine moieties were omitted, leaving only tertiary amine centers and aromatic rings. Given its radically altered structure and great reduction in bulk, we were pleased that (trunc)$_2$PYDZ led to surprisingly significant *ee*s (44, 61, and 35% *ee* for *R1*, *R2*, and *R3*, respectively) for a catalyst lacking any structural optimization. Beyond its value in reconfirming the role of the critical elements that the SER study has revealed, this proof-of-principle result demonstrates the value of SER in guiding the design of simplified catalyst motifs. As a bonus, mechanistic interpretation of these results indicates that for *R1*, the definition of the catalytic pocket plays a major role so that the lack of efficient π–π stacking in (trunc)$_2$PYDZ gives eroded enantioselectivity. On the other hand, *R2* is more dependent on local interactions with the stereogenic catalyst functionalities and less on the overall structure and ability to participate in π–π stacking interactions. For *R3*, the catalytic pocket is needed for efficient selectivity, and thus the absence of the bulky quinuclidine units results in poor enantioselectivity. This approach to catalyst design could enable rapid exploratory generation of libraries of truncated catalysts via routine chemical transformations, in contrast to the synthetic challenges of modifying a catalyst with the complexity of DHQD)$_2$PHAL.

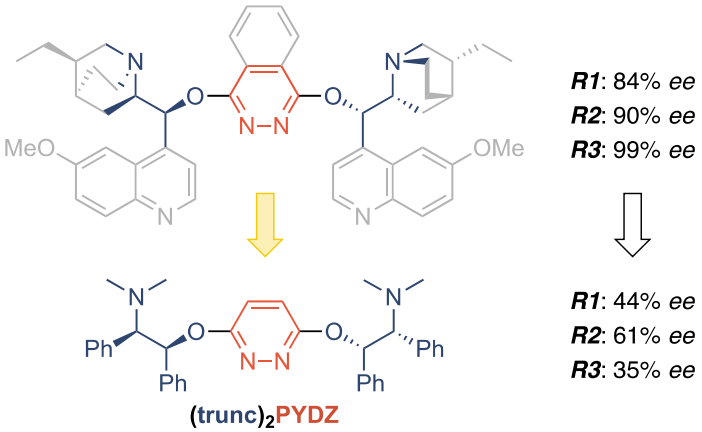


Figure 4 *Truncated catalyst retains the most critical elements identified in the SER study of (DHQD)2PHAL, leading to appreciable enantio-induction for the three reactions R1−R3 without structural or reaction optimization efforts. The (trunc)2PYDZ catalyst represents a minimalist approach to catalyst design.*

CONCLUSIONS

By exploring the effects of catalyst structural variations on the enantioselectivities of the three halocyclization reactions *R1*− *R3*, we have identified factors essential for effective asymmetric induction. One key issue is the structural definition conferred by the strong rotational preferences of the azaaromatic linkers; in fact, slight but measurable improvements were seen over the performance of $(DHQD)_2$PHAL itself for reactions *R1* with $(DHQD)_2$bzPHAL and *R2* with $(DHQD)_2$PYDZ. The relative configurations of C8 and C9 are also critical; epimerizing C9 severely eroded selectivity, especially for *R1* and *R3*. Figure 3 summarizes the contributions of different domains of the catalysts on the stereochemical outcome of the three reactions investigated.

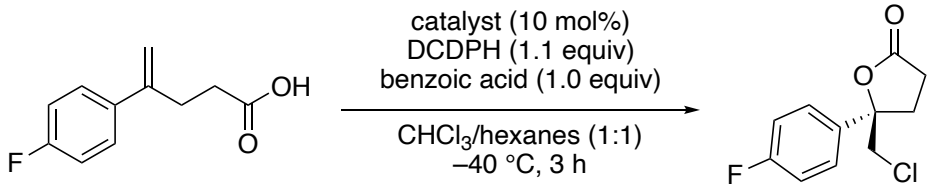
The three reactions show widely varying sensitivity to structural changes in the catalysts suggesting nontrivial differences in the details of their catalyzed reaction mechanisms. Reaction *R1* in particular shows a need for activation by catalysts with the two alkaloid moieties in rigid, structurally defined relationships, consistent with our recently reported analysis of its $(DHQD)_2$PHAL-catalyzed reaction mechanism.[14] On the other hand, even with only one alkaloid moiety available as in (QD)(Cl)PYDZ and effectively catalyst dimers constructed with alkyl diester linkers SUCC, GLUT, and ADI, *R2* shows enantioselectivities that are substantial, albeit not high enough to be of practical synthetic value. Extension of these ideas to the synthesis of new candidate catalyst forms showed that even simplified systems are capable of nontrivial asymmetric induction. Although none of the more severely altered catalysts or the new designs tested yielded significantly better enantioselectivities than the parent $(DHQD)_2$PHAL, the results described here have established the key variables and set the stage for more detailed mechanistic and simulation studies to guide the design of new, potent halofunctionalization reactions.

GENERAL PROCEDURES

All reagents were used without purification unless otherwise noted. Anhydrous chloroform stabilized with amylenes (Aldrich) and HPLC grade 95% *n*-hexanes (Spectrum) was used for all asymmetric halolactonizations. All other solvents were purchased from either Fisher Scientific or Mallinckrodt Chemicals and were used without further purification. NMR spectra were measured at 500 or 600 MHz on Varian Inova instruments. Chemical shifts are reported relative to residual solvent (δ7.24 ppm for $CDCl_3$). HRMS data were collected on a Waters Xevo G2-XS UPLC/MS/MS instrument at the MSU mass spec facility. Analytical thin layer chromatography (TLC) was performed using pre-coated silica gel 60 F_{254} plates. Compounds were visualized with UV light, potassium permanganate stain, *p*-anisaldehyde or phosphomolybdic acid in EtOH. Column chromatographic purifications were performed using Silicycle 40-60 Å, 30-75 μm silica gel. All compounds purified by chromatography were sufficiently pure for use in further experiments. Melting point values were recorded using a Mel-Temp II Laboratory Device and are uncorrected.

General procedure for lactonization catalyst screening (R1)

(*R*)-5-(Chloromethyl)-5-(4-fluorophenyl)dihydrofuran-2(3H)-one (2)[33]



1 **2**

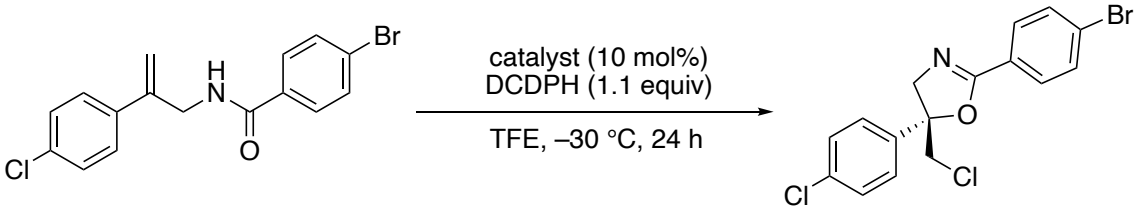
To a flame dried 30 mm × 100 mm disposable test tube was added catalyst (0.003 mmol, 0.10 equiv), chloroform (0.25 mL), and hexanes (0.25 mL). The reaction was cooled to –40 °C using an immersion cooler. DCDPH (9 mg, 0.3 mmol, 1.1 equiv) and benzoic acid (3 mg, 0.03 mmol, 1.0 equiv) were then added and the reaction was stirred for 30 min. 4-(4-fluorophenyl)pent-4-enoic acid (5 mg, 0.03 mmol) was then added and the reaction was stirred at –40 °C for 3 h. The reaction was monitored by TLC (20% ethyl acetate in hexanes, $KMnO_4$ charred). The reaction was quenched with 0.1 M aqueous sodium hydroxide (2.0 mL). The reaction was extracted with dichloromethane (3 × 5 mL), the combined organics were dried over anhydrous sodium sulfate, and concentrated. The crude residue was filtered through a Pasteur pipette packed with silica gel (20% ethyl acetate in hexanes), giving the product quantitively as a colorless oil.

Data for **(*R*)-5-(chloromethyl)-5-(4-fluorophenyl)dihydrofuran-2(3H)-one (2)**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.39-7.36 (m, 2H), 7.10-7.06 (m, 2H), 3.78 (d, J = 12.1 Hz, 1H), 3.71 (d, J = 12.1 Hz, 1H), 2.84-2.76 (m, 2H), 2.58-2.46 (m, 2H) ppm; ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$) δ 173.8, 162.6 (d, $J_{C\text{-}F}$ = 247 Hz), 136.4, 126.8 (d, $^{3}J_{C\text{-}F}$ = 8.6 Hz), 116.0 (d, $^{2}J_{C\text{-}F}$= 21.6 Hz), 86.6, 52.3, 31.7, 29.2 ppm. $[\alpha]^{20}_{D}$ = +18.0° (c = 10 mg/mL, $CHCl_3$). GC Resolution of enantiomers: GAMMA DEX 225; 90 °C for 10 min, 90 °C to 200 °C ramp (3 °C/min), 220 °C for 15 min; RT_1 = 52.78 min, RT_2 = 53.11 min.

General procedure for screening 1,1-disubstituted olefin amide cyclization (R2)

(*R*)-2-(4-Bromophenyl)-5-(chloromethyl)-5-(4-chlorophenyl)-4,5-dihydrooxazole (4)[34]

To a flame dried 30 mm × 100 mm disposable test tube was added catalyst (0.003 mmol, 0.10 equiv) and



3 **4**

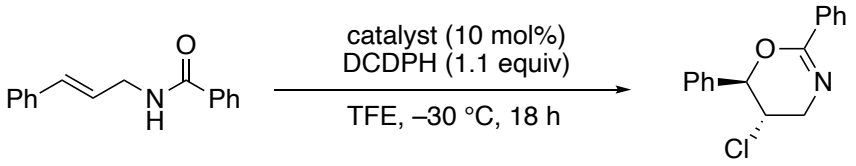
trifluoroethanol (0.63 mL). The reaction was cooled to –30 °C using an immersion cooler and then DCDPH (10 mg, 0.031 mmol, 1.2 equiv) was added and the reaction was stirred for 10 min. 4-Bromo-*N*-(2-(4-chlorophenyl)allyl)benzamide (9 mg, 0.03 mmol) was then added and the reaction was stirred at –30 °C for 24 h. The reaction was monitored by TLC (20% ethyl acetate in hexanes, $KMnO_4$ charred). The reaction was quenched with 10% aqueous sodium thiosulfite (2.0 mL). The reaction was then extracted with dichloromethane (3 × 5 mL), the combined organics were dried over anhydrous sodium sulfate, and concentrated. The crude residue was filtered through a Pasteur pipette packed with silica gel (20% ethyl acetate in hexanes), giving the product quantitively as a yellow gum.

Data for **(*R*)-2-(4-bromophenyl)-5-(chloromethyl)-5-(4-chlorophenyl)-4,5- dihydrooxazole (4):** ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 8.7 Hz, 2H), 7.37-7.32 (m, 4H), 4.47 (d, J = 15.1 Hz, 1H), 4.15 (d, J = 15.1 Hz, 1H), 3.88 (d, J = 12.0 Hz, 1H), 3.80 (d, J = 14.5 Hz, 1H) ppm; ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$) δ 162.0, 139.7, 134.4, 131.9, 129.7, 129.0, 128.8, 128.5, 126.8, 126.4, 87.5, 65.0, 50.7 ppm. $[\alpha]^{20}_D$ = –73.8° (c = 10 mg/mL, $CHCl_3$). LC Resolution of enantiomers: CHIRAL-CEL OJ-H; 5% iso-propyl alcohol in hexanes, 1.0 mL / min, 254 nm, RT_1= 18.80 min, RT_2= 19.10 min.

General procedure for screening *trans*-disubstituted olefin amide cyclization (R3)

(5*S*,6*R*)-5-Chloro-2,6-diphenyl-5,6-dihydro-4H-1,3-oxazine (6)[34]

To a flame dried 30 mm × 100 mm disposable test tube was added catalyst (0.003 mmol, 0.10 equiv) and



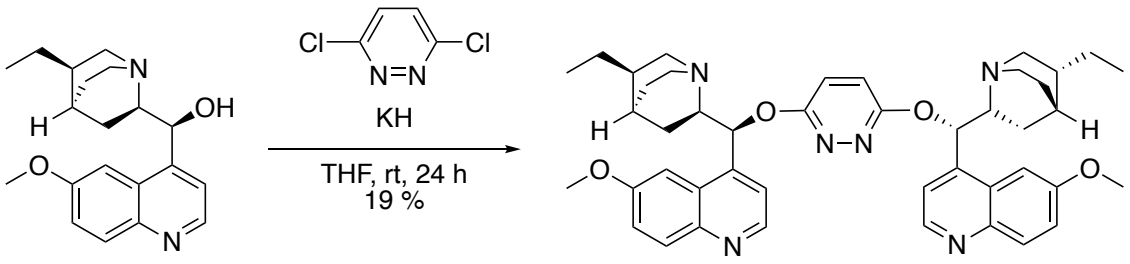
5 **6**

trifluoroethanol (0.63 mL). The reaction was cooled to –30 °C using an immersion cooler and then DCDPH (10 mg, 0.031 mmol, 1.2 equiv) was added and the reaction was stirred for 10 min. *N*-cinnamylbenzamide (6 mg, 0.03 mmol) was then added and the reaction was stirred at –30 °C for 18 h. The reaction was monitored by TLC (20% ethyl acetate in hexanes, $KMnO_4$ charred). The reaction was quenched with 10% aqueous sodium thiosulfite (2.0 mL). The reaction was then extracted with dichloromethane (3 × 5 mL), the combined organics were dried over anhydrous sodium sulfate, and concentrated. The crude residue was purified using a Pasteur pipette packed with silica gel (20% ethyl acetate in hexanes), giving the product quantitively as a colorless oil.

Data for **(5*S*,6*R*)-5-chloro-2,6-diphenyl-5,6-dihydro-4H-1,3-oxazine (6)**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.99 (dd, J = 8.4, 0.95 Hz, 2H), 7.49-7.39 (m, 8H), 5.27 (d, J = 7.7, 1H), 4.26-4.21 (m, 1H), 4.01 (dd, J = 17.1, 4.8 Hz, 1H) 3.82 (dd, J = 17.1, 7.9 Hz, 1H) ppm; ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$) δ 155.2, 137.2, 132.6, 130.9, 129.0, 128.7, 128.2, 127.3, 126.8, 80.7, 54.0, 50.0 ppm. $[\alpha]^{20}_D$ = –21.0° (c = 10 mg/mL, $CHCl_3$). LC Resolution of enantiomers: CHIRAL-CEL OJ-H; 3% iso-propanol in hexanes, 1.0 mL/min, RT_1 = 16.42 min, RT_2 = 20.68 min.

SYNTHESIS OF CATALYSTS

Synthesis of $(DHQD)_2PYDZ$



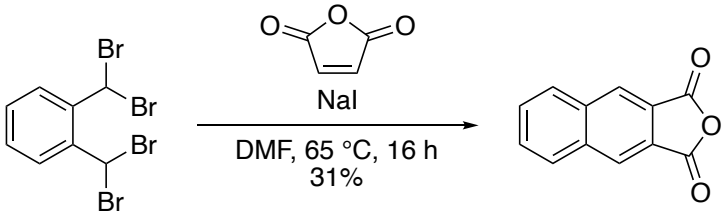
To a flame dried 100 mL round bottom flask was added KH (238 mg, 1.78 mmol, 4.36 equiv, 30% suspension in oil). The oil was removed from the potassium hydride by washing with hexanes (3 × 2 mL). THF (36 mL) was then added to the flask, followed by the addition of dihydroquinidine (302 mg, 0.925 mmol, 2.26 equiv) and 3,6-dichloropyridazine (61 mg, 0.409 mmol, 1.0 equiv). The reaction was stirred at room temperature under dry nitrogen for 24 h, during which time the color changed from colorless to orange. At the end of 24 h, TLC analysis (15% MeOH in $CHCl_3$) indicated that all the starting material was consumed. The reaction was quenched by adding saturated aqueous NH_4Cl (10 mL). The layers were then separated, the aqueous layer was washed with EtOAc (3 x 20 mL), the combined organics were washed with water (3 × 20 mL), dried over anhydrous Na_2SO_4, and concentrated. The product was purified using column chromatography ($CHCl_3$ to 3% MeOH in $CHCl_3$) to give the product as an off-white solid (56 mg, 0.077 mmol) in 19% yield.

Data for **$(DHQD)_2PYDZ$:** ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.67 (d, J = 4.5 Hz, 2H), 8.00 (d, J = 9.2 Hz, 2H), 7.44 (s, 2H), 7.37-7.34 (m, 4H), 6.97 (s, 2H), 6.74 (d, J = 6.2 Hz, 2H), 3.87 (s, 6H), 3.29 (dd, J = 15.8, 8.9 Hz, 2H), 2.81-2.62 (m, 8H), 1.85 (t, J = 12.3 Hz, 2H), 1.68 (s, 2H), 1.53-1.50 (m, 2H), 1.46-1.38 (m, 10H), 0.83 (t, J = 6.9 Hz, 6H) ppm; ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$) δ 161.19, 157.99, 147.74, 145.08, 144.98, 131.96, 127.63, 122.11, 121.64, 119.02, 102.37, 77.36, 60.34, 55.96, 51.29, 50.44, 37.79, 27.69, 26.46, 25.68, 23.61, 12.31 ppm. Expected signal for carbinol peak must be underneath $CDCl_3$ signal, so both ^{1}H-NMR and ^{13}C{^{1}H}-NMR were run in CD_3OD to confirm carbinol signal. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.74 (d, J = 4.7 Hz, 2H), 8.05 (d, J = 9.2 Hz, 2H), 7.67 (d, J = 4.7 Hz, 2H), 7.61-7.55 (m, 4H),

7.51 (s, 2H), 7.00 (d, J = 4.3 Hz, 2H), 4.01 (s, 6H), 3.43 (td, J = 9.1, 4.4 Hz, 2H), 3.05-2.85 (m, 6H), 2.93-2.82 (m, 2H), 2.34-2.28 (m, 2H), 1.90 (s, 2H), 1.78-1.62 (m, 10H), 1.56-1.48 (m, 2H), 1.06 (t, J = 7.1 Hz, 6H) ppm; $^{13}C\{^{1}H\}$-NMR (125 MHz, CD_3OD) δ 163.61, 161.13, 149.26, 147.64, 146.38, 132.72, 129.81, 125.23, 124.74, 120.93, 103.93, 80.90, 78.93, 61.84, 57.71, 53.30, 52.36, 39.72, 29.12, 27.67, 24.12, 13.63 ppm. IR (NaCl plate): $\tilde{\nu}$ 2951, 2934, 2872, 1622, 1509, 1474, 1407, 1282, 1228, 989 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{44}H_{52}N_6O_4H^+$ 729.4128, found 729.4144; $[\alpha]^{20}_D$ = –19.7° (c = 10 mg/mL, $CHCl_3$); mp = 97-99 °C.

Synthesis of (DHQD)$_2$bzPHAL

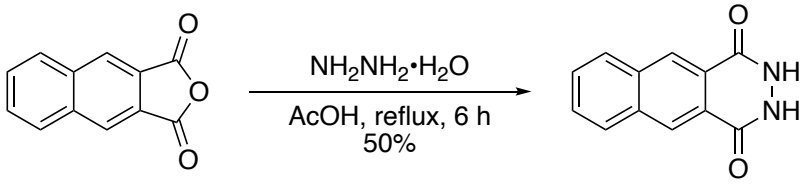
Naphtho[2,3-c]furan-1,3-dione[35]



To a flame dried 100 mL round bottom flask was added α,α,α',α'-tetrabromo-*o*-xylene (7.24 g, 17.2 mmol, 1.7 equiv), maleic anhydride (0.99 g, 10.1 mmol, 1.0 equiv), sodium iodide (16.1 g, 107.8 mmol, 10.6 equiv) and anhydrous DMF (40 mL). The reaction immediately turned dark brown and was heated to 65 °C for 16 h. When the reaction was complete, it was cooled to room temperature and poured onto ice. The reaction was then quenched by slowly adding aqueous sodium bisulfite (2% w/w) until the brown color dissipated, during which time a pale yellow precipitate formed. The precipitate was filtered and recrystallized from acetone/petroleum ether to give an off-white solid in 31% yield (0.616 g, 3.1 mmol).

Data for **naphtho[2,3-c]furan-1,3-dione:** ^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.79 (s, 2H), 8.36-8.33 (m, 2H), 7.89-7.86 (m, 2H) ppm; $^{13}C\{^{1}H\}$-NMR (125 MHz, DMSO-d_6) δ 163.4, 135.5, 130.4, 130.2, 127.4, 126.1 ppm; mp = 248-249 °C.

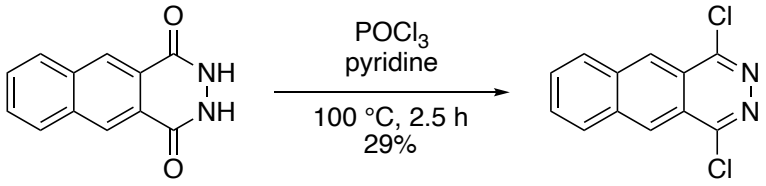
2,3-Dihydrobenzo[g]phthalazine-1,4-dione[36]



Hydrazine monohydrate (0.350 mL, 4.69 mmol, 3.1 equiv, 65% solution) was added in one portion to a solution of naphtho[2,3-c]furan-1,3-dione (0.238 g, 1.20 mmol, 1.0 equiv) in AcOH (6.0 mL). Following the addition of the hydrazine solution, the reaction became clear and was then heated to reflux. After approximately 5 min of heating, the solution went cloudy and then a white precipitate formed. The solution was refluxed for 6 h and was then cooled to room temperature, where it was allowed to stand overnight. The precipitate was filtered and washed with water. The white solid was dissolved in dichloromethane (5 mL) and concentrated. The precipitate was dried under vacuum, giving an off-white solid in 50% yield (0.128 g, 0.60 mmol).

Data for **2,3-dihydrobenzo[g]phthalazine-1,4-dione:** ^{1}H-NMR (500 MHz, DMSO-*d*$_6$) δ 12.52 (br, 2H), 9.73 (s, 2H), 9.29-9.26 (m, 2H), 8.76-8.72 (m, 2H) ppm; ^{13}C{^{1}H}-NMR (150 MHz, DMSO-*d*$_6$) δ 175.1, 137.2, 134.4, 132.2 131.6, 129.3 ppm; mp > 250 °C.

1,4-Dichlorobenzo[g]phthalazine[37]

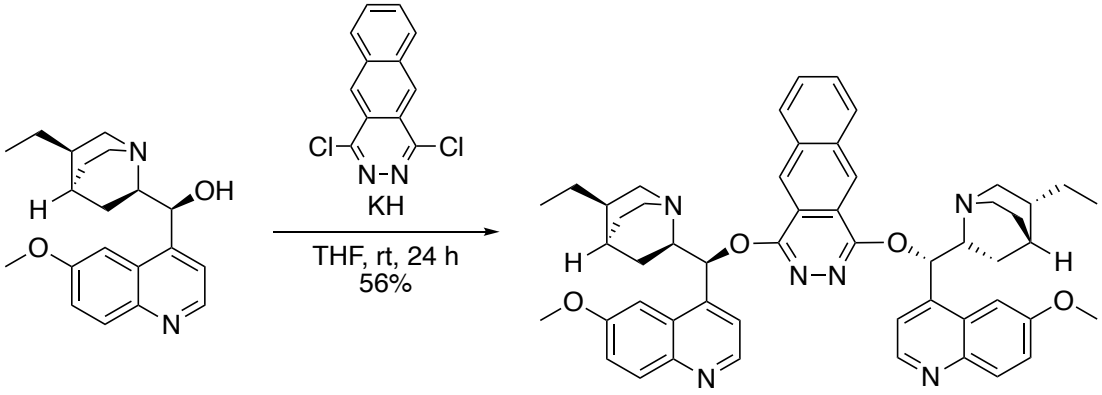


To a flame dried 25 mL round bottom flask was added 2,3-dihydrobenzo[g]phthalazine-1,4-dione (128 mg, 0.603 mmol), phosphoryl chloride (1.28 mL, 38 mmol, 22.7 equiv), and pyridine (80 µL, 1.6 equiv). The reaction was then heated to 100 °C for 2.5 h, during which time the reaction changed from clear to yellow. After the 2.5 h, the reaction was cooled to 60 °C and a short path distillation apparatus was attached to the flask. The liquids were distilled off under vacuum and the reaction contents were cooled to room temperature. The solids were triturated with diethyl ether (10 mL) and filtered. The solids were then added

to cold water (5 mL) and ethyl acetate (5 mL) and stirred vigorously for 10 min. The solid was filtered and washed with water, then ethyl acetate, and then dried under vacuum. The product was a white solid which was obtained in 29% yield (43 mg, 0.173 mmol). *The product decomposes within 1 h of being dissolved in DMSO-d_6.*

Data for **1,4-dichlorobenzo[g]phthalazine:** ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.08 (s, 2H), 8.51-8.49 (m, 2H), 7.92-7.90 (m, 2H) ppm; ^{13}C{^{1}H}-NMR (125 MHz, DMSO-d_6) δ 155.1, 135.3, 130.0, 129.4, 126.9, 122.7 ppm; mp = 223-225 °C.

$(DHQD)_2$bzPHAL

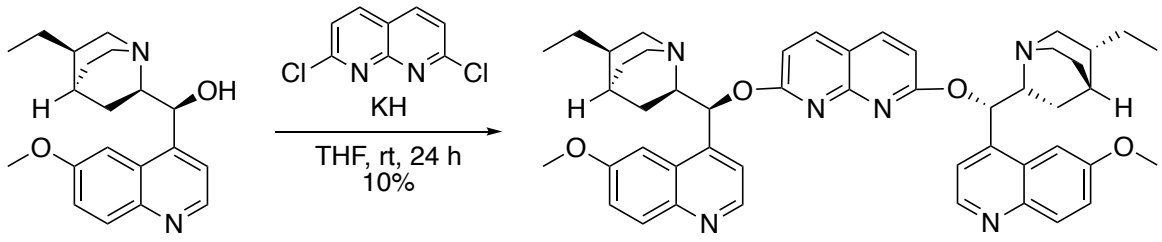


To a flame dried 100 mL round bottom flask was added KH (237 mg, 1.77 mmol, 4.36 equiv, 30% suspension in oil). The oil was removed from the potassium hydride by washing hexanes (3 × 2 mL). THF (36 mL) was then added to the flask, followed by the addition of dihydroquinidine (300 mg, 0.920 mmol, 2.26 equiv) and 1,4-dichlorobenzophthalazine (101 mg, 0.407 mmol, 1.0 equiv). The reaction was stirred at room temperature under dry nitrogen for 24 h. At the end of 24 h, TLC analysis (10% MeOH in $CHCl_3$) indicated that all the starting material was consumed. The reaction was quenched by adding saturated aqueous NH_4Cl (10 mL). The layers were then separated, the aqueous layer was washed with EtOAc (3 × 15 mL), the combined organics were washed with water (3 × 20 mL), dried over anhydrous Na_2SO_4, and concentrated. NMR analysis of the crude residue indicated complete conversion of the starting material to the desired product, however the product was purified using column chromatography ($CHCl_3$ to 5% MeOH

in $CHCl_3$) to give the product as an off-white solid (189 mg, 0.228 mmol) in 56% yield (yields are based only on the mass of the combined column fractions deemed clean via NMR analysis).

Data for **$(DHQD)_2$bzPHAL:** ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.88 (s, 2H), 8.65 (d, *J*= 4.6 Hz, 2H), 8.18 (dd, *J* = 3.3 Hz, 2H), 7.99 (d, *J* = 9.2 Hz, 2H), 7.76-7.73 (m, 2H), 7.60 (d, *J* = 2.5 Hz, 2H), 7.50 (d, *J* = 4.6 Hz, 2H), 7.36 (dd, *J* = 9.2, 2.7 Hz, 2H), 7.05 (d, *J* = 5.8 Hz, 2H), 3.91 (s, 6H), 3.46 (q, *J* = 8.9 Hz, 2H), 2.85-2.77 (m, 6H), 2.72-2.65 (m, 2H), 2.07 (t, *J* = 11.7 Hz, 2H), 1.74 (s, 2H), 1.59-1.41 (m, 12H), 0.83 (t, *J* = 7.3 Hz, 6H); ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$) δ 157.91, 156.57, 147.72, 145.21, 145.08, 131.89, 129.35, 128.76, 127.66, 123.50, 122.15, 119.94, 118.78, 102.43, 77.56, 76.64, 60.49, 55.97, 51.25, 50.37, 37.79, 27.59, 26.71, 25.71, 23.68, 12.25 ppm; IR (NaCl plate) $\tilde{\nu}$ 3047, 2934, 2872, 1620, 1593, 1543, 1510, 1462, 1433, 1350, 1228, 1145, 1062, 846, 734 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{52}H_{56}N_6O_4H^+$ 829.4441, found 829.4456; $[\alpha]^{20}_D$ = –312.5° (*c* = 10 mg/mL, $CHCl_3$); mp = 60-61 °C.

Synthesis of $(DHQD)_2$NAPY



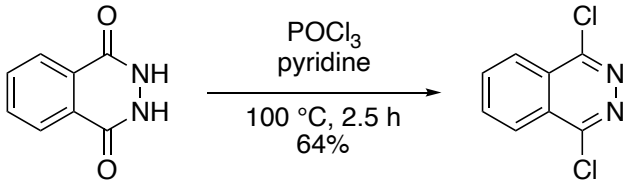
To a flame dried 100 mL round bottom flask was added KH (264 mg, 1.97 mmol, 4.36 equiv, 30% suspension in oil). The oil was removed from the potassium hydride by washing three times with hexanes (2 mL). THF (36 mL) was then added to the flask, followed by the addition of dihydroquinidine (302 mg, 0.925 mmol, 2.26 equiv) and 2,7-dichloro-1,8-naphthyridine (81 mg, 0.409 mmol, 1.0 equiv). The reaction was stirred at room temperature under dry nitrogen for 24 h. At the end of 24 h, TLC analysis (10% MeOH in $CHCl_3$) indicated that all the starting material was consumed. The reaction was quenched by adding sat. aq. NH_4Cl (15 mL). The layers were then separated, the aqueous layer was washed with EtOAc (3 × 20 mL), the combined organics were washed with water (3 × 20 mL), dried over Na_2SO_4, and concentrated.

The product was purified using column chromatography ($CHCl_3$ to 5% MeOH in $CHCl_3$) to give the product as an off-white solid (32 mg, 0.041 mmol) in 10% yield.

Data for **$(DHQD)_2NAPY$:** ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.68 (d, *J* = 4.5 Hz, 2H), 8.01 (d, *J* = 9.2 Hz, 2H), 7.88 (d, *J* = 8.6 Hz), 7.52 (d, *J* = 2.5, 2H), 7.43 (d, *J* = 4.5 Hz, 2H), 7.38 (dd, *J* = 9.2, 2.5 Hz, 2H), 7.18 (d, *J* = 5.1 Hz, 2H), 6.89 (d, *J* = 8.6, 2H), 3.84 (s, 6H), 3.32 (dd, *J* = 14.0, 8.9 Hz, 2H), 2.85-2.72 (m, 4H), 2.71 (dd, *J* = 17.3, 9.7 Hz, 4H), 1.99 (t, *J* = 11.2, 2H), 1.66 (s, 2H), 1.51-1.25 (m, 12H), 0.68 (t, *J* = 6.8 Hz, 6H) ppm; ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$) δ 163.98, 158.08, 154.38, 147.82, 145.08, 139.44, 131.99, 127.61, 122.16, 118.87, 116.12, 111.11, 102.05, 75.41, 59.50, 56.10, 51.20, 50.51, 37.79, 27.72, 26.15, 25.33, 22.50, 12.23 ppm; IR (NaCl plate) $\tilde{\nu}$ 3075, 3051, 2932, 2872, 1606, 1500, 1433, 1329, 1257, 1130, 1028, 989, 843 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{48}H_{54}N_6O_4H^+$ 779.4285, found 779.4286. $[\alpha]^{20}_D$ = –24.5° (*c* = 1.0 mg/mL, $CHCl_3$); mp = 190 °C (decomposed).

Synthesis of $(QD)_2PHAL$

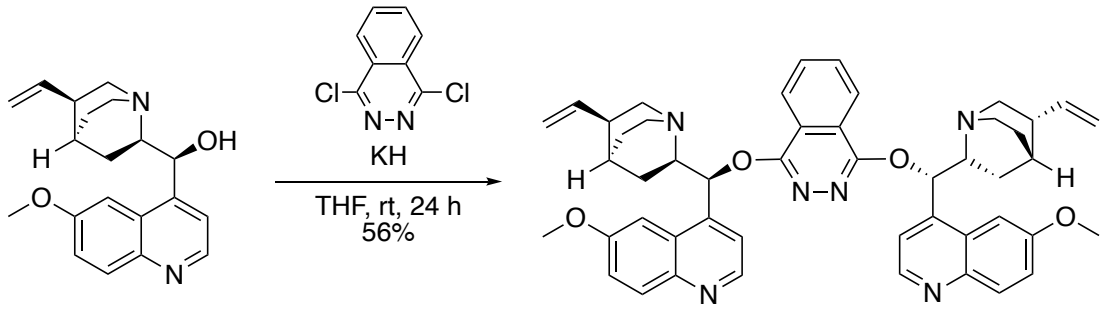
1,4-Dichlorophthalazine[38]



To a flame dried 25 mL round bottom flask was added phthalhydrazine (400 mg, 2.47 mmol, 1.0 equiv), phosphoryl chloride (5.25 mL. 56.1 mmol, 22.7 equiv), and pyridine (328 µL, 4.1 mmol, 1.6 equiv). The reaction was heated to reflux for 2.5 h, during which time it went from a clear to yellow solution. The reaction was then cooled to 60 °C and a short-path distillation apparatus was attached to the flask. The phosphoryl chloride was distilled off under vacuum. The white solid remaining in the flask was cooled to room temperature and filtered, washing with diethyl ether. Column chromatography (15% ethyl acetate in hexanes) was used to obtain the product as a white solid in 64% yield (315 mg, 1.59 mmol).

Data for **1,4-dichlorophthalazine:** ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.29-8.27 (m, 2H), 8.07-8.04 (m, 2H) ppm; ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$) δ 155.0, 134.5, 127.2, 125.8 ppm; mp = 151-153 °C.

(QD)$_2$PHAL

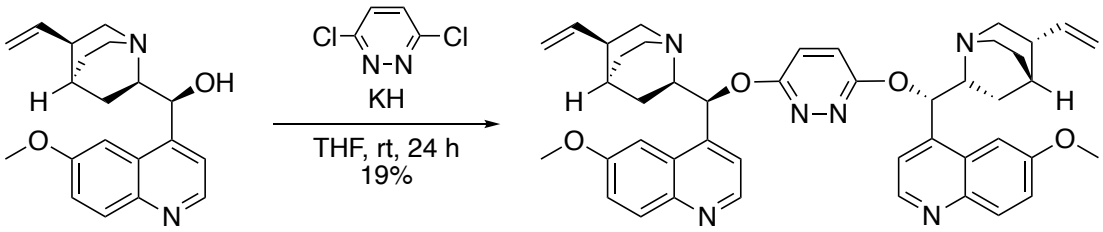


To a flame dried 100 mL round bottom flask was added KH (238 mg, 1.78 mmol, 4.36 equiv, 30% suspension in oil). The oil was removed from the potassium hydride by washing with hexanes (3 × 2 mL). THF (36 mL) was then added to the flask, followed by the addition of dihydroquinidine (300 mg, 0.925 mmol, 2.26 equiv) and 1,4-dichlorobenzophthalazine (81 mg, 0.409 mmol, 1.0 equiv). The reaction was stirred at room temperature under dry nitrogen for 24 h. At the end of 24 h, TLC analysis (10% MeOH in $CHCl_3$) indicated that all the starting material was consumed. The reaction was quenched by adding saturated aqueous NH_4Cl (10 mL). The layers were then separated, the aqueous layer was washed with EtOAc (3 × 15 mL), the combined organics were washed with water (3 × 20 mL), dried over anhydrous Na_2SO_4, and concentrated. NMR analysis of the crude residue indicated complete conversion of the starting material to the desired product, however the product was purified using column chromatography ($CHCl_3$ to 5% MeOH in $CHCl_3$) to give the product as an off-white solid (189 mg, 0.229 mmol) in 56% yield (yields are based only on the mass of the combined column fractions deemed clean via NMR analysis).

Data for **(QD)$_2$PHAL:** ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.64 (d, *J* = 4.6 Hz, 2H), 8.34 (dd, *J* = 6.2, 3.3 Hz, 2H), 7.99 (d, *J* = 9.2 Hz, 2H), 7.92 (dd, *J* = 6.1, 3.3 Hz, 2H), 7.55 (d, *J* = 2.7 Hz, 2H), 7.42 (d, *J* = 4.6 Hz, 2H), 7.36 (dd, *J* = 9.2, 2.7 Hz, 2H), 7.04 (d, *J* = 6.0 Hz, 2H), 5.96-5.90 (m, 2H), 4.99-4.95 (m, 4H), 3.90 (s, 6H), 3.41 (dd, *J* = 15.1, 8.9 Hz, 2H), 2.96-2.93 (m, 2H), 2.86-2.78 (m, 4H), 2.71-2.64 (m, 2H), 2.21 (q, *J* = 8.2 Hz, 2H), 2.11-2.07 (m, 2H), 1.80 (s, 2H), 1.57-1.51 (m, 6H) ppm; ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$) δ 157.99, 156.74, 147.69, 145.22, 145.03, 140.68, 132.45, 131.89, 127.62, 123.34, 122.77, 122.16, 118.62, 114.96, 102.38, 76.48, 60.44, 55.96, 50.18, 49.82, 40.01, 28.12, 26.84, 23.59 ppm; IR (NaCl plate) $\tilde{\nu}$ 3073,

3053, 2938, 2872, 2840, 1622, 1593, 1508, 1388, 1354, 1226, 1093, 1028, 985 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{48}H_{50}N_6O_4H^+$ 775.3972, found 775.3976; $[\alpha]^{20}_D = -194.7°$ (c = 10 mg/mL, $CHCl_3$); mp = 119-120 °C.

Synthesis of $(QD)_2PYDZ$[39]

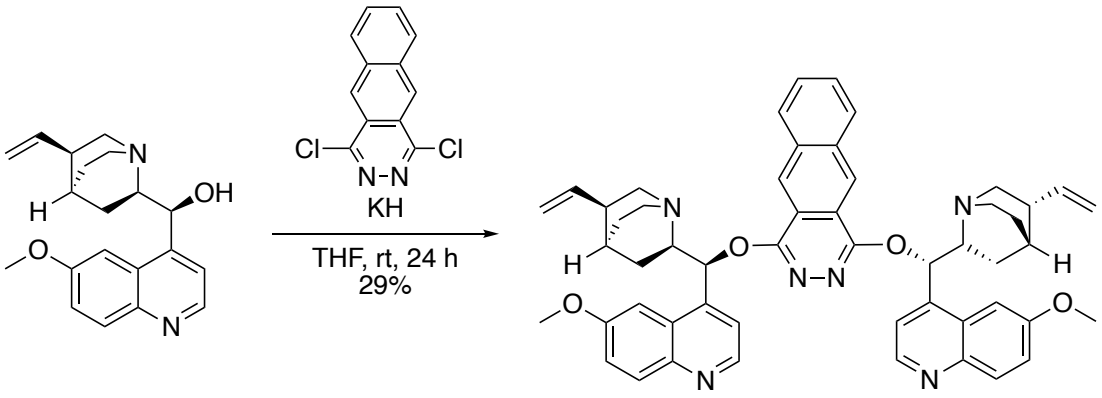


To a flame dried 100 mL round bottom flask was added KH (238 mg, 1.78 mmol, 4.36 equiv, 30% suspension in oil). The oil was removed from the potassium hydride by washing with hexanes (3 × 2 mL). THF (36 mL) was then added to the flask, followed by the addition of quinidine (300 mg, 0.925 mmol. 2.26 equiv) and 3,6-dichloropyridazine (61 mg, 0.409 mmol, 1.0 equiv). The reaction was stirred at room temperature under dry nitrogen for 24 h, during which time the color changed from colorless to orange. At the end of 24 h, TLC analysis (15% MeOH in $CHCl_3$) indicated that all the starting material was consumed. The reaction was quenched by adding saturated aqueous NH_4Cl (10 mL). The layers were then separated, the aqueous layer was washed with EtOAc (3 × 20 mL), the combined organics were washed with water (3 × 20 mL), dried over anhydrous Na_2SO_4, and concentrated. The product was purified using column chromatography ($CHCl_3$ to 5% MeOH in $CHCl_3$) to give the product as an off-white solid (57 mg, 0.079 mmol) in 19% yield.

Data for **$(QD)_2PYDZ$:** ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.66 (d, J = 4.5 Hz, 2H), 7.98 (d, J = 9.2 Hz, 2H), 7.42 (d, J = 2.6 Hz, 2H), 7.35-7.33 (m, 4H), 7.00 (s, 2H), 6.78 (d, J = 5.9 Hz, 2H), 5.98-5.91 (m, 2H), 5.00-4.96 (m, 4H), 3.85 (s, 6H), 3.28 (dd, J = 15.1, 8.8 Hz, 2H), 2.92-2.87 (m, 2H), 2.82-2.74 (m, 4H), 2.68-2.62 (m, 2H), 2.18 (dd, J = 16.5, 8.1 Hz, 2H), 1.97-1.93 (m, 2H), 1.74 (s, 2H), 1.48 -1.40 (m, 6H) ppm; $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$) δ 161.06, 157.92, 147.63, 144.97, 144.75, 140.76, 131.88, 127.45, 121.99, 121.59, 118.75, 114.85, 102.19, 77.03, 60.09, 55.84, 50.22, 49.70, 40.18, 28.24, 26.78, 23.41. ppm;

IR (NaCl plate): $\tilde{\nu}$ 2936, 1622, 1508, 1473, 1261, 1226, 1084, 1030, 991 cm^{-1}; HRMS(ESI) m/z: $[M+H]^+$ calcd. for $C_{44}H_{48}N_6O_4H^+$ 725.3815, found 725.3830; $[\alpha]^{20}_D = -26.0°$ (c = 10 mg/mL, $CHCl_3$); mp = 103-105 °C.

Synthesis of $(QD)_2$bzPHAL



To a flame dried 100 mL round bottom flask was added KH (101 mg, 0.752 mmol, 4.36 equiv, 30% suspension in oil). The oil was removed from the potassium hydride by washing with hexanes (3 × 2 mL). THF (15 mL) was added to the flask, followed by the addition of quinidine (126 mg, 0.390 mmol, 2.26 equiv) and 1,4-dichlorobenzophthalazine (43 mg, 0.173 mmol. 1.0 equiv). The reaction was stirred at room temperature under dry nitrogen for 24 h. At the end of 24 h, TLC analysis (10% MeOH in $CHCl_3$) indicated that all the starting material was consumed. The reaction was quenched by adding saturated aqueous NH_4Cl (10 mL). The layers were separated, the aqueous layer was washed with EtOAc (3 × 10 mL), the combined organics were washed with water (3 × 20 mL), dried over anhydrous Na_2SO_4, and concentrated. NMR analysis of the crude residue indicated complete conversion of the starting material to the desired product, however the product was purified using column chromatography ($CHCl_3$ to 5% MeOH in $CHCl_3$) to give the product as an off-white solid (41 mg, 0.050 mmol) in 29% yield (yields are based only on the mass of the combined column fractions deemed clean via NMR analysis).

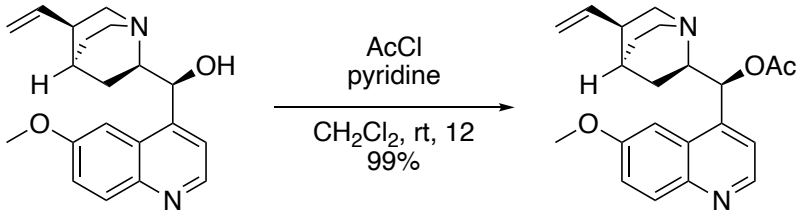
Data for **$(QD)_2$bzPHAL:** ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.91 (s, 2H), 8.63 (d, J = 4.6 Hz, 2H), 8.22-8.20 (m, 2H), 7.99 (d, J = 9.2 Hz, 2H), 7.77-7.75 (m, 2H), 7.56 (d, J = 2.5 Hz, 2H), 7.48 (d, J = 4.6 Hz, 2H), 7.36 (dd, J = 9.1, 2.6 Hz, 2H), 7.13 (d, J = 4.7 Hz, 2H), 6.06-6.00 (m, 2H), 5.05-5.01 (m, 4H), 3.91 (s, 6H),

3.45 (dd, J = 14.2, 8.8 Hz, 2H), 3.08-3.04 (m, 2H), 2.87 (t, J = 10.4 Hz, 4H), 2.75 -2.72 (m, 2H), 2.24-2.21 (m, 4H), 1.88 (s, 2H), 1.59-1.55 (m, 6H) ppm; $^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$) δ 158.08, 156.56, 147.68, 145.02, 140.68, 135.00, 131.90, 129.39, 128.82, 127.51, 123.73, 122.28, 119.92, 118.45, 115.06, 102.29, 76.48, 60.23, 56.05, 50.26, 49.87, 39.84, 28.02, 26.74, 23.23 ppm; IR (NaCl plate) $\tilde{\nu}$ 3089, 3053, 2936, 2870, 1620, 1593, 1508, 1433, 1348, 1228, 1145, 1060, 985, 844 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{52}H_{52}N_6O_4H^+$ 825.4128, found 825.4123; $[\alpha]^{20}_D$ = –266.8° (c = 10 mg/mL, $CHCl_3$); mp = 120 °C (decomposed).

Synthesis of $(Me_2QD)_2PYDZ$

***O*-Acetyl Quinidine**[40]

Quinidine (1.00 g, 3.08 mmol) was dissolved in anhydrous DCM (16 mL) in a 50 mL flame dried round

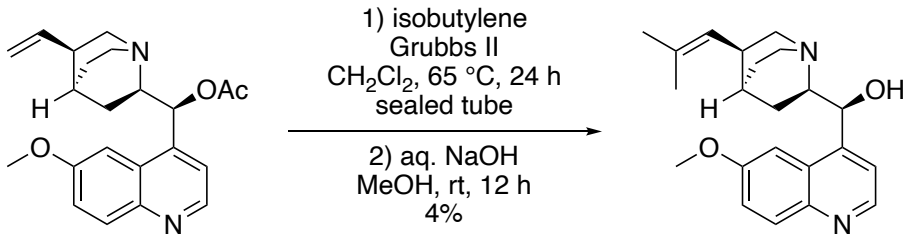


bottom flask. Anhydrous pyridine (250 μL, 3.08 mmol, 1.0 equiv) was added in, followed by the dropwise addition of acetyl chloride (0.23 mL, 3.23 mmol, 1.05 equiv). The reaction was stirred at room temperature for 12 h. Water (0.5 mL) was added and the reaction was stirred for 30 min. The reaction was then poured into aqueous 2M potassium carbonate (25 mL) and extracted with DCM (3 × 50 mL). The combined organics were dried over anhydrous sodium sulfate and concentrated. The product was purified using column chromatography (99:1 $CHCl_3$ / MeOH), giving the product as a yellow oil in 99% yield (1.12 g, 3.06 mmol).

Data for ***O*-acetyl quinidine**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.70 (d, J = 4.5 Hz, 1H), 7.97 (d, J = 9.2 Hz, 1H), 7.37-7.30 (m, 3H), 6.49 (d, J = 7.1 Hz, 1H), 6.02-5.95 (m, 1H), 5.08-5.03 (m, 2H), 3.91 (s, 3H), 3.25 (q, J = 8.8 Hz, 1H), 2.88 (d, J = 8.9 Hz, 2H), 2.80-2.65 (m, 2H), 2.22 (q, J = 8.7 Hz, 1H), 2.09 (s, 3H), 1.84-1.77 (m , 2H), 1.52-1.43 (m, 3H) ppm; $^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$) 169.8, 157.8, 147.4, 144.7, 143.7, 140.3, 131.7, 127.0, 121.7, 118.5, 114.7, 103.4, 73.5, 59.0, 55.5, 49.8, 49.1, 39.7, 27.8, 26.4, 23.4, 21.0

ppm; HRMS m/z: $[M+H]^+$ calcd. for $C_{22}H_{26}N_2O_3H^+$ 367.2022, found 367.2036; $[\alpha]^{20}_D$ = –24.2° (c = 5.7 mg/1 mL, $CHCl_3$).

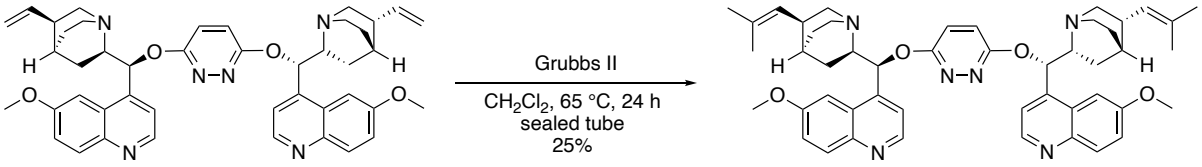
Me_2QD



To a flame dried 100 mL sealed tube was added *O*-acetyl quinidine (500 mg, 1.36 mmol, 1.0 equiv) and dry DCM (5 mL). The tube was sealed with a rubber septum and was subjected to three cycles of "freeze (using liquid nitrogen), pump, thaw" to degas the solution. The reaction was then cooled to –78 °C using a dry ice/acetone bath, the reaction was cautiously opened, and condensed isobutylene (8 mL) was added. The reaction was flushed with argon and Grubb's second-generation catalyst (232 mg, 0.136 mmol, 0.20 equiv) was added in one portion. The tube was sealed and warmed to room temperature, followed by subsequent heating to 65 °C for 24 h. The reaction was quenched by cooling to –78 °C, the sealed tube was carefully opened, and the reaction contents were allowed to slowly warm to room temperature, while also allowing the isobutylene to evaporate. The product was then extracted using 1 M HCl (3 × 25 mL), followed by basification of the combined aqueous layers with ammonium hydroxide (35%) to pH = 10. The neutralized product was then re-extracted into the organic layer by using $CHCl_3$ (5 × 30 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. Methanol (7.5 mL) and aqueous NaOH (1 M, 1.65 mL, 1.65 mmol) were added to the crude material and the reaction was stirred at room temperature for 12 h. The product was quenched by neutralizing the reaction by adding 1 M HCl solution. The product was extracted with ethyl acetate (3 × 50 mL), the combined organics were dried over anhydrous sodium sulfate, and concentrated. Column chromatography was used to purify the product (1% MeOH in $CHCl_3$ to 5% MeOH in $CHCl_3$), which was a brown solid in 4% yield (20 mg, 0.057 mmol).

Data for **Me_2QD:** ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.60 (d, *J* = 4.5 Hz, 1H), 7.90 (d, *J* = 9.2 Hz, 1H), 7.52 (d, *J* = 4.4 Hz, 1H), 7.23 -7.22 (m, 1H), 7.13 (s, 1H), 5.69 (s, 1H), 5.38 (d, *J* = 8.3 Hz, 1H), 4.54 (br, 1H), 3.77 (s, 3H), 3.30-3.26 (m, 1H), 3.05 (t, *J* = 9.7, 1H), 2.96-2.87 (m, 2H), 2.80-2.73 (m, 1H), 2.39 (dd, *J* = 17.3, 8.3 Hz, 1H), 2.09 (t, *J* = 11.9 Hz, 1H), 1.71 (s, 3H), 1.63 (s, 1H), 1.54-1.45 (m, 5H), 1.11-1.06 (m, 1H) ppm; ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$) δ 157.6, 147.4, 147.3, 144.1, 132.9, 131.4, 126.8, 126.4, 121.5, 118.5, 101.1, 71.2, 59.7, 55.7, 50.8, 49.9, 34.2, 28.4, 26.1, 25.9, 20.9, 18.2 ppm; IR (NaCl plate) $\tilde{\nu}$ 3166, 3005, 2934, 2867, 2840, 1622, 1591, 1510, 1472, 1433, 1242, 1107, 1032, 831, 736 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{22}H_{28}N_2O_2H^+$ 353.2229, found 353.2228; $[\alpha]^{20}_D$ = +149.5° (*c* = 10 mg/mL, $CHCl_3$); mp = 58-61 °C.

$(Me_2QD)_2$PYDZ



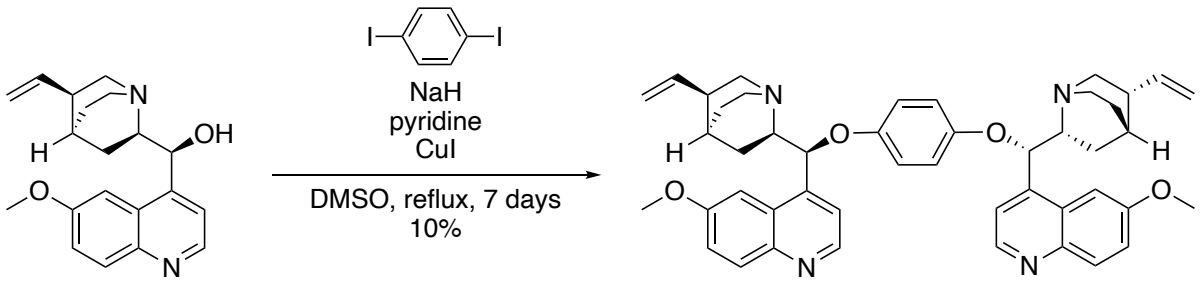
The $(QD)_2$PYDZ used is this reaction was prepared as described above. The material was not purified via column chromatography, but simply by filtration through a pad of silica gel in a frit funnel, which was thoroughly washed with 1:10 MeOH/$CHCl_3$.

To a flame dried 100 mL sealed tube was added $(QD)_2$PYDZ (738 mg, 1.02 mmol, 1.0 equiv) and dry DCM (12 mL). The tube was sealed with a rubber septum and was subjected to three cycles of "freeze (using liquid nitrogen), pump, thaw" to degas the solution. The reaction was then cooled to –78 °C using a dry ice/acetone bath, the reaction was cautiously opened, and condensed isobutylene (22 mL) was added. The reaction was flushed with argon and Grubb's second-generation catalyst (300 mg, 0.353 mmol, 0.35 equiv) was added in one portion. The tube was then sealed and warmed to room temperature, followed by subsequent heating to 65 °C for 24 h. The reaction was quenched by cooling to –78 °C, carefully opening the sealed tube, and allowing the tube to slowly reach room temperature, while allowing the isobutylene to evaporate. The product was extracted using 1 M HCl (3 × 50 mL), followed by basification of the combined

aqueous layers with ammonium hydroxide (35%) to pH=10. The neutralized product was re-extracted into the organic layer by using $CHCl_3$ (5 × 50 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. Column chromatography was used to purify the product (1% MeOH in $CHCl_3$ to 5% MeOH in $CHCl_3$), which was a red solid in 25% yield (200 mg, 0.256 mmol).

Data for **$(Me_2QD)_2PYDZ$:** ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.66 (d, *J* = 4.6 Hz, 2H), 7.97 (d, *J* = 9.2 Hz, 2H), 7.42 (d, *J* = 2.0 Hz, 2H), 7.36 -7.31 (m, 4H), 7.01 (s, 2H), 6.82 (d, *J* = 5.1 Hz, 2H), 5.36 (d, *J* = 8.6 Hz, 2H), 3.87 (s, 6H), 3.31 (q, *J* = 8.8, Hz, 2H), 2.85-2.64 (m, 8H), 2.35 (q, *J* = 8.6 Hz, 2H), 2.00 (t, *J* = 12.1 Hz, 2H), 1.64-1.39 (m, 20H) ppm; $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$) δ 161.24, 157.99, 147.71, 145.07, 144.79, 132.87, 131.97, 127.67, 127.50, 122.04, 121.73, 118.99, 102.38, 60.09, 55.97, 51.16, 50.25, 34.88, 28.62, 27.01, 26.25, 23.63, 18.49 ppm; IR (NaCl plate) $\tilde{\nu}$ 3080, 3048, 2938, 2870, 2840, 1622, 1593, 1501, 1473, 1437, 1261, 1228, 1084, 1028, 991, 846, 734 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{48}H_{56}N_6O_4H$ 781.4441, found 781.4465; $[\alpha]^{20}_D = -93.3°$ (*c* = 10 mg/mL, $CHCl_3$); mp = 107-109 °C.

Synthesis of $(QD)_2C_6H_4$

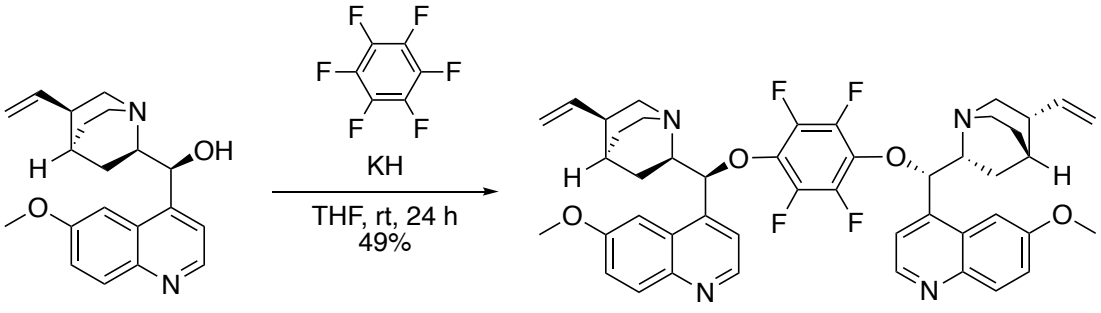


To a flame dried 3-neck round bottom was added quinidine (500 mg, 1.54 mmol, 3.0 equiv). The flask was flushed with argon for 30 min. Dry DMSO (4 mL) was added and the reaction was stirred until the solid dissolved. Sodium hydride (70 mg, 1.74 mmol, 3.39 equiv, 60% in oil) was added in one portion and the colorless solution became orange. The reaction was stirred for 30 min (until gas evolution ceased) and dry pyridine (0.250 mL, 3.08 mmol, 6.0 equiv) and copper iodide (293 mg, 1.54 mmol, 3.0 equiv) were added; the reaction instantly turned dark brown. The reaction was stirred at room temperature for 45 min, 1,4-diiodobenzene (169 mg, 0.51 mmol, 1.0 equiv) was added and the reaction was heated to 120 °C for 7 days. To quench the reaction, it was cooled to room temperature and 35% aqueous ammonium hydroxide (3 mL)

was carefully added. The reaction was stirred at room temperature for 10 min and ethyl acetate (50 mL) was added. The organic layer was repeatedly washed with 35% ammonium hydroxide solution until the persistent blue color of the aqueous layer dissipated. The organic layer was dried over anhydrous sodium sulfate and concentrated. Three columns were run to purify the desired compound: 1st column ($CHCl_3$ to 4% MeOH in $CHCl_3$), 2nd column (25% MeOH in EtOAc to 50% MeOH in EtOAc); 3rd column (DCM to 10% MeOH in DCM). The product was obtained as a tan solid (36 mg, 0.050 mmol) in 10% yield.

Data for **$(QD)_2C_6H_4$:** ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.62 (d, *J* = 4.5 Hz, 2H), 8.01 (d, *J* = 9.4 Hz, 2H), 7.36-7.33 (m, 6H), 6.62 (s, 4H), 6.15-6.08 (m, 2H), 5.15-5.10 (m, 4H), 3.96 (s, 6H), 3.40 (s, 2H), 3.16 (t, *J* = 8.5 Hz, 2H), 3.01 (t, *J* = 12.0 Hz, 4H), 2.84 (q, *J* = 9.4 Hz, 2H), 2.36-2.30 (m, 4H), 1.88 (s, 2H), 1.62 (s, 2H), 1.55–1.49 (m, 2H), 1.24–1.17 (m, 4H) ppm; $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$) δ 158.66, 151.69, 147.81, 144.89, 143.22, 139.93, 132.34, 126.60, 122.49, 118.84, 116.92, 115.71, 100.93, 59.96, 56.47, 50.36, 49.56, 39.70, 30.00, 28.37, 26.08, 20.78 ppm; IR (NaCl plate) $\tilde{\nu}$ 3042, 2870, 1602, 1504, 1473, 1433, 1226, 1028, 977, 825 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{46}H_{50}N_4O_4H^+$ 723.3910, found 723.3898. $[\alpha]^{20}_D = -92.9°$ (*c* = 10 mg/mL, $CHCl_3$); mp = 101-104 °C.

Synthesis of $(QD)_2C_6F_4$

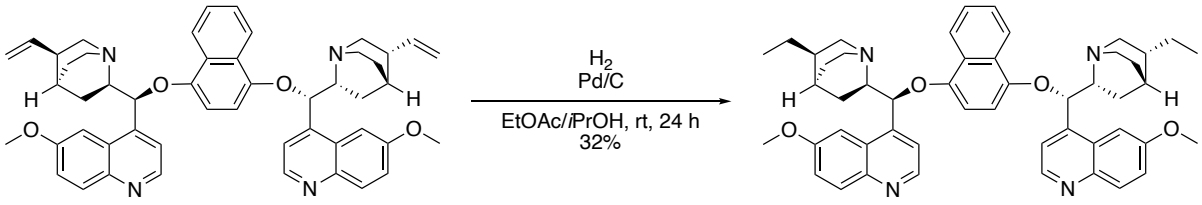


To a flame dried 100 mL round bottom flask was added KH (126 mg, 0.924 mmol, 2.0 equiv, 30% suspension in oil). The oil was removed from the potassium hydride by washing with hexanes (3 × 2 mL). THF (4.2 mL) was added to the flask, followed by the addition of quinidine (300 mg, 0.924 mmol, 2.0 equiv) and hexafluorobenzene (54 μL, 0.462 mmol, 1.0 equiv). The reaction was stirred at room temperature under dry nitrogen for 24 h. At the end of 24 h, TLC analysis (10% MeOH in $CHCl_3$) indicated

that all the starting material was consumed. The reaction was quenched by adding saturated aqueous NH_4Cl (15 mL). The layers were separated, the aqueous layer was washed with EtOAc (3 × 20 mL), the combined organics were washed with water (3 × 20 mL), dried over anhydrous Na_2SO_4, and concentrated. The product was purified using column chromatography ($CHCl_3$ to 3% MeOH in $CHCl_3$) to give the product as an off-white solid (181 mg, 0.228 mmol) in 49% yield.

Data for **$(QD)_2C_6F_4$:** ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.69 (d, *J* = 4.5 Hz, 2H), 7.97 (d, *J* = 9.2 Hz, 2H), 7.39 (s, 2H), 7.33 (dd, *J* = 9.2, 2.7 Hz, 2H), 7.23 (s, 2H), 6.04-5.98 (m, 4H), 5.08-5.04 (m, 4H), 3.87 (s, 6H), 3.27 (s, 2H), 2.97 (s, 2H), 2.87 (t, *J* = 10.1 Hz, 2H), 2.76-2.69 (m, 4H), 2.29 (q, *J* = 7.9 Hz, 2H), 2.16 (t, *J* = 10.7, 2H), 1.81 (s, 2H), 1.53 (s, 6H) ppm; $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$) δ 165.91, 158.26, 147.69, 144.96, 142.84, 142.53, 140.54, 132.19, 127.34, 122.17, 119.39, 115.13, 101.05, 84.26, 60.84, 55.83, 50.30, 49.69, 40.18, 28.26, 26.72, 23.43 ppm; ^{19}F-NMR (282 MHz, $CDCl_3$) δ -155.60 ppm; IR (NaCl plate) $\tilde{\nu}$ 2085, 2047, 2939, 2874, 1622, 1593, 1499, 1475, 1227, 1032, 997, 827 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{46}H_{46}F_4N_4O_4H^+$ 795.3533, found 795.3536; $[\alpha]^{20}_D = 30.0°$ (*c* = 10 mg/mL, $CHCl_3$); mp = 77-79 °C.

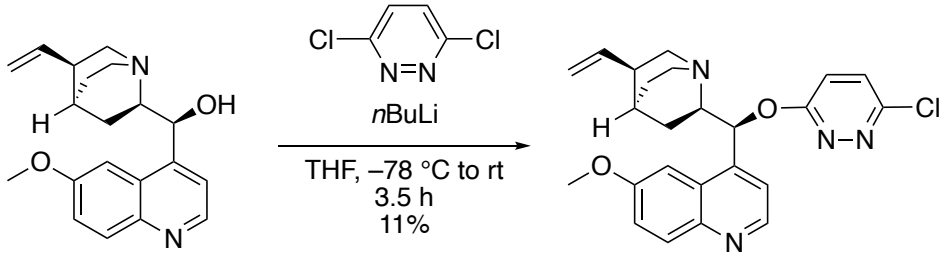
Synthesis of $(DHQD)_2NAPH$



To a 25 mL round bottom flask was added $(QD)_2NAPH$ (40 mg, 0.052 mmol, sample had trace impurities), Pd/C (20 mg, 10% activated palladium on carbon), ethyl acetate (1 mL) and isopropanol (1 mL). The reaction was stirred under hydrogen for 24 h at room temperature. The reaction was filtered through a pad of celite, which was washed thoroughly with 10% MeOH in $CHCl_3$. The filtrate was concentrated. Column chromatography ($CHCl_3$ to 5% MeOH in $CHCl_3$) was used to purify the product, which was obtained as a tan solid (13.1 mg, 0.017 mmol).

Data for **(DHQD)$_2$NAPH:** ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.58 (d, *J* = 4.5 Hz, 2H), 8.51 (dd, *J* = 6.4, 3.3 Hz, 2H), 8.02 (d, *J* = 9.2 Hz, 2H), 7.64 (dd, *J*= 6.3, 3.4 Hz, 2H), 7.47 (br, 2H), 7.38-7.35 (m, 4H), 6.33 (br, 2H), 6.11 (s, 2H), 3.96 (s, 6H), 3.30-3.22 (br, 4H), 3.01 (br, 4H), 2.83 (br, 2H), 2.03 (br, 2H), 1.85 (s, 2H), 1.74-1.59 (m, 10H), 1.38-1.34 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 6H) ppm; ^{13}C{^{1}H}-NMR (150 MHz, $CDCl_3$) δ 177.05, 158.74, 147.80, 146.50, 144.99, 132.37, 126.91, 126.89, 126.44, 122.65, 122.06, 118.49, 106.48, 101.09, 60.36, 56.46, 50.83, 50.05, 37.25, 26.88, 25.50, 22.99, 21.39, 12.13 ppm; IR (NaCl plate) $\tilde{\nu}$ 3080, 3042, 2972, 2934, 2872, 1620, 1597, 1510 ,1462, 1433, 1390, 1267, 1240, 1078, 1026, 825, 760 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{50}H_{56}N_4O_4H^+$calcd. 777.4380, found 777.4374; $[\alpha]^{20}_D$ = +195.6° (*c* = 10 mg/mL, $CHCl_3$).

Synthesis of (QD)(Cl)PYDZ[39]

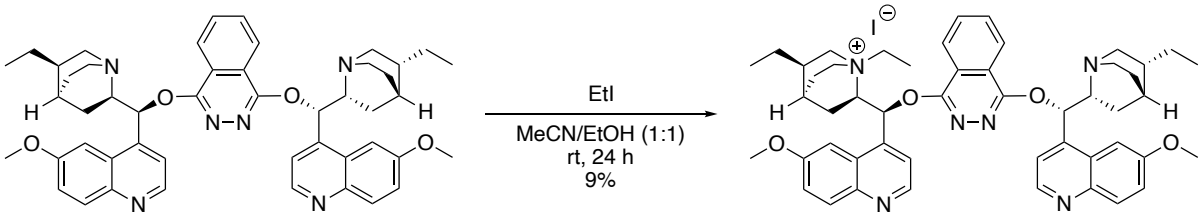


To a flame dried 100 mL round bottom was added quinidine (300 mg, 0.925 mmol) and dry THF (6 mL). The contents of the flask were cooled to –78 °C using a dry ice / acetone bath, and then *n*BuLi (0.70 mL, 0.96 mmol, 1.04 equiv, 1.38 M) was added dropwise. The reaction was stirred at –78 °C for 5 min, was warmed to room temperature, and 3,6-dichloropyridazine (149 mg, 0.999 mmol, 1.08 equiv) was added in one portion. The reaction was stirred at room temperature for 3.5 h and was quenched by adding saturated ammonium chloride (5 mL). The reaction was extracted using DCM (3 x 15 mL), the combined organics were washed with water (3 × 10 mL), dried over anhydrous sodium sulfate, and concentrated. Column chromatography (20% EtOAc in MeOH) was used to purify the product, which was obtained as a pale yellow solid in 11% yield (50 mg, 0.12 mmol).

Data for (**QD)(Cl)PYDZ**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.65 (d, *J* = 4.5 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.48 (d, *J* = 2.6 Hz, 1H), 7.36-7.33 (m, 3H), 7.05-7.02 (m, 2H), 6.06- 6.00 (m, 1H), 5.10-5.06 (m, 2H), 3.95

(s, 3H), 3.38 (q, *J* = 8.6 Hz, 1H), 3.03-3.00 (m, 1H), 2.94-2.89 (m, 1H), 2.87-2.81 (m, 1H), 2.77-2.71 (m, 1H), 2.26 (q, *J* = 8.3 Hz, 1H), 2.02 (t, J = 11.2 Hz, 1H), 1.81 (s, 1H), 1.56-1.49 (m, 3H) ppm; $^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$) δ 163.3, 157.9, 151.4, 147.3, 144.7, 143.5, 140.4, 131.8, 131.1, 127.1, 121.8, 119.9, 118.5, 114.8, 101.6, 59.6, 55.2, 50.0, 49.4, 39.8, 27.9, 26.5, 23.3 ppm; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{24}H_{25}N_4O_2ClH^+$ 437.1744, found 437.1737 $[\alpha]^{20}_D = -46.5°$ (c = 10 mg/mL, $CHCl_3$); mp = 60-62 °C.

Synthesis of (DHQD)(DHQD-EtI)PHAL

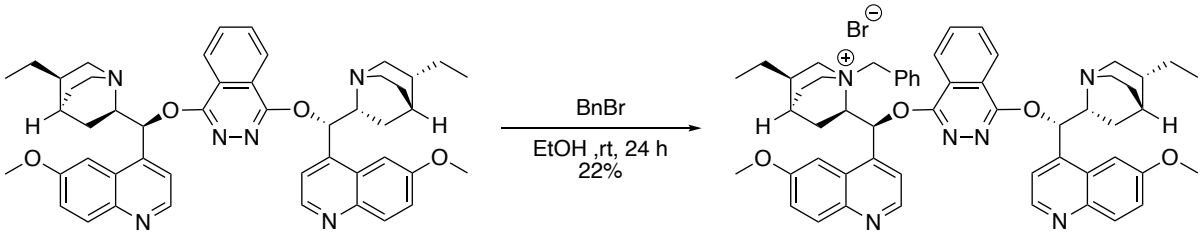


$(DHQD)_2PHAL$ (200 mg, 0.257 mmol) was dissolved in anhydrous ethanol (0.4 mL) and acetonitrile (1.2 mL). Ethyl iodide (21 μL, 0.264 mmol) was added in using a microsyringe and the resulting reaction was stirred at room temperature. After 24 h, the reaction was concentrated and purified via column chromatography (10% MeOH in DCM) giving the product as a pale yellow solid in 9% yield (22 mg, 0.023 mmol).

Data for **(DHQD)(DHQD-EtI)PHAL:** ^{1}H-NMR (600 MHz, $CDCl_3 + CD_3OD$) δ 8.58 (dd, *J* = 10.0, 4.8 Hz, 2H), 8.43 (dd, *J* = 6.4, 3.1 Hz, 1H), 8.27 (dd, *J* = 7.5, 3.5 Hz, 1H), 8.09 (dd, *J* = 6.1, 3.1 Hz, 2H), 8.03 (d, *J* = 9.3Hz, 1H), 7.95 (d, *J* = 9.2 Hz, 1H), 7.72 (s, 1H), 7.45 -7.34 (m, 6H), 7.13 (d, *J* = 2.9 Hz, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 3.70-3.67 (m, 1H), 3.58-3.28 (m, 2H), 3.27 (m, 2H), 2.62 (t, *J* = 12.8 Hz, 1H), 2.26 (s, 4H), 1.97-1.82 (m, 2H), 1.72-1.64 (m, 4H), 1.58-1.51 (m, 6H), 1.39-1.36 (m, 2H), 1.29-1.22 (m, 6H), 0.99 (t, *J* = 7.5 Hz, 3H), 0.88 (t, 3H) ppm; $^{13}C\{^{1}H\}$-NMR (150 MHz, $CDCl_3 + CD_3OD$) δ 159.13, 158.84, 156.99, 155.06, 147.03, 146.94, 144.27, 138.90, 134.00, 133.97, 131.90, 131.25, 131.19, 128.96, 126.73, 125.96, 123.36, 123.04, 122.78, 122.48, 122.10, 122.08, 119.10, 118.23, 101.60, 101.38, 69.60, 68.45, 65.86, 59.72, 58.79, 56.70, 56.57, 50.72, 50.25, 38.91, 35.55, 29.82, 26.05, 25.23, 24.89, 24.71, 24.03, 22.81, 22.13,

14.17, 14.10, 11.65, 11.31, 9.22 ppm; IR (NaCl plate) $\tilde{\nu}$ 2963, 2924, 2851, 1726, 1620, 1552, 1510, 1462, 1352, 1261, 1095, 800 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{50}H_{58}N_6O_4H^+$ 807.4598, found 807.4604; $[\alpha]^{20}_D = -56.5°$ (*c* 1.0 mg/mL, $CHCl_3$); mp = 170-174 °C.

Synthesis of (DHQD)(DHQD-BnBr)PHAL[39]



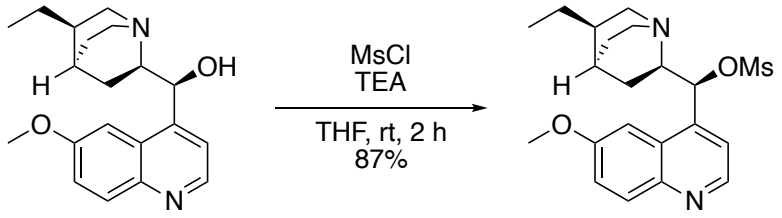
$(DHQD)_2PHAL$ (300 mg, 0.385 mmol) was dissolved in anhydrous ethanol (3.6 mL) and benzyl bromide (47 μL, 0.392 mmol) was added in one portion. The reaction was stirred at room temperature for 24 h and was concentrated. The resulting residue was purified via column chromatography (10% DCM in MeOH). A second column was run using (3% MeOH in $CHCl_3$) giving the mono-alkylated product in 22% yield as an off-white solid (80 mg, 0.085 mmol).

Data for **(DHQD)(DHQD-BnBr)PHAL:** ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.56 (d, *J* = 4.7 Hz, 1H), 8.48 (d, *J* = 4.6 Hz, 1H), 8.40 (dd, *J* = 9.2, 6.8 Hz, 1H), 8.31 (dd, *J* = 5.3, 2.3 Hz, 1H), 8.10-8.08 (m, 2H), 7.98 (s, 1H), 7.90 (d, *J* = 9.2 Hz, 1H), 7.84 (d, *J* = 9.2 Hz, 1H), 7.61 (d, *J* = 4.6 Hz, 1H), 7.49 (s, 1H), 7.37 (d, *J* = 4.6 Hz, 1H), 7.35 -7.25 (m, 7H), 7.20 (t, *J*= 7.6 Hz, 2H), 4.96 (d, *J* = 12.1 Hz, 1H), 4.65 (d, *J* = 10.2 Hz, 1H), 4.57 (t, *J* = 11.9 Hz, 1H), 4.48 (t, *J* = 9.2 Hz, 1H), 3.97 (s, 3H), 3.86 (s, 3H), 3.44-2.35 (m, 9H), 3.04 (s, br, 2H), 2.95-2.86 (m, br, 2H), 2.70 (t, *J* = 12.1 Hz, 1H), 2.31 (s, 1H), 2.03 (s, 1H), 1.98-1.94 (m, 1H), 1.87 (s, 1H), 1.75-1.47 (m, 11H), 0.86-0.78 (m, 6H) ppm; $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$) δ 159.04, 158.81, 157.01, 155.56, 146.78, 146.73, 144.28, 139.18, 134.04, 133.98, 133.58, 131.47, 131.17, 130.95, 129.50, 126.82, 126.28, 126.23, 123.30, 123.12, 122.78, 122.72, 122.25, 122.10, 119.53, 101.85, 70.22, 67.03, 64.27, 59.74, 57.43, 56.43, 50.57, 35.87, 29.81, 25.97, 25.24, 24.84, 24.68, 24.23, 22.32, 11.65, 11.32 ppm; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{55}H_{60}N_6O_4H^+$869.4754, found 869.4775; $[\alpha]^{20}_D = -165.9°$ (*c* 1.0 mg/mL, $CHCl_3$); mp = 160 °C (decomposed).

Synthesis of *(*C9-*epi*-DHQD)$_2$PYDZ

Dihydroquindine mesylate[41]

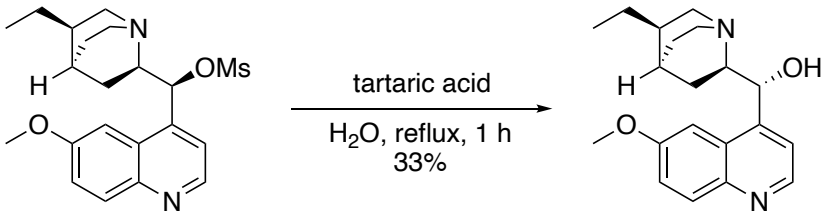
To a flame dried 50 mL round bottom flask was added dihydroquinidine (1.00 g, 3.40 mmol) and anhydrous



THF (20 mL). In parallel, triethylamine (0.950 mL, 6.80 mmol, 2 equiv) and mesyl chloride (0.48 mL, 6.11 mmol, 1.8 equiv) were added and the reaction was stirred at room temperature for 2 h. The reaction was quenched by adding saturated aqueous sodium bicarbonate (10 mL). The product was extracted with DCM (3 × 25 mL), the combined organics were washed with water (3 × 100 mL), dried over anhydrous sodium sulfate, and concentrated. The product was a yellow syrup, which was obtained in 87% yield (1.20 g, 2.97 mmol). The crude product was taken on to the next step without any further purification.

Data for **dihydroquinidine mesylate**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.78 (d, J = 4.3 Hz, 1H), 8.03 (d, *J* = 9.2 Hz, 1H), 7.43 (s, 1H), 7.39 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.32 (s, 1H), 6.18 (br, 1H), 3.95 (s, 3H), 3.36-3.12 (m, 1H), 2.88-2.84 (m, 1H), 2.62-2.48 (m, 6H), 1.89-1.81 (m, 1H), 1.78 (s, 1H), 1.64-1.23 (m, 6H), 0.90 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$) δ 158.2, 147.4, 145.0, 141.8, 132.1, 126.5, 122.1, 119.3, 101.2, 60.3, 55.6, 50.6, 49.9, 39.3, 38.9, 37.4, 27.2, 25.8, 25.4, 24.2, 12.0 ppm; $[\alpha]^{20}_{D}$ = +124.3° (c = 9.4 mg/1 mL, DCM).

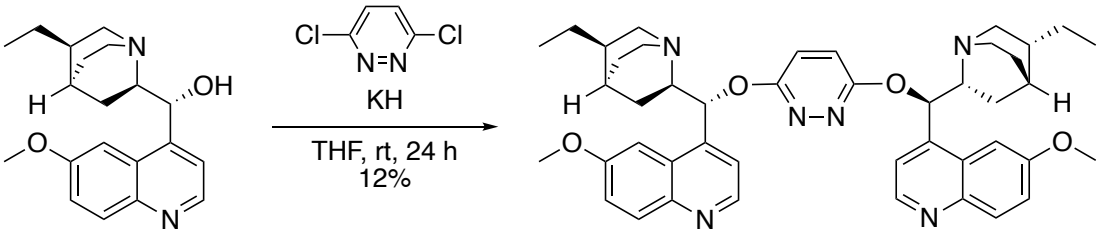
C9-*epi*-Dihydroquinidine[36]



To a 50 mL round bottom flask was added dihydroquinidine mesylate (1.13 g, 2.79 mmol, 1.0 equiv), tartaric acid (433 mg, 2.89 mmol, 1.03 equiv) and water (13 mL). The reaction was heated to 100 °C for 1 h, during which time the reaction turned orange in color. To quench the reaction, it was cooled to room temperature and saturated aqueous $NaHCO_3$ (30 mL) was slowly added. The product was extracted using $CHCl_3$ (3 × 50 mL), the combined organics were dried over anhydrous sodium sulfate and concentrated. The product was purified using column chromatography (20% MeOH in EtOAc to 50% MeOH in EtOAc) giving the product as a white solid in 33% yield (300 mg, 0.919 mmol).

Data for **C9-*epi*-dihydroquinidine**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.73 (d, *J* = 4.5 Hz, 1H), 8.00 (d, *J* = 8.8 Hz, 1H), 7.62 (d, *J* = 2.8 Hz, 1H), 7.41 (d, *J* = 4.5 Hz, 1H), 7.33 (dd, *J* = 9.2, 2.7 Hz, 1H), 5.04 (d, *J* = 9.9 Hz, 1H), 4.68 (br, 1H), 3.90 (s, 3H), 2.98-2.88 (m, 4H), 2.58 (dd, *J* = 13.6, 7.4 Hz, 1H), 1.58-1.36 (m, 7H), 1.00-0.95 (m, 1H), 0.87 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$) δ 157.3, 147.5, 144.9, 144.7, 131.6, 128.0, 121.5, 120.0, 102.1, 70.5, 62.0, 55.3, 49.2, 49.0, 37.2, 27.4, 25.7, 25.7, 23.8, 11.9 ppm; $[\alpha]^{20}_D$ = +87.8° (*c* = 5.9 mg/mL, $CHCl_3$); mp = 121-123 °C.

(C9-*epi*-DHQD)$_2$PYDZ



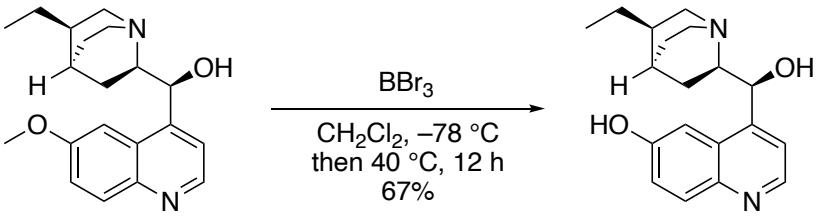
To a flame dried 100 mL round bottom flask was added KH (221 mg, 1.66 mmol, 4.36 equiv, 30% suspension in oil). The oil was removed from the potassium hydride by washing with hexanes (3 × 2 mL). THF (36 mL) was then added to the flask, followed by the addition of C9-*epi*-dihydroquinidine (280 mg, 0.858 mmol) and 2,6-dichloropyridazine (57 mg, 0.380 mmol). The reaction was stirred at room temperature under dry nitrogen for 24 h. At the end of 24 h, TLC analysis (10% MeOH in $CHCl_3$) indicated that all the starting material was consumed. The reaction was quenched by adding saturated aqueous NH_4Cl (10 mL). The layers were separated, the aqueous layer was washed with EtOAc (3 × 10 mL), the combined

organics were washed with water (3 × 20 mL), dried over anhydrous Na_2SO_4, and concentrated. NMR analysis of the crude residue indicated complete conversion of the starting material to the desired product, however the product was purified using column chromatography ($CHCl_3$ to 5% MeOH in $CHCl_3$) to give the product as an off-white solid (32 mg, 0.044 mmol) in 12% yield (yields are based only on the mass of the combined column fractions deemed clean via NMR analysis).

Data for **(C9-*epi*-DHQD)$_2$PYDZ:** ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.68 (d, *J* = 4.5 Hz, 2H), 8.01 (d, *J* = 9.2 Hz, 2H), 7.59 (d, *J* = 2.3 Hz, 2H), 7.45 (d, *J* = 4.6 Hz, 2H), 7.40 (dd, *J* = 2.7, 9.2 Hz, 2H), 6.90 (s, 2H), 6.51 (d, *J* = 9.8 Hz, 2H), 3.82 (s, 6H), 3.35 (q, *J* = 9.4 Hz, 2H), 2.98-2.93 (m, 2H), 2.88-2.84 (m, 4H), 2.61-2.57 (m, 2H), 1.51-1.25 (m, 14H), 1.06 (t, *J* = 9.4 Hz, 2H), 0.81 (t, *J* = 7.4 Hz, 6H) ppm; ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$) δ 161.31, 158.09, 147.80, 145.00, 144.27, 131.84, 128.68, 122.42, 121.75, 120.29, 102.18, 60.65, 55.90, 50.14, 49.67, 37.73, 27.61, 26.17, 26.04, 24.04, 12.27 ppm; IR (NaCl plate) $\tilde{\nu}$ 3075, 2932, 2872, 1622, 1508, 1435, 1259, 1226, 1035, 933, 852 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{44}H_{52}N_6O_4H^+$ 729.4128, found 729.4150; $[\alpha]^{20}_D$ = 130.1° (*c* = 10 mg/mL, $CHCl_3$); mp = 174-176 °C.

Synthesis of (*i*PrDHQD)$_2$PYDZ

6'-Hydroxy-10,11-dihydrocinchonine[42]

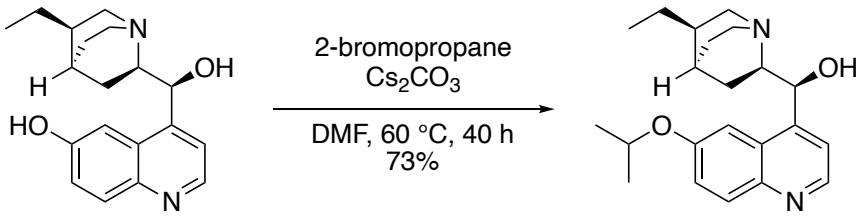


Dihydroquinidine (1.50 g, 4.60 mmol) and anhydrous dichloromethane (230 mL) were added to a flame dried 500 mL round bottom flask and the contents were cooled to –78 °C using a dry ice/acetone bath. In a separate flame dried 25 mL round bottom flask was added boron tribromide (2.61 mL, 27.6 mmol, 6.0 equiv) and anhydrous dichloromethane (5.5 mL). This solution was added to the dihydroquinidine solution dropwise. Following the addition, the reaction was stirred at –78 °C for 10 min and was then warmed to room temperature. The solution was refluxed for 12 h. The reaction was monitored by TLC (15% methanol

in chloroform, $KMnO_4$ charred). Upon completion, the reaction was cooled to 0 °C using an ice bath and 10% aqueous NaOH (50 mL) was slowly added. The reaction was poured into a separatory funnel and the organic layer was washed with aqueous 2% HCl (2 × 100 mL). The combined aqueous layers were basified to a pH of 9.5 using aqueous ammonium hydroxide (30% w/w). The aqueous layer was extracted with chloroform (5 × 200 mL), the combined organics were dried over anhydrous sodium sulfate, and concentrated. The product was obtained as a white solid in 67% yield (0.96 g, 3.07 mmol).

Data for **6'-hydroxy-10,11-dihydrocinchonine**: ^{1}H-NMR (500 MHz, DMSO-d_6 + $CDCl_3$) δ 8.57 (d, J = 4.5 Hz, 1H), 7.83 (d, J = 9.1 Hz, 1H), 7.51-7.49 (m, 1H), 7.37 (d, J = 2.3 Hz, 1H), 7.22 (dd, J = 9.1, 2.5 Hz, 1H), 6.23 (br, 2H), 5.70 (s, 1H), 3.36 (t, J = 12.2 Hz, 1H), 2.89 (t, J = 8.8 Hz, 1H), 2.72 (t, J = 10.5 Hz, 1H), 2.61-2.56 (m, 1H), 2.28-2.22 (m, 1H), 2.06-2.02 (m, 1H), 1.57 (s, 1H), 1.44-1.40 (m, 2H), 1.27-1.26 (m, 3H), 0.84- 0.76 (m, 4H) ppm; ^{13}C{^{1}H}-NMR (125 MHz, DMSO-d_6 + $CDCl_3$) δ 156.1, 147.1, 145.9, 142.6, 130.8, 126.2, 121.6, 117.5, 103.5, 70.0, 58.7, 49.8, 48.9, 36.3, 25.9, 25.3, 24.2, 18.7, 11.4 ppm; $[\alpha]^{20}_D$ = 130.1° = +230.4° (c = 10 mg/mL, MeOH); mp = 171-173 °C.

6'-Isopropoxy-10,11-dihydrocinchonidine[42]

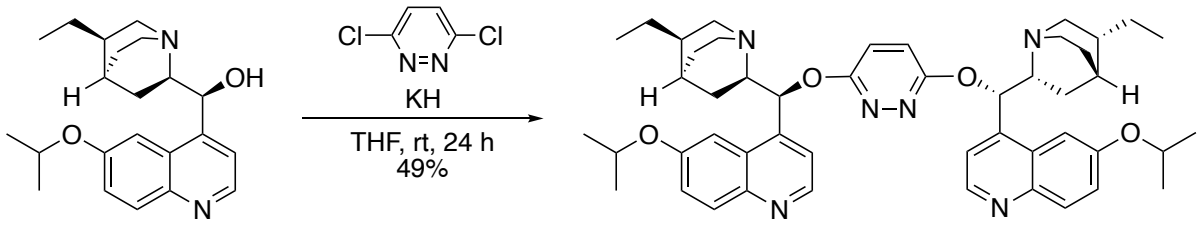


6'-Hydroxy-10,11-dihydrocinchonine (480 mg, 1.54 mmol, 1.0 equiv) was dissolved in DMF (76 mL) in a 300 mL round bottom flask and cesium carbonate (1.25 g, 3.85 mmol, 2.5 equiv) was added. The reaction was stirred at room temperature for 10 min and 2-bromopropane (0.29 mL, 3.08 mmol, 2.0 equiv) was added in one portion and the reaction was heated to 60 °C for 40 h. The reaction was cooled to room temperature and concentrated. The yellow residue was purified via column chromatography (1% MeOH in $CHCl_3$ to 10% MeOH in $CHCl_3$) giving the product as a yellow solid in 73% yield (400 mg, 1.13 mmol).

Data for **6'-isopropoxy-10,11-dihydrocinchonidine**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.63 (d, J = 4.5 Hz, 1H), 7.94 (d, J = 9.2 Hz, 1H), 7.48 (d, J = 4.6 Hz, 1H), 7.26-7.19 (m, 2H), 5.52 (d, J = 4.5 Hz, 1H), 4.58

(pent, J = 6.1 Hz, 1H), 4.08 (br, 1H), 3.02-2.95 (m, 2H), 2.86-2.78 (m, 2H), 2.73-2.67 (m, 1H), 2.23 (br, 1H), 1.91-1.87 (m, 1H), 1.65 (s, 1H), 1.45-1.35 (m, 5H), 1.31-1.29 (m, 6H), 0.83 (t, J = 7.1 Hz, 3H) ppm; $^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$) δ 155.9, 147.7, 147.6, 144.1, 131.7, 126.8, 122.7, 118.6, 103.7, 72.2, 70.3, 60.0, 51.4, 50.5, 37.6, 27.4, 26.5, 25.3, 22.2, 21.7, 21.3, 12.1 ppm; $[\alpha]^{20}_{D}$ = +187.5° (c = 20 mg / mL, EtOH); mp = 176-178 °C.

(*i*PrDHQD)$_2$PYDZ

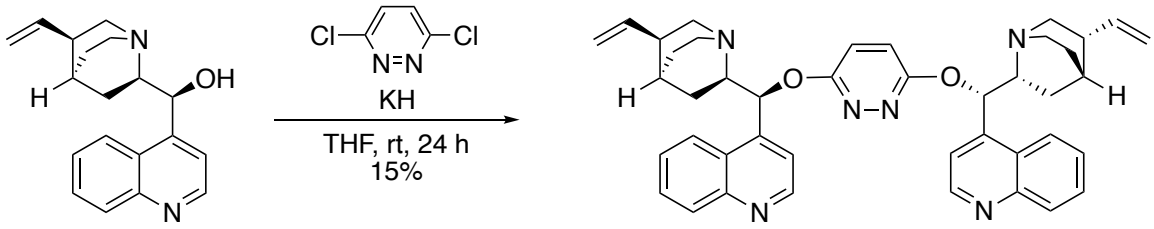


To a flame dried 100 mL round bottom flask was added KH (290 mg, 2.17 mmol, 4.36 equiv, 30% suspension in oil). The oil was removed from the potassium hydride by washing three times with hexanes (3 mL). THF (44 mL) was added to the flask, followed by the addition of *i*PrDHQD (400 mg, 1.12 mmol, 2.26 equiv) and 3,6-dichloropyridazine (74 mg, 0.497 mmol, 1.0 equiv). The reaction was stirred at room temperature under dry nitrogen for 36 h. At the end of 36 h, TLC analysis (15% MeOH in $CHCl_3$) indicated that all the starting material was consumed. The reaction was quenched by adding saturated aqueous NH_4Cl (15 mL). The layers were separated, the aqueous layer was washed with EtOAc (3 × 20 mL), the combined organics were washed with water (3 × 20 mL), dried over anhydrous Na_2SO_4, and concentrated. The product was purified using column chromatography ($CHCl_3$ to 7% MeOH in $CHCl_3$) to give the product as a pale yellow solid (190 mg, 0.242 mmol) in 49% yield.

Data for **(*i*PrDHQD)$_2$PYDZ:** ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.64 (d, J = 4.5 Hz, 2H), 7.97 (d, J = 9.2 Hz, 2H), 7.45 (d, J = 2.2 Hz, 2H), 7.34-7.30 (m, 4H), 6.96 (s, 2H), 6.73 (d, J = 4.2 Hz, 2H), 4.70 (pentet, J = 4.9 Hz, 2H), 3.28 (dd, J = 15.0, 8.7 Hz, 2H), 2.81-2.64 (m, 8H), 2.29 (br, 2H), 1.89-1.85 (m, 2H), 1.68 (s, 2H), 1.51-1.45 (m, 2H), 1.42-1.25 (m, 20H), 0.83 (t, J = 6.9 Hz, 6H) ppm; $^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$) δ 161.17, 156.18, 147.55, 144.84, 144.54, 131.97, 127.47, 123.22, 121.58, 119.14, 104.53, 77.47,

70.43, 60.24, 51.19, 50.48, 37.74, 27.63, 26.46, 25.64, 23.35, 22.33, 22.05, 12.26 ppm; IR (NaCl plate) $\tilde{\nu}$ 3047, 2934, 2872, 1618, 1506, 1435, 1260, 1224, 1113, 968 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{48}H_{60}N_6O_4H^+$ 785.4749, found 785.4754; $[\alpha]^{20}_D$ = –9.4° (*c* = 10 mg/mL, $CHCl_3$); mp = 94-96 °C.

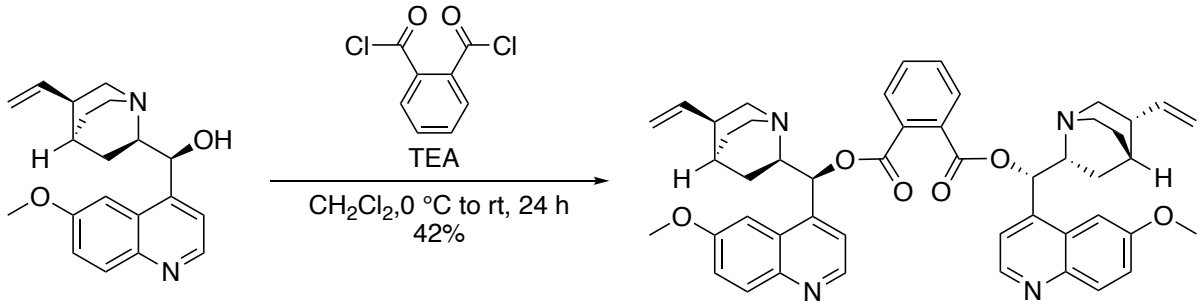
Synthesis of $(CN)_2$PYDZ



To a flame dried 100 mL round bottom flask was added KH (262 mg, 1.96 mmol, 4.36 equiv, 30% suspension in oil). The oil was removed from the potassium hydride by washing three times with hexanes (3 × 2 mL). THF (40 mL) was added to the flask, followed by the addition of cinchonine (300 mg, 1.02 mmol, 2.26 equiv) and 3,6-dichloropyridazine (67 mg, 0.450 mmol, 1.0 equiv). The reaction was stirred at room temperature under dry nitrogen for 24 h, during which time the color changed from colorless to orange. At the end of 24 h, TLC analysis (15% MeOH in $CHCl_3$) indicated that all the starting material was consumed. The reaction was quenched by adding saturated aqueous NH_4Cl (10 mL). The layers were separated, the aqueous layer was washed with EtOAc (3 × 20 mL), the combined organics were washed with water (3 × 20 mL), dried over anhydrous Na_2SO_4, and concentrated. The product was purified using column chromatography ($CHCl_3$ to 3% MeOH in $CHCl_3$) to give the product as an off-white solid (44 mg, 0.066 mmol) in 15% yield.

Data for **$(CN)_2$PYDZ:** ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.81 (d, *J* = 4.5 Hz, 2H), 8.22 (d, *J* = 8.6 Hz, 2H), 8.10 (d, *J* = 8.5 Hz, 2H), 7.70 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 2H), 7.55 (ddd, *J* = 8.3, 6.8, 1.3 Hz. 2H), 7.41 (d, *J* = 4.5 Hz, 2H), 6.99 (s, 2H), 6.84 (d, *J* = 6.3 Hz, 2H), 5.97-5.89 (m, 2H), 5.01-4.96 (m, 4H), 3.31 (dd, *J* = 15.2, 8.7 Hz, 2H), 2.92-2.88 (m, 2H), 2.82-2.72 (m, 4H), 2.68-2.61 (m, 2H), 2.19 (q, *J* = 8.4 Hz, 2H), 1.94-1.90 (m, 2H), 1.74 (s, 2H), 1.50-1.42 (m, 6H) ppm; $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$) δ 161.19, 150.23, 148.96, 146.24, 140.82, 130.70, 129.32, 126.86, 126.57, 124.36, 121.78, 119.14, 114.93, 77.44, 60.56, 50.32, 49.69, 40.31, 28.32, 26.85, 23.70 ppm; IR (NaCl plate) $\tilde{\nu}$ 3063, 2940, 2872, 1437, 1394, 1261,

987 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ for $C_{42}H_{44}N_6O_2H^+$ 665.3604, found 665.3602. $[\alpha]^{20}_D = +75.9°$ (*c* = 10 mg/mL, $CHCl_3$); mp = 99-102 °C.



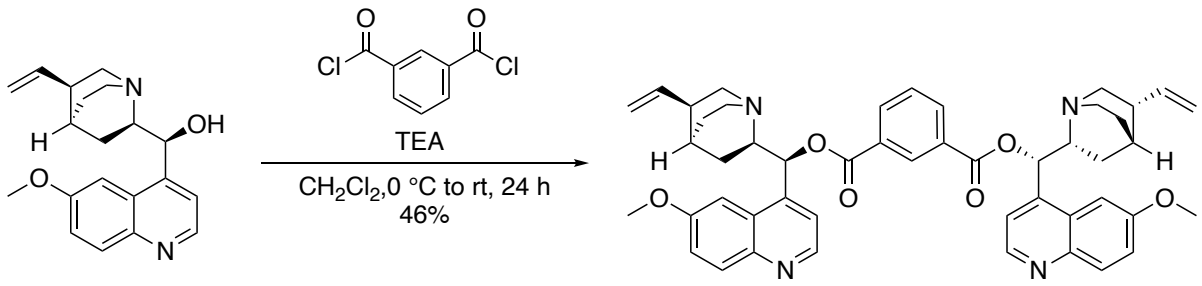
Synthesis of $(QD)_2PHTHAL$

To a flame dried 3-neck round bottom flask equipped with an addition funnel was added quinidine (300 mg, 0.925 mmol, 2.0 equiv) and dry DCM (6 mL). Freshly distilled triethylamine (0.925 mL, 6.61 mmol, 14.3 equiv) was added to the quinidine solution and it was subsequently cooled to 0 °C. To the addition funnel was added phthaloyl chloride (67 µL, 0.462 mmol) and DCM (5 mL). The acyl chloride solution was then added drop wise to the cooled quinidine solution. Following addition, the reaction slowly turned yellow in color, was warmed to room temperature and stirred overnight. The reaction was quenched by adding saturated aqueous ammonium chloride (10 mL). The reaction was extracted with DCM (3 x 20 mL), the combined organics were washed with water (3 × 20 mL), dried over anhydrous sodium sulfate, and concentrated. The product was purified using column chromatography (first column: 20% MeOH in EtOAc, second column: 5% MeOH in $CHCl_3$) giving the product as an off-white solid (151 mg, 0.194 mmol) in 42% yield (yields are based only on the mass of the combined fractions deemed clean via NMR analysis).

Data for **$(QD)_2PHTHAL$:** ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.73 (d, *J* = 4.6 Hz, 2H), 8.0 (d, *J* = 9.2 Hz, 2H), 7.72-7.70 (m, 2H), 7.59-7.56 (m, 2H), 7.42 (d, *J* = 2.6 Hz, 2H), 7.35 (dd, *J* = 9.2, 2.7 Hz, 2H), 7.30 (d, *J* = 4.6 Hz, 2H), 6.58 (d, *J* = 7.9 Hz, 2H), 5.87-5.81 (m, 2H), 4.98-4.94 (m, 4H), 3.90 (s, 6H), 3.19 (q, *J* = 8.6 Hz, 2H), 2.83-2.76 (m, 4H), 2.74-2.59 (m, 4H), 2.15 (q, *J* = 8.1 Hz, 2H), 1.75 (dd, *J* = 13.5, 8.9 Hz, 2H), 1.56 (s, 2H), 1.45-1.40 (m, 4H), 1.36-1.31 (m, 2H) ppm; $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$) δ 166.40,

158.19, 147.78, 145.10, 144.38, 140.53, 132.11, 131.75, 129.16, 127.54, 122.28, 119.06, 114.96, 75.20, 60.04, 55.88, 50.02, 49.44, 40.03, 27.88, 26.71, 24.50 ppm; IR (NaCl plate) $\tilde{\nu}$ 3076, 3042, 3004, 2937, 2872, 1730, 1622, 1508, 1261, 1228, 1064, 916, 736 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{48}H_{50}N_4O_6H^+$ $[M+H]^+$ 779.3809, found 779.3817; $[\alpha]^{20}_D$ = +45.4° (*c* = 10 mg/mL, $CHCl_3$); mp = 97-99 °C.

Synthesis of (QD)$_2$*iso*PHTHAL

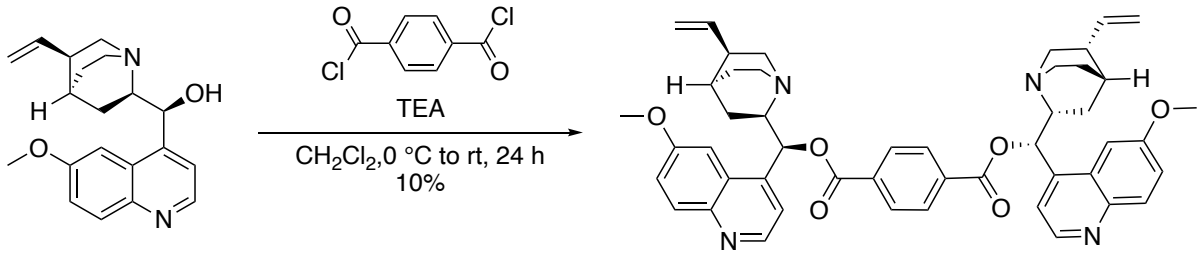


To a flame dried 3-neck round bottom flask equipped with an addition funnel was added quinidine (300 mg, 0.925 mmol, 2.0 equiv) and dry DCM (6 mL). Freshly distilled triethylamine (0.925 mL, 6.61 mmol, 14.3 equiv) was added to the quinidine solution and it was subsequently cooled to 0°C. To the addition funnel was added isophthaloyl chloride (68 µL, 0.463 mmol) and DCM (5 mL). The acyl chloride solution was added drop wise to the cooled quinidine solution. Following addition, the reaction slowly turned yellow in color, was warmed to room temperature, and stirred overnight. The reaction was quenched by adding saturated aqueous ammonium chloride (15 mL). The reaction was extracted with DCM (3 × 20 mL), the combined organics were washed with water (3 × 20 mL), dried over anhydrous sodium sulfate, and concentrated. The product was purified using column chromatography (1% MeOH in DCM to 6% MeOH in DCM) giving the product as an off-white solid (164 mg, 0.211 mmol) in 46% yield (yields are based only on the mass of the combined fractions deemed clean via NMR analysis).

Data for **(QD)$_2$*iso*PHTHAL:** ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.77 (t, *J* = 1.2 Hz, 1H), 8.71 (d, *J* = 4.2 Hz, 2H), 8.30 (dt, *J* = 7.8, 1.8 Hz, 2H), 8.00 (d, *J* = 9.2 Hz, 2H), 7.57 (t, *J* = 3.9 Hz, 1H), 7.47 (d, *J* =2.6 Hz, 2H), 7.40 (d, *J* = 4.6 Hz, 4H), 6.74 (d, *J* = 7.4 Hz, 2H), 6.04-5.98 (m, 2H), 5.10-5.04 (m, 4H), 3.94 (s, 6H),

3.44 (q, J = 8.8 Hz, 2H), 2.95 (d, J = 9.0 Hz, 4H), 2.85-2.80 (m, 2H), 2.76-2.70 (m, 2H), 2.28 (q, J = 8.7 Hz, 2H), 1.95 (dd, J = 13.3, 9.0 Hz, 2H), 1.87 (s, 2H), 1.67-1.50 (m, 6H) ppm; $^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$) δ 164.95, 158.29, 147.74, 145.10, 143.90, 140.44, 134.42, 132.20, 131.35, 130.76, 129.28, 127.36, 122.19, 118.90, 115.24, 101.69, 74.99, 59.78, 55.87, 50.11, 49.54, 39.87, 27.99, 26.69, 24.20, 12.20 ppm; IR (NaCl plate) $\tilde{\nu}$ 3076, 2937, 2872, 1726, 1622, 1593, 1508, 1300, 1228, 1130, 1030, 731 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{48}H_{50}N_4O_6H^+$ 779.3809, found 779.3821; $[\alpha]^{20}_D$ = –59.4° (c = 10 mg/mL, $CHCl_3$); mp = 78-80 °C.

Synthesis of $(QD)_2$TERE

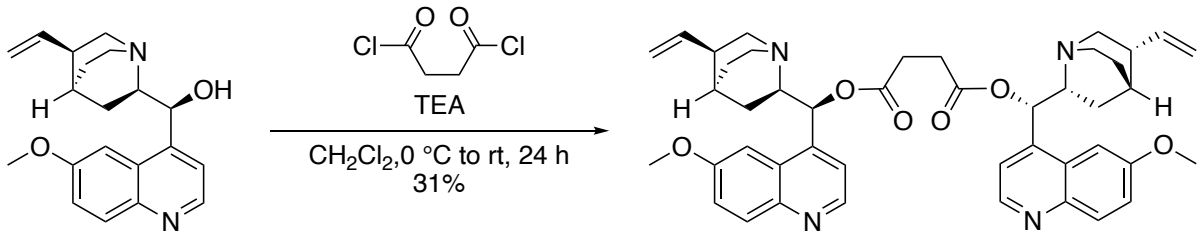


To a flame dried 3-neck round bottom flask equipped with an addition funnel was added quinidine (300 mg, 0.924 mmol, 2.0 equiv) and dry DCM (6 mL). Freshly distilled triethylamine (0.925 mL, 6.61 mmol, 14.3 equiv) was added to the quinidine solution and it was subsequently cooled to 0°C. To the addition funnel was added terephthaloyl chloride (70 µL, 0.462 mmol, 1.0 equiv) and DCM (5 mL). The acyl chloride solution was added drop wise to the cooled quinidine solution. Following addition, the reaction slowly turned yellow in color, was warmed to room temperature, and stirred overnight. The reaction was quenched by adding saturated aqueous ammonium chloride (10 mL). The reaction was extracted with DCM (3 × 20 mL), the combined organics were washed with water (3 × 20 mL), dried over anhydrous sodium sulfate, and concentrated. The product was purified using column chromatography (20% MeOH in EtOAc) giving the product as an off-white solid (35 mg, 0.045 mmol) in 10% yield (yields are based only on the mass of the combined fractions deemed clean via NMR analysis).

Data for **$(QD)_2$TERE:** ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.70 (d, J = 4.5 Hz, 2H), 8.15 (s, 4H), 8.00 (d, J = 9.2 Hz, 2H), 7.47 (d, J = 2.5 Hz, 2H), 7.38-7.36 (m, 4H), 6.76 (d, J = 6.7 Hz, 2H), 6.03-5.96 (m, 2H), 5.12-

5.05 (m, 4H), 3.96 (s, 6H), 3.45-3.42 (m, 2H), 2.97-2.95 (m, 4H), 2.86-2.68 (m, 4H), 2.24 (q, J = 8.5 Hz, 2H), 2.02-1.94 (m, 2H), 1.86 (s, 2H), 1.59-1.56 (m, 6H) ppm; $^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$) δ 164.6, 158.0, 147.4, 144.8, 143.4, 140.1, 133.9, 131.9, 129.8, 126.9, 121.9, 118.5, 115.0, 101.3, 74.8, 59.3, 55.6, 49.8, 49.2, 39.4, 27.6, 26.3, 23.6 ppm; IR (NaCl plate) $\tilde{\nu}$ 3075, 2936, 2872, 1724, 1622, 1508, 1287, 1228, 1103, 1018, 729 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{48}H_{50}N_4O_6H^+$ 779.3809, found 779.3772; $[\alpha]^{20}_D$ = –70.5° (c = 10 mg/mL, $CHCl_3$); mp = 85 °C (decomposed).

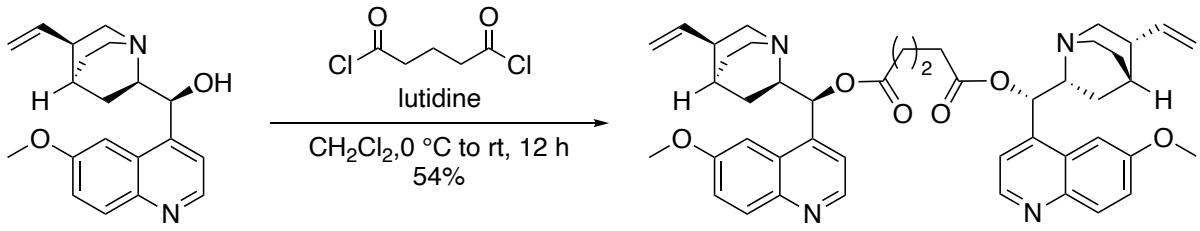
Synthesis of $(QD)_2SUCC$



To a flame dried 3-neck round bottom flask equipped with an addition funnel was added quinidine (400 mg, 1.232 mmol, 2.0 equiv) and dry DCM (6 mL). Freshly distilled triethylamine (1.232 mL, 14.3 equiv) was added to the quinidine solution and it was subsequently cooled to 0 °C. To the addition funnel was added succinyl chloride (68 µL, 0.616 mmol) and DCM (5 mL). The acyl chloride solution was added drop wise to the cooled quinidine solution. Following addition, the reaction slowly turned dark in color, was warmed to room temperature, and stirred for 24 h. The reaction was quenched by adding saturated aqueous ammonium chloride (10 mL). The reaction was extracted with DCM (3 × 20 mL), the combined organics were washed with water (3 x 20 mL), dried over anhydrous sodium sulfate, and concentrated. The product was purified using column chromatography (1% MeOH in DCM to 6% MeOH in DCM) giving the product as an off-white solid (139 mg, 0.190 mmol) in 31% yield.

Data for **$(QD)_2SUCC$:** ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.68 (d, J = 4.5 Hz, 2H), 7.99 (d, J = 10.0 Hz, 2H), 7.36-7.33 (m, 4H), 7.25 (s, 2H), 6.49 (d, J = 7.4 Hz, 2H), 6.00-5.93 (m, 2H), 5.08-5.03 (m, 4H), 3.89 (s, 6H), 3.19 (q, J =9.0 Hz, 2H), 2.86-2.84 (m, 4H), 2.73-2.63 (m, 8H), 2.21 (q, J = 8.2 Hz, 2H), 1.76-1.72 (m, 4H), 1.49-1.39 (m, 6H) ppm; $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$) δ 171.41, 158.21, 147.74, 145.05, 143.88, 140.59, 132.17, 127.32, 118.94, 115.18, 101.63, 74.20, 55.86, 50.10, 49.46, 40.05, 29.34, 26.65, 23.97 ppm; IR (NaCl plate) $\tilde{\nu}$ 3080, 2999, 2937, 2872, 1740, 1622, 1508, 1508, 1475, 1361, 1263, 1226, 1153, 1030, 989 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{44}H_{50}N_4O_6H^+$ 731.3809, found 731.3789; $[\alpha]^{20}_D$ = +88.4° (c = 10 mg/mL, $CHCl_3$); mp = 68-70 °C.

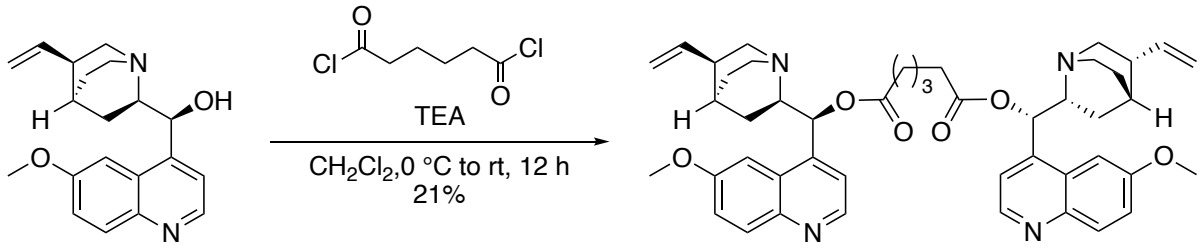
Synthesis of $(QD)_2GLUT$



To a flame dried 3-neck round bottom flask equipped with an addition funnel was added quinidine (300 mg, 0.925 mmol, 2.0 equiv) and dry DCM (6 mL). Freshly distilled lutidine (0.160 mL, 1.386 mmol, 3.0 equiv) was added to the quinidine solution and it was subsequently cooled to 0°C. To the addition funnel was added glutaroyl chloride (60 µL, 0.463 mmol, 1.0 equiv) and DCM (5 mL). The acyl chloride solution was added drop wise to the cooled quinidine solution. Following addition, the reaction slowly turned yellow in color, was warmed to room temperature and stirred overnight. The reaction was quenched by adding saturated aqueous ammonium chloride (10 mL). The reaction was extracted with DCM (3 × 20 mL), the combined organics were washed with water (3 × 20 mL), dried over anhydrous sodium sulfate, and concentrated. The product was purified using column chromatography (20% MeOH in EtOAc) giving the product as an off-white solid (187 mg, 0.249 mmol) in 54% yield.

Data for **$(QD)_2GLUT$:** ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.68 (dd, J = 3.8, 0.7 Hz, 2H), 7.97 (d, J = 7.1 Hz, 2H), 7.37-7.32 (m, 4H), 7.23 (s, 2H), 6.47 (d, J = 6.2 Hz, 2H), 5.98-5.92 (m, 2H), 5.05-5.02 (m, 4H), 3.91 (s, 6H), 3.24 (q, J = 7.2 Hz, 2H), 2.86-2.83 (m, 4H), 2.77-2.73 (m, 2H), 2.69-2.64 (m, 2H), 2.41-2.32 (m, 4H), 2.24 (q, J = 6.8 Hz, 2H), 1.92 (pent, J = 6.2 Hz, 2H), 1.76-1.71 (m, 4H), 1.52-1.43 (m, 6H) ppm; $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$) δ 171.8, 157.9, 147.4, 144.7, 143.7, 140.1, 131.8, 127.0, 121.8, 118.5, 114.9, 101.3, 73.4, 59.0, 55.5, 49.7, 49.1, 39.7, 33.1, 27.7, 26.3, 23.6, 19.9 ppm; IR (NaCl plate) $\tilde{\nu}$ 3083, 3045, 2939, 2874, 1740, 1622, 1593, 1508, 1228 1165, 1030, 988, 734 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{45}H_{52}N_4O_6H^+$ 745.3965, found 745.3951; $[\alpha]^{20}_D$ = 66.2° (c = 10 mg/mL, $CHCl_3$); mp = 53-55 °C.

Synthesis of $(QD)_2ADI$

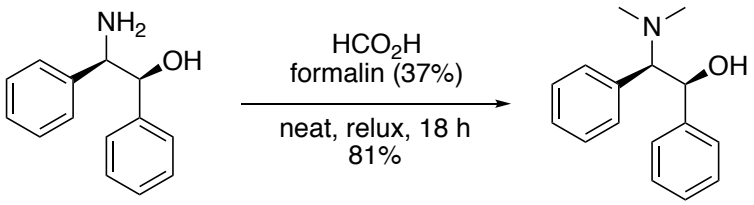


To a flame dried 3-neck round bottom flask equipped with an addition funnel was added quinidine (300 mg, 0.925 mmol, 2.0 equiv) and dry DCM (6 mL). Freshly distilled triethylamine (0.925 mL, 14.3 equiv) was added to the quinidine solution and it was subsequently cooled to 0 °C. To the addition funnel was added adipoyl chloride (68 µL, 0.462 mmol) and DCM (5 mL). The acyl chloride solution was added drop wise to the cooled quinidine solution. Following addition, the reaction slowly turned yellow in color, was warmed to room temperature, and stirred overnight. The reaction was quenched by adding 10 mL saturated ammonium chloride. The reaction was extracted with DCM (3 × 20 mL), the combined organics were washed with water (3 × 20 mL), dried over anhydrous sodium sulfate, and concentrated. The product was purified using column chromatography (1% EtOH in DCM to 3% EtOH in DCM) giving the product as an off-white solid (74 mg, 0.098 mmol) in 21% yield.

Data for **$(QD)_2ADI$:** ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.70 (d, J = 4.5 Hz, 2H), 7.99 (d, J = 9.2 Hz, 2H), 7.37-7.33 (m, 4H), 7.27 (d, J = 4.5 Hz, 2H), 6.49 (d, J = 6.7 Hz, 2H), 5.97-5.95 (m, 2H), 5.09-5.04 (m, 4H), 3.92 (s, 6H), 3.24 (q, J = 7.8 Hz, 2H), 2.88-2.86 (m, 4H), 2.76-2.68 (m, 6H), 2.36-2.35 (m, 6H), 1.80-1.74 (m, 4H), 1.61 (q, J = 6.9 Hz, 4H), 1.52-1.43 (m, 6H) ppm; $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$) δ 172.1, 157.9, 147.3, 144.7, 143.8, 140.1, 131.7, 127.0, 121.8 118.5, 114.9, 101.3, 73.4, 59.0, 55.6, 49.7, 49.1, 39.6, 33.9, 27.7, 26.3, 24.1, 23.5 ppm; IR (NaCl plate) $\tilde{\nu}$ 3092, 3040, 2937, 2872, 1740, 1022, 1500, 1473, 1361, 1228, 1167, 1030, 734 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{46}H_{54}N_4O_6H^+$ 759.4122, found 759.4156; $[\alpha]^{20}_D$ = 68.4° (c = 10 mg/mL, $CHCl_3$); mp = 43-45 °C.

Synthesis of (trunc)$_2$PYDZ

(1*S*,2*R*)-2-(Dimethylamino)-1,2-diphenylethan-1-ol: truncated monomer ("trunc") [42]

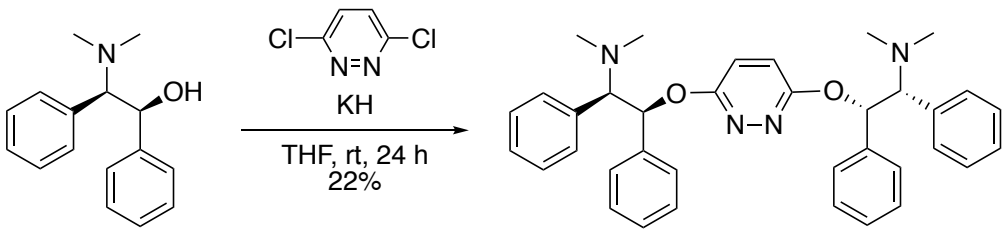


"trunc"

To a 5 mL round bottom flask was added (1*S*, 2*R*)-(+)-2-amino-1,2-diphenyethanol (200 mg, 0.938 mmol), formic acid (0.355 mL, 9.38 mmol, 10 equiv), and formalin (0.457 mL, 5.63 mmol, 6.0 equiv, 37% in water). The reaction was refluxed for 18 h. The reaction was cooled to room temperature and basified to pH = 10 using 1 M aqueous sodium hydroxide. The reaction was extracted with diethyl ether (3 x 20 mL). The combined organic fractions were washed with water (10 mL), dried over anhydrous sodium sulfate, and concentrated. The product was purified using column chromatography (1% AcCN in $CHCl_3$ to 5% MeOH/1% AcCN/94% $CHCl_3$). The product was isolated as a white solid in 81% yield (184 mg, 0.763 mmol).

Data for **truncated monomer:** ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.13-7.08 (m, 6H), 6.98-6.94 (m, 4H), 5.29 (d, J = 3.6 Hz, 1H), 3.30 (br, 1H), 3.19 (d, J = 3.6 Hz, 1H), 2.33 (s, 6H) ppm; ^{13}C{^{1}H}-NMR (150 MHz, $CDCl_3$) δ 141.3, 136.8, 129.6, 127.7, 127.6, 127.3, 126.9, 126.3, 77.7, 72.7, 44.3 ppm; $[\alpha]^{20}_D$ = +122.3° (*c* = 10 mg/mL, EtOH); mp = 91-93 °C

(trunc)$_2$PYDZ



"trunc" **(trunc)$_2$PYDZ**

To a flame dried 100 mL round bottom flask was added KH (185 mg, 1.39 mmol, 4.36 equiv, 30% suspension in oil). The oil was removed from the potassium hydride by washing with hexanes (3 × 2 mL). THF (28 mL) was added to the flask, followed by the addition of (1*S*,2*R*)-2-(dimethylamino)-1,2-diphenylethanol (174 mg, 0.722 mmol, 2.26 equiv) and 3,6-dichloropyridazine (48 mg, 0.319 mmol). The reaction was stirred at room temperature under dry nitrogen for 24 h. At the end of 24 h, TLC analysis (10% MeOH in $CHCl_3$) indicated that all the starting material was consumed. The reaction was quenched by adding saturated aqueous NH_4Cl (10 mL). The layers were separated, the aqueous layer was washed with EtOAc (3 × 15 mL), the combined organics were washed with water (3 x 15 mL), dried over anhydrous Na_2SO_4, and concentrated. The product was purified using column chromatography (EtOAc to 40% MeOH in EtOAc) to give the product as an off-white solid (40 mg, 0.072 mmol) in 22% yield.

Data for **(trunc)$_2$PYDZ:** ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.19-712 (m, 20H), 6.89 (d, J = 5.1 Hz, 2H), 6.77 (s, 2H), 3.51 (d, J = 5.1 Hz, 2H), 2.21 (s, 12H), 1.96 (s, 2H) ppm; ^{13}C{^{1}H}-NMR (150 MHz, $CDCl_3$) δ 161.10, 139.71, 136.60, 130.07, 129.80, 128.64, 128.03, 127.62, 127.42, 127.37, 127.35, 122.24, 76.35, 76.01, 43.88 ppm; IR (NaCl plate) $\tilde{\nu}$ 3063, 3030, 2938, 2862, 2826, 2779, 1666, 1595, 1454, 1437, 1278, 1263, 1020 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{36}H_{38}N_4O_2H^+$ 559.3073, found 559.3088; $[\alpha]^{20}_D$ = 27.7° (c = 10 mg/mL, $CHCl_3$); mp = 84-85 °C.

QUNTUM CHEMICAL CALCULATIONS

As summarized in the plots in Figure 2 (main text), computational analysis at the wB97X-D/6-31+G* level of theory was used to explore the rotational potential energy functions for ethers flanking the central linkers explored in this work. Specifically, one of the two methoxy groups in these sites was rotated in 10° increments from a dihedral angle of 0° to 180° with all other geometrical parameters allowed to fully relax. A more detailed study was performed in the case of 1,4-dimethoxy-9,10-anthraquinone, motivated by the surprisingly low barrier to rotation, and the multiple minima noted in the potential energy surface study for this case. We had initially reasoned that, as in the phthalazine and other linkers containing a pyridazine ring, resonance delocalization of the ether oxygen's 2p lone pair as shown in Figure S1 would strongly prefer a coplanar orientation of the ether with the attached ring. Even without p-electron withdrawing group, the methoxy moiety in anisole prefers the coplanar arrangement. In addition, the phthalazine system includes the synergistic contributions from the in-plane oxygen lone pair to C-N s* donation and the electrostatic attraction between the O-CH_3 and nitrogen sites, both of which also favor the planar structure. In contrast, in the anthraquinone system, the planar structure is destabilized by the orientation of the O-CH_3 dipole in conflict with the partially negative carbonyl oxygen, whereas in the out-of-plane rotamers, the electrostatic attraction between the partially positive methyl group and partially negative carbonyl oxygen is stabilizing (see Figure S1). These effects evidently counterbalance any loss of p resonance stabilization.

Conformers of 1,4-dimethoxy-9,10-anthraquinone[44]

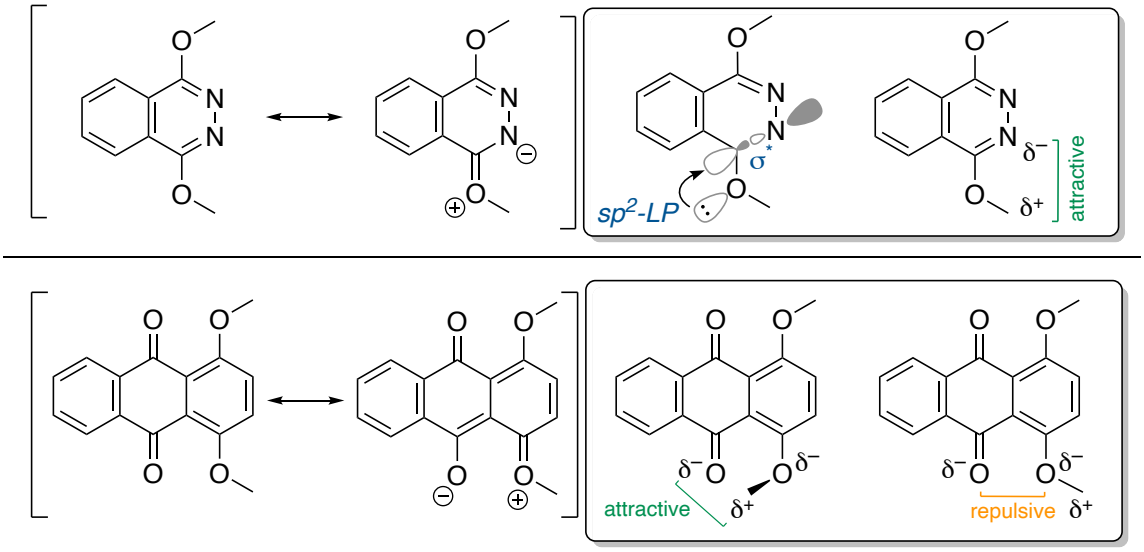
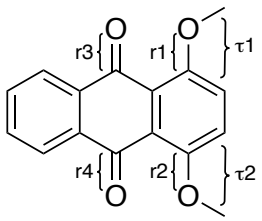


Figure S1 *Left: Resonance structures suggesting partial double bonding of ether oxygen atoms favoring planar aryl ether structures. Right: Additional stereoelectronic and electrostatic factors that reinforce ether planarity for the phthalazine, but stabilize nonplanar rotamers in the case of the dimethoxyanthraquinone.*

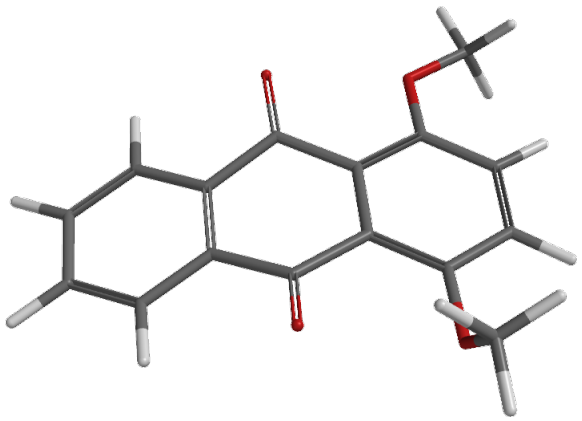
Structure	Energy (au)	$E_{relative}$	Point Group	r1	r2	r3	r4	t1	t2
Conformer 1	-917.52516	[0.00]	C1	1.363	1.344	1.218	1.218	91.0	0.2
Conformer 2	-917.52483	0.21	Cs	1.348	1.348	1.217	1.217	-1.2	1.2
Conformer 3	-917.52428	0.55	Cs	1.361	1.361	1.218	1.218	-93.0	93.0
Conformer 4	-917.52344	1.08	C1	1.344	1.353	1.219	1.221	0.5	-132.3
Conformer 5	-917.52293	1.40	C1	1.362	1.349	1.219	1.221	85.4	-130.4
Conformer 6	-917.52277	1.50	C2	1.361	1.361	1.219	1.219	-88.8	-88.8
Conformer 7	-917.52271	1.53	C1	1.361	1.351	1.219	1.221	-94.8	-133.7
Conformer 8	-917.52255	1.64	C2	1.350	1.350	1.222	1.222	-136.1	-136.1
Conformer 9	-917.52104	2.58	Cs	1.352	1.352	1.221	1.221	130.1	-130.1

Table S1 *Summary of conformational minima for 1,4-dimethoxy-9,10-anthroquinone ($E_{relative}$ is in kcal/mol).* Computational level: wB97X-D/6-31+G*[45, 46]

As defined in the structure at right, the above table lists selected CO bond lengths (r1-r4) and C=C-O-C dihedral angles (t1,t2) for the nine symmetry distinct minima found for 1,4-dimethoxy-9,10-anthroquinone. Though the implied transition structures that would link these structures have not explicitly been mapped out, it is clear from the simple dihedral driving energy plot shown in the main text that the barriers between these minima are low. The resulting lack of a strongly preferred conformation is consistent with the poor performance of the $(DHQD)_2$ catalyst connected by this linker.



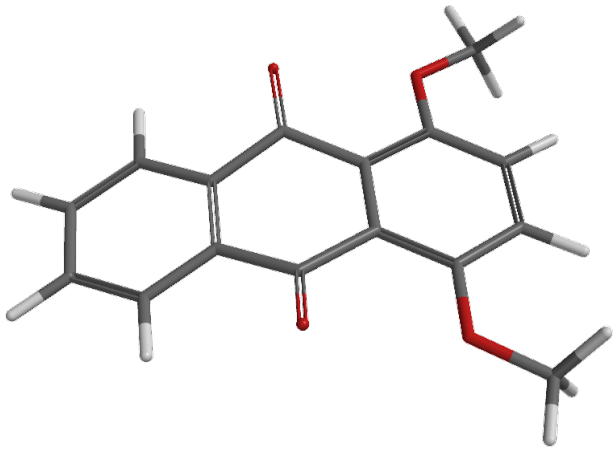
Conformer structures: coordinates and energies:



Conformer 1: E = -917.52516 H; $E_{relative}$ = [0]; Point Group = C_1

O	-1.5978	-2.8852	0.5125
C	-1.6705	-1.5495	0.2509
C	-1.9512	1.2332	-0.0842
C	-2.9137	-0.9336	0.3800
C	-0.5434	-0.7666	-0.0444
C	-0.6765	0.6357	-0.2014
C	-3.0617	0.4310	0.2098
C	3.2543	-1.0958	0.1777
C	2.9976	1.6705	-0.1159
C	1.9970	-0.5279	-0.0375
C	4.3733	-0.2777	0.2712
C	4.2445	1.1059	0.1238
C	1.8670	0.8546	-0.1844
C	0.8050	-1.4090	-0.1705
C	0.5346	1.4744	-0.4624
O	0.9434	-2.6019	-0.3763

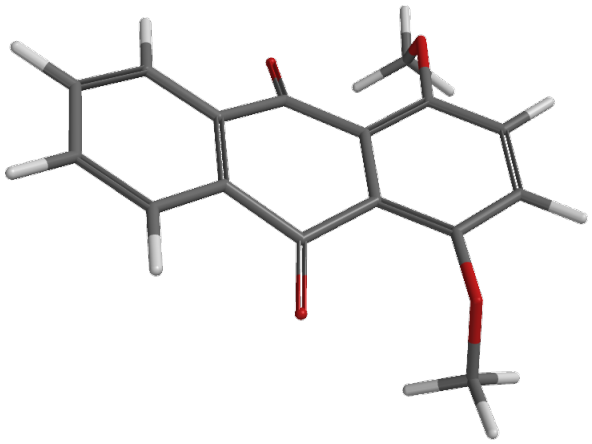
O	0.4776	2.6215	-0.8669
C	-1.7992	-3.7335	-0.6109
O	-2.0449	2.5658	-0.2330
C	-3.3021	3.1918	-0.0851
H	-3.7695	-1.5523	0.6334
H	-4.0457	0.8703	0.3202
H	3.3348	-2.1742	0.2686
H	2.8794	2.7404	-0.2533
H	5.3502	-0.7160	0.4531
H	5.1220	1.7425	0.1904
H	-1.0265	-3.5644	-1.3666
H	-2.7967	-3.5723	-1.0419
H	-1.7231	-4.7548	-0.2357
H	-3.1162	4.2533	-0.2486
H	-3.7090	3.0445	0.9234
H	-4.0195	2.8304	-0.8324



Conformer 2: E = -917.52483 H; $E_{relative}$ = 0.21; Point group = C_s

O	-1.7291	0.0316	2.7609
C	-1.7673	0.0065	1.4139
C	-1.7673	0.0065	-1.4139
C	-2.9548	0.1460	0.6928
C	-0.5535	-0.1403	0.7079
C	-0.5535	-0.1403	-0.7079
C	-2.9548	0.1460	-0.6928
C	3.1928	0.1516	1.3965
C	3.1928	0.1516	-1.3965
C	1.9984	-0.0341	0.6976
C	4.3755	0.3621	0.6988
C	4.3755	0.3621	-0.6988
C	1.9984	-0.0341	-0.6976
C	0.7375	-0.2834	1.4558
C	0.7375	-0.2834	-1.4558
O	0.7906	-0.5799	2.6355

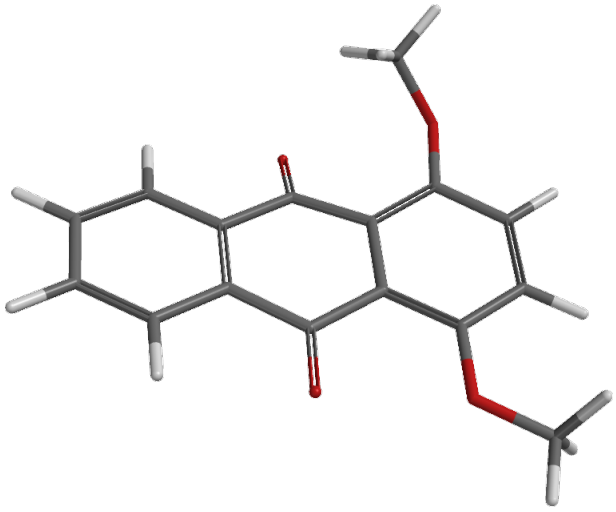
O	0.7906	-0.5799	-2.6355
C	-2.9274	0.2310	3.4776
O	-1.7291	0.0316	-2.7609
C	-2.9274	0.2310	-3.4776
H	-3.9016	0.2605	1.2069
H	-3.9016	0.2605	-1.2069
H	3.1737	0.1263	2.4813
H	3.1737	0.1263	-2.4813
H	5.3030	0.5204	1.2414
H	5.3030	0.5204	-1.2414
H	-3.6433	-0.5815	3.2990
H	-3.3908	1.1948	3.2291
H	-2.6392	0.2297	4.5289
H	-3.3908	1.1948	-3.2291
H	-3.6433	-0.5815	-3.2990
H	-2.6392	0.2297	-4.5289



Conformer 3: E = -917.52428 H; $E_{relative}$ = 0.55; Point group = C_s

O	-1.9008	-0.4356	2.7595
C	-1.8489	-0.3341	1.4034
C	-1.8489	-0.3341	-1.4034
C	-3.0136	-0.6304	0.6910
C	-0.6627	-0.0475	0.7092
C	-0.6627	-0.0475	-0.7092
C	-3.0136	-0.6304	-0.6910
C	3.0860	-0.1212	1.3974
C	3.0860	-0.1212	-1.3974
C	1.8847	0.0063	0.6988
C	4.2770	-0.2781	0.6986
C	4.2770	-0.2781	-0.6986
C	1.8847	0.0063	-0.6988
C	0.6124	0.2030	1.4516
C	0.6124	0.2030	-1.4516
O	0.6380	0.5441	2.6208

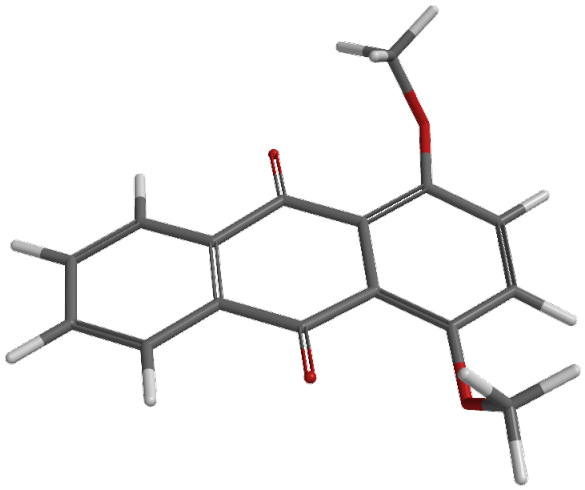
O	0.6380	0.5441	-2.6208
C	-2.2202	0.7689	3.4468
O	-1.9008	-0.4356	-2.7595
C	-2.2202	0.7689	-3.4468
H	-3.9081	-0.8832	1.2523
H	-3.9081	-0.8832	-1.2523
H	3.0674	-0.0965	2.4823
H	3.0674	-0.0965	-2.4823
H	5.2107	-0.3949	1.2408
H	5.2107	-0.3949	-1.2408
H	-2.2405	0.5143	4.5070
H	-3.2068	1.1375	3.1359
H	-1.4543	1.5293	3.2686
H	-3.2068	1.1375	-3.1359
H	-2.2405	0.5143	-4.5070
H	-1.4543	1.5293	-3.2686



Conformer 4: E = -917.52344 H; $E_{relative}$ = 1.08; Point group = C_1

O	2.4191	-2.2971	-0.0520
C	2.1496	-0.9802	-0.0724
C	1.5311	1.7745	-0.0676
C	3.1658	-0.0123	-0.1163
C	0.8022	-0.5644	-0.0577
C	0.4941	0.8266	-0.1207
C	2.8567	1.3305	-0.0915
C	-2.7460	-1.9865	0.2525
C	-3.3291	0.7031	-0.2148
C	-1.7076	-1.0737	0.0564
C	-4.0654	-1.5527	0.2257
C	-4.3581	-0.2065	-0.0088
C	-2.0013	0.2709	-0.1736
C	-0.2964	-1.5709	0.0653
C	-0.9101	1.2557	-0.3928

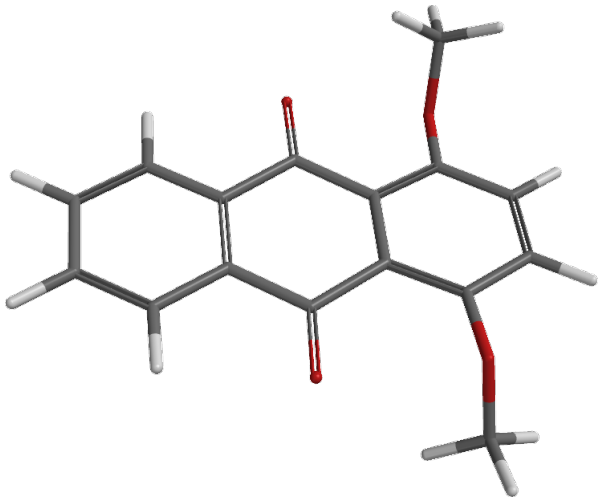
O	-0.0916	-2.7652	0.1966
O	-1.1705	2.3687	-0.8226
C	3.7625	-2.7315	-0.0636
O	1.3909	3.1193	-0.0138
C	0.4990	3.7109	0.9222
H	4.2076	-0.3080	-0.1387
H	3.6418	2.0796	-0.0804
H	-2.4977	-3.0294	0.4198
H	-3.5322	1.7514	-0.4089
H	-4.8712	-2.2640	0.3820
H	-5.3907	0.1293	-0.0328
H	4.3091	-2.3718	0.8172
H	4.2805	-2.4158	-0.9779
H	3.7122	-3.8201	-0.0362
H	1.0505	4.5203	1.4078
H	0.1821	2.9829	1.6778
H	-0.3780	4.1036	0.4063



Conformer 5: E = -917.52293 H; $E_{relative}$ = 1.40; Point group = C_1

O	-2.1578	-2.5413	0.5288
C	-2.0017	-1.1998	0.3562
C	-1.7822	1.5955	0.1533
C	-3.1183	-0.3797	0.5561
C	-0.7571	-0.6197	0.0897
C	-0.6223	0.7990	0.0694
C	-3.0161	0.9884	0.4267
C	2.9075	-1.6953	-0.1163
C	3.1989	1.0595	0.2296
C	1.7791	-0.8750	-0.0582
C	4.1741	-1.1391	0.0104
C	4.3195	0.2397	0.1823
C	1.9230	0.5041	0.1117
C	0.4281	-1.4837	-0.2028
C	0.7356	1.4082	0.1579
O	0.3131	-2.6372	-0.5794

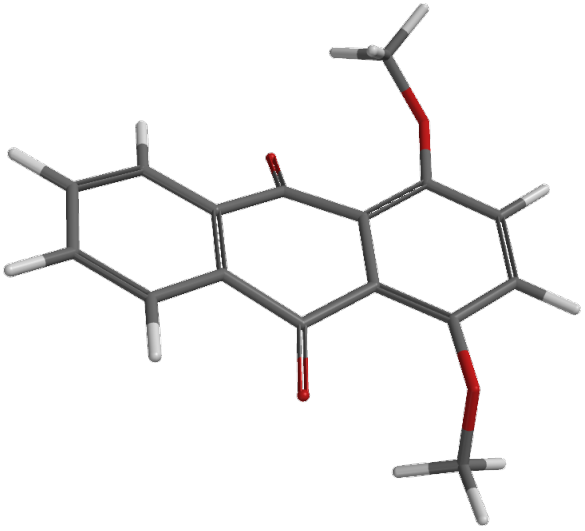
O	0.9006	2.6051	0.3359
C	-2.6382	-3.2492	-0.6070
O	-1.8302	2.9390	0.0369
C	-1.2303	3.5814	-1.0845
H	-4.0677	-0.8485	0.7970
H	-3.8830	1.6321	0.5346
H	2.7707	-2.7626	-0.2566
H	3.2904	2.1331	0.3572
H	5.0518	-1.7778	-0.0247
H	5.3106	0.6734	0.2784
H	-1.9243	-3.1772	-1.4329
H	-3.6201	-2.8670	-0.9172
H	-2.7329	-4.2902	-0.2960
H	-1.9978	4.2253	-1.5227
H	-0.9011	2.8478	-1.8278
H	-0.3748	4.1708	-0.7554



Conformer 6: E = -917.52277 H; $E_{relative}$ = 1.50; Point group = C_2

O	0.5539	-2.7021	-1.9771
C	0.2384	-1.3812	-1.8953
C	-0.2384	1.3812	-1.8953
C	0.1315	-0.6776	-3.0972
C	0.0938	-0.7050	-0.6712
C	-0.0938	0.7050	-0.6712
C	-0.1315	0.6776	-3.0972
C	0.1167	-1.3904	3.1029
C	-0.1167	1.3904	3.1029
C	0.0585	-0.6958	1.8924
C	0.0599	-0.6960	4.3043
C	-0.0599	0.6960	4.3043
C	-0.0585	0.6958	1.8924
C	0.0966	-1.4687	0.6176
C	-0.0966	1.4687	0.6176
O	0.0875	-2.6870	0.6534

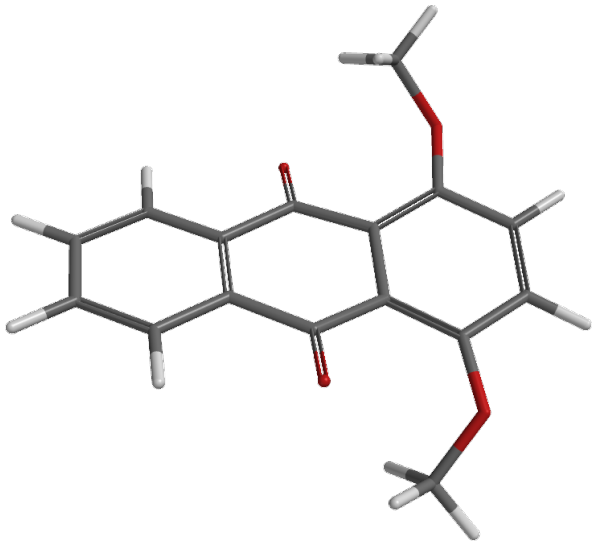
O	-0.0875	2.6870	0.6534
C	-0.5507	-3.5888	-2.1018
O	-0.5539	2.7021	-1.9771
C	0.5507	3.5888	-2.1018
H	0.2551	-1.2260	-4.0263
H	-0.2551	1.2260	-4.0263
H	0.2055	-2.4715	3.0793
H	-0.2055	2.4715	3.0793
H	0.1075	-1.2375	5.2446
H	-0.1075	1.2375	5.2446
H	-1.1891	-3.5406	-1.2146
H	-0.1257	-4.5891	-2.1889
H	-1.1334	-3.3550	-3.0029
H	1.1334	3.3550	-3.0029
H	1.1891	3.5406	-1.2146
H	0.1257	4.5891	-2.1889



Conformer 7: E = -917.52271 H; $E_{relative}$ = 1.53; Point group = C_1

O	2.4591	-2.3572	0.4675
C	2.1530	-1.0521	0.2337
C	1.6777	1.7109	-0.0083
C	3.2100	-0.1350	0.2810
C	0.8453	-0.5911	0.0321
C	0.6076	0.8064	-0.1243
C	2.9786	1.2175	0.1671
C	-2.7614	-1.8109	0.3874
C	-3.2005	0.8856	-0.1988
C	-1.6817	-0.9744	0.1004
C	-4.0506	-1.2922	0.4081
C	-4.2708	0.0555	0.1125
C	-1.9017	0.3741	-0.1885
C	-0.3059	-1.5482	0.0257
C	-0.7556	1.2658	-0.5165
O	-0.1591	-2.7567	-0.0310
O	-0.9443	2.3223	-1.0979

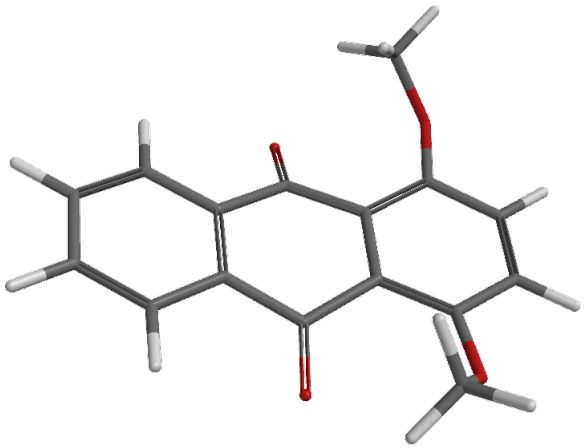
C	2.7005	-3.1429	-0.6934
O	1.5947	3.0587	-0.0485
C	0.6043	3.7515	0.7013
H	4.2118	-0.5185	0.4490
H	3.7877	1.9371	0.2398
H	-2.5722	-2.8607	0.5871
H	-3.3527	1.9304	-0.4498
H	-4.8897	-1.9392	0.6461
H	-5.2808	0.4547	0.1202
H	3.5598	-2.7472	-1.2511
H	1.8143	-3.1750	-1.3338
H	2.9255	-4.1482	-0.3359
H	1.1150	4.5892	1.1824
H	0.1686	3.1020	1.4693
H	-0.1838	4.1138	0.0400



Conformer 8: E = -917.52255 H; $E_{relative}$ = 1.64; Point group = C_2

O	-0.0034	-2.7510	-2.1547
C	0.0150	-1.4113	-1.9933
C	-0.0150	1.4113	-1.9933
C	-0.0081	-0.6862	-3.1982
C	0.0634	-0.7142	-0.7779
C	-0.0634	0.7142	-0.7779
C	0.0081	0.6862	-3.1982
C	0.4220	-1.3307	2.9834
C	-0.4220	1.3307	2.9834
C	0.2083	-0.6666	1.7740
C	0.2114	-0.6658	4.1851
C	-0.2114	0.6658	4.1851
C	-0.2083	0.6666	1.7740
C	0.4153	-1.4014	0.4941
C	-0.4153	1.4014	0.4941

O	0.9143	-2.5168	0.5090
O	-0.9143	2.5168	0.5090
C	-0.8380	-3.5719	-1.3467
O	0.0034	2.7510	-2.1547
C	0.8380	3.5719	-1.3467
H	-0.0241	-1.2486	-4.1261
H	0.0241	1.2486	-4.1261
H	0.7485	-2.3653	2.9602
H	-0.7485	2.3653	2.9602
H	0.3747	-1.1835	5.1257
H	-0.3747	1.1835	5.1257
H	-0.2458	-4.0777	-0.5834
H	-1.2942	-4.2987	-2.0229
H	-1.6227	-2.9764	-0.8660
H	1.6227	2.9764	-0.8660
H	0.2458	4.0777	-0.5834
H	1.2942	4.2987	-2.0229



Conformer 9: E = -917.52104 H; $E_{relative}$ = 2.58; Point group = C_s

O	-2.1415	0.0553	2.7485
C	-1.9803	0.1394	1.4090
C	-1.9803	0.1394	-1.4090
C	-3.1820	0.2177	0.6867
C	-0.7597	0.1763	0.7161
C	-0.7597	0.1763	-0.7161
C	-3.1820	0.2177	-0.6867
C	2.9899	-0.0710	1.3969
C	2.9899	-0.0710	-1.3969
C	1.7934	0.0990	0.6978
C	4.1748	-0.2685	0.6987
C	4.1748	-0.2685	-0.6987
C	1.7934	0.0990	-0.6978
C	0.5293	0.3345	1.4494
C	0.5293	0.3345	-1.4494
O	0.5776	0.6661	2.6235

O	0.5776	0.6661	-2.6235
C	-1.4667	-0.9512	3.4944
O	-2.1415	0.0553	-2.7485
C	-1.4667	-0.9512	-3.4944
H	-4.1100	0.2292	1.2492
H	-4.1100	0.2292	-1.2492
H	2.9727	-0.0421	2.4815
H	2.9727	-0.0421	-2.4815
H	5.1044	-0.4142	1.2410
H	5.1044	-0.4142	-1.2410
H	-0.6750	-0.5024	4.0948
H	-1.0362	-1.7091	2.8302
H	-2.2187	-1.4164	4.1370
H	-2.2187	-1.4164	-4.1370
H	-1.0362	-1.7091	-2.8302
H	-0.6750	-0.5024	-4.0948

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