SYNTHESIS OF CHIRAL CATALYSTS: STRUCTURE ENANTIOSELECTIVITY RELATIONSHIP STUDIES OF VARIOUS $(DHQD)_2PHAL$ CATALYZED HALOCYCLIZATIONS AND SYNTHESIS OF NOVEL C_2-SYMMETRIC PYRIDINE LIGANDS

By

Sarah Elizabeth Marshall

A DISSERTATION

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

Chemistry – Doctor of Philiosophy

2013

ABSTRACT

SYNTHESIS OF CHIRAL CATALYSTS:
STRUCTURE ENANTIOSELECTIVITY RELATIONSHIP STUDIES OF VARIOUS $(DHQD)_2PHAL$ CATALYZED HALOCYCLIZATIONS AND
SYNTHESIS OF NOVEL C_2-SYMMETRIC PYRIDINE LIGANDS

By

Sarah Elizabeth Marshall

The dimeric *cinchona* alkaloid catalyst, $(DQHD)_2PHAL$, used in conjunction with chlorinated hydantoins, has proven to be an efficient catalyst for enantioselective chlorocyclizations, including lactonizations and cyclizations of various amides and carbamates. In efforts to better understand the underlying mechanism(s), a number of *cinchona* alkaloid dimers have been synthesized for structure enantioselectivity relationship studies. The goals from this study were to acquire a better understanding of the structural features of $(DHQD)_2PHAL$ responsible for high enantioinduction and to search for more effective catalyst scaffolds.

Chapter 4 will unveil the design of a novel, chiral C_2-symmetric pyridine scaffold. The design of this ligand used a combination of computational and synthetic results to determine an optimal scaffold. After discovering an efficient route to access the desired scaffold as a racemate, the enantiomers were separated via fractional crystallization. Additional efforts were then placed on synthesizing a more activated analog of the catalyst scaffold by installing a 4-amino group.

To my parents, my siblings, my husband, and my teachers for always believing in me.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

KEY TO ABBREVIATIONS

Å	angstrom
[α]	specific rotation
δ	chemical shift
μW	microwave
Ac	acetyl
Alk	alkyl
AQN	anthraquinone
Ar	aryl
benzoPHAL	benzophthalazine
br	broad (spectral peak)
CD	cinchonidine
CN	cinchonine
D	day
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 ether

$(DHQ)_2PHAL$	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
DIAD	Diisopropyl diazadicarboxylate
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	minutes
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
PHATHAL	phthaloyl
PHN	phenanthroline
ppm	parts per million
PYDZ	pyridazine
QD	quinidine
QN	quinidine
R	substituent
rt	room temperature
SER	structure enantioselectivity relationship

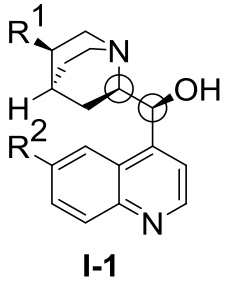
TEA	triethylamine
Tf	triflyl
$(Tf)_2O$	triflic anhydride
THF	tetrahydrofuran
*t*Bu	*tert*-butyl
TBAB	tetrabutylammonium bromide
TERE	terephthaloyl
TFE	2,2,2-trifluoroethanol
TLC	thin layer chromatography
TMEDA	Tetramethylethylenediamine

Chapter I: *Cinchona* Alkaloids - A Brief Introduction

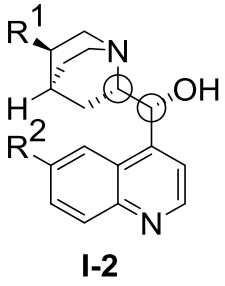
I-1 Introduction

Although there are a plethora of compounds isolated from the bark of *cinchona* trees, generally the 4 main components are cinchonine (CN), cinchonidine (CD), quinidine (QD), and quinine (QN) (Table I-1).[1] These four natural products belong to a class of compounds known as the *cinchona* alkaloids. During the last 400 years, these four alkaloids have been utilized in a variety of applications; including use as an antimalarial agent, bitter additive in the food and beverage industry and cardiac depressant. Additionally, these compounds have played a pivotal role in the field of organic chemistry, primarily being used as resolving agents or chiral catalysts for a large number and range of transformations.[2]

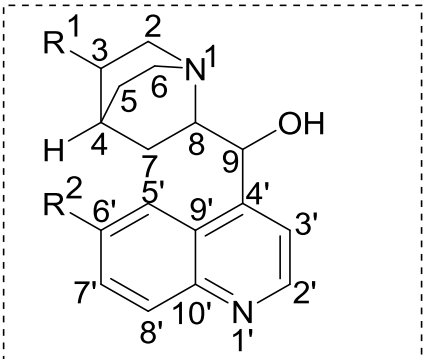
Table I-1. Eight most common *cinchona* alkaloids and general numbering system.



I-1



I-2

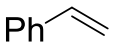
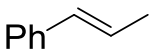
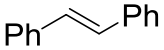


General Numbering System

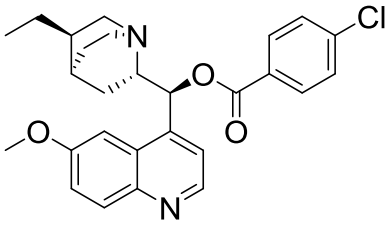
Structure **I-1**	R^1	R^2	Structure **I-2**	R^1	R^2
a Quinine	$-CH=CH_2$	-OMe	**a** Quinidine	$-CH=CH_2$	-OMe
b Cinchonidine	$-CH=CH_2$	-H	**b** Cinchonine	$-CH=CH_2$	-H
c Dihydroquinine	$-CH_2CH_3$	-OMe	**c** Dihydroquinidine	$-CH_2CH_3$	-OMe
d Dihydrocinchonidine	$-CH_2CH_3$	-H	**d** Dihydrocinchonine	$-CH_2CH_3$	-H

The structures of the eight most common *cinchona* alkaloids utilized in synthetic chemistry are depicted in Table I-1. As mentioned cinchonine (CN), cinchonidine (CD), quinidine (QD) and quinine (QN) are naturally occurring; however four other popular derivatives of these compounds are their hydrogenated analogs, which can be isolated in trace quantities from natural sources (**I-1c-d** and **I-2c-d)**. The structures of these alkaloids are centered on a chiral 1,2-aminoalcohol moiety. The quinuclidine ring

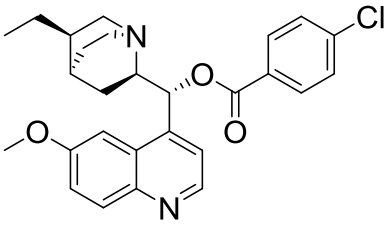
Table I-2. Example of *pseudo*-enantiomeric relationship between DHQD and DHQ derived catalysts in Sharpless Asymmetric Dihydroxylation.

Entry	Olefin	Catalyst	% *ee*	Config. of diol
1	 **I-3**	**I-6**	60	*R*
		I-7	53	*S*
2	 **I-4**	**I-6**	65	*R,R*
		I-7	55	*S,S*
3	 **I-5**	**I-6**	85	*R,R*
		I-7	78	*S,S*

catalyst:



I-6 O-*p*-chlorobenzoyl DHQD



I-7 O-*p*-chlorobenzoyl DHQ

system, containing the amino group, is connected to a quinoline ring via the C_9-carbinol. The quinoline ring system is one site of variation amongst the alkaloids, which remains unsubstituted in cinchonidine and cinchonine, but contains a methoxy-substituent in quinine and quinidine. In total, each alkaloid has 5 chiral centers: C_3, C_4, C_8, C_9, and N_1. The stereochemistry of all the alkaloids in Table I-1 is identical at C_3, C_4, and N_1, but varies at positions C_8 and C_9. Although this makes the general structures **I-1** and **I-2** diastereomeric, their behavior as chiral catalysts has revealed an enantiomeric relationship. So if quinine delivers a chiral product favoring one enantiomer, then use of quinidine will favor the formation of the other enantiomer. Generally speaking, the diastereomeric relationship between quinine and quinidine (or cinchonine and cinchonidine) is exposed by a small but consistent difference in the *ee*'s of products. For example, in the Sharpless asymmetric dihydroxylation, acylated derivatives of DHQD and DHQ were screened as catalysts. In every example, the DHQD derived catalyst gave slightly better *ee's* (Table I-2).[3] Based on consistent observation of this behavior, *cinchona* alkaloid literature refers to the relationship between general structures **I-1** and **I-2** as "pseudo" or "quasi" enantiomers.[4]

In taking a more detailed look at the basic structure of the *cinchona* alkaloids, the most prominent site of functionality is the 1,2-aminoalcohol moiety. The rigid tertiary amine provides a beautiful chiral scaffold which has been exploited in a variety of reactions.[2] These include use as chiral ligands for metals, participating in conjugate addition reactions, or serving as a chiral proton source. The alcohol moiety on the other

hand can serve as a Lewis acid, be coordinated to a metal, or can be used as a handle to derivatize the *cinchona* alkaloid unit. [2]

As mentioned previously, *cinchona* alkaloids and their derivatives are used to induce chirality in a number of transformations. In order to optimize these transformations, it is beneficial to understand two elements of the alkaloid catalyst: the conformation of the alkaloid under the reaction conditions and the role of the alkaloid in the reaction mechanism. If these two things are known, in some transformations it may be possible to design and synthesize a more efficient derivative of the *cinchona* alkaloid catalyst. Our group recently disclosed three asymmetric halocyclization reactions catalyzed by a dimeric *cinchona* alkaloid catalyst. [5-8] Although a variety of experiments were conducted, including kinetic studies and a thorough investigation of the halogen source, details pertaining to the alkaloid catalyst in the reaction were absent. Model kits were used to supplement mechanistic considerations, however the plethora of conformations possible for the alkaloid catalyst was befuddling. The remainder of this chapter will discuss what is known about the conformations of *cinchona* alkaloids and their derivatives in various reaction conditions and how structural alterations to the alkaloid can affect its conformation. The literature contains a number of detailed studies regarding the conformations of alkaloids in the gas phase, solution phase, and solid state, [4, 9, 10] but in the interest of brevity, this chapter will only address the effects that are related to our results. Chapter II will discuss these connections, along with the results from our structure enantioselectivity relationship (SER) studies for the various halocyclization reactions.

I-2 Conformations of Monomeric *Cinchona* Alkaloids and Derivatives Thereof

A number of studies pertaining to the conformations of various *cinchona* alkaloids have focused on the monomeric scaffolds.[4, 9-16] Although our SER studies featured mainly dimeric scaffolds, a brief discussion of the monomeric alkaloids is provided, to explain the fundamental concepts regarding alkaloid conformations.

In 1989, the first report examining the preferred conformation of monomeric *cinchona* alkaloids and derivatives thereof in various solvents was published. In this seminal publication, through the use of calculations and NMR studies, the rotation about the C_8 - C_9 and C_9 – $C_{4'}$ bonds was found to have the strongest influence on the alkaloid's conformation.[2, 4] With this knowledge in hand, Wynberg's group found that

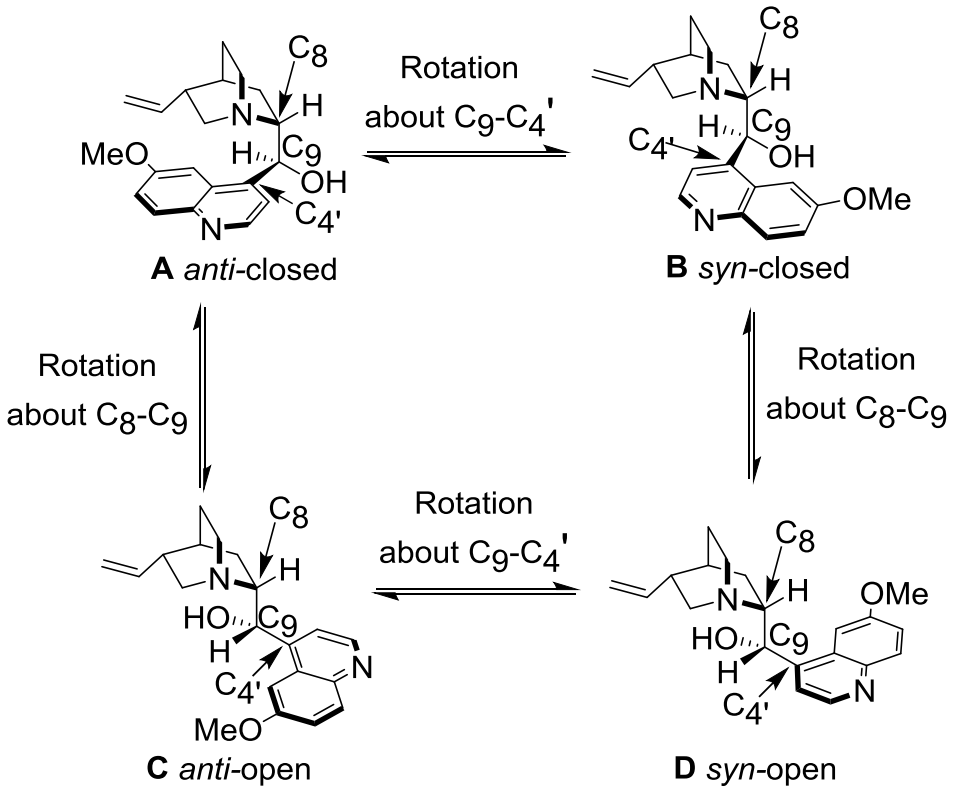
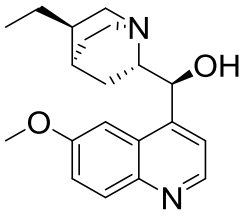


Figure I-1. Four lowest energy conformations for quinidine.

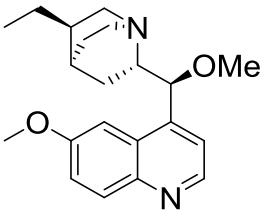
there are four minimum energy conformations for quinidine: *syn*-closed, *syn*-open, *anti*-closed, and *anti*-open (Figure I-1). The terms *anti* and *syn* refer specifically to the quinoline moiety, which could be fundamentally described as whether the bulk of the quinoline moiety is on the same side as the C_9-OH (*syn)* or pointed away from the C_9-OH (*anti).* The terms closed and open refer to the conformation resulting from rotation about the C_8 - C_9 bond. When the quinuclidine nitrogen lone pair is located over the quinoline ring, this is referred to as the closed conformation; and when the quinuclidine nitrogen lone pair is away from the quinoline ring, this is referred to as the open conformation.[4, 11]

Further analysis found that the conformation of the alkaloid was heavily influenced by the substituent on the C_9 oxygen, solvent, and protonation state of the quinuclidine nitrogen.[4, 11] To summarize the effect of the C_9-substituent, three representative compounds will be discussed: alkaloids with a C_9-OH (**I-8**), methyl (**I-9**), or acyl group (**I-10**). The conformations of each alkaloid were investigated in the following deuterated solvents: chloroform, dichloromethane, acetone, benzene, and methanol. With a free C_9-OH (**I-8**) group, the conformation was independent of solvent, with approximately 90% of the alkaloid adopting the *anti*-open conformation (**C)**. There was a small amount of flexibility about the C_9-C_4 bond, which permited rotation of the quinuclidine ring.[11] When the C_9-O was methylated (**I-9**), the conformation was found to be a mixture of both the *syn*-closed and *syn*-open conformations. Interestingly, a combination of NMR and molecular mechanics found that with more polar solvents the equilibrium shifted to favor the *syn*-open conformation, while non-coordinating solvents



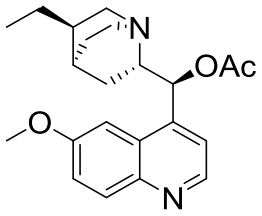
I-8 DHQD

Favors *anti*-open conformation in chloroform, dichloromethane, acetone, benzene and methanol



I-9 DHQD-Me

Both *anti*-open and *syn*-closed are favored, with polar solvents favoring *anti*-open and nonpolar solvents favoring *syn*-closed



I-10 DHQD-Ac

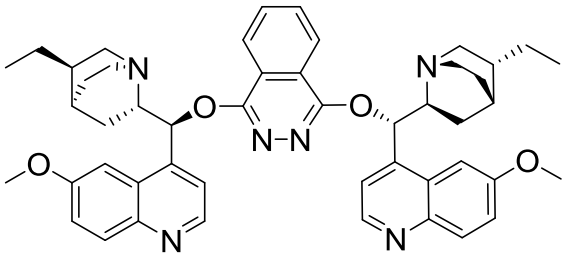
Favors *syn*-closed in chloroform, dichloromethane, acetone, and benzene, but *anti-open* conformation in methanol

Figure I-2. Four lowest energy conformations for quinidine.

slightly favored the *syn*-closed conformation.[11] When the C_9-hydroxyl was acylated (**I-10**), in all solvents except for methanol, the predominant conformation was *syn*-closed, but in methanol, the alkaloid exclusively took on the *anti*-open form.[11] The other significant influence on alkaloid conformation was the protonation of the quinuclidine nitrogen. Independent of the solvent, all the alkaloids (**I-8, I-9,** and **I-10**) adopted the *anti*-open conformation when protonated.[11, 16] Calculations (AM1) looking at the relative energies for each of the conformations with the various alkaloid derivatives is in agreement with experimental data, showing that for **I-8,** the *anti*-open conformation (**C**) is 2.0 kcal / mol more stable than the *syn*-closed (**D**), for **I-9,** the difference in energy between **C** and **D** is smaller, being approximately 0.9 kcal / mol, and for **I-10** the difference is neglible, being only 0.3 kcal / mol.[11] The stabilization acquired when the quinuclidine nitrogen interacts, via hydrogen bonding or protonation, with solvent or acid, is approximated to be 1-3 kcal / mol and requires the alkaloid to be in the an open

conformation. This offers an explanation for why the conformational preference for **I-9** and **I-10** is solvent dependent, since the energy barrier for conversion between **B** and **C** is small.[11]

Having a rudimentary understanding of basic *cinchona* alkaloid conformations in mind, we began to investigate what was known about the conformations of dimeric alkaloid catalysts. Thorough investigations regarding this class of catalysts are lacking in comparison to the extensive studies of the monomers. The dimeric alkaloid catalyst, (DHQD)q_2PHAL (**I-11**), the catalyst developed for and commonly used in the Sharpless asymmetric dihydroxylation, is the most well understood in regards to conformation.[17] Structurally, (DHQD)$_2$PHAL is a C_2-symmetric molecule, comprised of two *cinchona* alkaloid subunits which are connected by a phthalazine linker (Figure I-3). Specifically addressing the effect of the heterocyclic linker, its electron withdrawing nature causes



I-11 (DHQD)$_2$PHAL

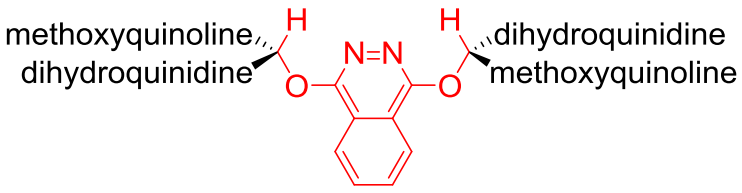
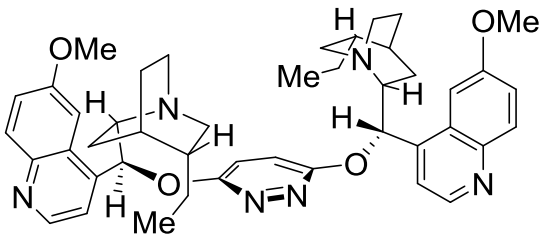


Figure I-3. Co-planar atoms (labeled in red) about phthalazine linker in (DHQD)$_2$PHAL. For interpretation of the references to color in this and al other figures, the reader is referred to the electronic version of this dissertation.

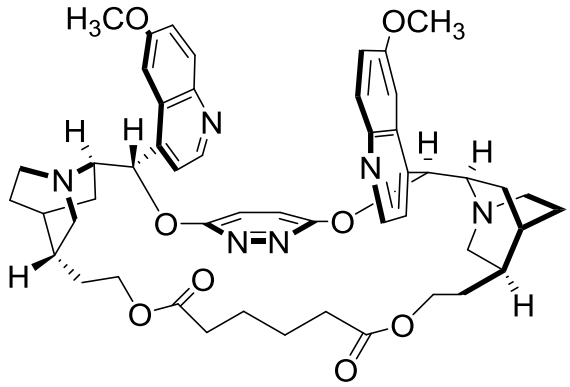
the C_9-oxygen to take on partial sp^2 character, which in turn, forces the C_9-O-C=N atoms to become co-planar. In an attempt to minimize steric interactions with the phthalazine ring, the C_9-proton adopts a co-planar arrangement with the heterocyclic linker (Figure I-3).[18, 19] A number of studies by Corey revealed that the conformation of the alkaloids under the aqueous alcoholic reaction conditions was *anti*-open.[20] One clever way this was firmly resolved was by synthesizing a rigidified pyridazine linked dimeric alkaloid catalyst (**I-13)**, which gave nearly identical *ee*'s in comparison to the simple dimeric scaffold (Table I-3).[21] It is worth noting that a similar rigidified scaffold was reported by Lohray's group, tethering the two alkaloids via an alkyl chain attached to the quinoline alkoxy group.[22]

Another dimeric scaffold warranting discussion is $(DHQD)_2AQN$ (**I-20**), a scaffold that looks similar to $(DHQD)_2PHAL$. We were interested in understanding the conformation of this scaffold because it yielded interesting results that played a pivotal role in directing our SER studies. Although there are no reports specifically discussing the conformation of this catalyst, in a roundabout way, its conformation can be inferred. In 2010, Li, *et al.* elucidated the active conformation of a different *cinchona* alkaloid catalyst, DHQD-PHN (**I-19**).[23] The interest in the conformation of this catalyst stemmed from elucidating its role in the desymmetrization of *meso* cyclic anhydrides with alcohols. Although DHQD-PHN is monomeric, when the authors used $(DHQD)_2AQN$ as a catalyst, the reaction yielded identical results.

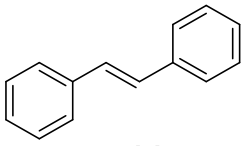
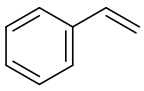
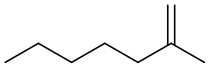
Table I-3. Corey's rigidified dimer (**I-13**) in the Sharpless asymmetric dihydroxylation reaction in comparison to $(DHQD)_2PYDZ$ (**I-12**).



I-12



I-13

Entry	Olefin	Catalyst I-11 Yield (*ee*)	Catalyst I-13 Yield (*ee*)	Catalyst I-14 Yield (*ee*)
1		**I-12**	>99	*R,R*
	 **I-14**	**I-12**	>99	*R,R*
2		**I-11**	96	*R*
	 **I-15**	**I-12**	97	*R*
3		**I-11**	62	*R,R*
	 **I-16**	**I-12**	68	*R,R*

*Reaction conditions: 1mol% catalyst, 3 equiv $K_3Fe(CN)_6$, 3 equiv of K_2CO_3, 0.1 mol% OsO_4, 1 equiv $CH_3SO_2NH_2$, *t*buOH / H_2O, 0°C.

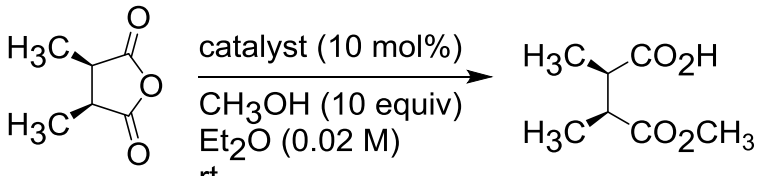
As mentioned, various C_9-substituted alkaloids are known to favor different conformations (Figure I-1) based on their energetic preference.[11] Interestingly, when Li, *et al.* conducted ^{1}H NMR studies to determine the preferred conformation for DHQD-PHN, they found that in toluene all of the conformations shown in Figure I-1 were readily adopted. The crystal structure for **I-19** is also reported, showing the alkaloid adopts an *anti*-open conformation in the crystalline state.[24] To test whether this was the active conformation of the catalyst, Li, *et al.* synthesized a rigidified scaffold (**I-21**), which was known to lock the alkaloid in an *anti*-conformation (**A *or* C**).[25] The enantioinduction was significantly lower with this scaffold than with simple DHQD-PHN, suggesting that *anti*-open was not the active conformation. Therefore a novel rigidified alkaloid inducing the *syn*-closed conformation was synthesized (**I-22**). This scaffold delivered their product in similar *ee*'s as DHQD-PHN, elucidating that the active conformation of their catalyst was **B**.[23]

The authors of this paper hypothesize that DHQD-PHN's sterically bulky phenanthryl group induces the *syn*-closed conformation.[23] Under the assumption that $(DHQD)_2AQN$ takes on the same conformation, it is possible to hypothesize that the diketones in the anthraquinone linker may create a similar sterically encumbered environment, in comparison to the less hindered phthalazine linker. It is important to note that this suggested analogy is inferred here and is not directly stated in Li, *et al.'s* publication.

The conformational flexibility of *cinchona* alkaloids makes them an interesting, complex class of catalysts. By using NMR, computations, and rigidified derivatives it is

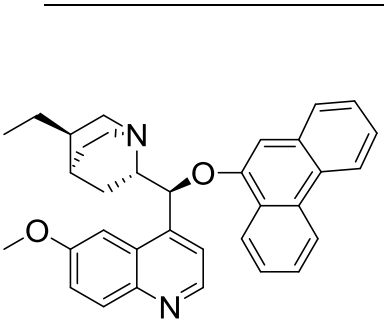
possible to gain a better understanding of the active conformation. Chapter II will discuss the SER studies from our $(DHQD)_2PHAL$ catalyzed chlorocyclization reactions, which will include discussions of the conformation of the *cinchona* alkaloid.

Table I-4. Catalyst screening in the desymmetrization of *meso*-cyclic anhydrides.

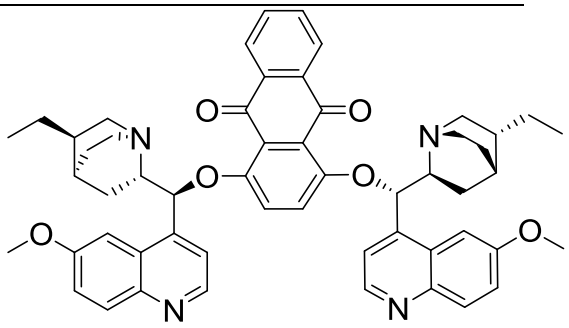


I-17 **I-18**

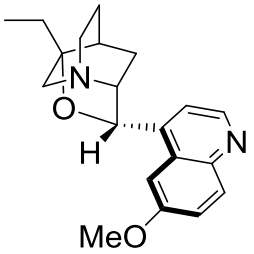
Entry	Catalyst	*ee*
1	**I-19**	96%
2	**I-20**	94%
3	**I-21**	20%
4	**I-22**	93%



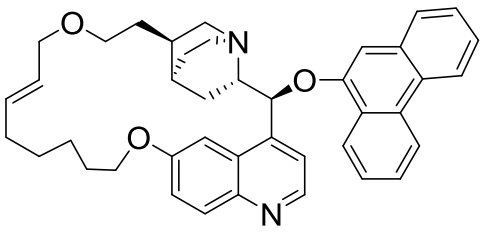
I-19 $(DHQD)_2PHN$



I-20 $(DHQD)_2AQN$



I-21 (locked in **A** and **C**)



I-22 (locked in **B**)

REFERENCES

REFERENCES

1. McCalley, D. V., *Analyst* **1990,** *115*, 1355-1358.

2. Song, C. E., *Cinchona Alkaloids in Synthesis and Catalysis*. Wiley-VCH: Wenheim, 2009; p 526.

3. Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroeder, G.; Sharpless, K. B., *J. Am. Chem. Soc.* **1988,** *110*, 1968-1970.

4. Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H.; Svendsen, J. S.; Marko, I.; Sharpless, K. B., *J. Am. Chem. Soc.* **1989,** *111*, 8069-8076.

5. Whitehead, D. C. The development of a novel asymmetric halolactonization and the investigation of peptidic ligands for osmium tetroxide mediated transformations. Michigan State University, ProQuest Dissertation and Thesis, 2009.

6. Whitehead, D. C.; Yousefi, R.; Jaganathan, A.; Borhan, B., *J. Am. Chem. Soc.* **2010,** *132*, 3298-3300.

7. Jaganathan, A.; Garzan, A.; Whitehead, D. C.; Staples, R. J.; Borhan, B., *Angew. Chem. Int. Ed.* **2011,** *50*, 2593-2596.

8. Garzan, A. Asymmetric Electrophilic Halocyclization Reactions. Michigan State University, East Lansing, Michigan, 2012.

9. Marcelli, T., *Wiley Interdisciplinary Reviews: Computational Molecular Science* **2011,** *1*, 142-152.

10. Busygin, I.; Nieminen, V.; Taskinen, A.; Sinkkonen, J.; Toukoniitty, E.; Sillanpää, R.; Murzin, D. Y.; Leino, R., *The Journal of Organic Chemistry* **2008,** *73*, 6559-6569.

11. Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H., *The Journal of Organic Chemistry* **1990,** *55*, 6121-6131.

12. Oleksyn, B. J.; Suszko-Purzycka, A.; Dive, G.; Lamotte-Brasseur, J., *J. Pharm. Sci.* **1992,** *81*, 122-127.

13. Thiel, J.; Fiedorow, P., *J. Mol. Struct.* **1997,** *405*, 219-230.

14. Bürgi, T.; Baiker, A., *J. Am. Chem. Soc.* **1998,** *120*, 12920-12926.

15. Caner, H.; Biedermann, P. U.; Agranat, I., *Chirality* **2003,** *15*, 637-645.

16. Olsen, R. A.; Borchardt, D.; Mink, L.; Agarwal, A.; Mueller, L. J.; Zaera, F., *J. Am. Chem. Soc.* **2006,** *128*, 15594-15595.

17. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M., *The Journal of Organic Chemistry* **1992,** *57*, 2768-2771.

18. Bruckner, R., *Organic Mechanisms: Reactions, Stereochemistry and Synthesis*. Springer: 2010.

19. Corey, E. J.; Noe, M. C.; Sarshar, S., *Tetrahedron Lett.* **1994,** *35*, 2861-2864.

20. Corey, E. J.; Noe, M. C.; Sarshar, S., *J. Am. Chem. Soc.* **1993,** *115*, 3828-3829.

21. Corey, E. J.; Noe, M. C., *J. Am. Chem. Soc.* **1993,** *115*, 12579-12580.

22. Lohray, B. B.; Singh, S. K.; Bhushan, V., *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2002,** *41B*, 1226-1233.

23. Li, H.; Liu, X.; Wu, F.; Tang, L.; Deng, L., *Proceedings of the National Academy of Sciences* **2010,** *107*, 20625-20629.

24. Amberg, W.; Bennani, Y. L.; Chadha, R. K.; Crispino, G. A.; Davis, W. D.; Hartung, J.; Jeong, K. S.; Ogino, Y.; Shibata, T.; Sharpless, K. B., *The Journal of Organic Chemistry* **1993,** *58*, 844-849.

25. Braje, W.; Frackenpohl, J.; Langer, P.; Hoffmann, H. M. R., *Tetrahedron* **1998,** *54*, 3495-3512.

Chapter II: Structure Enantioselectivity Relationship Studies of Various $(DHQD)_2PHAL$ Catalyzed Halocyclizations

II-1 Introduction

Transformations centered on asymmetric halogenations are becoming increasingly prevalent in the literature.[1-3] Although the fundamental principle in these reactions is the delivery of a halenium to an alkene, the array of nucleophiles which which can react with the resulting intermediate is diverse. This class of reactions encompasses a variety of different methodologies; including halocyclizations,[1] semi-Pinacol rearrangements,[4, 5] and dihalogenations.[6] The acquired functionality from this class of reactions is complementary to asymmetric methodologies which are staples in the field of synthetic organic chemistry, including the asymmetric dihydroxylations,[7] epoxidations,[8-10] and aminohydroxylations.[11]

II-2 Unique Reactivities of Halogens

This chapter will begin by addressing the mechanistic challenges that must be overcome with the various halogens during an asymmetric halogenation. In looking at various asymmetric halogenations in the literature, one notable, but often overlooked difference is the halogen utilized in the reaction. Generally speaking, the identity of the halogen is key to the success of the asymmetric reaction, meaning that it is not possible to substitute one halogen for another in most of these methodologies. This selectivity is the result of the unique reactivity of each of the halogens.

Classically the reaction of an olefin with an electrophilic halogen species is believed to go through a halonium intermediate, which then undergoes attack by a

nucleophile. This halonium species can exist in two forms, being either a bridged 3-membered ring (**II-2**) or an open ion form (**II-3**), bearing a carbocation at the more substituted carbon and the halogen on the other. The halogen used in the reaction as well as the substitution pattern of the alkene dictates which intermediate is favored by equilibrium. Although the substitution pattern of the olefin does have an effect, generally speaking the larger halogens, bromine and iodine, tend to favor the cyclic halonium intermediate; whereas chlorine and fluorine tend to favor the open ion form (Figure II-1).[12] The reason for the observed selectivity can be traced back to the relative electronegativities of the halogens. Since fluorine and chlorine are more electronegative, equilibrium favors the open ion form where the carbon bears the positive charge and the halogen is neutral.[13]

Simply delivering a halenium to an alkene in an enantioselective manner does not ensure that the product will be obtained in high stereoselectivity. Each of the halonium intermediates described above has challenges to overcome. For fluorine and chlorine, typically proceeding via the open ion form, the concern is bond rotation causing racemization at the carbon bearing the positive charge. If this rotation is

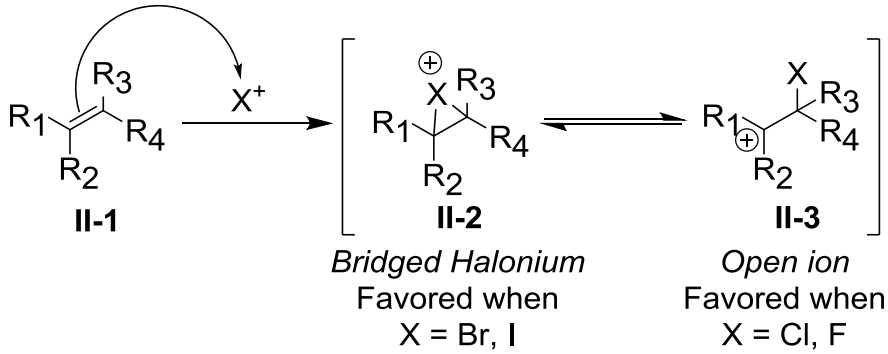


Figure II-1. Formation of the two possible halonium intermediates.

permitted, then the configurational memory of the stereochemistry at this carbon will be lost. With bromine and iodine the concern is a process known as olefin to olefin transfer (Figure II-2), during which the unreacted olefinic starting materials intercept the halogen from the intermediate halonium species. If the transfer of the halonium proceeds in the absence of the chiral catalyst, then this transfer could lead to racemization. Alternatively, it is possible for other nucleophiles in solution to behave in a similar way, removing the electrophilic halogen and regenerating the starting material. This process is a challenge that must be overcome when using bromine and iodine in catalytic asymmetric halogenations, fundamentally because throughout most of the reaction course, the large excess of starting olefinic residue will be competing for the intermediate halonium species. More specifically, once the chiral catalyst delivers the halogen to the alkene enantioselectively, if the intermediate chiral halonium undergoes the process of olefin to olefin transfer, it can result in loss of chirality and ultimately lead to formation of racemic products.[13]

One last variable in terms of reactivity observed in the halogen series is their "hotness." This term describes how reactive the halogen is towards olefins, with iodine typically being regarded as the most reactive and fluorine as the least. This reactivity is

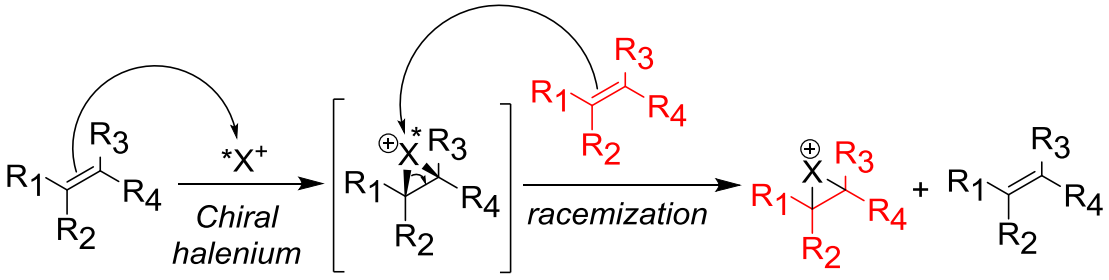
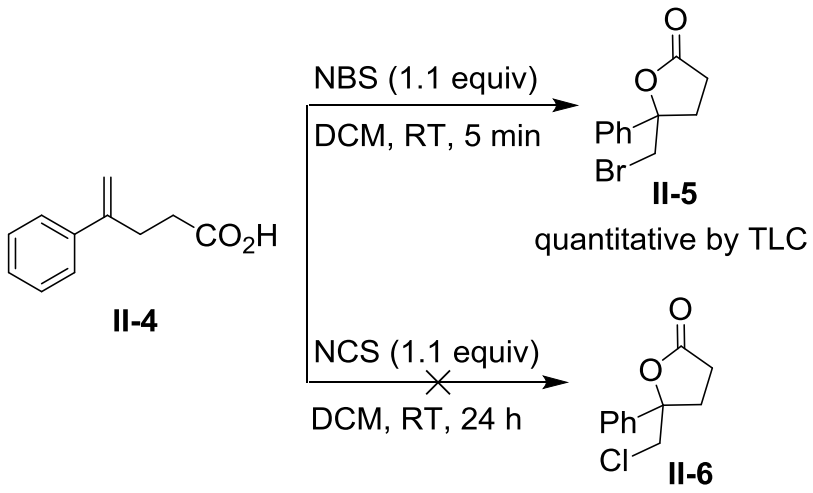


Figure II-2. Olefin to olefin racemization process.



Scheme II-1. Uncatalyzed bromolactonization versus chlorolactonization.

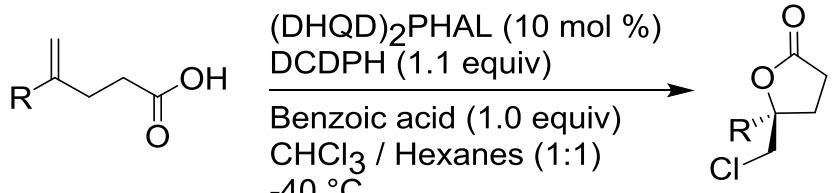
very important to account for because ideally the uncatalyzed reaction should be very sluggish. If the uncatalyzed reaction, also known as the background reaction, is relatively fast, then the catalyzed reaction will be competing with it, leading to reduced overall stereoselectivity. For example, it was observed by Whitehead *et al.* during optimization of a halolactonization reaction that with NBS, the uncatalyzed reaction was done at room temperature in 5 minutes, whereas with NCS, there was no detectable reaction even after 24 hours (Scheme II-1).[14] The presence of a chiral catalyst in the reaction with bromine, does not result in high *ee's* since there was a competitive background reaction. However with chlorine, any product formed had to arise via a pathway involving the catalyst and therefore it is possible to determine the catalyst's effect on enantio-induction.

II-3 Overview of $(DHQD)_2PHAL$ Catalyzed Asymmetric Chlorolactonization

In 2010, the Borhan laboratory published the first example of a synthetically useful catalytic, asymmetric halolactonization. In this methodology, 4-substituted-4-

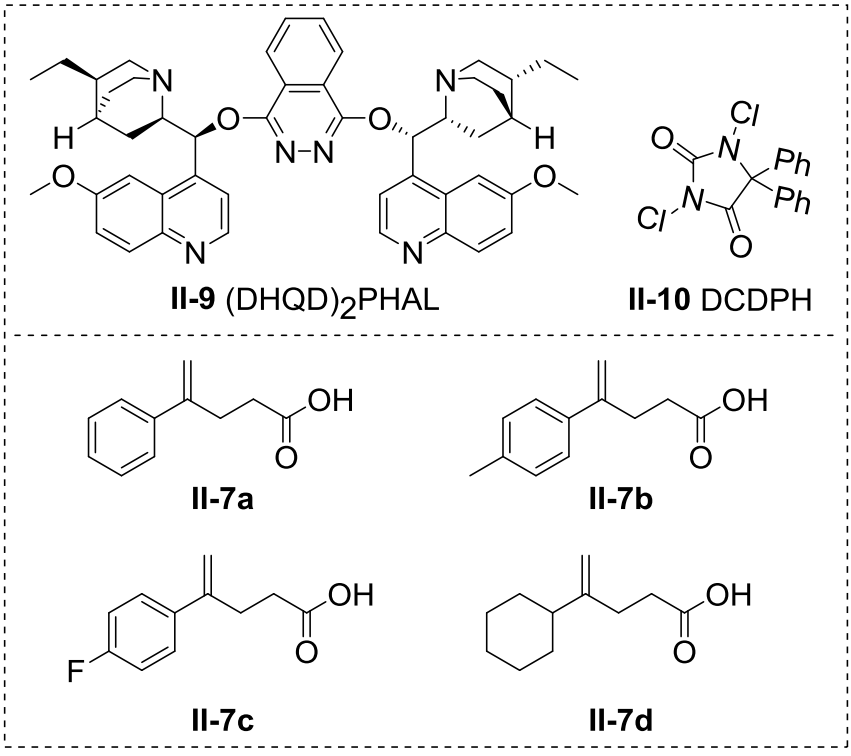
pentenoic acids are cyclized to the corresponding chlorolactones using 1,3-dichloro-5,5-diphenylhydantoin (DCDPH) (**II-10**) as the chlorinating agent and commercially available $(DHQD)_2PHAL$ (**II-9**) as the catalyst (Table II-1). Both the yields and enantioselectivities

Table II-1. Substrate scope for asymmetric chlorolactonization.



II-7a-d **II-8a-d**

Entry	Substrate	Time (min)	Yield	*% ee*
1	**II-7a**	30	86	89
2	**II-7b**	30	86	80
3	**II-7c**	30	81	89
4	**II-7d**	180	55	43

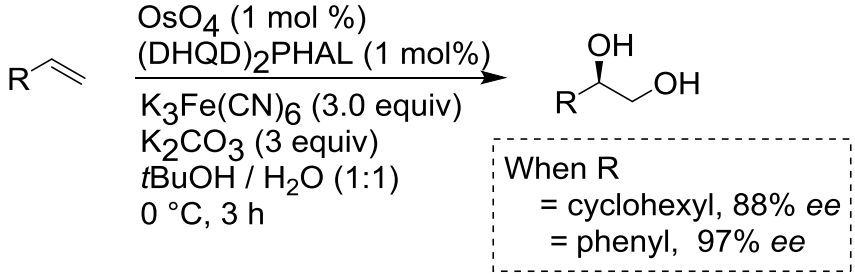


II-9 $(DHQD)_2PHAL$ **II-10** DCDPH

II-7a **II-7b**

II-7c **II-7d**

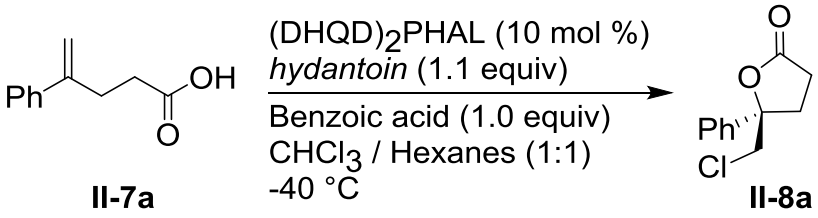
obtained in this reaction are good; however substrate scope is a limitation. The olefin tolerates a variety of aryl substituents (Table II-1, entries 1-3); but a marked drop in enantioselectivity is observed when this substituent is alkyl (Table II-1, entry 4).[15] The observed drop in *ee* in going from an aryl to an alkyl substituent on the double bond is reminiscent of the results obtained with the same catalyst scaffold in the Sharpless asymmetric dihydroxylation (Scheme II-2). Sharpless attributed the better results for aromatic olefins to π-π stacking interactions between the phthalazine of the catalyst and the substrate's aromatic substituent.[16] In our methodology however, an alternate proposal pertaining to the electronic stabilization of the transition state is possible, with an aryl substituent providing more stabilization of the open ion intermediate. In efforts to expand the scope and improve the robustness of this organocatalytic system, our group turned to mechanistic studies. To date, the underlying mechanism of this reaction has been extensively investigated by performing kinetic[17] and deuterium labeling studies,[18] in conjunction with a thorough examination of structural variations in both the chlorinating agent[19] and catalyst. This chapter will unveil the results from the studies pertaining to variations in the catalyst structure.



Scheme II-2. Comparison of aromatic versus alkyl substituent results using Sharpless asymmetric dihydroxylation.

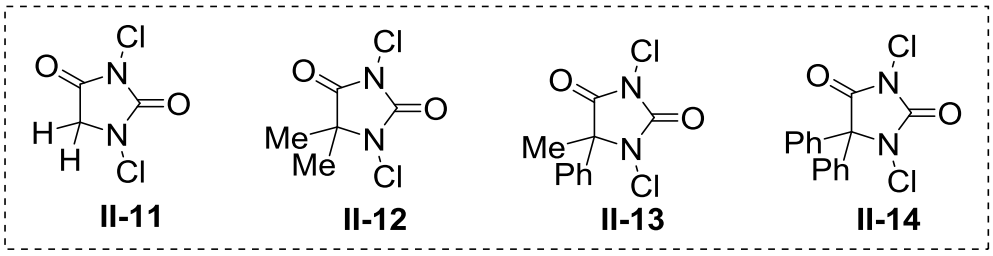
Preliminary thoughts that the hydantoin was simply transferring the chlorenium to the catalyst were ruled out during a number of early studies. It was first alluded to during optimization studies when structural variation in the chlorinating agent was found to affect the *ee,* with increased sterics leading to increased *ee*'s (Table II-2). Later, a ^{1}H NMR study using unsubstituted dichlorohydantoin **II-11** revealed that the two hydantoin protons resolved into an AB quartet in the presence of a stoichiometric amount of the $(DHQD)_2PHAL$ (Scheme II-3). Additionally, detailed studies unveiled a matched / mismatched case with respect to the catalyst chirality when chiral hydantoins were used

Table II-2. Effect of varying sterics in hydantoin structure.



II-7a **II-8a**

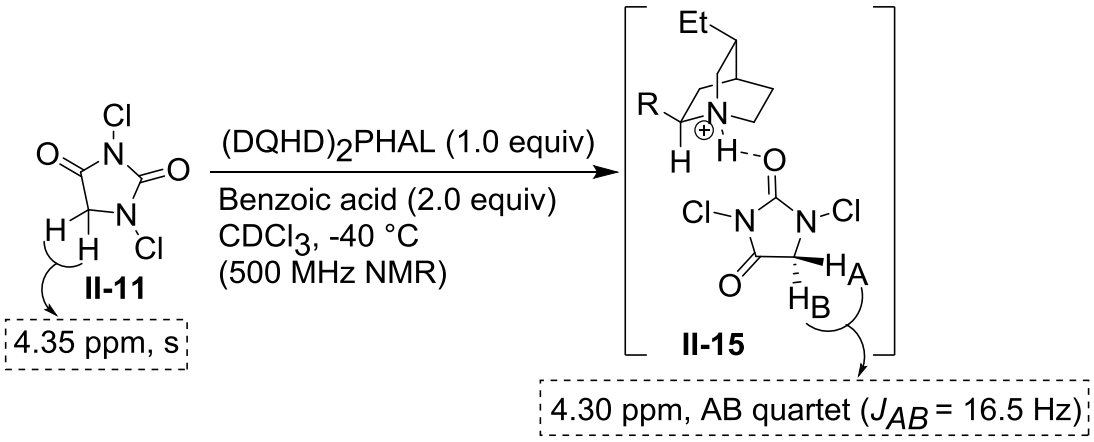
Entry	Hydantoin	Yield	% ee
1	**II-11**	76	81
2	**II-12**	87	84
3	**II-13**	82	85
4	**II-14**	81	89



II-11 **II-12** **II-13** **II-14**

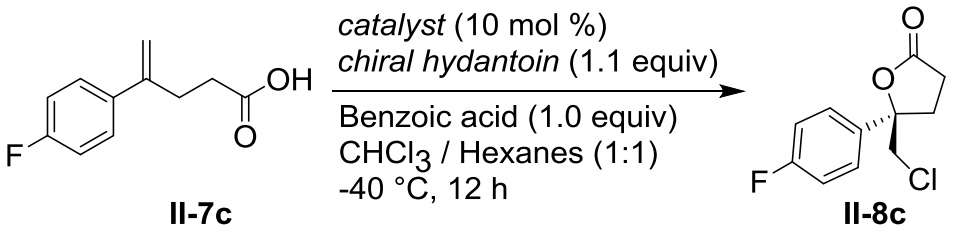
(Table II-3).[19] It was found that chiral hydantoin **II-16** delivered higher *ee's* when used with $(DHQD)_2PHAL$, in comparison to when the catalyst's pseudo enantiomer, $(DHQ)_2PHAL$ was used. The opposite selectively was observed when the other enantiomer of hydantoin, **II-17**, was used. All of these results corroborated that the source of the chiral halenium in this organocatalytic system involves an association between the chiral catalyst and hydantoin; however the mode of association between them was not clear. Since the optimized reaction conditions included one equivalent of benzoic acid in addition to one equivalent of acid starting material, it was assumed that both of the quinuclidine nitrogens of the C_2-symmetric catalyst should be protonated. Based on this idea, it is reasonable to propose that the associative complex could be based on a hydrogen bond between a protonated quinuclidine and the more electron rich carbonyl of the hydantoin (**II-15**).

It is important to mention one more pertinent discovery regarding the mechanism of the chlorolactonization reaction. In the products from the lactonization reaction, there



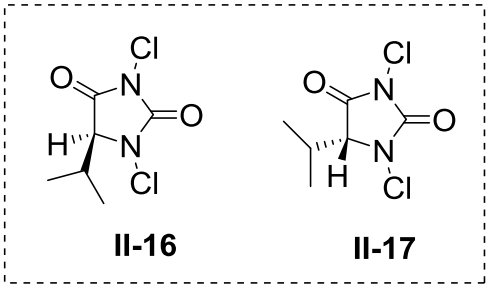
Scheme II-3. ^1H NMR studies suggesting an associative complex between catalyst and hydantoin.

Table II-3. Matched / mismatched case observed with chiral hydantoins.



II-7c **II-8c**

Entry	Hydantoin	Catalyst	Yield	% ee
1	**II-16**	$(DHQD)_2PHAL$	78	83
2	**II-17**	$(DHQD)_2PHAL$	44	69
3	**II-16**	$(DHQ)_2PHAL$	30	-55
4	**II-17**	$(DHQ)_2PHAL$	65	-62



II-16 **II-17**

is only 1 chiral center (**II-8a-d**). However an important question to address is whether the chlorenium delivery is asymmetric, or is it simply the attack of the nucleophile that proceeds asymmetrically? By doing deuterium labeling studies, Yousefi *et al.* was able to prove that both the delivery of the halenium and the attack of the nucleophile are highly enantioselective.[17] One other very interesting result from this study concerns the relative stereochemistry of the chlorine and nucleophile, which were surprisingly found to be *syn.* Ultimately from this study, they concluded that chlorination of the olefin and attack of the carboxylate nucleophile occurred independently of each other. This points to an asymmetric chlorenium delivery, equilibration favoring the open ion halonium

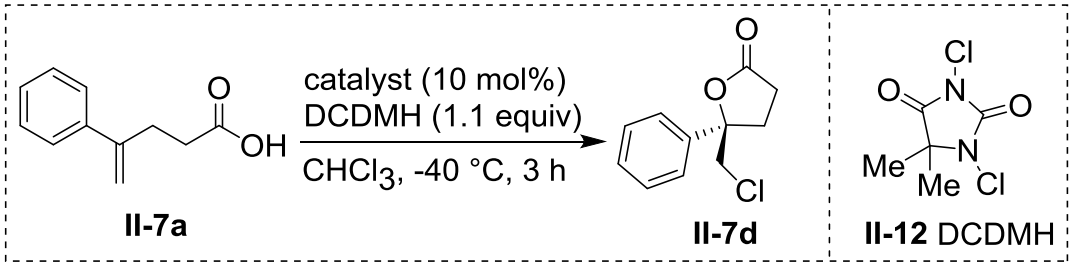
intermediate, and either stabilization of the carbocation via interaction with the catalyst or control of the closure geometry.[18]

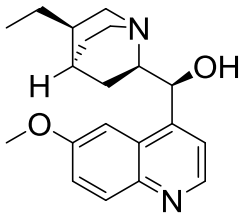
All of these results support the existence of a catalyst / hydantoin / substrate complex. Since detailed studies regarding the chlorinating agent had been carried out, a detailed study focusing on the catalyst structure would be complimentary. We therefore decided to conduct thorough structure enantioselectivity relationship (SER) studies in efforts to acquire a better understanding of the essential moieties of the catalyst.

II-4 Introduction to Structure Enantioselectivity Relationship Studies

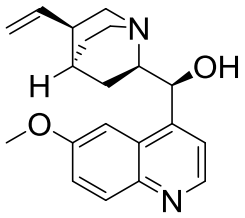
Early on in the development of the asymmetric chlorolactonization, several commercially available *cinchona* alkaloid based scaffolds were screened, including simple alkaloid monomers, monomeric derivatives and also a variety of dimers.[14] The conclusions from this study were indicative of the reaction's sensitivity to variations in the catalyst structure. It is pertinent to keep in mind that under these unoptimized conditions, $(DHQD)_2PHAL$ gives 83% *ee.* The monomers, dihydroquinidine (DHQD), quinidine (QD), quinine (QN), and cinchonidine (CD) all gave marginal stereoselectivites, with *ee*'s ranging from -14 to 22 %. Next, commercially available monomeric catalyst derivatives were screened, all of which were in the same nominal range. Two things to consider when comparing the results in Scheme II-4 are whether a change in the conformation of the alkaloid is leading to a decrease in *ee* or whether the structural changes are altering the reaction mechanism, for example perhaps the aryl linker in $(DHQD)_2PHAL$ could be π-stacking with the acid substrate. This links us

back to Chapter 1, which discussed how the substituent on the C_9-O affected the preferred conformation of the alkaloid, with simple DHQD favoring the *anti*-open conformation in all solvents and the electron withdrawing acyl group having preference for the *syn*-closed conformation in chloroform. Based on the results from the monomers and monomeric derivatives shown in Scheme II-4, the conformation does not seem to have a significant role in delivering high steroselectivities. This conclusion was drawn by comparing DHQD (**II-18),** DHQD-CLB **(II-23),** and DHQD-PHN (**II-24).** The conformations of these alkaloids have been studied and are known to prefer the *anti*-open, *syn*-closed, and *syn*-closed, respectively.[20, 21] Although preliminary, none of these scaffolds, having various conformations, gave significant increase in *ee*, suggesting that the success of $(DHQD)_2PHAL$ is not based solely on the alkaloid's conformation. Mechanistically this is stimulating, begging the question of whether the second alkaloid in $(DHQD)_2PHAL$ is serving purely as a steric wall, or if both alkaloid units have a unique role. The last set of catalysts screened during the development of this reaction were commercially available dimers, with clearly the most satisfying result being that of $(DHQD)_2PHAL$ and its *pseudo*-enantiomer $(DHQ)_2PHAL$, giving 83% and -77% *ee* respectively. The drop observed in going from $(DHQD)_2PHAL$ to $(DHQ)_2PHAL$ is not surprising, since they are diastereomeric in relationship. In using $(DHQ)_2PYR$, the observed drop is most likely attributable to the significant overall conformational changes induced by the pyrimidinyl linker, whereby the alkaloids are *meta* to each other. A somewhat unexpected result is the stark difference between $(DHQ)_2PHAL$ and $(DHQ)_2AQN$, giving a difference of 65% *ee.* An initial comparison of these two scaffolds

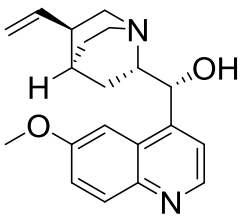




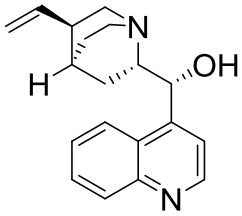
II-18 dihydroquinidine (DHQD)
-14% *ee*



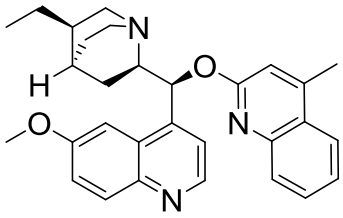
II-19 quinidine (QD)
0% *ee*



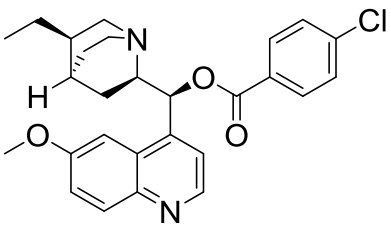
II-20 quinine (QN)
0% *ee*



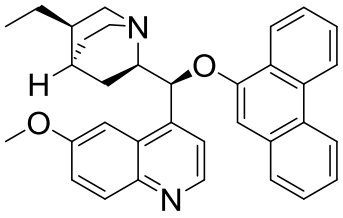
II-21 cinchonidine (CD)
22% *ee*



II-22 DHQD-MEQ
17% *ee*



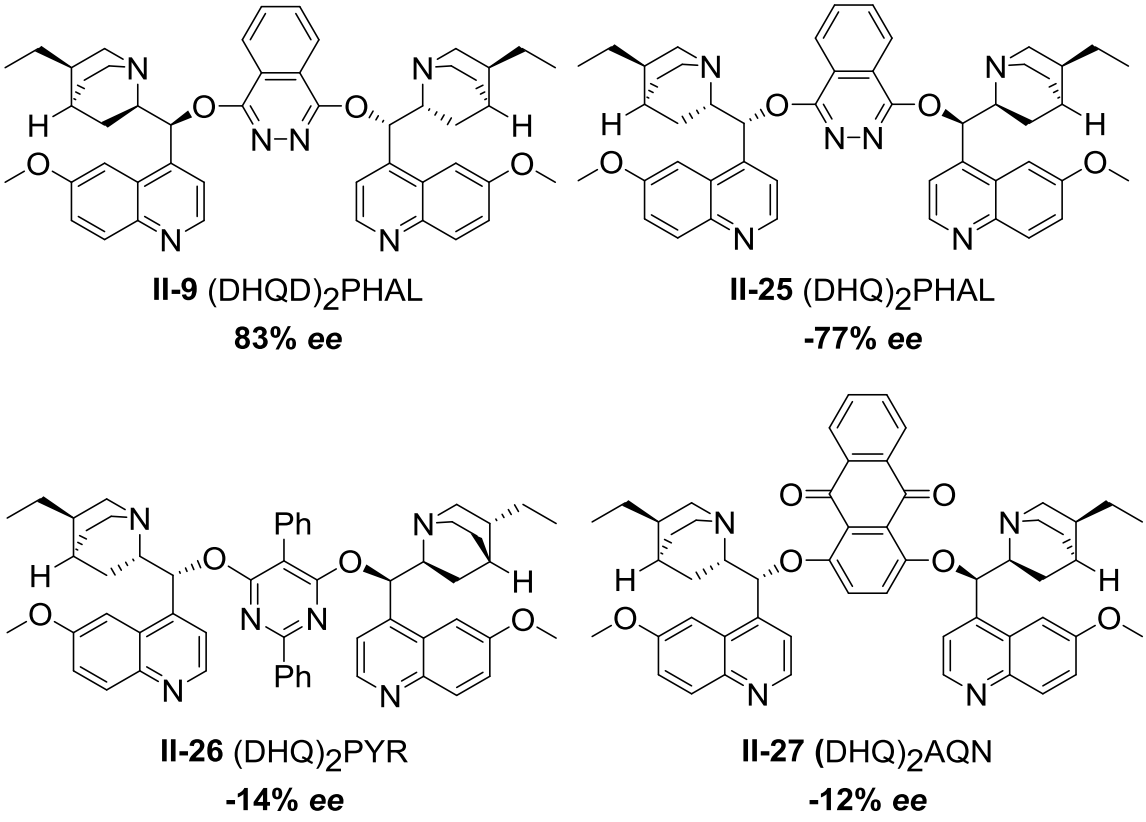
II-23 DHQD-CLB
17% *ee*



II-24 DHQD-PHN
3% *ee*

Scheme II-4. Preliminary *cinchona* alkaloid screening results for asymmetric chlorolactonization.

**The conditions used in this preliminary screening are not the optimized conditions.*



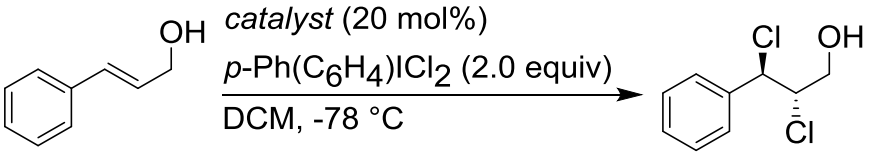
Scheme II-4 (cont'd). Preliminary *cinchona* alkaloid screening results for asymmetric chlorolactonization.

shows that they are very similar, both having a 1,4-substituted aryl linker and with the same alkaloid units attached. The most obvious difference between these two scaffolds, however, is the two nitrogens in the PHAL linker which are absent in AQN, which in turn has two carbonyl sites not present in the PHAL linker. This started to arouse questions regarding the role of the two nitrogens in the phthalazine linker in the catalyst of our asymmetric chlorolactonization methodology. Was the nitrogen in the catalyst serving a mechanistic role, or changing the conformation of the alkaloid? It is important to point out that all of these scaffolds catalyzed the reaction, since the background reaction at this temperature is negligible. Therefore, the resulting *ee*'s are

all the more intriguing since these chiral molecules had a role in the reaction but did not induce enantioselectivity, providing a very subtle hint in regards to the mechanism.

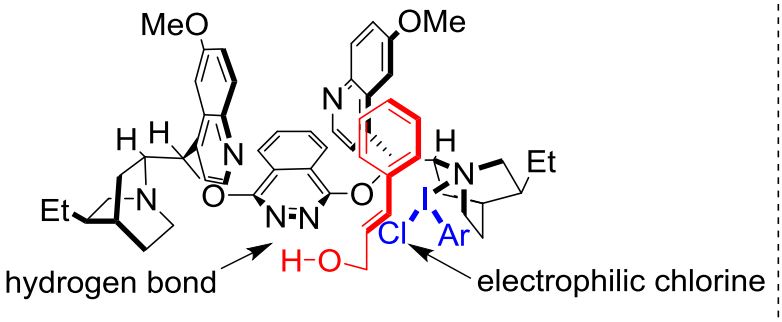
At this time, it is important to mention a strikingly similar observation from the asymmetric dichlorination of allylic alcohols methodology recently reported by Nicolaou.[6] In this methodology, a chlorinated hypervalent iodine species, used in conjunction with $(DHQ)_2PHAL$, stereoselectively generates the *anti*-dichloride product in decent yields (32-90%) and moderate to good *ee*'s (25-81%) (Table II-4). The interesting aspect of this reaction is that when the catalyst was changed from

Table II-4. Asymmetric dichlorination methodology and proposed model for stereoinduction.



II-28 **II-29**

Entry	Catalyst	% ee
1	$(DHQD)_2PHAL$	85
2	$(DHQ)_2AQN$	-10



Proposed stereoinduction model

$(DHQ)_2PHAL$ to $(DHQ)_2AQN$, the *ee* dropped from 85% to -10%, similar to the 77 to -12 % *ee* drop seen in Scheme II-4. The authors postulate that the observed stereospecificity could be based on the allylic alcohol of the substrate hydrogen bonding with the phthalazine nitrogens of the catalyst (Table II-4). They suggest that the chlorenium is delivered enantioselectively by the hypervalent iodine which is bound to one of the quinuclidine nitrogens. Although this mechanism is purely speculative, it resembles our observation with $(DHQ)_2PHAL$ and $(DHQ)_2AQN$. One cannot rule out that the mechanism of our chlorolactonization and this dichlorination mechanism are similar. This creates another possible mechanistic proposal for our reaction, where the carboxylic acid of the substrate is hydrogen bonded to the catalyst's phthalazine nitrogens.

The conclusion from all of these studies and observations is that the structure of the catalyst has a significant effect on the enantioselectivities in the asymmetric chlorolactonization methodology. In efforts to acquire a better understanding of the mechanism, specifically regarding the catalyst and also to search for better catalyst scaffolds, we began the SER studies of $(DHQD)_2PHAL$ in the asymmetric chlorolactonization reaction.

II-5 Structure Enantioselectivity Relationship Studies of the Asymmetric Chlorolactonization Reaction

The term SER was coined by Sharpless and co-workers during the development of the Sharpless asymmetric dihydroxylation.[22] This type of study involves the synthesis of a variety of catalysts, which can then be screened in the desired reaction.

Based on the *ee* of the product, conclusions about the mechanism or predictions of more potent catalyst structures can be made. Since our understanding of the catalyst's role in the asymmetric chlorolactonization was deficient, we hoped that this study would help us attain a firmer grasp of the essential structural aspects of the catalyst responsible for the delivery of high enantioselectivity. This chapter will discuss the results obtained from catalyst screening, with the details regarding the synthesis of these catalyst scaffolds being disclosed in Chapter 3.

All catalyst screening reactions were carried out using 0.026 mmol of substrate (~5 mg) and 0.003 mmol catalyst (~1-3 mg). This approach was taken since many of the acquired catalysts were obtained in milligram quantities. The products were purified via a plug of silica gel in a pipette column. Determination of the isolated yields from these reactions was not feasible based on the small scale; however TLC analysis indicated that all reactions went to completion before work-up.

During this study approximately 25 catalyst analogs were screened. Fundamentally, these analogs can be classified into 5 categories, regarding their site of variation. These 5 categories include changes to: the linker, the sterics of the quinoline substituent, the sterics of the quinuclidine substituent, the quinuclidine nitrogens, and the stereochemistry of the C_9-carbinol center. Each of these variations will be discussed in detail as the chapter unfolds, however a brief summary of the questions we were hoping to find answers to can be found in Figure II-3.

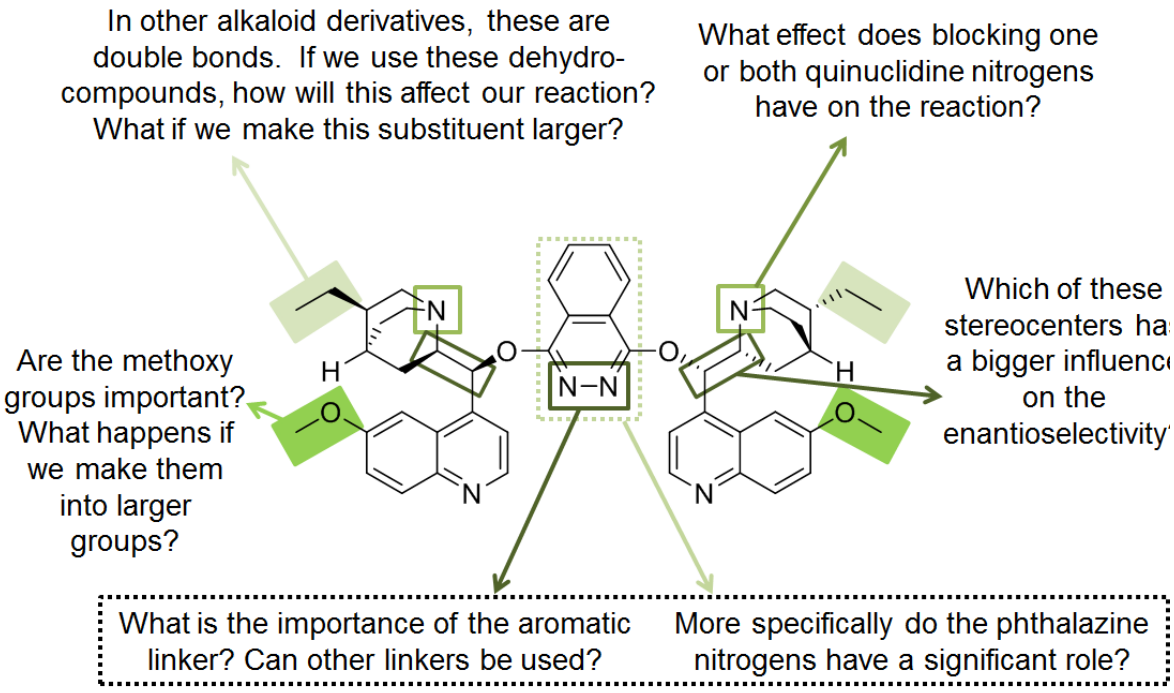
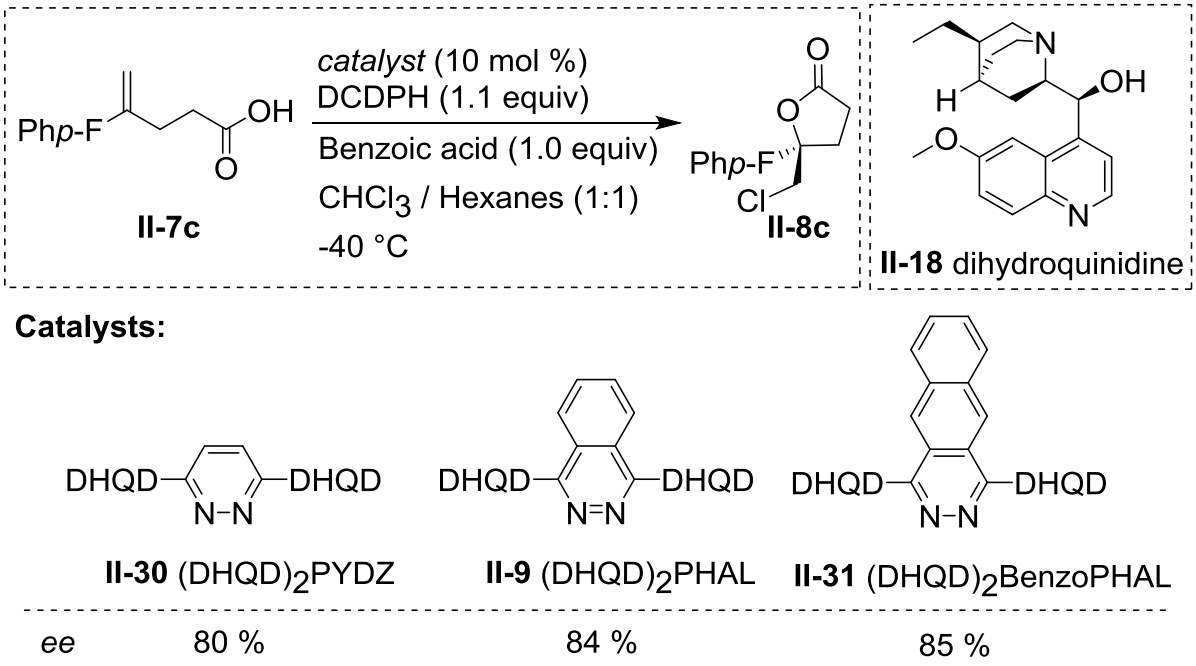


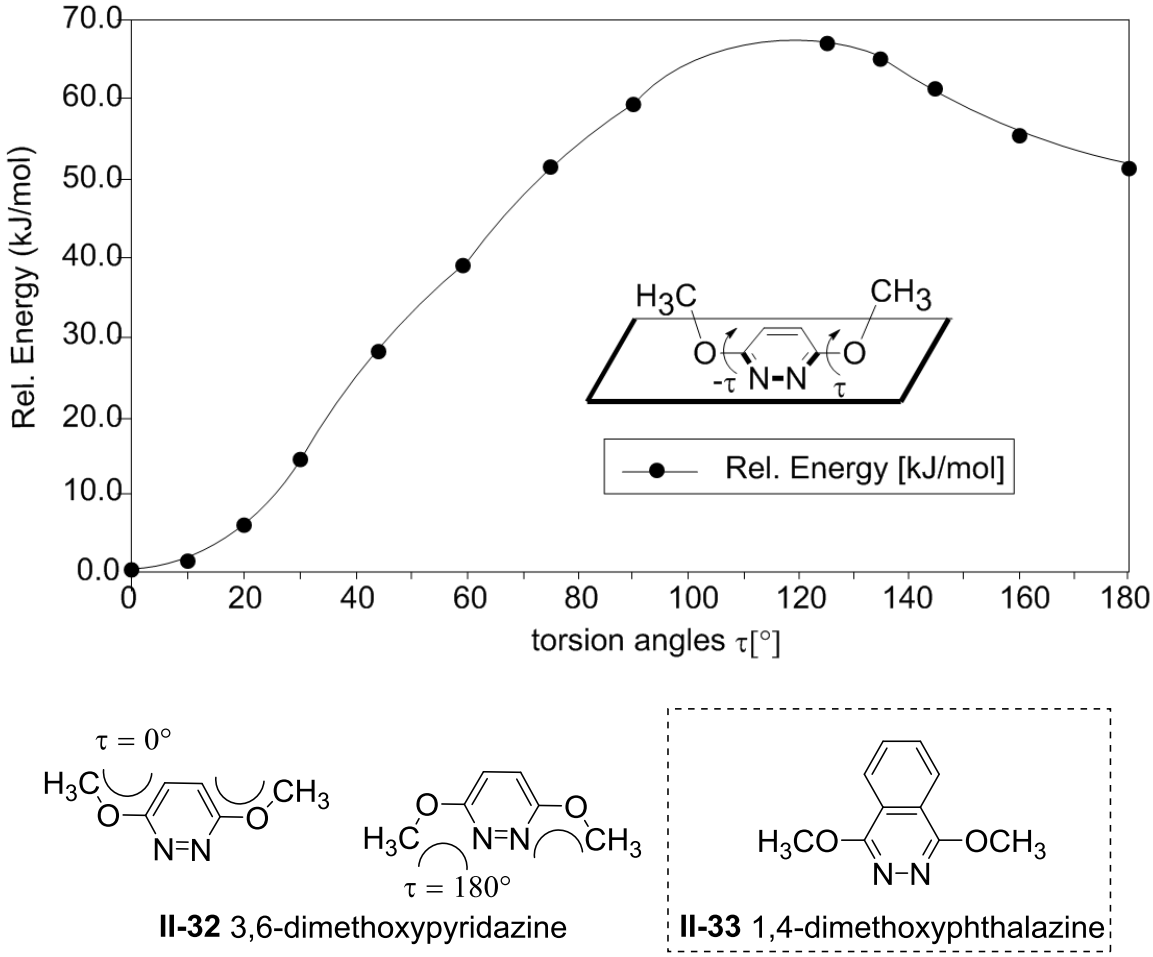
Figure II-3. Questions we set out to answer during our SER studies.

We began our studies by screening the systematic variations of the phthalazine linker, pyridazine and benzophthalazine. These two dimeric DHQD scaffolds linked by 2,6-pyridazine (PYDZ) (**II-30)** and 1,4-benzophthalazine (**II-31**) gave 80% *and* 85% *ee* respectively. In comparison with $(DHQD)_2PHAL$, which gave 84% *ee,* the slight drop observed with the PYDZ linker in conjunction with the slight increase with the 1,4-benzophalazine linker could be attributed to the conformational rigidity of the catalyst, specifically regarding the torsional angle about the alkaloid carbinol – oxygen – aryl linker bonds. In a computational study involving a truncated scaffold, 3,6-dimethoxypyridazine, Sharpless found that the preferred torsion angle about the CH_3-O-C=N bonds had the lone pairs of the oxygen pointing opposite the lone pair of the



Scheme II-5. Systematic catalyst variations of phthalazine linker.

nitrogen, with the calculated plot of energy versus torsion angle being shown in Figure II-4. Although no details were provided, they state that the same trend was observed for 1,4-dimethoxy phthalazine, being nearly identical from 0° to 60°, however at angles greater than 60° a significant increase in energy was observed. This calculation could indicate that the active conformation of the catalyst in our mechanism has the lone pair of the aromatic linker nitrogen pointed in the opposite direction as that of the carbinol oxygen. By introducing a larger aromatic linker, from pyridazine, to phthalazine, to benzophthalazine, the optimal conformation could be more rigidified, leading to stronger enantioinduction.



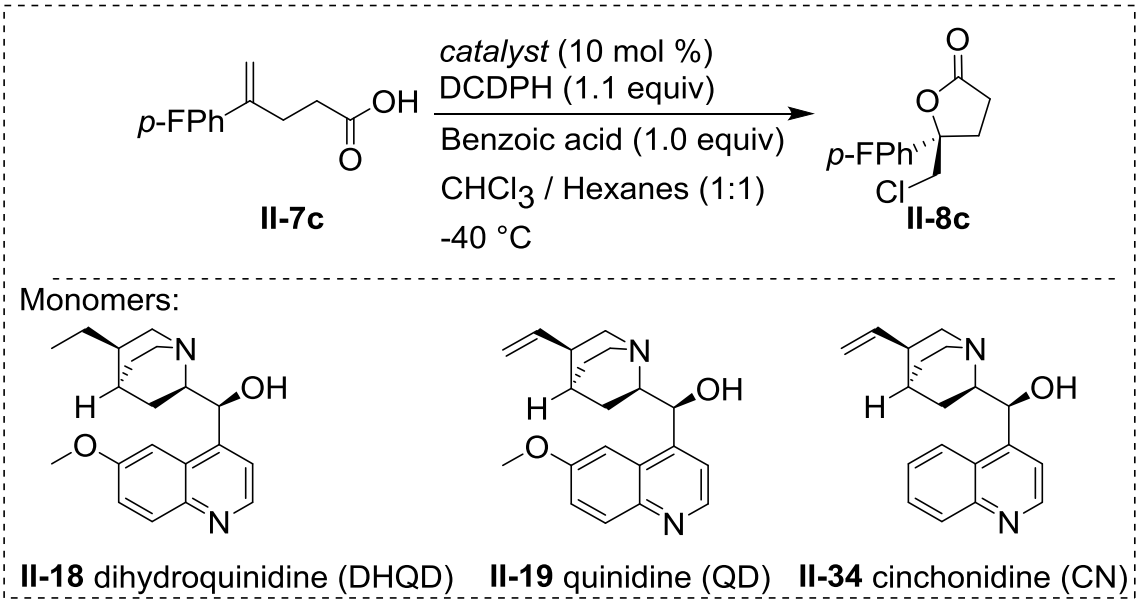
II-32 3,6-dimethoxypyridazine

II-33 1,4-dimethoxyphthalazine

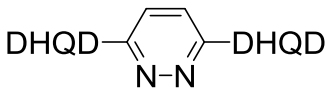
Figure II-4. Torsional angle versus energy plot of rotation about 3,6-dimethoxypyridazine CH_3-O-C=N.

Reprinted from Becker, H.; *et al.*[23]

Next we chose to synthesize PYDZ dimeric catalysts containing the various commercially available *cinchona* alkaloids monomers. Initially we looked at the series: $(DHQD)_2PYDZ$, $(QD)_2PYDZ$, and $(CN)_2PYDZ$. From this study we were able to get an approximate cost of enantioselectivity per modification. In comparing $(DHQD)_2PYDZ$ (**II-30**) to $(QD)_2PYDZ$ (**II-35**), we found that there was a drop of 5% *ee,* which equates to the cost of substituting the quinuclidine ethyl group for a vinyl moiety. We then

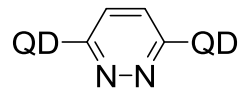


Catalysts:



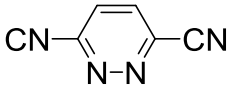
II-30 $(DHQD)_2PYDZ$

ee 80 %



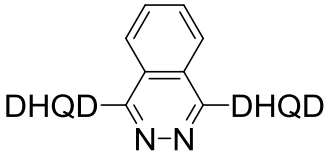
II-35 $(QD)_2PYDZ$

76 %



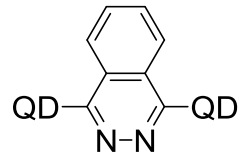
II-36 $(CN)_2PYDZ$

65 %



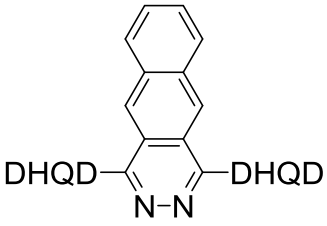
II-9 $(DHQD)_2PHAL$

ee 84 %



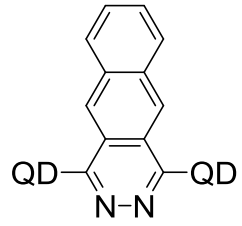
II-37 $(QD)_2PHAL$

81 %



II-31 $(DHQD)_2benzoPHAL$

ee 85 %



II-38 $(QD)_2benzoPHAL$

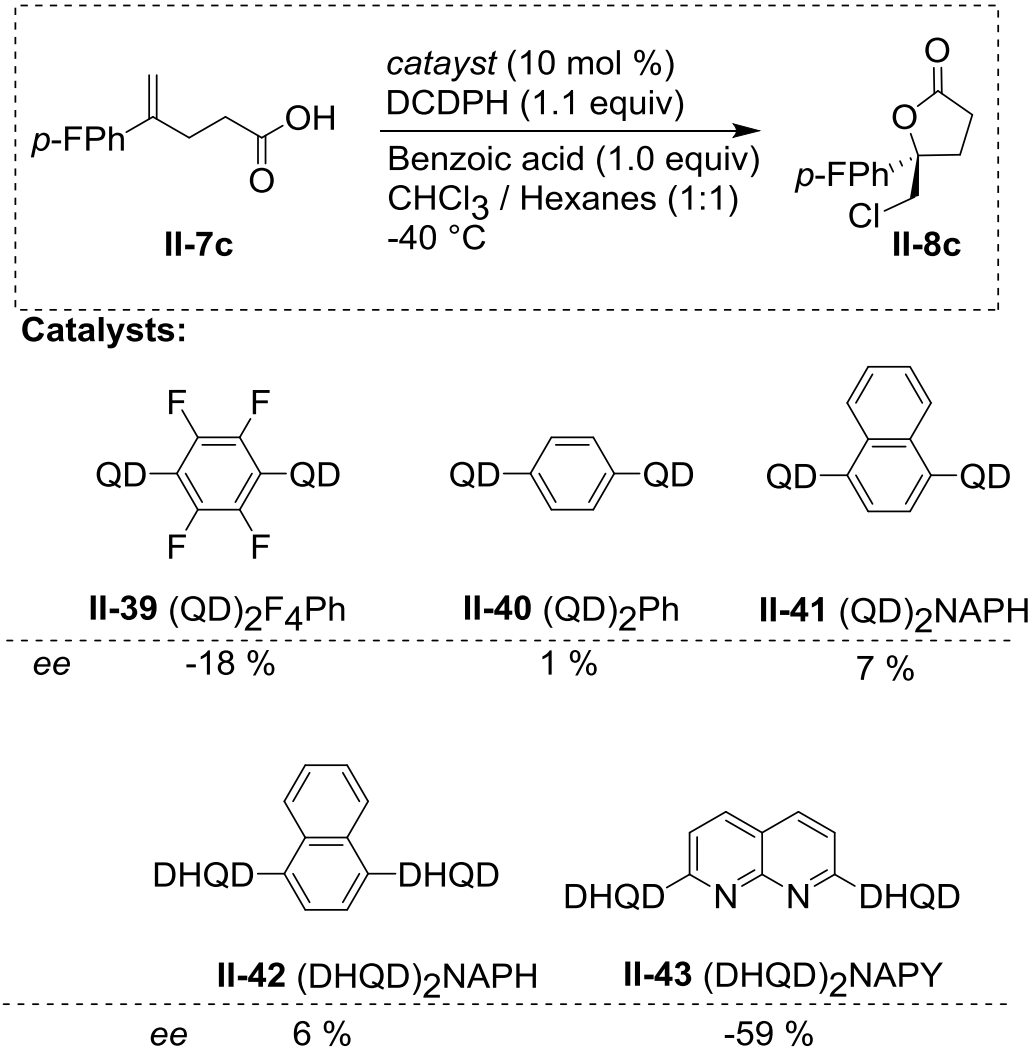
80 %

Scheme II-6. Additive effect study with various catalysts.

compared $(QD)_2$PYDZ (**II-35)**) to $(CN)_2$PYDZ (**II-36**), with the only difference being the quinoline methoxy group, whose removal led to a 11% drop in *ee.* At this point, we were curious as to whether it was a safe assumption to apply this "additive effect" to catalyst alterations. Therefore looked at the results obtained with $(QD)_2$PHAL (**II-37**), $(DHQD)_2$benzophthalazine (**II-31**) and $(QD)_2$benzophthalazine (**II-38**). Indeed with all of these scaffolds we found a nearly perfect "additive effect." To summarize, the substituent of the quinuclidine ethyl with a vinyl group costs 5% *ee,* substitution of the quinoline methoxy with hydrogen costs 11% *ee,* the substitution of phthalazine with pyridazine costs 4% *ee,* and the substitution of phthalazine with benzophthalazine adds 1% *ee.* Although these conclusions provoke a number of hypotheses, they will be discussed with their respective related catalyst structures. From this preliminary catalyst screening, we ultimately concluded that we would use pyridazine as a linker in screening analogs, since it is the only commercially available linker in the series of PYDZ, PHAL, and benzophthalazine. Also, we concluded that although DHQD appears to be the optimal alkaloid subunit for this reaction, the cheaper, naturally occurring QD is also acceptable.

Returning our focus back to screening linker analogs, we decided to investigate the role of the phthalazine nitrogens. As was previously discussed, in substituting $(DHQ)_2$PHAL (**II-25**) with $(DHQ)_2$AQN (**II-27**) (Scheme II-4), a significant change in *ee* was observed. We proposed that the ideal catalyst to test the role of the nitrogens would include two DHQD alkaloids linked by a naphthalene unit; however this scaffold proved to be a synthetic challenge. The first catalyst we were able to acquire lacking

these nitrogens featured a tetrafluorophenyl linker (**II-39**). This catalyst led to a significant drop in enantioselectivity, giving -18% *ee.* Since this linker contained fluorine, which is capable of hydrogen bonding, we wanted reassurance that the erosion of *ee* was not attributable to this significant electronic alteration. Therefore, we synthesized the phenyl linked dimer **II-40**, which gave only 1% *ee.* In efforts to complete this series of catalysts naphthalene linked **II-41** was acquired**,** which also gave



Scheme II-7. Catalysts screened to test the role of the phthalazine nitrogens in $(DHQD)_2PHAL$.

near racemic product (7% *ee*). Since **II-40** and **II-41** both utilized QD, instead of the optimal DHQD, we completed the series with $(DHQD)_2NAPH$ (**II-42**) as a final test, which also gave near racemic product (5% *ee*). Based on all of these results, it's clear that the phthalazine nitrogens are structurally essential to $(DHQD)_2PHAL$ in our chlorolactonization reaction, but their exact role in the mechanism however is unclear. It is possible to propose two hypotheses regarding the role of these nitrogens. The first is that the conformations of these catalysts are different from that of $(DHQD)_2PHAL$. This proposal would agree with the calculations done by Sharpless concerning the torsional angle about the pyridazine or phthalazine C_9-O-C=N bonds.[23] With the nitrogens missing from the aryl linker, there would be no rigidity about the C_9-O-C=C bond since there are no lone pair repulsions, permitting the linker of the catalyst to be free to rotate. Also, the phthalazine linker was electron withdrawing causing the carbinol oxygen to be partially sp^2 hybridized. In the phenyl / naphthyl case, the linker is more electron rich; therefore the carbinol oxygen should have less sp^2-character. This would most likely disrupt the planarity about the C_9-O-C=C bond, which $(DHQD)_2PHAL$ possesses. An alternate hypothesis relates to the unexpected mechanistic discovery found by Yousefi regarding the *syn* stereochemistry of the chlorine and carboxylate in the product. One possible explanation would be that a double inversion is taking place, with the phthalazine nitrogen's attacking the carbocation / halonium intermediate, which then is displaced by the carboxylate. This mechanism would account for the observed *syn* stereochemistry.[18]

One last catalyst that probed the role of the phthalazine nitrogens is **II-43**. This linker was designed to mimic the two aromatic rings and two nitrogens in phthalazine, however this was done by using a naphthyridine linker. This catalyst delivered a modest *ee* of the opposite enantiomer (-59% *ee*). The is a remarkable result, since the chirality of the alkaloids is the same in $(DHQD)_2PHAL$ and this catalyst, but the difference in ee's is 143%. This result can most likely be explained by the significantly different conformation induced by the wider linker, but reiterates the idea that nitrogens are necessary. A crystal structure of this catalyst was obtained, which does reveal that **II-43** has an overall C-shape, with the two alkaloids being oriented towards each other. Compared to the crystal structure for $(DHQD)_2PHAL$,[24] $(DHQD)_2NAPY$ places the two alkaloids further apart but more tightly angled toward each other (Figure II-5).

The last set of linker analog catalysts tested was built around a series of acyl linkers. The goal was to see if flexible linkers of various lengths or various substituted phthalic acid acyl linkers would be tolerated. Four flexible acyl linkers of various chain

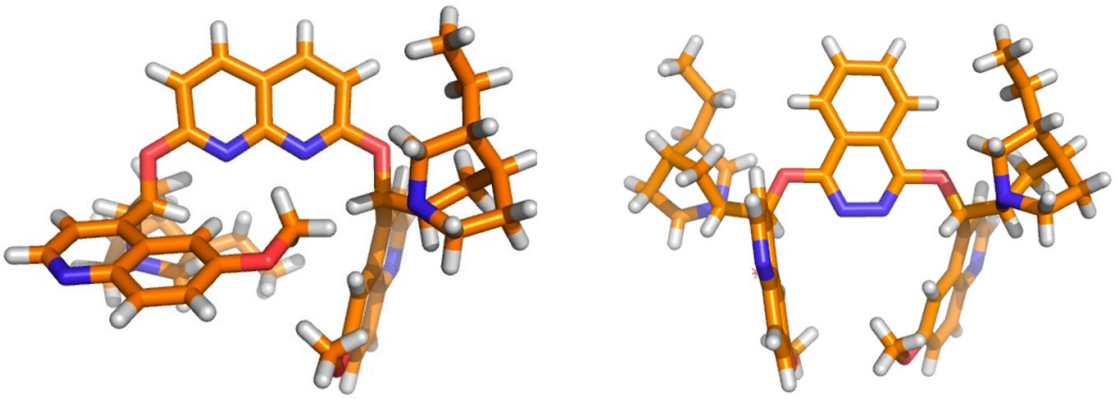
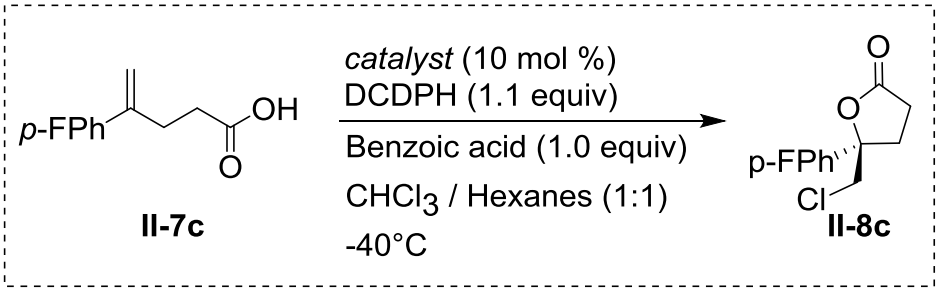
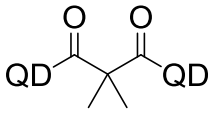


Figure II-5. Comparison of the crystal structures of $(DHQD)_2NAPY$ (left) and $(DHQD)_2PHAL$ (right).[24]

lengths were screened, having 3, 4, 5, or 6 carbons; all of these gave near racemic products (Scheme 8, **II-44** thru **II-47**). This was not surprising, based on the present results indicating the reaction's sensitivity to structural alterations of the linker in $(DHQD)_2PHAL$. The three aromatic acyl linkers gave somewhat more exciting results, with the para (**II-48**) and meta (**II-49**) acyl linkers giving near racemic values but the ortho acyl linker **(II-50)** jumping to 38% *ee.* Although it is possible to imagine the ortho

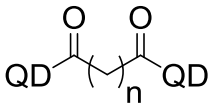


Catalysts:



II-44 $(QD)_2MALMe_2$

ee 10 %

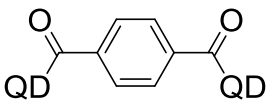


ee

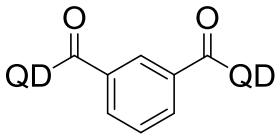
II-45 (n=1) $(QD)_2SUCC$ 1 %

II-46 (n=2) $(QD)_2GLUT$ 2 %

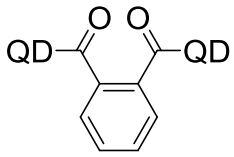
II-47 (n=3) $(QD)_2ADI$ 1 %



II-48 $(QD)_2TERE$



II-49 $(QD)_2isoPHTHAL$



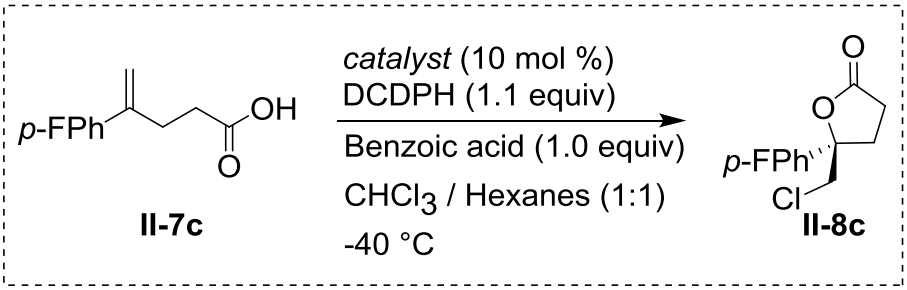
II-50 $(QD)_2PHTHAL$

ee 2 3 38

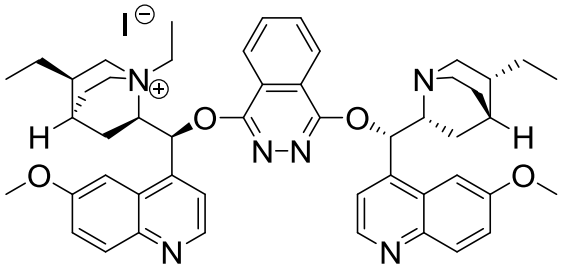
Scheme II-8. Catalyst screening results for acyl linkers.

acyl linker in a conformation which bears a striking resemblance to phthalazine in terms of electronics, where the two carbonyls mimic the two phthalazine nitrogens, the predicted geometry for 1,2-phthalic acids is not predicted to be planar. Computational studies have shown that the two carbonyls electronically repel each other, which results in a conformation where one carbonyl is nearly planar (~10° out of plane) and the other is perpendicular to the plane of the aromatic ring.[25] Therefore from these results, it is hard to draw any conclusions, except perhaps to investigate electronically varied phthalic acid dimers in the chlorolactonization methodology. Although presumptive, it is quite possible that this reaction proceeds via a different mechanism than the reaction with $(DHQD)_2PHAL$, which could possibly offer a wider substrate scope than the $(DHQD)_2PHAL$ catalyzed reaction. It is also worth noting here that the solvent had a significant effect on the $(DHQD)_2PHAL$ catalyzed chlorolactonization and a solvent screen may be able to increase the *ee*'s observed with this ortho acyl linked catalyst.

We then set out to screen what effect blocking the quinuclidine nitrogens had on the reaction. Based on the assumption that both quinuclidine nitrogens should be protonated under the reaction conditions, we hypothesized that unless hydrogen bonding is important, alkylation should not lead to a significant drop in *ee.* Unfortunately the di-alkylated $(DHQD)_2PHAL$ was not attained, due to its instability, however two different mono-alkylated derivatives of $(DHQD)_2PHAL$ were acquired. These two scaffolds, being the mono-ethylated and mono-benzylated salts, gave the product in modest enantioselectivity, being 57% and 51% *ee,* respectively (Scheme II-9). A number of reasons can be proposed for the drop in *ee* observed with these catalysts

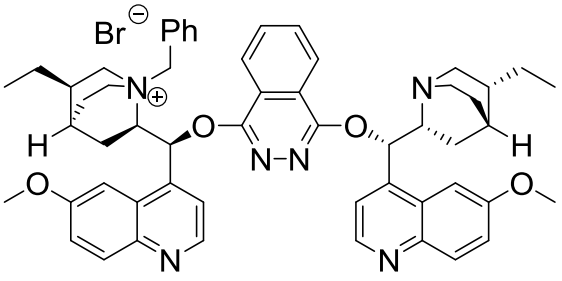


Catalysts:



II-51 $(DHQD)_2PHAL+EtI$

ee 57%



II-52 $(DHQD)_2PHAL + BnBr$

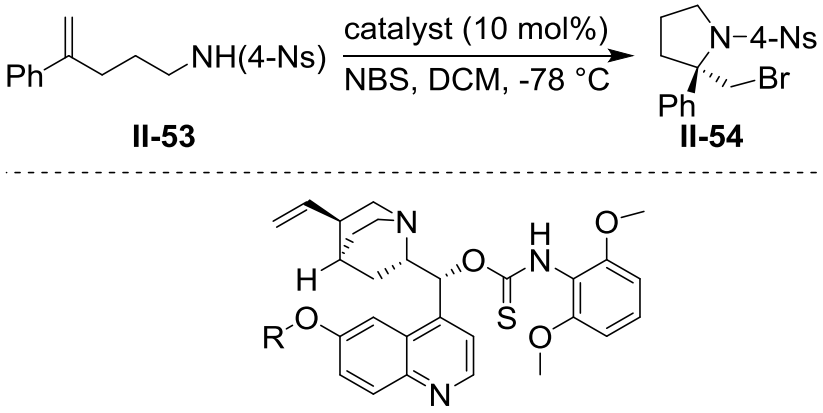
ee 51%

Scheme II-9. Catalyst screening of mono-alkylated salts of $(DHQD)_2PHAL$.

with respect to $(DHQD)_2PHAL$, including interference with hydrogen bonding, conformational changes, or sterics. Since the ethyl salt gives slightly better *ee*'s than the benzyl salt, this could suggest that these alkyl groups are interfering with a binding site in the catalyst.

Our next site of variation was the quinoline substituent. This idea was brought about during the preliminary catalyst screening when the difference between $(QD)_2PYDZ$ (**II-35**) and $(CN)_2PYDZ$ (**II-36**) caused an 11% drop in *ee.* The only difference between these two scaffolds is that QD has a methoxy substituent on the quinoline, whereas CN has a H. In a similar fashion, we recalled that Zhou, *et al.* screened four *cinchona* alkaloid catalysts (**55a-d**) with various groups on the quinoline alkoxy in an asymmetric bromoaminocyclization reaction. These analogs did affect the *ee,* with the optimal catalyst containing an isoamyl group on the quinoline alkoxy (Scheme II-10).[26] Therefore, we proposed that by making this group larger, we might be able to see an increase in *ee.* We therefore chose to add an isopropyl group at this position. Unfortunately, this catalyst gave 58% *ee* (**II-56**). This is suggestive that either

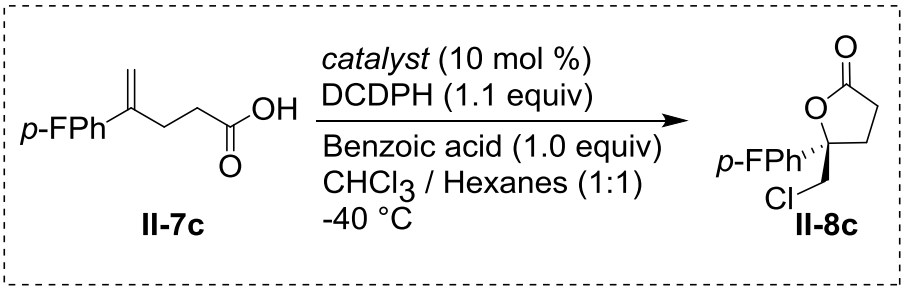
Table II-5. Results from Zhou, *et al.* for alkaloid catalysts with various quinoline alkoxy groups.



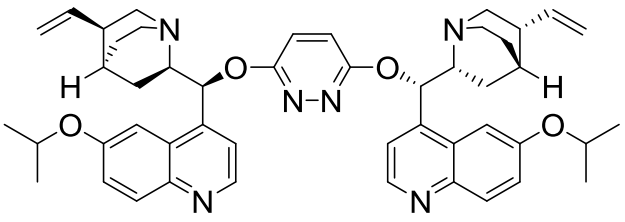
Entry	Catalyst	R =	*ee*
1	**II-55a**	Me	71
2	**II-55b**	Et	75
3	**II-55c**	*n*Bu	78
4	**II-55d**	isoamyl	80

the larger group causes a conformational change in the catalyst, but more likely that this group is sterically clashing with the acid substrate. This would correlate with the intramolecular ROESY studies obtained by Yousefi, revealing that the alkyl CH_2's of the acid substrate are in proximity to the quinoline methoxy moiety.[17]

One last site of steric variation was the ethyl moiety of the quinuclidine. As was noted earlier in going from $(DHQD)_2PYDZ$ (**II-30**) to $(QD)_2PYDZ$ (**II-35**), a drop of 5% *ee* was observed. Two hypothesis were proposed to account for this drop in *ee*, either that the double bond was being chlorinated under the reaction conditions, causing the catalyst to become deactivated or have different reactivity, or that it could simply be a matter of sterics, with the vinyl group being smaller than the ethyl group. To test this hypothesis we initially screened a catalyst with two methyls on the olefin and a PYDZ



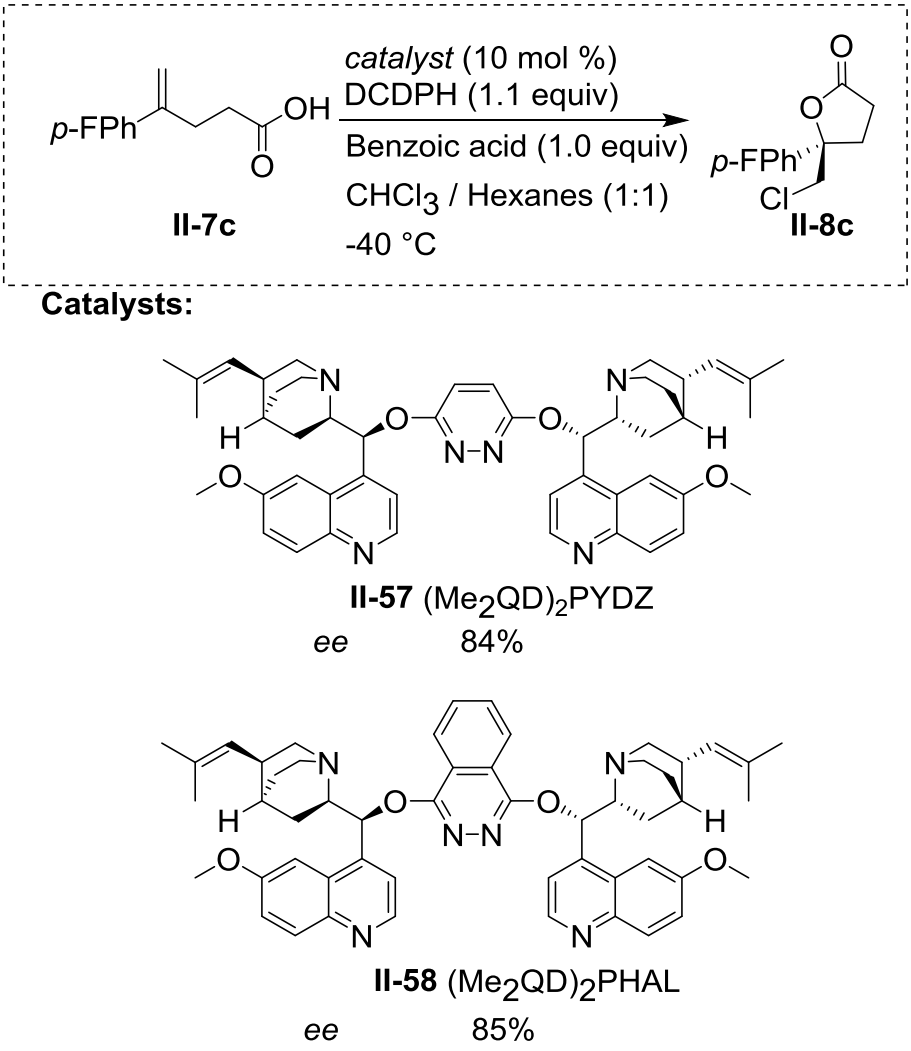
Catalyst:



II-56 $(iPrQD)_2PYDZ$
ee 58%

Scheme II-10. Catalyst screening of quinidine derivatives with a larger quinoline alkoxy group.

linker (**II-57**). This catalyst provided products with identical *ee*'s as that obtained with $(DHQD)_2PHAL$, 84%. Based on the "additive effect" observed earlier, we proposed that substitution of pyridazine with phthalazine should lead to an increase of 4% *ee*, therefore the catalyst bearing the larger olefinic residue and phthalazine linker was made, which delivered the product in 85% *ee* (**II-58**). This was slightly disappointing, but we hypothesize that increasing the size of the olefinic residue may have the same



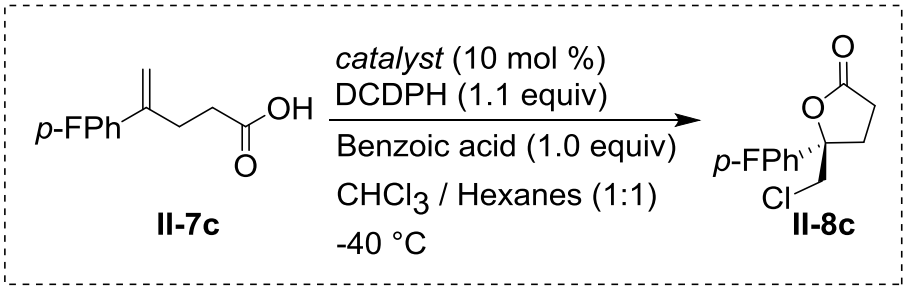
Scheme II-11. Catalyst screening of quinidine derivatives with larger olefinic residues.

effect as increasing the size of the linker. As discussed earlier, the larger aromatic heterocyclic linker could lead to increased rigidity about the C_9-O-C=N bonds, which ultimately leads to higher *ee.* All attempts to hydrogenate the olefin in catalyst **II-58** led to decomposition.

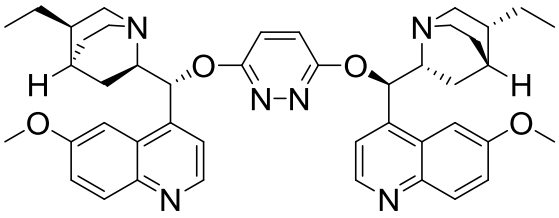
To finish our SER studies, three catalysts were made in efforts to probe the essential parts of the catalyst. The first of these three catalysts utilized epimeric quinidine units linked by pyridazine. In this dimer, the C_9-carbinol was inverted, to give the unnatural stereochemistry at this site (**II-59**). We believed that by inverting this stereochemistry, a conclusion could be made about which stereocenter has more of an influence in delivering enantioselectivity; is the chirality about the quinuclidine nitrogen more important, or the chirality about the C_9-carbinol center? Inverting this stereocenter also allows the catalyst to take on different conformations. Catalyst **II-59** yielded the product with only 11% *ee*, which could indicate that the chirality around the nitrogen is more important, since the catalyst gives the same enantiomer of product as $(DHQD)_2PHAL$. The next dimer only had one alkaloid attached to the pyridazine linker. Ultimately, we wanted to understand the essential parts of the catalyst, which included whether both alkaloid units were necessary. The results from this clearly showed that both are, with an *ee* of 1%, obtained for products of the reaction catalyzed by **II-60.** The last catalyst made was based on the idea of taking a minimalist approach. The catalyst made mimicked $(DHQD)_2PHAL$, having two chiral amino alcohol units linked by pyridazine (**II-61**). The configurations at the amino and alcohol sites were identical to those in dihydroquinidine. The results from catalyst **II-61** were promising, giving 44%

ee. This was an exciting discovery because it opens the door to a number of diverse catalyst scaffolds, instead of being limited to commercially available alkaloids.

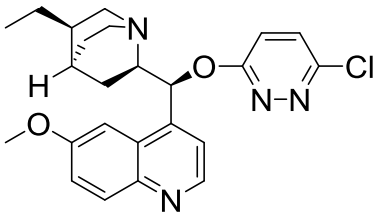
A summary from the SER studies of the $(DHQD)_2PHAL$ catalyzed asymmetric chlorolactonization can be seen in Figure II-6. It seems the recurring theme from these studies is catalyst conformation. The benzophthalazine linker may be more efficient



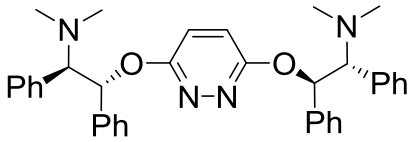
Catalysts:



II-59 (*epi*DHQD)$_2$PYDZ
ee 11%



II-60 (QD)PYDZ
ee 1%



II-61 (trunc)$_2$PYDZ
44%

Scheme II-12. Screening of catalysts investigating stereochemistry about C_9-carbinol, monomeric pyridazine, and truncated scaffold.

than the PYDZ linker, simply because the larger linker allows for a more rigid conformation. In agreement with this is the improvement seen between the tri-substituted olefinic catalysts **II-57** and **II-68.** It is possible that by bulking up this moiety of the catalyst, it creates a more rigidified scaffold, which would offer an explanation for why the substitution of PYDZ for PHAL does not give the expected increase in enantioselectivity as was seen in the analogous comparison of **II-30** to **II-9**. The observed drop in *ee* for bulking up the quinoline alkoxy substituent most likely is attributable to steric repulsions between the catalyst and the carboxylic acid substrate (catalyst **II-56**). Although the role of the phthalazine nitrogens is not clear, their presence is essential to delivering high enantioselectivities. In the future, detailed NMR and computational studies could aid in investigating the preferred conformation for

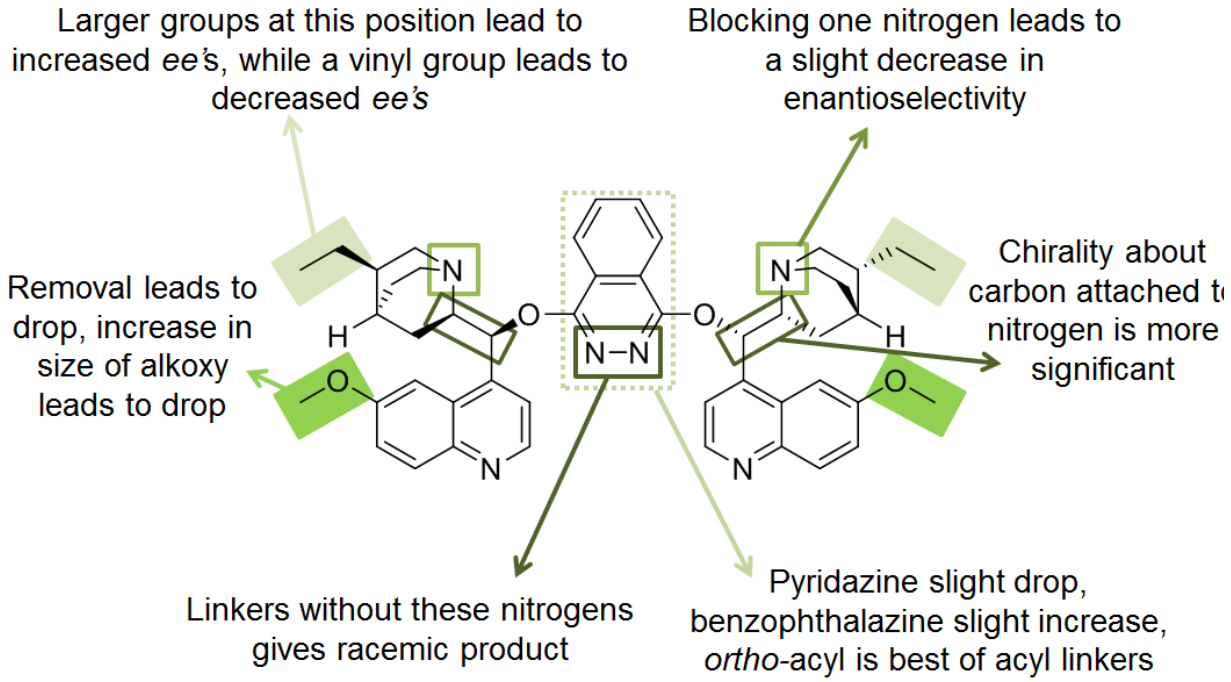


Figure II-6. Summary of asymmetric chlorolactonization SER studies.

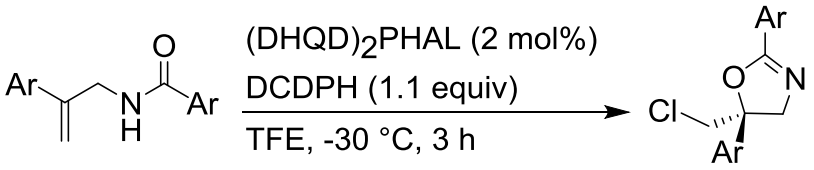
some of these catalyst analogs in an effort to get a better mechanistic understanding.

II-6 Introduction to Other $(DHQD)_2PHAL$ Chlorocyclization Reactions

In 2011 and 2012, our group developed two other asymmetric chlorocyclization methodologies, the chlorocyclization of various amides and a chlorocyclization of carbamates, respectively.[27] These two extensions to our chlorolactonization reaction used quite different reaction conditions and favored the opposite enantiomer of product, in comparison to the product from the chlorolactonization reaction. This sparked our interest in extending our SER studies to these classes of compounds to see their results with our catalyst analogs.

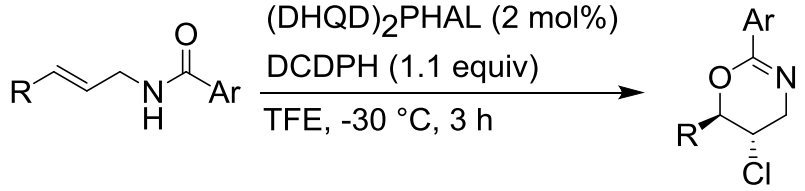
The chlorocyclization of various amides was found to be much more robust than the chlorolactonization, with a much larger substrate scope and *ee*'s commonly exceeding 90% (Scheme II-13). This reaction proceeded under different conditions

1,1-olefins



Up to 98% *ee*

trans-olefins

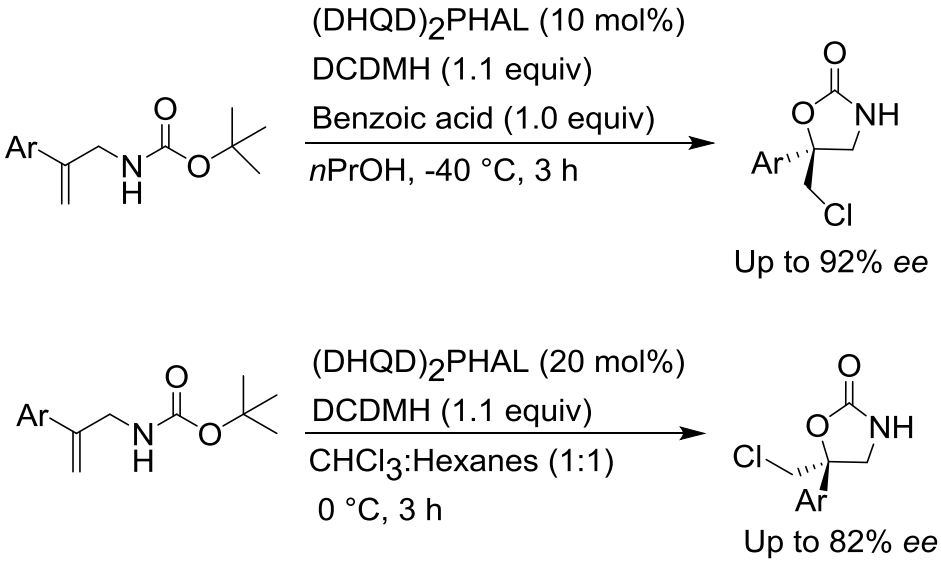


Up to >99% *ee*

Scheme II-13. Chlorocyclization of various unsaturated amides.

than the chlorolactonization reaction, with the optimized conditions including the use of the fluorinated, protic solvent trifluoroethanol, and the substrate scope including both 1,1- and *trans*- disubstituted olefins. One very interesting discovery concerning the 1,1-disubstituted olefins in this reaction was that the attack of the nucleophile occurred from the opposite face of the olefin than it did in the chlorolactonization reaction. This is suggestive of a different binding mode between the catalyst / substrate or an entirely different mechanism.[27]

The chlorocyclization of carbamates was found to be an extremely interesting class of reactions as well (Scheme II-14). The most remarkable aspect of this reaction is that the stereoselectivity of the reaction changes based on the solvent. With $(DHQD)_2PHAL$ as the catalyst, in *n*-propanol, the *S*-enantiomer is favored, whereas in chloroform / hexanes (1:1) the *R*-enantiomer is favored. This is astonishing; the same chirality of catalyst can selectively generate either one of the two enantiomers of the



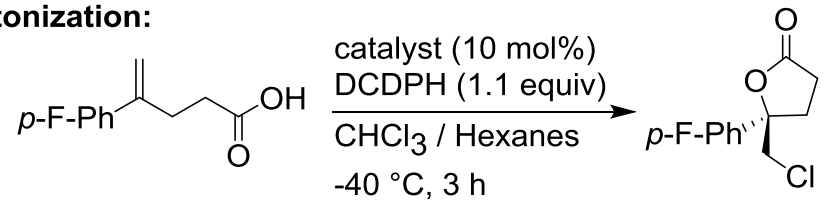
Scheme II-14. Chlorocyclization of carbamates.

product! This system, in either solvent, is generally less robust than either the chlorolactonization or chlorocylization of amides, but it is mechanistically intriguing. Ultimately it was found that in *n*-propanol, the reaction was governed by enthalpy, whereas in chloroform / hexanes (1:1) it was governed by entropy.

II-7 SER results for Chlorocyclization of Various Amides and Carbamates

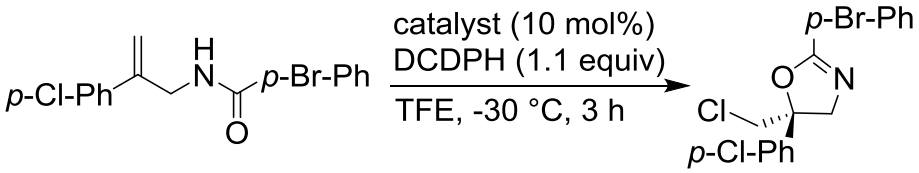
Comparison of the reaction conditions and the stereochemistry of the products resulting from the chlorolactonization and chlorocyclization of amides and carbamates revealed that these reactions are very different. The results from the SER studies reiterate this conclusion, with some catalysts being much more successful for certain classes of reactions. This section will summarize the results from the SER studies of the chlorocyclization of amides and carbamates in table format, followed by a brief discussion for each class of substrates. For ease of side-by-side comparison, the lactonization results will be included in the summary tables.

Lactonization:



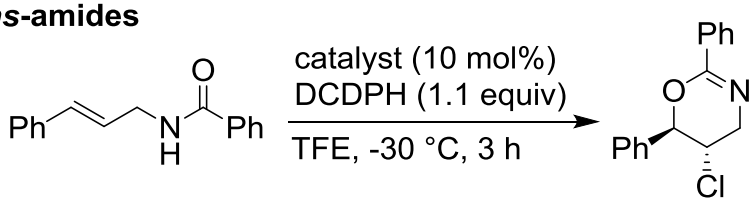
II-7c **II-8c**

1,1-amides:



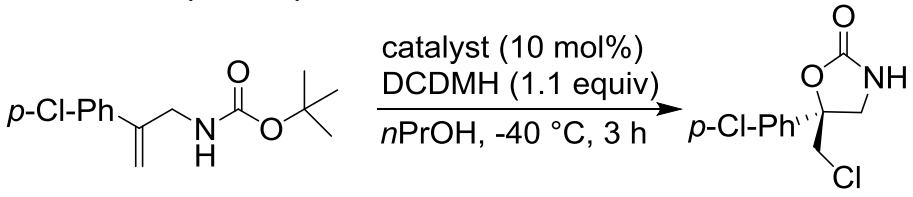
II-62 **II-63**

***trans*-amides**



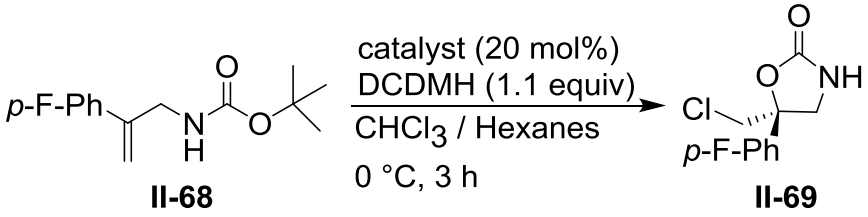
II-64 **II-65**

Carbamates (*n*PrOH):



II-66 **II-67**

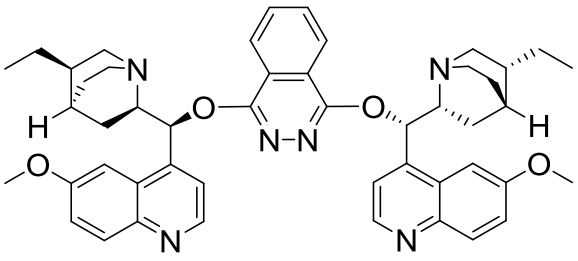
Carbamates ($CHCl_3$/hexanes):



II-68 **II-69**

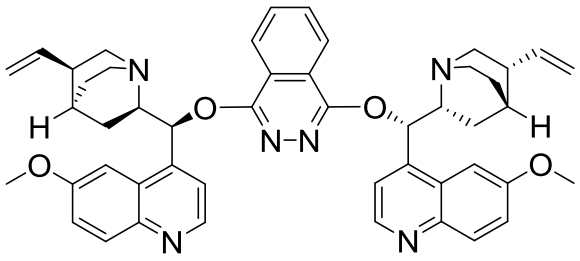
Scheme II-15. All the reactions screened during SER studies.

Table II-6. Summary of SER studies with all classes of substrates.



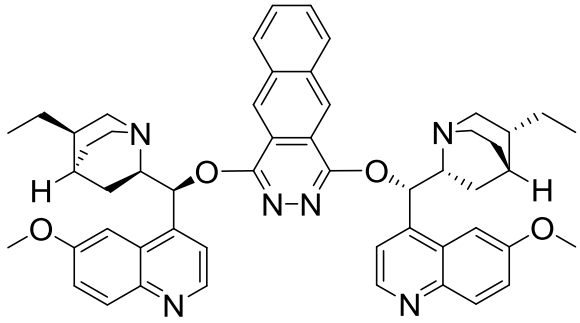
II-9 ($(DHQD)_2PHAL$

Reaction	% ee
Lactonization	84
1,1-Amides	90
trans-amides	99
Carbamates (*n*PrOH)	80 (*R*)
Carbamates ($CHCl_3$/hex)	56 (*S*)



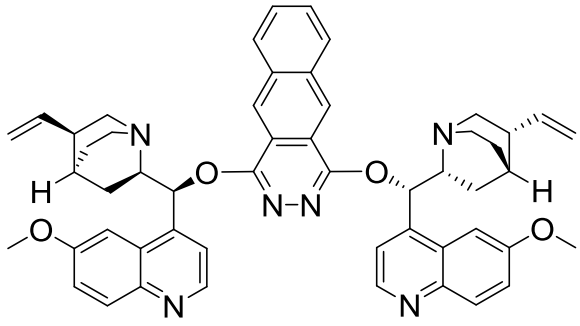
II-37 $(QD)_2PHAL$

Reaction	% ee
Lactonization	81
1,1-Amides	86
trans-amides	>99
Carbamates (*n*PrOH)	-
Carbamates ($CHCl_3$/hex)	-



II-31 $(DHQD)_2benzoPHAL$

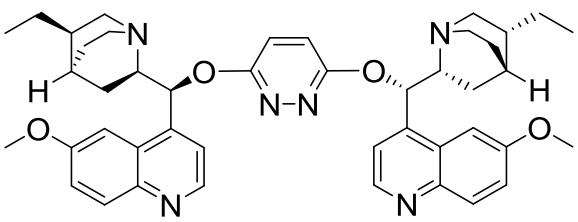
Reaction	% ee
Lactonization	85
1,1-Amides	86
trans-amides	>99
Carbamates (*n*PrOH)	-
Carbamates ($CHCl_3$/hex)	-



II-38 $(QD)_2benzoPHAL$

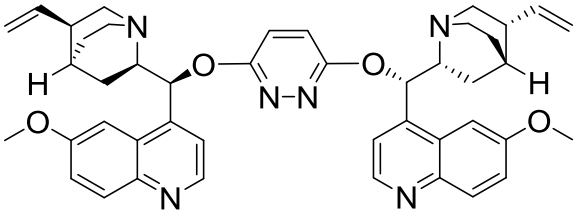
Reaction	% ee
Lactonization	80
1,1-Amides	86
trans-amides	>99
Carbamates (*n*PrOH)	-
Carbamates ($CHCl_3$/hex)	-

Table II-6. (cont'd).



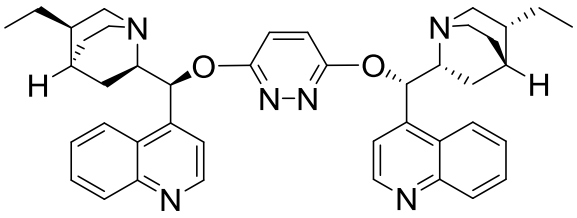
II-30 $(DHQD)_2PYDZ$

Reaction	% ee
Lactonization	80
1,1-Amides	93
trans-amides	98
Carbamates (*n*PrOH)	76 (*R*)
Carbamates ($CHCl_3$/hex)	42 (*S*)



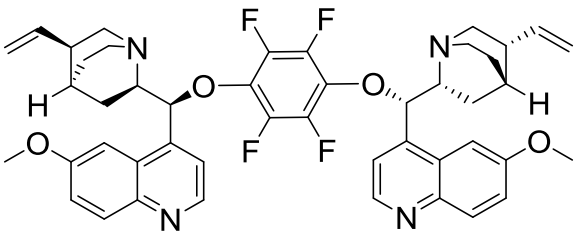
II-35 $(QD)_2PYDZ$

Reaction	% ee
Lactonization	76
1,1-Amides	88
trans-amides	>99
Carbamates (*n*PrOH)	-
Carbamates ($CHCl_3$/hex)	-



II-36 ($(CN)_2PYDZ$

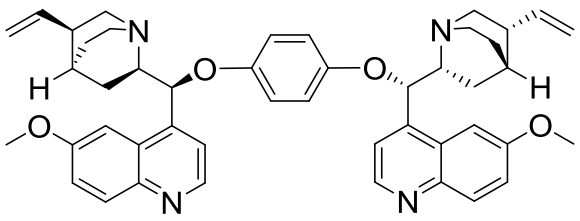
Reaction	% ee
Lactonization	65
1,1-Amides	91
trans-amides	98
Carbamates (*n*PrOH)	58 (*R*)
Carbamates ($CHCl_3$/hex)	20 (*S*)



II-39 $(QD)_2F_4Ph$

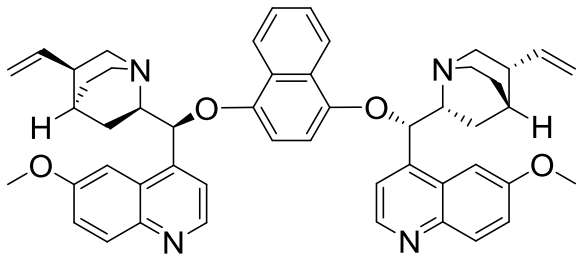
Reaction	% ee
Lactonization	-18
1,1-Amides	-9
trans-amides	0
Carbamates (*n*PrOH)	4 (*R*)
Carbamates ($CHCl_3$/hex)	0

Table II-6. (cont'd).



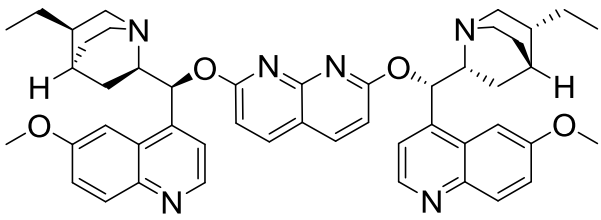
II-40 $(QD)_2Ph$

Reaction	% ee
Lactonization	0
1,1-Amides	12
trans-amides	0
Carbamates (*n*PrOH)	-
Carbamates ($CHCl_3$/hex)	-



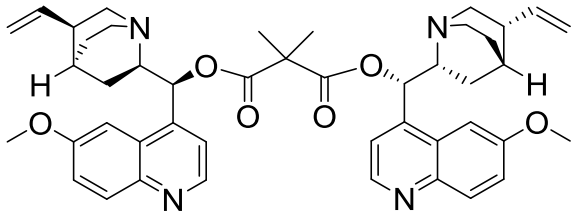
II-41 $(QD)_2NAPH$

Reaction	% ee
Lactonization	7
1,1-Amides	-14
trans-amides	15
Carbamates (*n*PrOH)	-
Carbamates ($CHCl_3$/hex)	-



II-43 ($DHQD)_2NAPY$

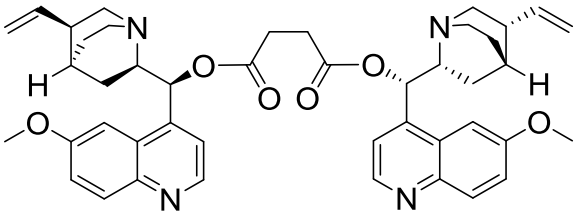
Reaction	% ee
Lactonization	-59
1,1-Amides	12
trans-amides	4
Carbamates (*n*PrOH)	50 (*R*)
Carbamates ($CHCl_3$/hex)	0



II-44 $(QD)_2MALMe_2$

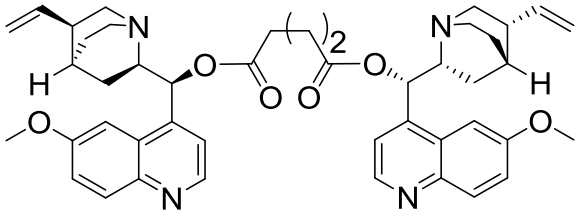
Reaction	% ee
Lactonization	10
1,1-Amides	42
trans-amides	22
Carbamates (*n*PrOH)	-
Carbamates ($CHCl_3$/hex)	6 (*S*)

Table II-6. (cont'd).



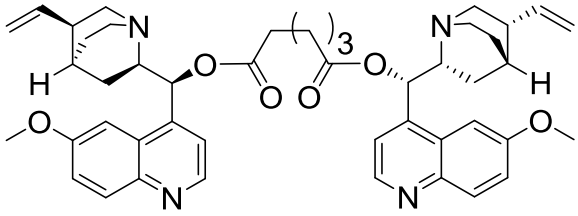
II-45 $(QD)_2SUCC$

Reaction	% ee
Lactonization	1
1,1-Amides	75
trans-amides	66
Carbamates (*n*PrOH)	43 (*R*)
Carbamates ($CHCl_3$/hex)	-20 (*S*)



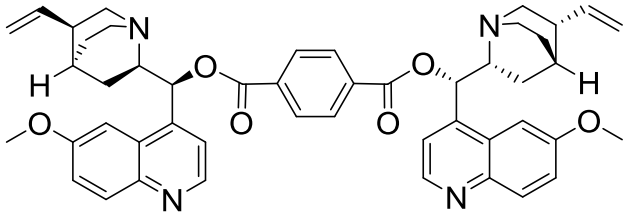
II-46 $(QD)_2GLUT$

Reaction	% ee
Lactonization	2
1,1-Amides	46
trans-amides	48
Carbamates (*n*PrOH)	-
Carbamates ($CHCl_3$/hex)	-17 (*S*)



II-47 $(QD)_2ADI$

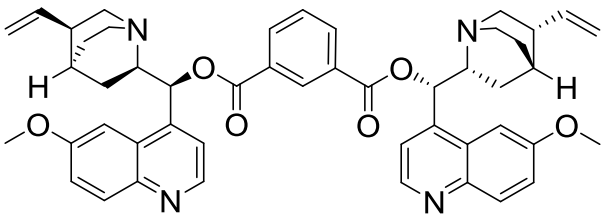
Reaction	% ee
Lactonization	1
1,1-Amides	57
trans-amides	43
Carbamates (*n*PrOH)	39 (*R*)
Carbamates ($CHCl_3$/hex)	-



II-48 $(QD)_2TERE$

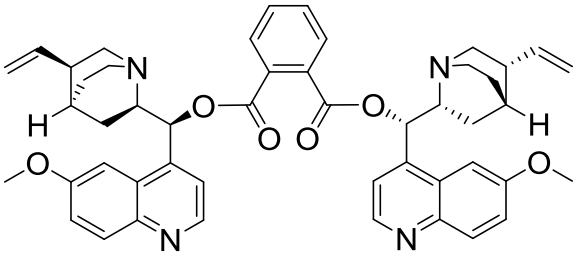
Reaction	% ee
Lactonization	2
1,1-Amides	47
trans-amides	51
Carbamates (*n*PrOH)	15 (*R*)
Carbamates ($CHCl_3$/hex)	-

Table II-6. (cont'd).



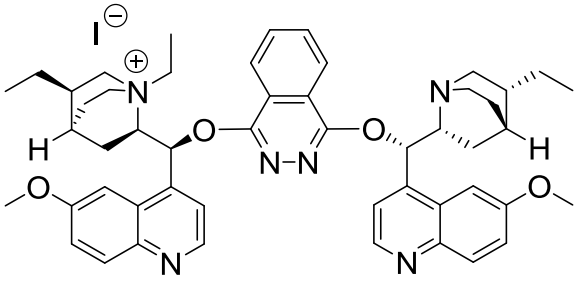
II-49 $(QD)_2$*iso*PHTHAL

Reaction	% ee
Lactonization	38
1,1-Amides	15
trans-amides	44
Carbamates (*n*PrOH)	-
Carbamates ($CHCl_3$/hex)	2 (*S*)



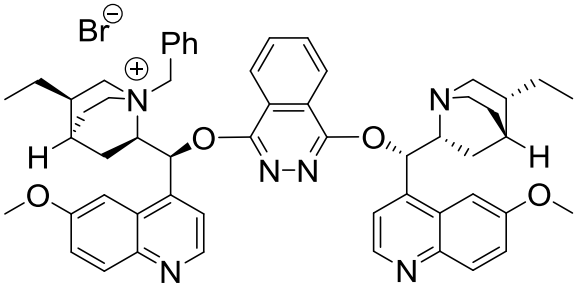
II-50 $(QD)_2$PHTHAL

Reaction	% ee
Lactonization	3
1,1-Amides	48
trans-amides	48
Carbamates (*n*PrOH)	-
Carbamates ($CHCl_3$/hex)	-



II-51 ($(DHQD)_2$PHAL + EtI

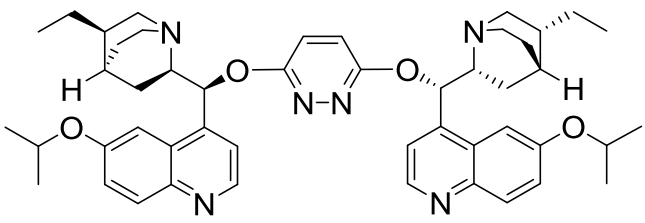
Reaction	% ee
Lactonization	57
1,1-Amides	80
trans-amides	98
Carbamates (*n*PrOH)	74(*R*)
Carbamates ($CHCl_3$/hex)	-



II-52 $(DHQD)_2$PHAL+BnBr

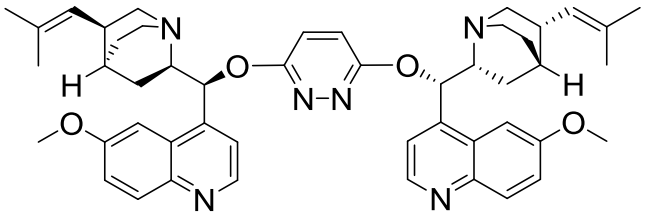
Reaction	% ee
Lactonization	51
1,1-Amides	87
trans-amides	86
Carbamates (*n*PrOH)	78 (*R*)
Carbamates ($CHCl_3$/hex)	8 (*S*)

Table II-6. (cont'd).



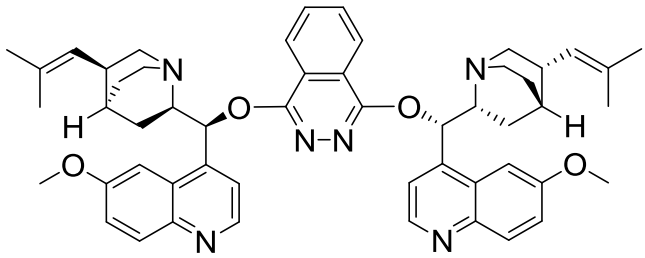
II-56 (*iPr*DHQD)$_2$PYDZ

Reaction	% ee
Lactonization	58
1,1-Amides	97
trans-amides	>99
Carbamates (*n*PrOH)	-
Carbamates ($CHCl_3$/hex)	-



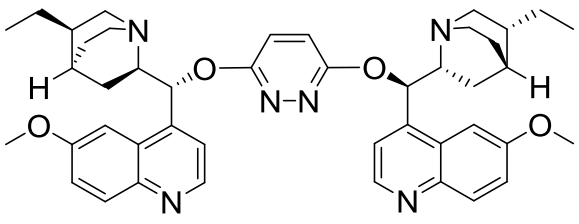
II-57 (Me$_2$QD)$_2$PYDZ

Reaction	% ee
Lactonization	84
1,1-Amides	81
trans-amides	>99
Carbamates (*n*PrOH)	-
Carbamates ($CHCl_3$/hex)	-



II-58 (Me$_2$QD)$_2$PHAL

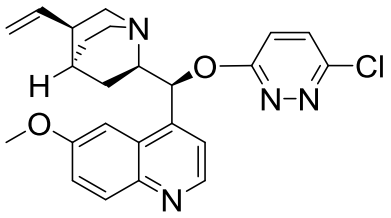
Reaction	% ee
Lactonization	85
1,1-Amides	62
trans-amides	-
Carbamates (*n*PrOH)	-
Carbamates ($CHCl_3$/hex)	-



II-59 (*epi*DHQD)$_2$PYDZ

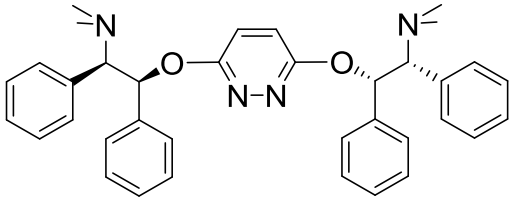
Reaction	% ee
Lactonization	11
1,1-Amides	57
trans-amides	17
Carbamates (*n*PrOH)	-
Carbamates ($CHCl_3$/hex)	-

Table II-6. (cont'd).



II-60 (QD)PYDZ

Reaction	% ee
Lactonization	1
1,1-Amides	51
trans-amides	24
Carbamates (*n*PrOH)	-
Carbamates ($CHCl_3$/hex)	10 (*S*)



II-61 $(trunc)_2$PYDZ

Reaction	% ee
Lactonization	44
1,1-Amides	-
trans-amides	-
Carbamates (*n*PrOH)	-
Carbamates ($CHCl_3$/hex)	0

Table II-6 presents a large amount of information which will be graphically summarized for each class of substrate, beginning with 1,1-amides (Scheme II-7). The smaller PYDZ linker showed improved enantioselectivities over the larger phthalazine and benzophthalazine linkers (**II-30** vs. **II-9** vs. **II-31**), which quite possibly is in agreement with the larger quinuclidine olefinic catalysts (**II-57** and **II-58**) giving worse enantioselectivities. Both of these results contradict the chlorolactonization results, with possible explanations being that more rigidity about the C_9-O-C=N bond is detrimental to 1,1-amides or that the larger linkers interfere with the substrate binding to the catalyst. Also differing from the chlorolactonization results is the increase in *ee*

observed with the larger quinoline alkoxy catalyst **II-56,** which delivered the best overall stereoselectivity for the 1,1-amides. Two other noteworthy results were from the epimeric catalyst **II-59** and monomeric pyridazine catalyst **II-60,** which gave the product in 57% and 51% *ee,* respectively. These moderate *ee*'s were in contrast to those for the chlorolactonization, which were near racemic. Since the product obtained from the reaction with the epimeric catalyst **II-59** had the same stereochemistry as the product with $(DHQD)_2PHAL$ (**II-9**), clearly the stereochemistry about the quinuclidine nitrogen has a strong effect on inducing enantioselectivity. The fact that the monomeric pyridazine catalyst gives such high *ee's* could be indicative that monomers would be well tolerated in this reaction, however in relation to this, the linkers without nitrogens (**II-**

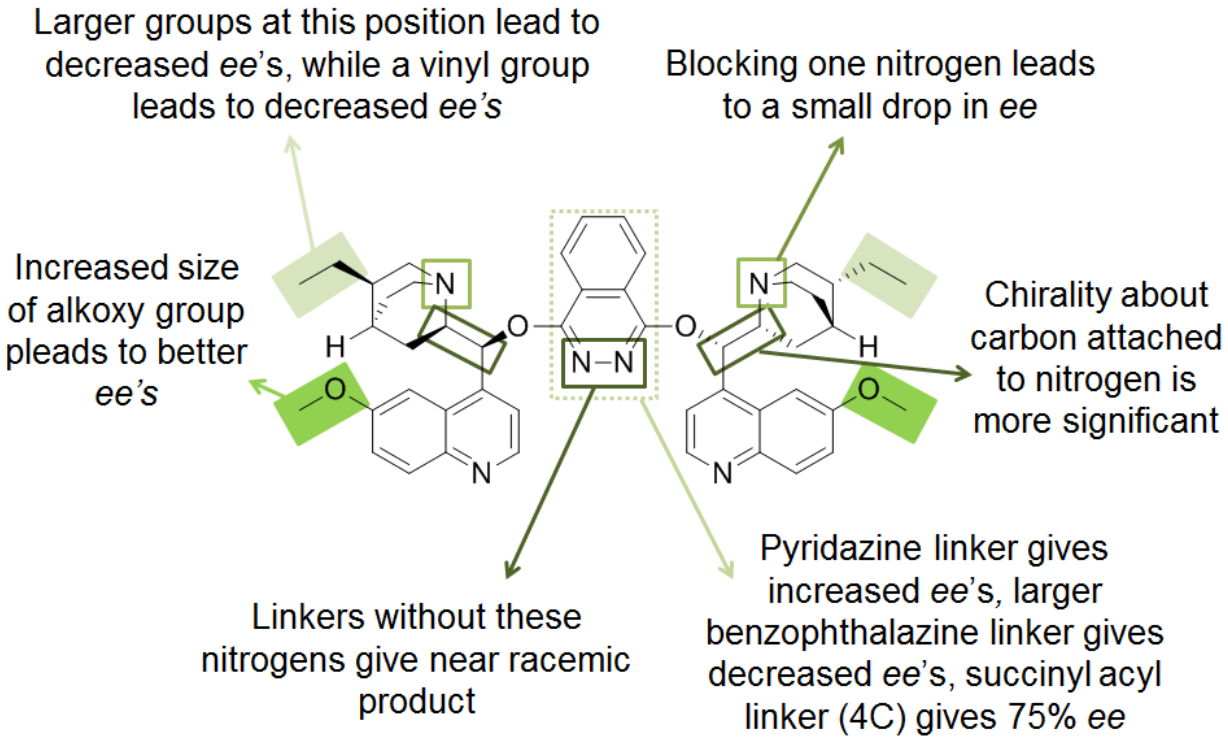


Figure II-7. Summary of asymmetric chlorocyclization of 1,1-amides SER studies.

39 to **II-41)** all gave the product in near racemic values. This reiterates the observation from the chlorolactonization study, that the linker nitrogens have a significant role in this reaction. The last series of catalysts screened, the acyl linkers (**II-44** through **II-50**) gave surprisingly hopeful results, with the succinyl acyl linker **II-45** delivering the 1,1-amide cyclization product in 75% *ee.* This is particularly stimulating, because the optimization of all the halocyclizations has shown that solvents have a strong influence. Having said this, no optimization has been applied to this screening, so a result of 75% is hopeful as a potential catalyst scaffold. Most of the other acyl linkers from this series of catalysts gave the product in moderate *ee.*

Overall, the *trans*-amides SER studies were less conclusive, since the system

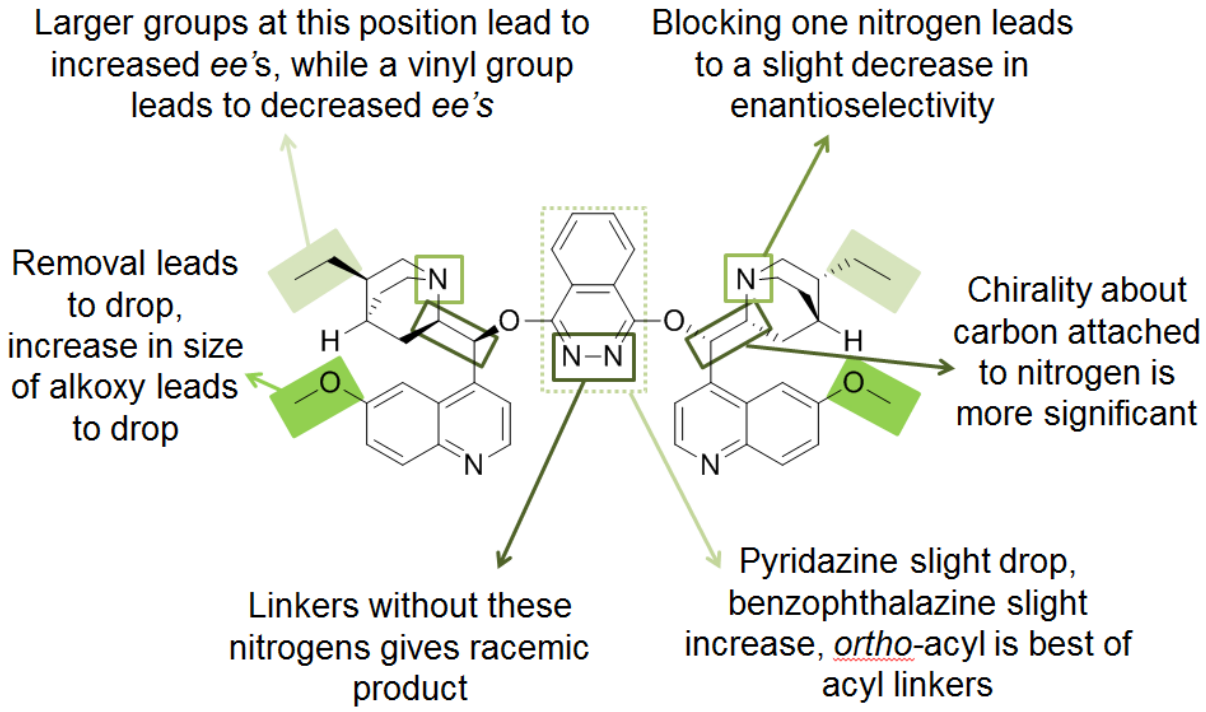


Figure II-8. Summary of asymmetric chlorocyclization of *trans*-amides SER studies.

was robust, and several catalysts gave the product in >99% *ee* (Scheme II-8). There are a few noteworthy finds. First of all, the larger quinuclidine olefinic catalysts (**II-57** and **II-58)** gave markedly decreased *ee's* (81 and 62% respectively). Increasing the sterics at this site of the catalyst must interfere quite strongly with the active site of the catalyst, since several other modications were well tolerated. Secondly, the catalysts missing the linker nitrogens (**II-39** through **II-41)** gave the product in near racemic values, in agreement with the other reactions screened. The acyl linkers for this class also proved successful with the succinyl linker providing the product in 66% *ee.* All other acyl linkers delivered the product in moderate *ee's.*

The class of amide substrates revealed very different results from the SER studies in comparison to the chlorolactonization. While the catalysts with larger quinuclidine olefinic groups proved most effective for the chlorolactonization, this change was detrimental for the amides. Similarly, increasing the sterics of quinoline alkoxy group was unfavorable for the chlorolactonization but optimal for the amides. This reiterates our hypothesis that the chlorolactonization and chlorocyclization of amides could have different binding modes between the substrate and catalyst. One strong agreement between these two classes of substrates is the fact that the catalyst's linker nitrogens are essential to high enantioselectivities.

The library of catalysts was then screened against the carbamates in the two solvent systems. Not all of the catalysts were screened for this class of substrates, mainly because the chloroform and hexanes screening required 20 mol% of each catalyst. From these studies it is clear that the reaction in *n*PrOH is more robust to

variations in the catalyst structure than the corresponding reaction in $CHCl_3$/hexanes. This can be related to the fact that Garzan found that the *n*PrOH reaction was enthalpy driven, most likely involving strong catalyst/substrate interactions in the transition state, while in $CHCl_3$/hexanes the reaction was found to be entropy driven, implying a much weaker interaction of the catalyst and substrate during the transition state.[28] The stronger interaction between the catalyst and substrate in nPrOH suggests that the active site of the catalyst may be much more defined in this system, with alterations surrounding the active site only having a weak influence on delivering enantioselectivity. In comparison, in $CHCl_3$/hexanes, the system that is entropy controlled, small changes

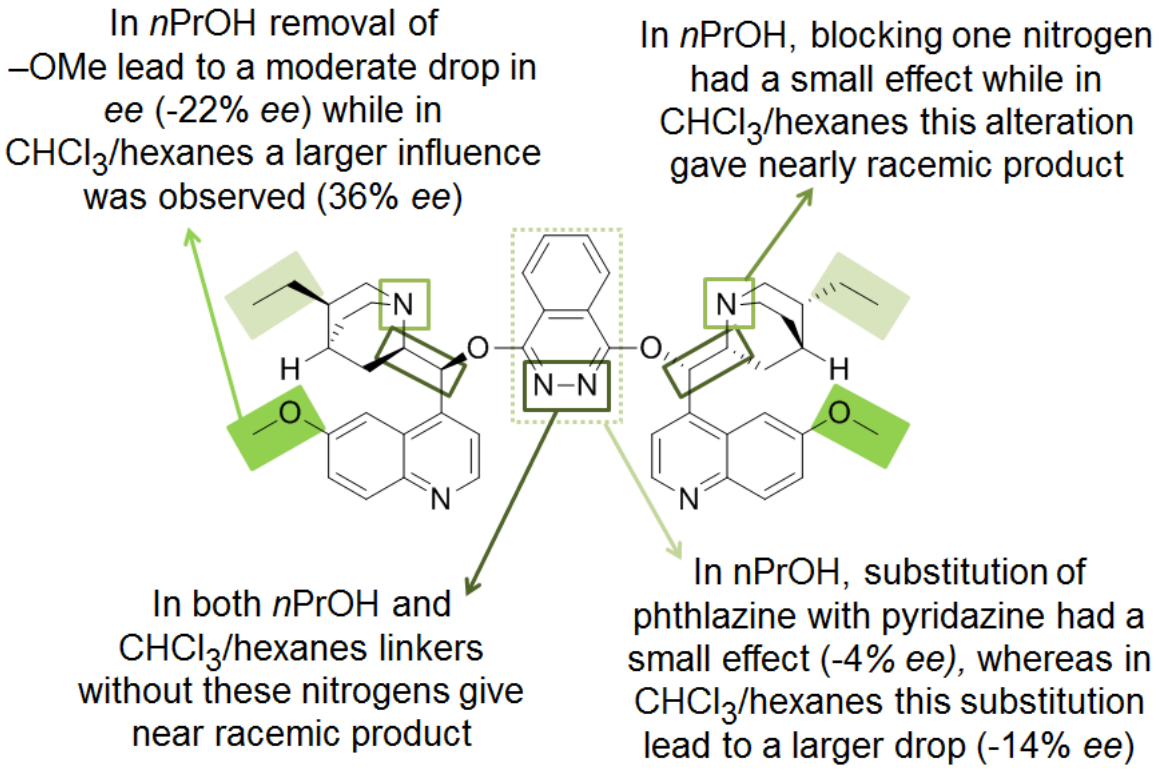


Figure II-9. Summary of asymmetric chlorocyclization of carbamates in both *n*ProH or $CHCl_3$/hexanes in SER studies.

to the catalyst strongly influence enantioselectivity perhaps because the enantioinducing site is less defined. For example by changing the linker from PHAL to PYDZ, the *n*PrOH system drops by a negligible amount (4% *ee)* while the $CHCl_3$/hexanes system drops by nearly 40% *ee.* This trend is fairly consistent throughout the screening, but there are a few things worth mentioning. In *n*PrOH, $(DHQD)_2$NAPY (**II-43**) gives 50% *ee* of the same enantiomer as $(DHQD)_2$PHAL (**II-9**) gives, which is noteworthy. The chlorolactonization and chlorocylization of carbamates in *n*PrOH deliver decent *ee's* with this catalyst, while the other substrates are nearly racemic. This could suggest that the structural features necessary for the substrate to interact with the catalyst are permitted in this catalyst, while not being favorable with the other substrates. Another set of catalysts that was interesting, especially for the *n*PrOH reaction, was the acyl linked dimeric scaffolds which delivered the cyclized product in modest *ee*'s, up to 58%.

From screening the chlorocyclization of carbamates in the two solvent systems, it was found that the reaction in nPrOH behaves similar to the chlorolactonization while the reaction in the mixture of chloroform and hexanes is intolerant to nearly every change in the catalyst. The similarity observed between the chlorolactonization and the chlorocyclization of carbamates in *n*PrOH may suggest that the way these substrates bind to the catalyst are similar.

II-8 Conclusions and Future Directions

The SER studies were helpful to provide clues hinting which parts of the catalyst were responsible for delivering high enantioselectivities in each class of substrates;

chlorolactonization and chlorocyclization of amides and carbamates. These results were also reiterative of our hypothesis that these reactions, most specifically the chlorolactonization and chlorocyclization of amides have different binding modes between the substrate and catalyst.

Linkers:

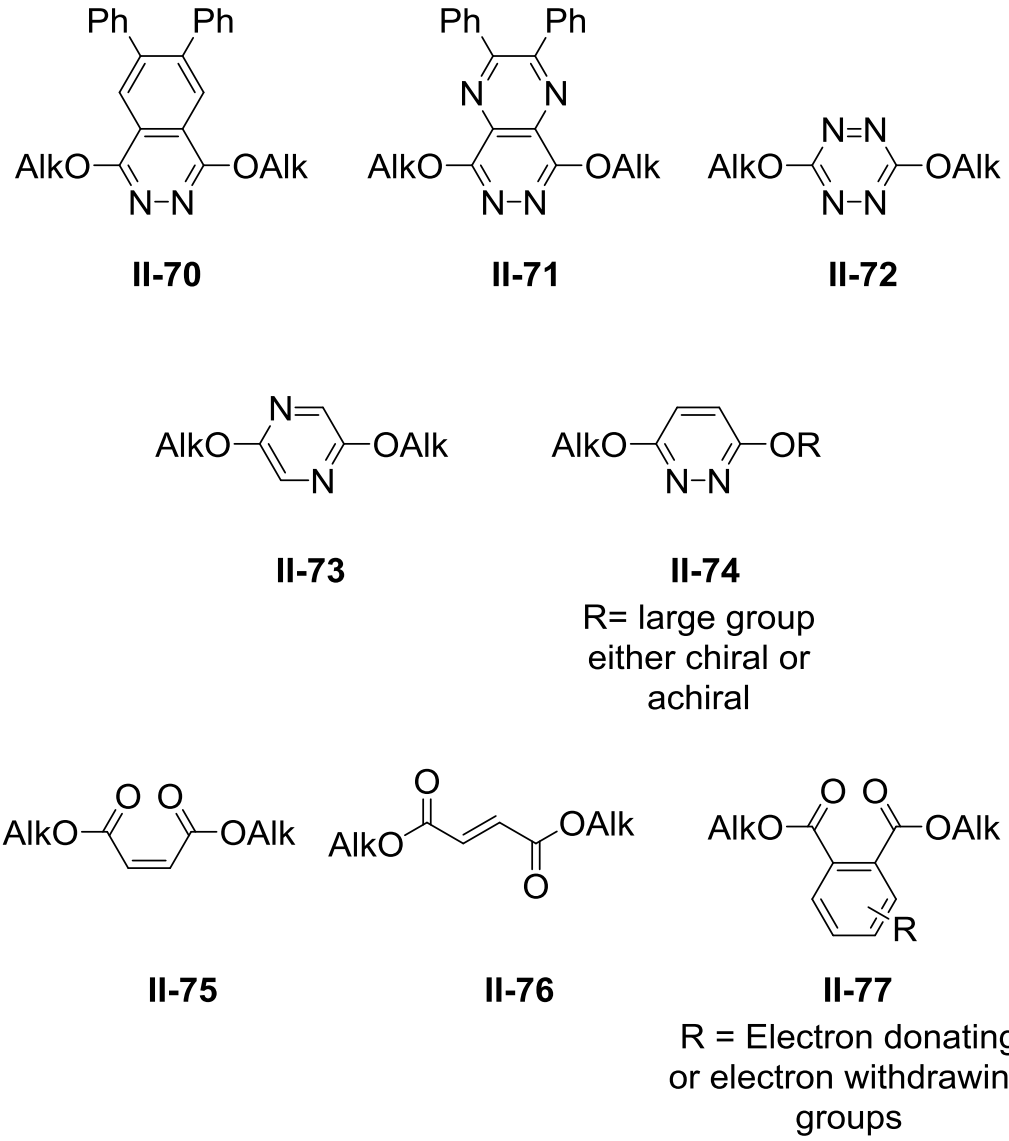


Figure II-10. Possible linkers to screen in future SER studies.

A number of other linkers can be proposed for future SER studies, which are shown in Figure II-10. Linkers **II-70** and **II-71** were made by Sharpless, and were found to place a steric wall behind the phthalazine linker. Because of the success with the phthalazine linker, these may be worth making.[29] Linker **II-72** having 4 nitrogens, should cause the synonymous bond rotation about the C_9-O-C=N to be less rigidified due to the symmetrical nature of the nitrogens. In relation to this, **II-73** should do the same. If the nitrogen- oxygen lone pair repulsion makes the catalyst take on an optimal conformation, then this catalyst should most likely give racemic product, however if the nitrogen is stabilizing the chloronium intermediate, this catalyst should still give respectable *ee's.* The last three, **II-75** through **II-75,** are various acyl linkers with **II-75** and **II-76** being more applicable to the amides SER studies, since succinyl linkers were found to deliver moderate *ee's.* Catalyst **II-77** is more applicable to the chlorolactonization reaction which gave a significant improvement with the *ortho*-acyl linker.

One last set of catalysts which have vast possibilities is scaffolds based on the truncated catalyst **II-61.** Various alkylations of the amino-alcohol starting material would be a good starting point, allowing a variety of groups not possible with *cinchona* alkaloids to be introduced, such as ureas, thioureas, sulfonyl, etc. An efficient route to synthesize a variety of these catalysts would be to start with a symmetrical olefin, do an asymmetric expoxidation, open the epoxide with the desired amine, and then link two units together.

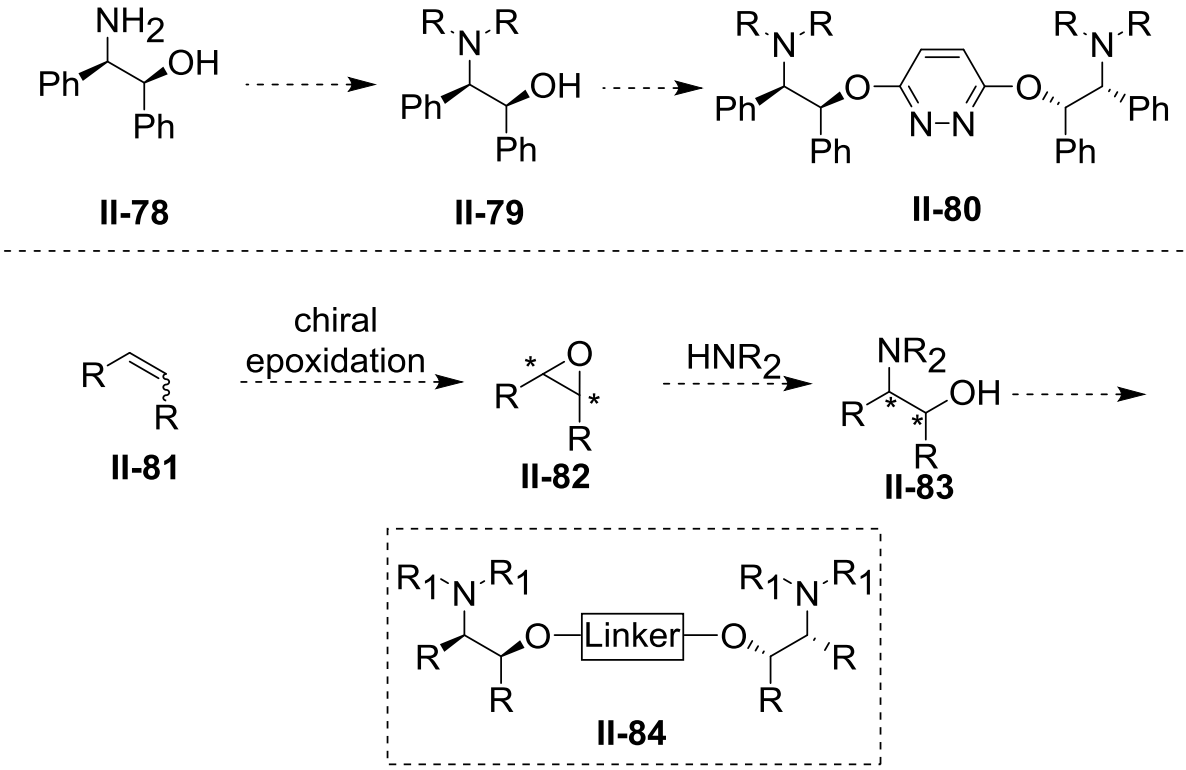
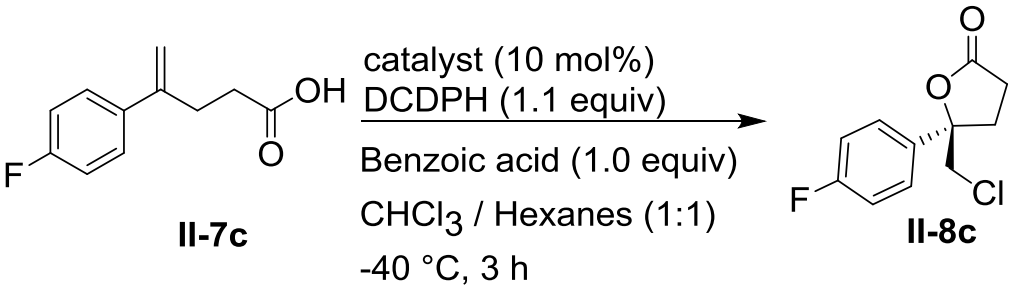


Figure II-11. Potential synthetic route to make a library of truncated catalysts.

II-9 Experimentals

All reagents were used without purification. 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 Fischer Scientific or Mallinckrodt Chemicals and were used without further purification. ^{1}H NMR spectra were measured at 300 or 500 MHz on a Varian Gemini-300 or a Varian VXR-500 instrument, respectively. Chemical shifts are reported relative to residual solvent (δ7.24 ppm for $CDCl_3$). 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.

(R)-5-(chloromethyl)-5-(4-fluorophenyl)dihydrofuran-2(3H)-one[15]



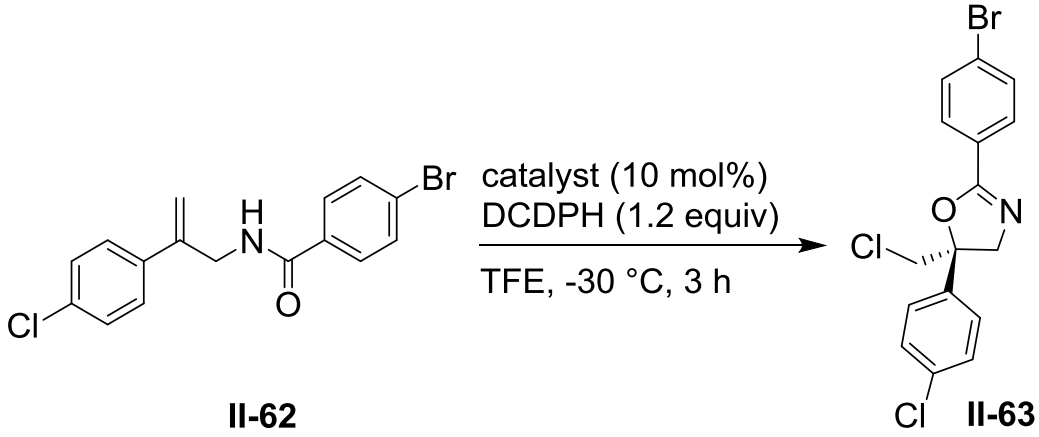
General Procedure for Lactonization Catalyst Screening: To a flame dried 30 mm x 100 mm disposable test tube was added catalyst (0.003 mmol, 0.10 equiv), chloroform (0.25 mL), and hexanes (0.25 mL). The reaction was cooled to -40°C using an immersion cooler. DCDPH (9 mg, 0.3 mmol, 1.1 equiv) and benzoic acid (3 mg, 0.03 mmol, 1.0 equiv) were then added and the reaction was stirred for 30 minutes. 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 hours. 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 then extracted with dichloromethane (3 x 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 as a colorless oil.

Data for (R)-5-(chloromethyl)-5-(4-fluorophenyl)dihydrofuran-2(3H)-one (**II-8c**): ^{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); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 173.8, 162.6 (d, $J_{C,F}$ = 247 Hz), 136.4, 126.8 (d, $^3J_{C,F}$ = 8.6 Hz), 116.0 (d, $^2J_{C,F}$ = 21.6 Hz), 86.6, 52.3, 31.7, 29.2; $[\alpha]^{20}_D$ = + 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.

(R)-2-(4-bromophenyl)-5-(chloromethyl)-5-(4-chlorophenyl)-4,5-dihydrooxazole[27]



II-62 **II-63**

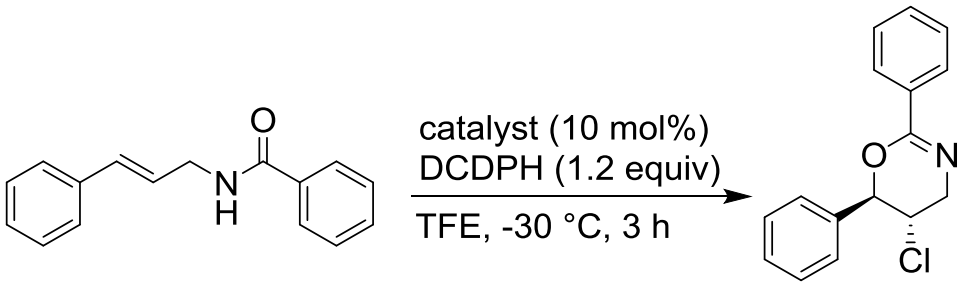
General Procedure for Screening 1,1-Disubstituted Olefin Amide Cyclization: To a flame dried 30 mm x 100 mm disposable test tube was added catalyst (0.003 mmol, 0.10 equiv) and trifluoroethanol (0.63 mL). The reaction was cooled to -30°C using an immersion cooler and then DCDPH (10 mg, 0.031 mmol, 1.2 equiv) was added and the reaction was stirred for 10 minutes. 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 3 hours. 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 x 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 as a yellow gum.

Data for (R)-2-(4-bromophenyl)-5-(chloromethyl)-5-(4-chlorophenyl)-4,5-dihydrooxazole(**II-63**): ^{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); ^{13}C 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; $[\alpha]^{20}_{D}$ = -73.8° (*c* = 10 mg / mL, $CDCl_3$).

LC Resolution of enantiomers: CHIRAL-CEL OJ-H; 5% *iso*-propyl alcohol in hexanes, 1.0 mL / min, 254 nm, RT_1 = 18.81 min, RT_2 = 21.59 min.

(5S,6R)-5-chloro-2,6-diphenyl-5,6-dihydro-4H-1,3-oxazine[27]



II-64 **II-65**

General Procedure for Screening *trans*-Disubstituted Olefin Amide Cyclization: To a flame dried 30 mm x 100 mm disposable test tube was added catalyst (0.003 mmol, 0.10 equiv) and trifluoroethanol (0.63 mL). The reaction was cooled to -30 °C using an

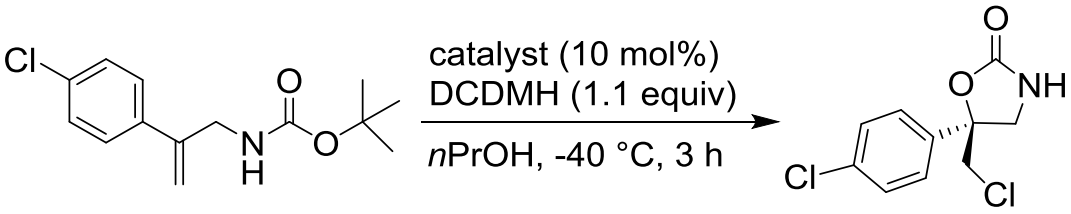
immersion cooler and then DCDPH (10 mg, 0.031 mmol, 1.2 equiv) was added and the reaction was stirred for 10 minutes. N-Cinnamylbenzamide (6 mg, 0.03 mmol) was then added and the reaction was stirred at -30 °C for 3 hours. The reaction was monitored by TLC (20% ethyl acetate in hexanes, $KMnO_4$ charred). The reaction was quenched with 10% aqueous sodium thiosulfite (2.0 mL). The reaction was then extracted with dichloromethane (3 x 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 as a colorless oil.

Data for (5S,6R)-5-chloro-2,6-diphenyl-5,6-dihydro-4H-1,3-oxazine (**II-65**):

^{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); ^{13}C 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; $[\alpha]^{20}_D$ = -21.0° (*c* = 10 mg / mL, $CDCl_3$).

LC Resolution of enantiomers: CHIRAL-CEL OD-H; 100% hexanes, 1.5 mL / min, RT_1 = 46.12 min, RT_2 = 53.76 min.

(S)-5-(chloromethyl)-5-(4-chlorophenyl)oxazolidin-2-one[28]



II-66 **II-67**

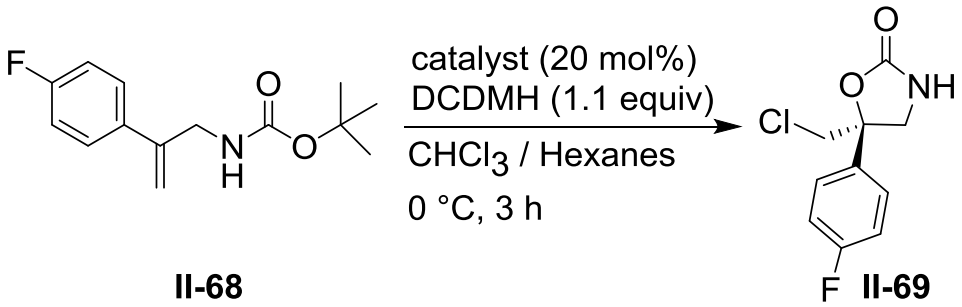
General Procedure for Screening Carbamate Cyclization in *n*PrOH: To a flame dried 30 mm x 100 mm disposable test tube was added catalyst (0.003 mmol, 0.10 equiv) and *n*PrOH (0.50 mL). The reaction was cooled to -40 °C using an immersion cooler and then DCDMH (6 mg, 0.03 mmol, 1.1 equiv) was added and the reaction was stirred for 10 minutes. Tert-butyl (2-(4-chlorophenyl)allyl)carbamate (7 mg, 0.03 mmol) was then added and the reaction was stirred at -40 °C for 3 hours. The reaction was monitored by TLC (20% ethyl acetate in hexanes, $KMnO_4$ charred). *The product is not visible using UV or any stain, so reaction completion was based on disappearance of starting material.* The reaction was quenched with 10% aqueous sodium hydroxide (2.0 mL). The reaction was then extracted with dichloromethane (3 x 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, elute 10 mL, then 50% ethyl acetate, elute 10 mL), giving the product as a colorless oil.

Data for (S)-5-(chloromethyl)-5-(4-chlorophenyl)oxazolidin-2-one (**II-67**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.29 (m, 4H), 5.13 (br, 1H), 4.09 (d, *J* = *8.7* Hz, 1H), 3.83-3.71 (m,

3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 145.5, 133.9, 128.8, 127.5, 112.7, 43.8, 28.1; $[\alpha]^{20}_D$ = + 3.0° (*c* = 10 mg / mL, $CDCl_3$).

GC Resolution of enantiomers: GAMMA DEX 225; 90 °C for 2 min, 90°C to 220 °C ramp (5 °C / min), 220 °C for 90 min; RT_1 = 27.67 min, RT_2 = 27.90 min.

(R)-5-(chloromethyl)-5-(4-fluorophenyl)oxazolidin-2-one[28]



II-68 **II-69**

General Procedure for Screening Carbamate Cyclization in $CHCl_3$ / Hexanes: To a flame dried 30 mm x 100 mm disposable test tube was added catalyst (0.003 mmol, 0.10 equiv), chloroform (0.49 mL), and hexane (0.49 mL). The reaction was cooled to 0 °C using an immersion cooler and then DCDMH (6 mg, 0.03 mmol, 1.1 equiv) was added and the reaction was stirred for 10 minutes. Tert-butyl (2-(4-fluorophenyl)allyl)carbamate (7 mg, 0.03 mmol) was then added and the reaction was stirred at 0 °C for 3 hours. The reaction was monitored by TLC (20% ethyl acetate in hexanes, $KMnO_4$ charred). *The product is not visible with UV light or any type of stain.* The reaction was quenched with 10% aqueous sodium hydroxide (2.0 mL). The reaction was then extracted with dichloromethane (3 x 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, elute ~ 10 mL, then 50% ethyl acetate in hexanes, elute 10 mL), giving the product as a colorless oil.

Data for (R)-5-(chloromethyl)-5-(4-fluorophenyl)oxazolidin-2-one (**II-69**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.36 (m, 2H), 7.09 (t, *J* = 8.5 Hz, 2H), 5.45 (br, 1H), 4.11 (d, *J* = 8.7 Hz, 1H), 3.82 (d, *J* = 12.1 Hz, 1H), 3.76 (d, *J* = 8.7 Hz, 1H), 3.71 (d, *J* = 12.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4 (d, $^{1}J_{C,F}$ = 246 Hz), 155.5, 145.5, 128.0 (d, $^{3}J_{C,F}$ = 8 Hz), 116.1, (d, $^{2}J_{C,F}$ = 22 Hz), 112.6, 43.6. 28.2; $[\alpha]^{20}_{D}$ = - 6° (*c* = 10 mg / mL, $CDCl_3$).

GC Resolution of enantiomers: GAMMA DEX 225; 90 °C for 2 min, 90 °C to 220°C ramp (5 °C / min), 220 °C for 90 min; RT_1 = 37.74 min, RT_2 = 38.59 min.

REFERENCES

REFERENCES

1. Castellanos, A.; Fletcher, S. P., *Chemistry – A European Journal* **2011,** *17*, 5766-5776.

2. Ibrahim, H.; Togni, A., *Chem. Commun.* **2004**, 1147-1155.

3. Moyano, A.; Rios, R., *Chem. Rev.* **2011,** *111*, 4703-4832.

4. Chen, Z.-M.; Zhang, Q.-W.; Chen, Z.-H.; Li, H.; Tu, Y.-Q.; Zhang, F.-M.; Tian, J.-M., *J. Am. Chem. Soc.* **2011,** *133*, 8818-8821.

5. Wang, B.; Tu, Y. Q., *Acc. Chem. Res.* **2011,** *44*, 1207-1222.

6. Nicolaou, K. C.; Simmons, N. L.; Ying, Y.; Heretsch, P. M.; Chen, J. S., *J. Am. Chem. Soc.* **2011,** *133*, 8134-8137.

7. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B., *Chem. Rev.* **1994,** *94*, 2483-2547.

8. Katsuki, T., *Adv. Synth. Catal.* **2002,** *344*, 131-147.

9. Katsuki, T.; Martin, V., Asymmetric Epoxidation of Allylic Alcohols: the Katsuki–Sharpless Epoxidation Reaction. In *Organic Reactions*, John Wiley & Sons, Inc.: 2004.

10. Wong, O. A.; Shi, Y., *Chem. Rev.* **2008,** *108*, 3958-3987.

11. O'Brien, P., *Angew. Chem. Int. Ed.* **1999,** *38*, 326-329.

12. Olah, G. A.; Bollinger, J. M., *J. Am. Chem. Soc.* **1968,** *90*, 947-953.

13. Denmark, S. E.; Burk, M. T., *Proceedings of the National Academy of Sciences* **2010,** *107*, 20655-20660.

14. Whitehead, D. C. The development of a novel asymmetric halolactonization and the investigation of peptidic ligands for osmium tetroxide mediated transformations. Michigan State University, ProQuest Dissertation and Thesis, 2009.

15. Whitehead, D. C.; Yousefi, R.; Jaganathan, A.; Borhan, B., *J. Am. Chem. Soc.* **2010,** *132*, 3298-3300.

16. Kolb, H. C.; Andersson, P. G.; Sharpless, K. B., *J. Am. Chem. Soc.* **1994,** *116*, 1278-1291.

17. Yousefi, R. Michigan State University, East Lansing, MI, 2012.

18. Yousefi, R. A., K.D.; Whitehead, D.C.; Jackson, J.E.; Borhan, B., *Submitted.* **2012**.

19. Yousefi, R.; Whitehead, D. C.; Mueller, J. M.; Staples, R. J.; Borhan, B., *Org. Lett.* **2011,** *13*, 608-611.

20. Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H., *The Journal of Organic Chemistry* **1990,** *55*, 6121-6131.

21. Li, H.; Liu, X.; Wu, F.; Tang, L.; Deng, L., *Proceedings of the National Academy of Sciences* **2010,** *107*, 20625-20629.

22. Ogino, Y.; Chen, H.; Manoury, E.; Shibata, T.; Beller, M.; Lübben, D.; Barry Sharpless, K., *Tetrahedron Lett.* **1991,** *32*, 5761-5764.

23. Becker, H.; Tong Ho, P.; Kolb, H. C.; Loren, S.; Norrby, P.-O.; Sharpless, K. B., *Tetrahedron Lett.* **1994,** *35*, 7315-7318.

24. Amberg, W.; Bennani, Y. L.; Chadha, R. K.; Crispino, G. A.; Davis, W. D.; Hartung, J.; Jeong, K. S.; Ogino, Y.; Shibata, T.; Sharpless, K. B., *The Journal of Organic Chemistry* **1993,** *58*, 844-849.

25. Markovic, Z. B., Dalibor; Gutman, Ivan, *J. Serb. Chem. Soc.* **2004,** *69*, 877-882.

26. Zhou, L.; Chen, J.; Tan, C. K.; Yeung, Y.-Y., *J. Am. Chem. Soc.* **2011,** *133*, 9164-9167.

27. Jaganathan, A.; Garzan, A.; Whitehead, D. C.; Staples, R. J.; Borhan, B., *Angew. Chem. Int. Ed.* **2011,** *50*, 2593-2596.

28. Garzan, A. Asymmetric Electrophilic Halocyclization Reactions. Michigan State University, East Lansing, Michigan, 2012.

29. Becker, H.; King, S. B.; Taniguchi, M.; Vanhessche, K. P. M.; Sharpless, K. B., *The Journal of Organic Chemistry* **1995,** *60*, 3940-3941.

Chapter III: Synthesis of *Cinchona* Alkaloid Catalysts for Structure Enantioselectivity Relationship Studies

III-1 Introduction

Chapter II disclosed the SER studies of various chlorocyclizations using a number of *cinchona* alkaloid catalysts. This chapter will unveil the synthetic efforts towards each of these catalyst scaffolds. Fundamentally the syntheses of these scaffolds can be broken down into 2 classifications; those pertaining to linkers and those pertaining to the *cinchona* alkaloid. The linkers category can be further broken down into the synthesis of catalysts with aryl or acyl tethers; whereas the alkaloid variations include the quinoline substituent, the vinyl group of the quinuclidine, the stereochemistry of the C_9-carbinol, alkylation of the quinuclidine nitrogens, and the synthesis of a truncated alkaloid mimic. This chapter will detail the synthesis of these catalyst analogs, with each section including a brief literature summary pertaining to relevant work.

III-2 Synthesis of Catalysts with Aryl Linkers

A variety of aryl linker catalysts were desired for the SER studies of the different $(DHQD)_2PHAL$ catalyzed chlorocyclizations. Initially we envisioned several aryl linked scaffolds, having various electronics, ranging from relatively electron deficient pyridazine to electronically neutral phenyl (Figure III-1). As with any synthetic venture, we proposed a general retrosynthetic scheme to access all of these dimers, involving an S_NAr reaction between the *cinchona* alkaloid subunits and respective dihalogenated

linker in the presence of base (Figure III-1). To acquire a better understanding of S_NAr reactions, we turned to the literature to thoroughly investigate related efforts.

The literature contains two general methods for conducting an S_NAr between two *cinchona* alkaloids and an electron deficient aryl linker, either the use of a weaker base and the azeotropic distillation of water or the use of a strong base, such as sodium hydride or *n*-butyl lithium. The classic example of a weaker base, driven by the azeotropic distillation of water, comes from the Sharpless lab who published the first synthesis of $(DHQD)_2PHAL$. Their synthesis of this scaffold involves DHQD, 1,4-dichlorophthalazine, potassium carbonate, and potassium hydroxide in toluene, giving the product in 88% yield (Scheme III-1a).[1-4]

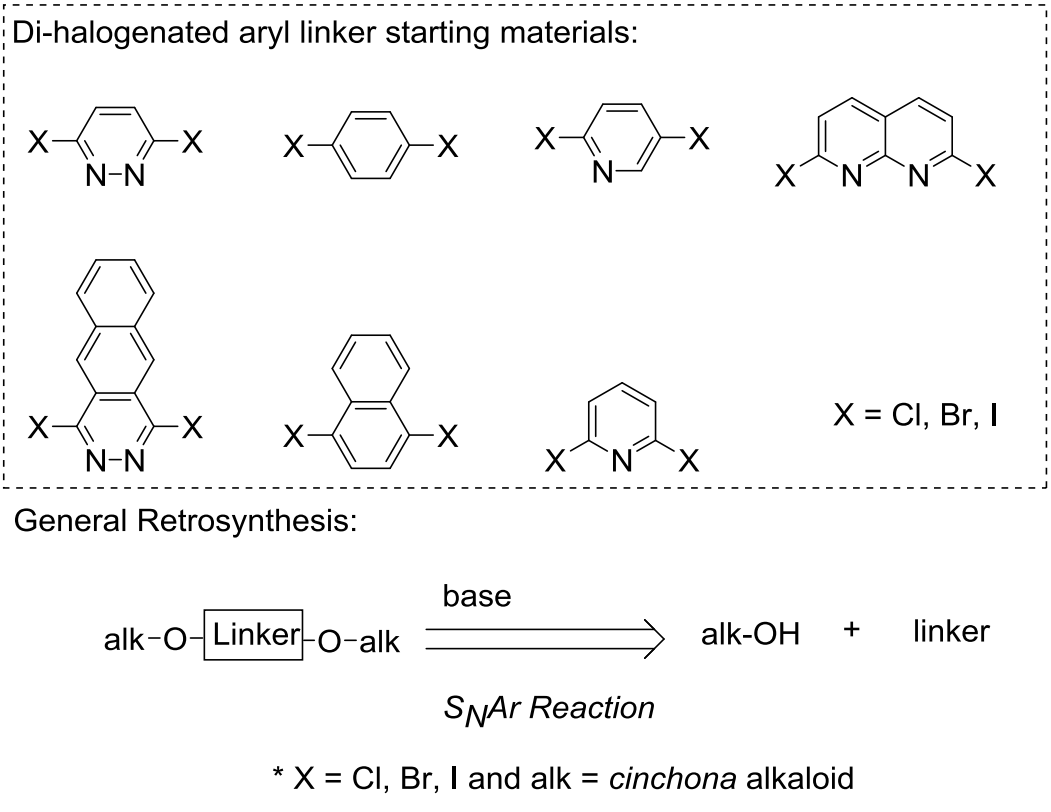
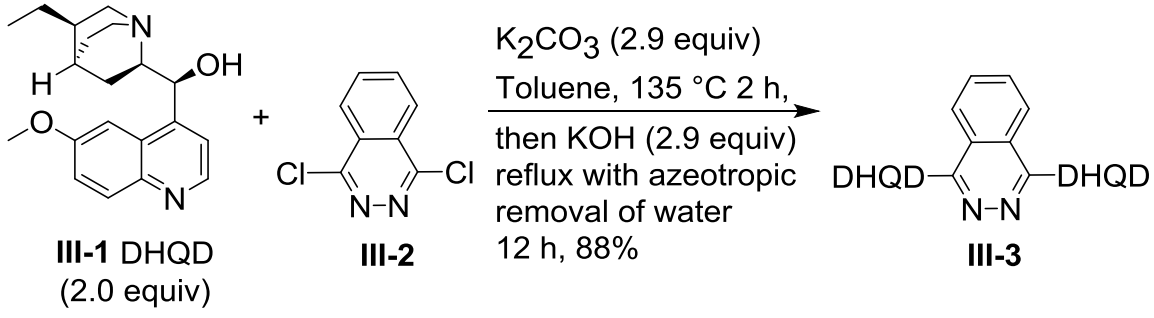


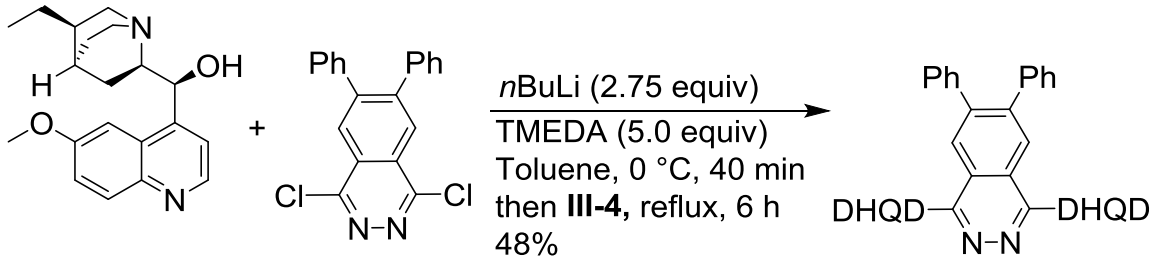
Figure III-1. Linker starting materials and general retrosynthetic route to access various aryl linked dimeric catalysts.

a) *Sharpless (1993):*



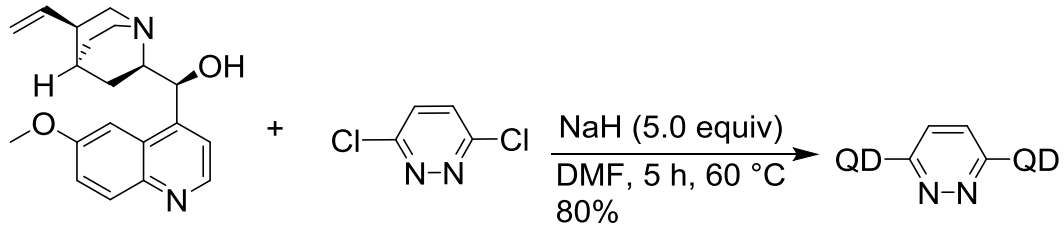
III-1 DHQD (2.0 equiv) **III-2** **III-3**

b) *Sharpless (1995):*



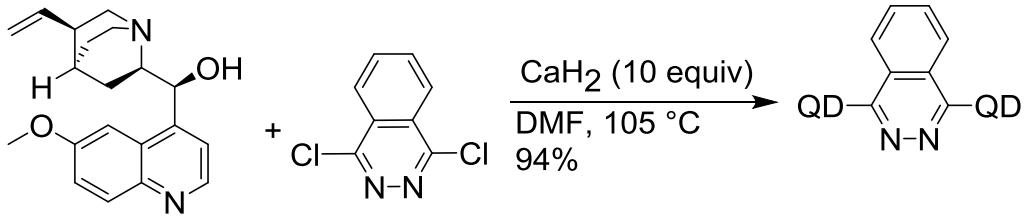
III-1 DHQD (2.5 equiv) **III-4** **III-5**

c) *Zhang (2007):*



III-6 QD (2.0 equiv) **III-7** **III-8**

d) *Zhang (2008):*



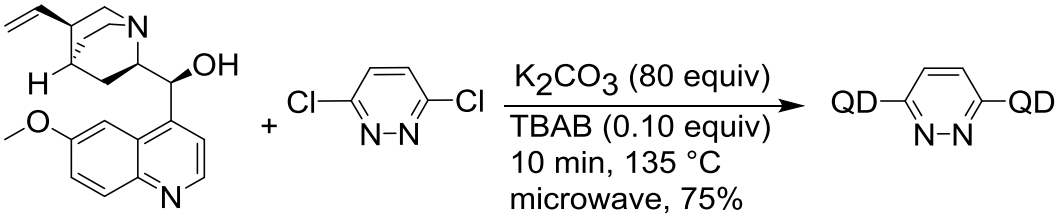
III-6 QD (2.2 equiv) **III-2** **III-9**

Scheme III-1. Literature precedent S_NAr reactions using electron deficient aryl linkers.

In 1995, Sharpless reported a different procedure utilizing a strong base to synthesize a similar scaffold (Scheme III-1b**)**. This procedure used *n*-butyl lithium in a mixture of TMEDA and toluene, to give the product in 48% yield.[5] In 2007 and 2008, Zhang's group reported two similar procedures, using sodium hydride or calcium hydride to give the desired dimeric scaffold in good to excellent yields (Scheme III-1c-d).[6, 7]

One other recently developed reaction from the Zhang group requires the use of a microwave and is solvent-free. This reaction uses a large excess of potassium carbonate and a catalytic amount of tetrabutylammonium bromide (TBAB), as a phase transfer catalyst, to give the dimeric alkaloid product in 75% yield (Scheme III-2).[8, 9]

All the dimerizations discussed until now have contained pyridazine or phthalazine linkers, which are relatively electron deficient aromatics. This makes the S_NAr more favorable since these linkers are better electrophiles. However, when the linker is changed to a weaker electrophile, such as a 1,4-dihalogenated benzene, the analogous reactions are not reported. In fact a dimeric *cinchona* alkaloid catalyst linked by phenyl is absent from the literature, with the most similar structure being a

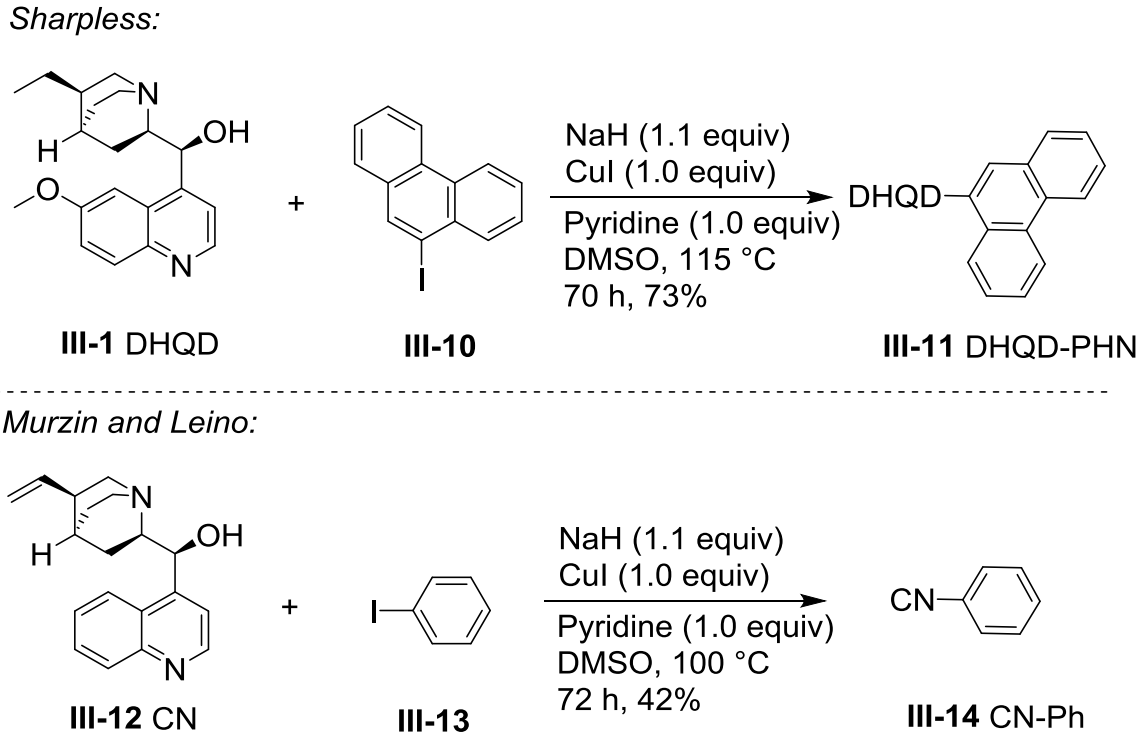


III-6 QD (2.0 equiv) **III-7** **III-8**

Scheme III-2. S_NAr reaction between alkaloid and electron deficient linker requiring use of a microwave.

monomeric alkaloid bearing a phenyl on the C_9-hydroxyl (**III-14**).[10] All reported syntheses of alkaloids bearing hydrocarbon aromatics on the C_9-hydroxyl utilize an Ullman coupling, with the procedure originating from the Sharpless group in their synthesis of a C_9-phenanthroline substituted alkaloid (Scheme III-3).[2]

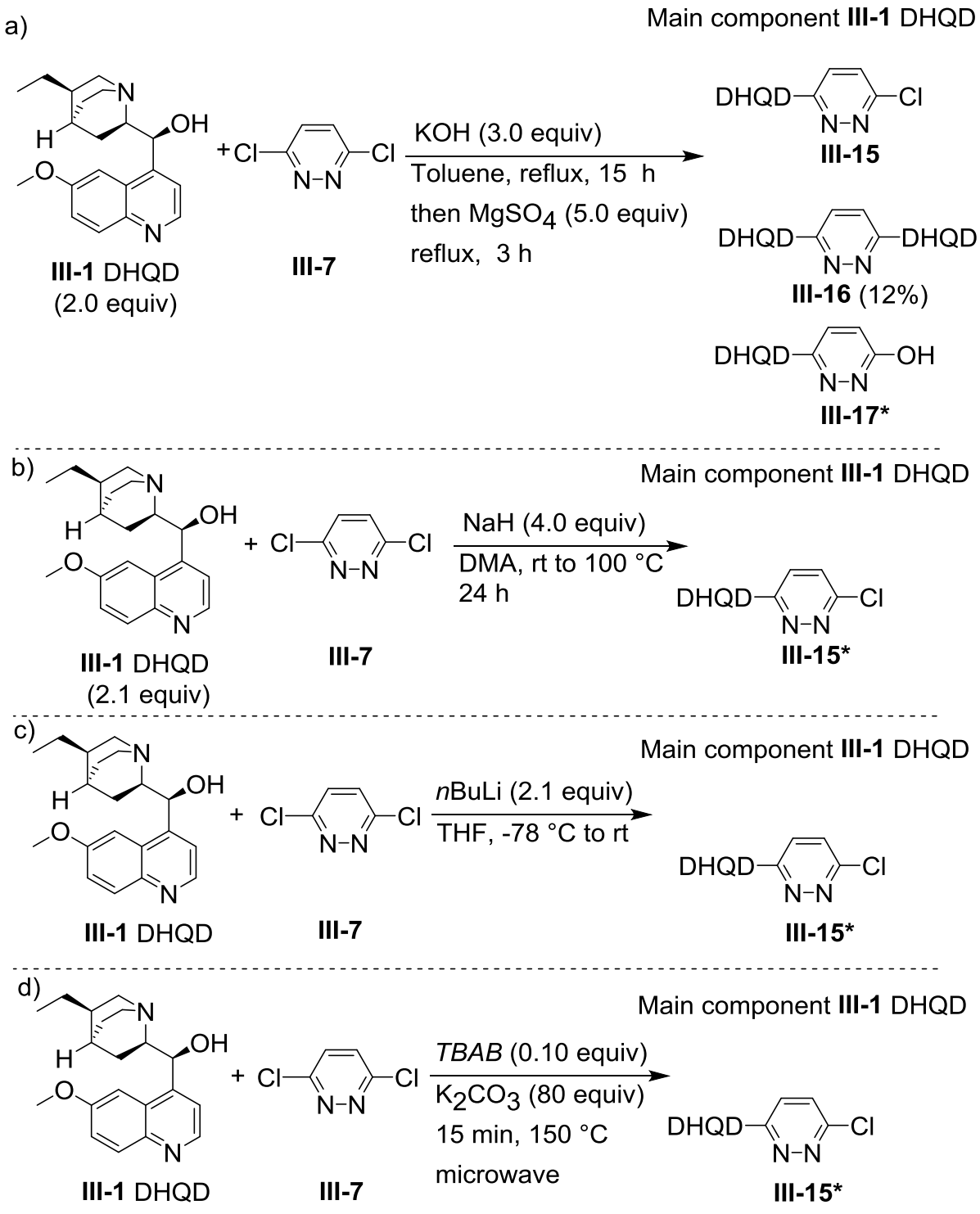
Having this information in hand, we hypothesized that the synthesis of dimers featuring heterocyclic aromatic linkers should be attainable via basic conditions (*n*BuLi, NaH, CaH_2, etc); while the hydrocarbon aromatics would most likely require an Ullman coupling. We began our synthetic investigations towards dimers with heterocyclic aromatic linkers (pyridazine, naphthyridine, pyridine, etc.) *The success of most of these reactions was determined via MS since the catalysts are C_2-symmetric dimers, which makes ^{1}H NMR analysis difficult. If the mass of the desired product was not observed,*



Scheme III-3. Ullman coupling of aryl halides and *cinchona* alkaloids.

no further characterization was pursued.

Initially we screened the literature precedent reactions with 2,6-dichloropyridazine and DHQD, which all had limited success. The first reaction used the procedure from Sharpless' lab involving the azeotropic distillation of water (Scheme III-4a).[2] Initially we tried this reaction on small scale (300 mg DHQD, 0.9 mmol) and after 24 hours, MS indicated the mass of our desired product, in conjunction with DHQD (**III-1**), mono-addition (**III-15**) and the mono-addition which underwent an S_NAr with hydroxide (**III-17**). The problem, however, was that even after 36 hours at reflux, the reaction would not go to completion and purification of the product proved to be challenging. Therefore, since azeotropic distillation can be difficult on small scale, the scale of the reaction was increased (1 gram DHQD, 1.1 mmol) in hopes of improving water removal and also providing more material for purification. This reaction also would not proceed to completion (even with a small Dean-Stark trap the azeotropic distillation mainly led to solvent evaporation) so after 15 hours, anhydrous magnesium sulfate was added to the reaction. This did seem to help the reaction progress however the reaction still did not proceed to completion. From this reaction 12% of the desired product (**III-16**) was obtained, with the mass balance containing a mixture of DHQD, **III-15**, and **III-17.** Because we were hoping to include a number of substrates in the SER studies, this large reaction scale was not amenable to acquire the desired scaffolds in such low yield. Therefore we decided to screen other literature precedent reactions.

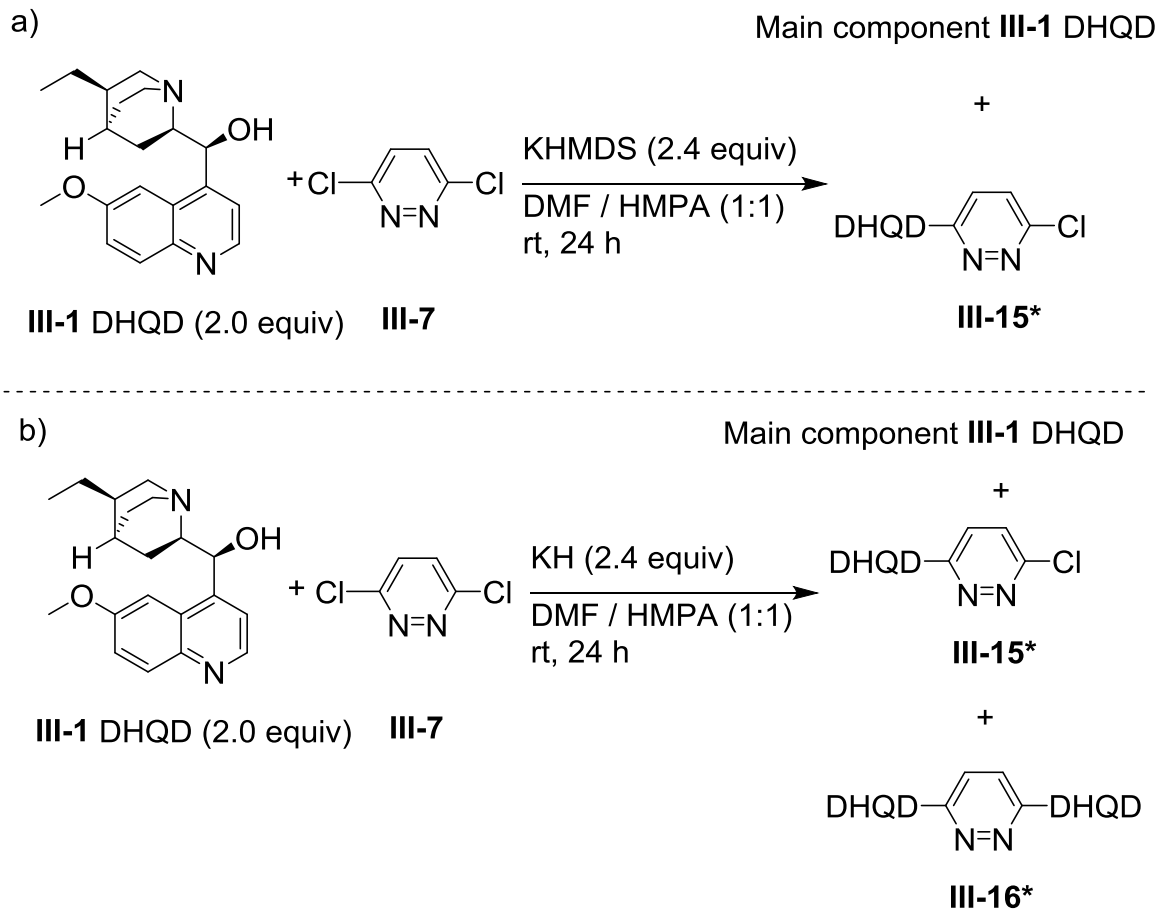


Scheme III-4. Preliminary screening of literature precedent S_NAr reactions.
*MS determined existence of product.

Since it seemed that the azeotropic removal of water was the problem in the previous method, we tried sodium hydride as the base, which should resolve the issue (Scheme III-4b). Following the precedent procedure,[6] MS analysis of this reaction indicated only trace amounts of the mono-addition product (**III-15**), with the main component being the starting alkaloid. Even with high temperatures and excess base, this reaction would not progress. In related efforts, we also tried the reaction with *n*-butyl lithium, which gave the same low conversion to the mono-addition product (**III-15**) (Scheme III-4c).[5]

As a last attempt, the solvent-free microwave reaction was tried (Scheme III-4d).[9] Even after heating the reaction up to 250 °C, the only observed product from this reaction was trace amounts of the mono-addition product. Two hypotheses for why this method failed could be attributable to our microwave reactor. The authors of the paper cite that their microwave was set at 850 Watts for 10 minutes, however a temperature is not specified. Our microwave reactor has an upper limit of 400 Watts, but allows for temperature variation up to 250 °C. In conjunction with this, the IR sensor in the reactor may not be able to accurately monitor the temperature since it is a solid phase reaction.

At this point, we tried to draw conclusions from our limited successes to direct our optimization studies. The only reaction that formed the dimer used potassium carbonate as a base; and when sodium hydride or *n*-butyl lithium was used, no dimerized product was detected. (The microwave studies were somewhat inconclusive due to the inconsistencies in microwave reactors.) From this, we ultimately concluded that the counterion of the base may be playing a significant role, with potassium working

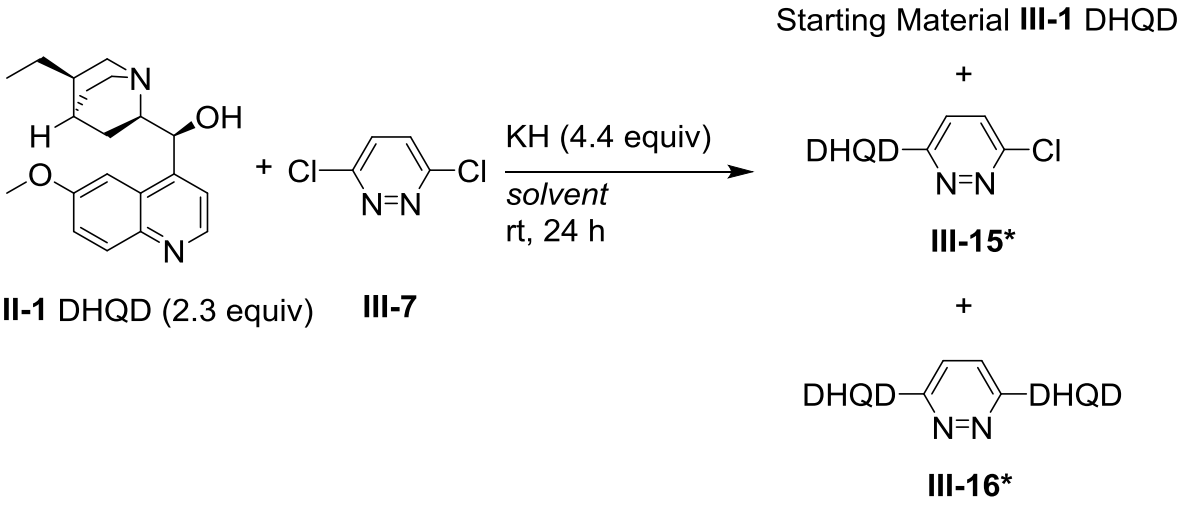


Scheme III-5. Screening of potassium bases in dimerization reaction.
*MS analysis determined existence of compound.

the best. This is a rational hypothesis since potassium, being the largest cation, should create the most dissociated metal - alkoxide species. Therefore we decided to investigate the use of various potassium bases.

The two bases that we decided to pursue were potassium hexamethyl disilazide (KHMDS) and potassium hydride (KH). Initially we screened these reactions in a solvent mixture of DMF and HMPA, since there are reported S_NAr procedures using this blend (Scheme III-5).[11, 12] With KHMDS, a mixture of DHQD and mono-addition (**III-15**) was obtained, however with KH, in addition to DHQD and the mono-addition product

Table III-1. Solvent screening for dimerization reaction.

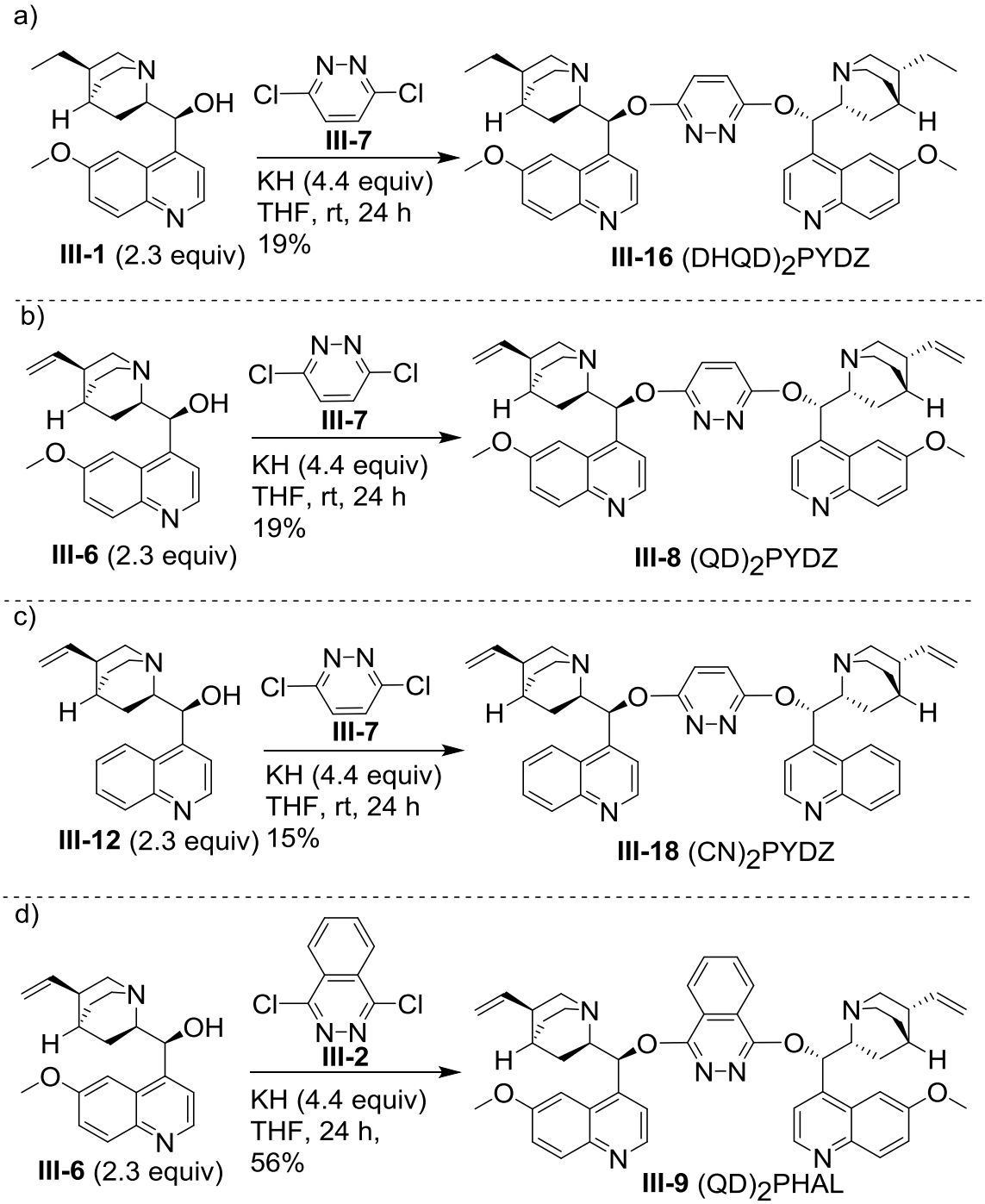


Entry	Solvent	III-1	III-15	III-16
1	DMSO / HMPA (1:1)	68%	32%	-
2	DMF / HMPA (1:1)	56%	22%	22%
3	DMF	74%	17%	9%
4	HMPA	93%	7%	-
4	DMF / TMEDA (1 equiv)	61%	39%	-
6	DMF / HMPA (1:2)	90%	10%	-
7	DMF / HMPA (2:1)	50%	28%	22%
8	DMF / HMPA (2.5 / 0.5)	75%	25%	-
9	DMF / HMPA (2.75 / 0.25)	44%	50%	5%
10	DMF / HMPA (2.99 / 0.01)	45%	45%	10%
11	THF (3.0)	-	-	100%

*Product ratio determined by crude ^{1}H NMR analysis. Solvent ratios based on total volume of solvent (3 mL). All reactions used 25 mg (0.08 mmol) of DHQD.

(**III-15)**, the desired dimer had also formed **(III-16)**. We therefore turned to optimizing this reaction with KH. We began our optimization studies by investigating a number of solvent systems. We envisioned a polar, aprotic solvent should be favorable since it should provide stabilization of the polar transition state. We initially began by screening DMSO and DMF with additives such as TMEDA or HMPA. Initially we found that a mixture of DMF / HMPA was better than a mixture of DMSO / HMPA (Table III-1, entries 1-2). We then investigated if DMSO or HMPA alone worked better, with both of these leading to none of the desired product. Since HMPA as an additive worked, we also looked at TMEDA which is known to chelate cations, in turn increasing the nucleophilicity of the alkoxide anion; however this was detrimental (Table III-1, entry 4). We therefore screened a range of ratios of DMF to HMPA (Table III-1, entries 6-10) to find that the best conditions (DMF / HMPA, 2:1) gave only 22% conversion to the desired product. Since there was no apparent trend in this optimization, we decided to look at other solvents, beginning with THF. Surprisingly we found that the reaction proceeded cleanly to full conversion (Table III-1, entry 11).

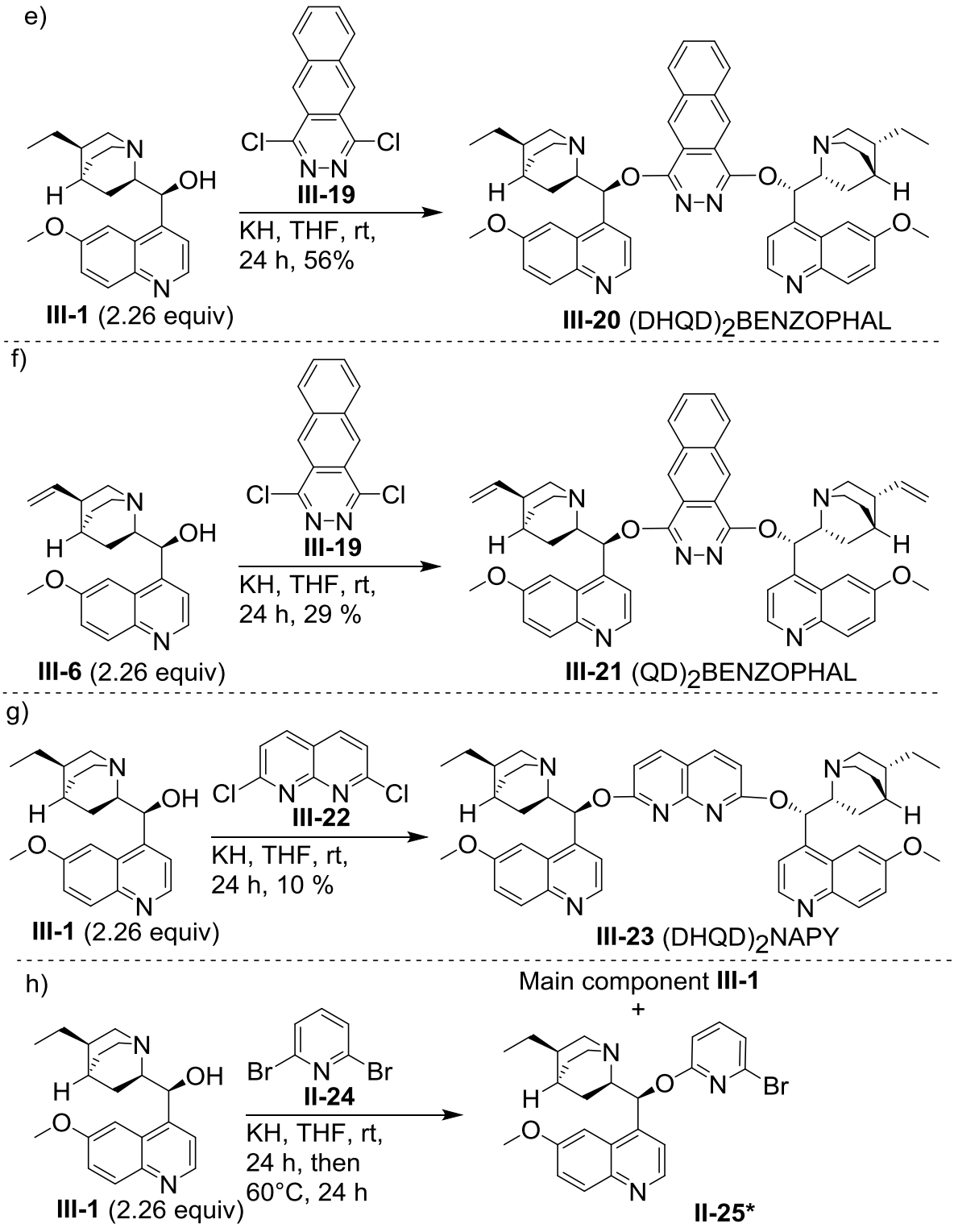
These reactions conditions for the S_NAr proved to be applicable to a variety of electron deficient linkers and alkaloids. These conditions cleanly carried most analogous reactions to full conversion. Scheme III-6 lists the dimers comprised of commercially available alkaloids synthesized with the methodology. The isolated yields for most of these reactions are low, simply because only the fractions deemed pure by ^1H NMR analysis were accounted for. The 1,4-dichlorophthalazine and 1,4-dichlorobenzophthalazine linkers were synthesized using literature procedures which



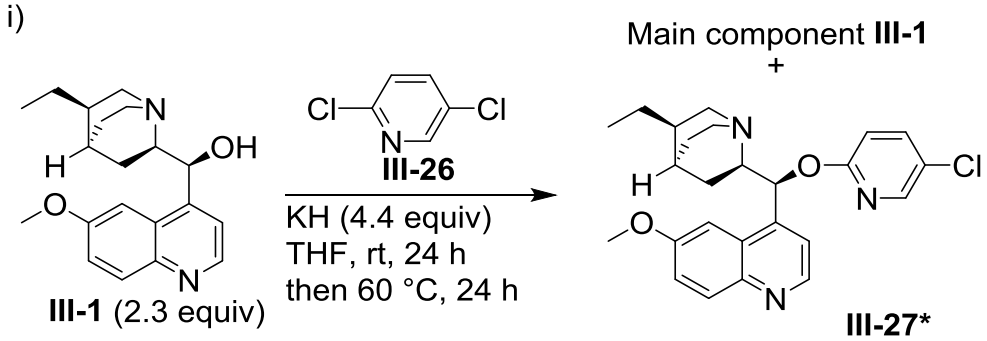
Scheme III-6. Synthesis of various dimers with electron deficient linkers.

*MS analysis determined existence of compound.

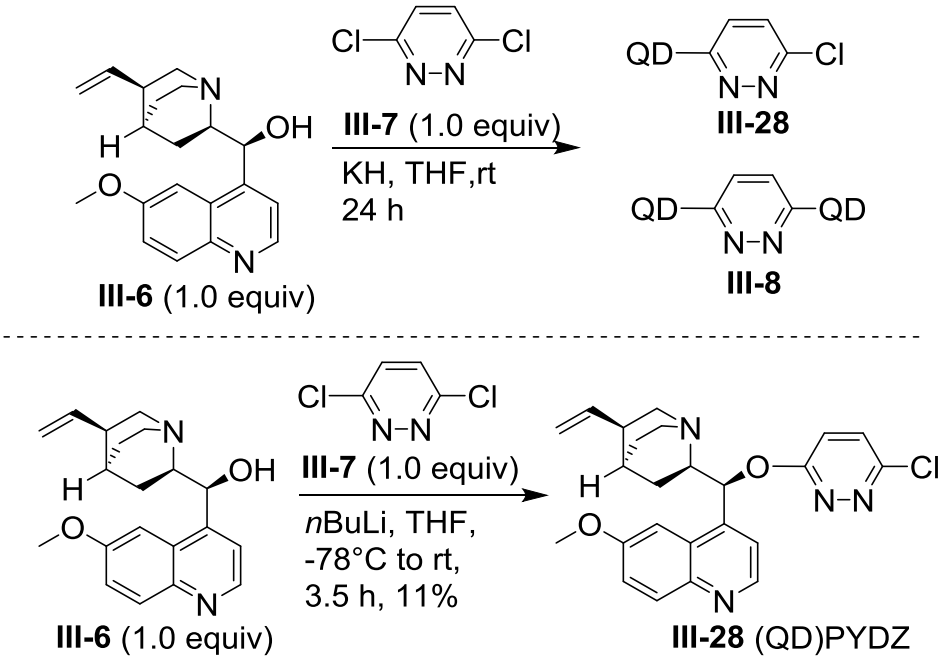
Scheme III-6 (cont'd).



Scheme III-6 (cont'd).



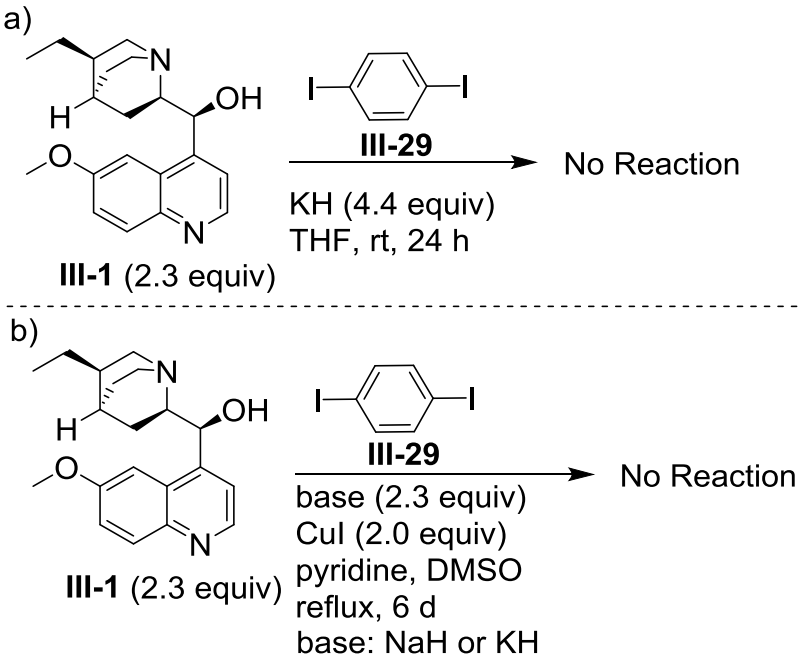
can be found in the experimental section.[13-16] There were two desired dimers which were not successfully synthesized using this methodology (Scheme III-6, h-i), featuring linkers with 2,6-dibromo- and 2,5-dichloro- pyridine moieties. Even after heating, the MS of these reactions only indicated the monoaddition product and starting material. This is most likely due to the linker not being electron deficient enough after the monoaddition to promote the second S_NAr reaction.



Scheme III-7. Synthesis of monomeric pyridazine-alkaloid scaffold.

One other catalyst scaffold we desired featuring an electron deficient linker was a monomeric alkaloid – pyridazine scaffold. Using a 1 to 1 quinidine / 2,6-dichloropyridazine equivalency in KH and THF yielded a mixture of mono- and dimeric addition products, which as we already knew were difficult to separate. Therefore, we decided to generate the less reactive lithium alkoxide, using *n*-butyl lithium as the base, which we already knew exclusively gave the monoaddition product.[17] This reaction cleanly gave the desired compound (Scheme III-7).

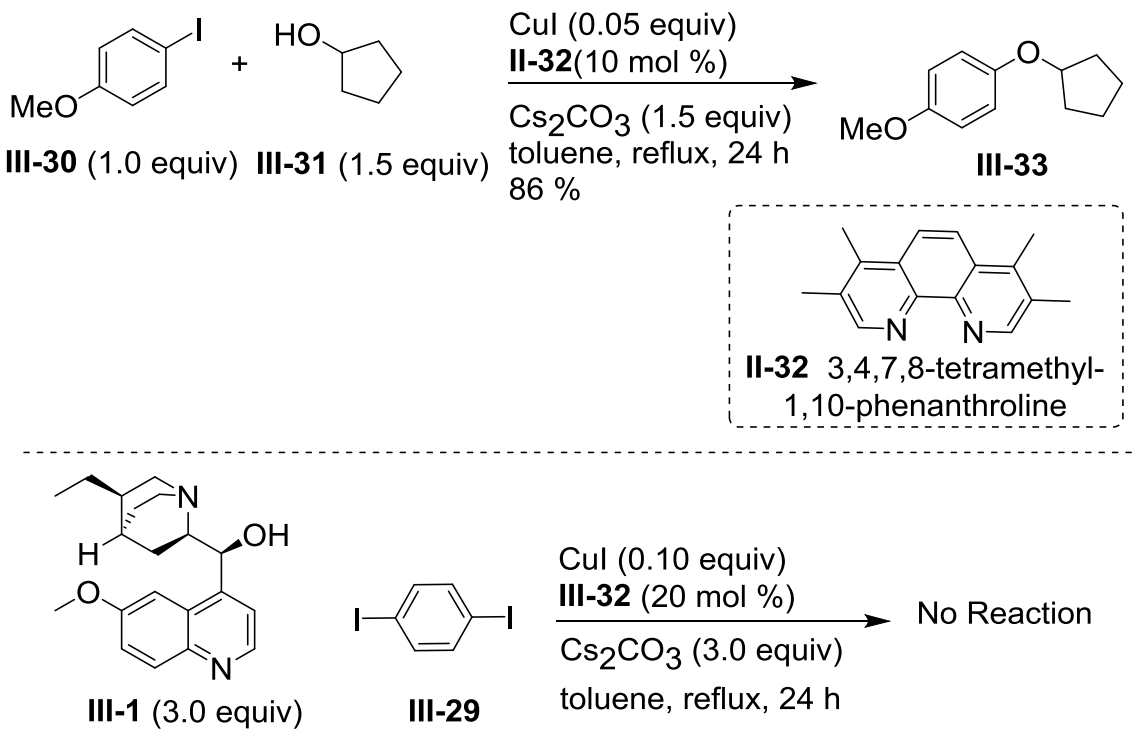
The failure to synthesize the two pyridine linked dimers (Scheme 6, entries h-i) was somewhat foreboding of the challenge we would face synthesizing dimers with hydrocarbon linkers. We began by screening the reaction we developed for electron deficient linkers with optimistic hopes (Scheme III-8a). Not to our surprise these reaction conditions with 1,4-diiodobenzene only returned starting materials, with not



Scheme III-8. Attempts to synthesize dimer with a hydrocarbon aryl linker.
*MS analysis determined that no reaction had occurred.

even a trace of the monoaddition product being observed in MS. We turned to screening the Ullman reaction using the optimized conditions from Sharpless' lab to form a phenyl-*cinchona* alkaloid bond.[2] With either sodium hydride or potassium hydride this coupling gave back only starting materials with no traces of monoaddition or product being observed in MS (Scheme III-8b). Since Sharpless had not reported the Ullman coupling with 1,4-diiodobenzene, at the time the reason for the failed reaction was attributed to the dihalogenated linker.

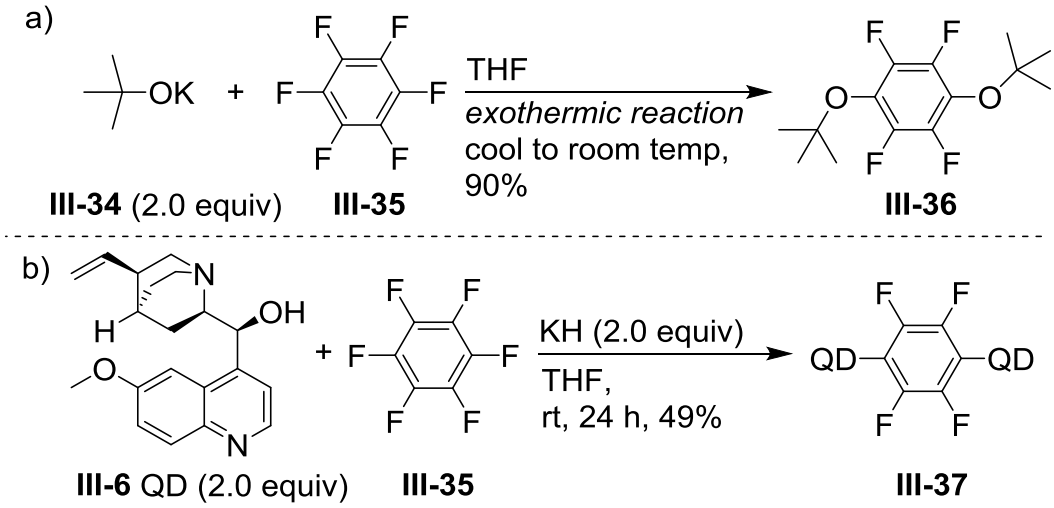
The next reaction we tried came from the Buchwald lab which was a copper based coupling used to make alkyl-aryl ether bonds, with the key feature of this reaction being the ligand: 3,4,7,8-tetramethyl-1,10-phenanthroline (**III-32** Me_4Phen).[18] Although



Scheme III-9. Buchwald alkyl-aryl ether coupling reaction using 3,4,7,8-tetramethyl-1,10-phenanthroline as a ligand.

the substrate scope given in the paper did not include any acyclic secondary alcohols or dihalides, there was one encouraging example involving the coupling of cyclopentanol to 4-iodo-1-methoxybenzene (Scheme III-9). Unfortunately, when DHQD and 1,4-diiodobenzene were used, this reaction did not form any of our desired product, with only starting materials being detected (Scheme III-9).

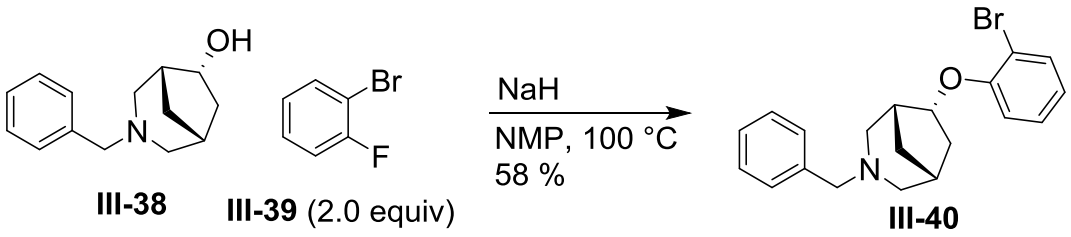
Since the copper reactions had not given us any of the mono-addition or dimerized product, we turned our focus back to an S_NAr reaction, with the idea being to increase the electrophilicity of the aryl linker. Initially upon screening the literature we found that perfluorobenzene was known to react with potassium *tert*-butoxide to give the *para*-disubstituted product in good yield (Scheme III-10).[19] The authors attributed the observed *para*-selectivity to the known activation of polyfluorinated compounds, with fluorines in the *ortho*- and *meta*- positions relative to the fluorine being displaced being activating, whereas fluorines in the *para*- position being regarded as deactivating. This behavior in polyfluorinated compounds is based on the early transition state of the



Scheme III-10. S_NAr reactions with perfluorobenzene (a) literature precedent reaction. (b) *Cinchona* alkaloid and perfluorobenzene dimerization.

reaction, whereby the *ortho*- and *meta*- fluorines stabilize the attack of the nucleophile.[20] Since potassium tert-butoxide was used in the precedent reaction, we decided to generate the analogous alkoxide of the *cinchona* alkaloid using potassium hydride. After 24 hours, we were excited to find our reaction had proceeded to completion, cleanly giving the *para*-substituted tetrafluorophenyl linked quinidine dimer (**III-37**). This was the first dimer we were able to acquire lacking nitrogens in the linker and after screening this catalyst in the SER studies, it gave us the encouragement we needed to continue our synthetic pursuit of a simple phenyl linked *cinchona* alkaloid dimer.

Upon acquiring the tetrafluorophenyl dimer, we scanned the literature for ways to de-fluorinate the linker, but unfortunately these reactions are not common. We did recognize, however, that the analogous dehalogenation with chlorine, bromine, or iodine could be easier, via a halogen metal exchange. Initially we looked in the literature for bis-S_NAr reactions with hexachloro- or hexabromobenzene, but they were not precedent. Therefore we started looking at tetra-halogenated benzenes, bearing fluorines for the S_NAr and two other halogens (chlorine, bromine, or iodine) to promote the S_NAR reaction. These extra halogens could then be removed after the S_NAR via a halogen-metal exchange reaction followed by protonation, to give our desired phenyl linked dimer. A brief literature scan revealed that 1-bromo-2-fluorobenzenes undergo S_NAr reactions specifically at the fluorine, indicating that the *ortho*-bromine substituent is electron withdrawing enough to promote the reaction (Scheme III-11).[21] We were happy to find that 1,4-dibromo-2,5-difluorobenzene was commercially available. Upon

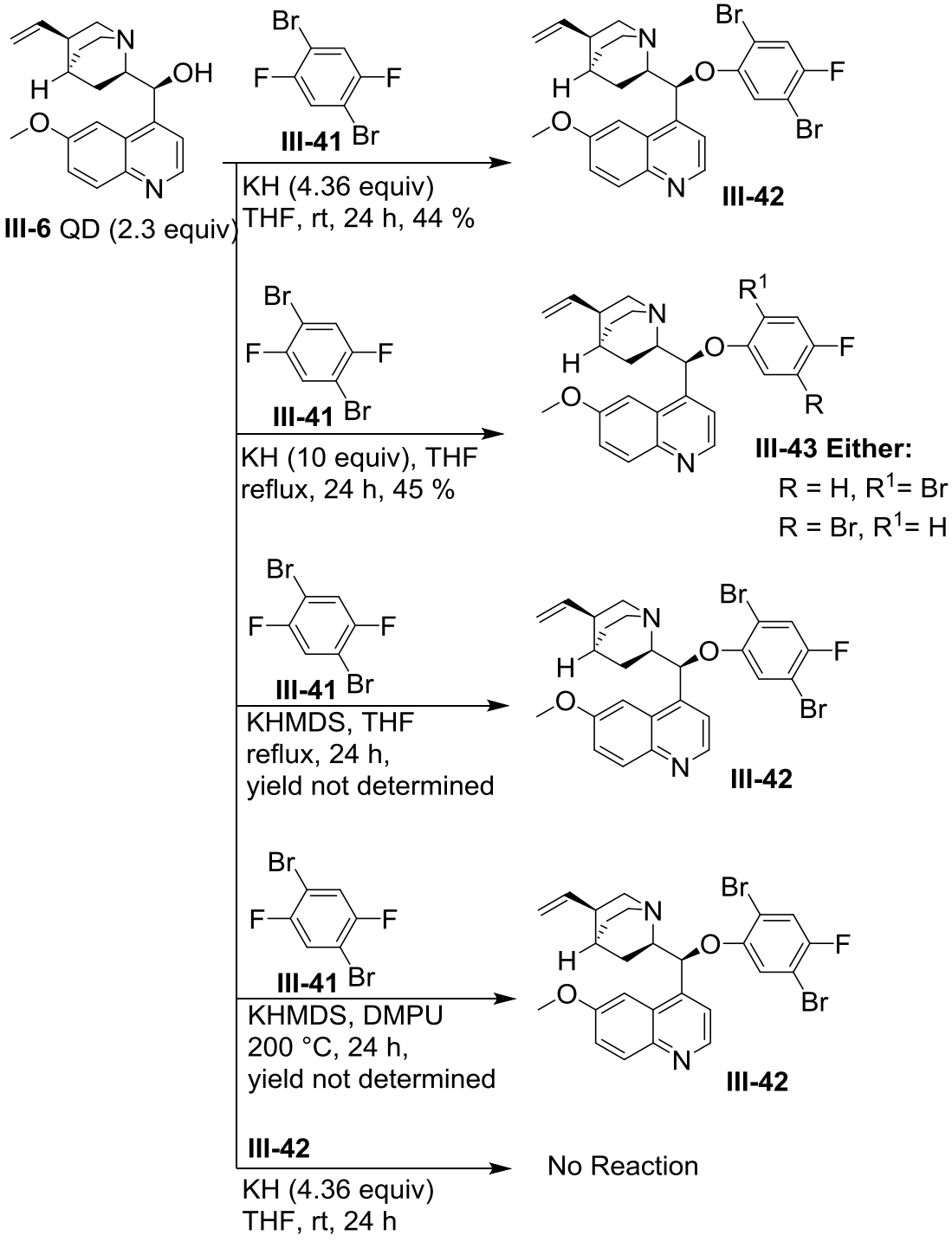


III-38 **III-39** (2.0 equiv) **III-40**

Scheme III-11. One example of an S_NAr reactions with 2-bromo-1-fluorobenzene.

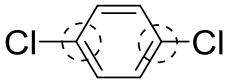
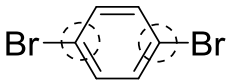
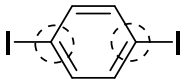
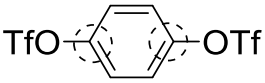
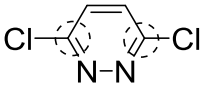
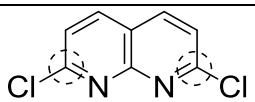
trying this reaction, we found that the mono-addition proceeded easily, however the second alkaloid would not add, in fact, the mass of the desired dimer was never observed using MS. In one reaction, a large excess of base was used and the reaction was heated to reflux; still MS indicated none of the desired dimer, but the mass of the product where the hydride from KH displaced one of the bromines on the aromatic ring was found (**III-43**). At that point, the base was changed to potassium hexamethyldisilazide (KHMDS), in hopes that the more sterically encumbered base would prevent formation of this side product. Use of KHMDS gave the monoaddition product, but again none of the desired dimer was detected via MS. The solvent was then changed to 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), a high boiling point solvent and the reaction was carried out in a sealed tube; again only the mono-addition product was observed. The last reaction we tried to make a dimer with this polyhalogenated linker used the isolated mono-addition product (**III-42**) with standard reaction conditions, which again proved fruitless (Scheme III-12).

Because of our successful dimerization with perfluorobenzene, we decided to further investigate S_NAr reactions with various leaving groups attached to the phenyl



Scheme III-12. All attempts to dimerize using 1,4-dibromo-2,5-difluorobenzene.

Table III-2. ^{13}C NMR shifts for various para-disubstituted phenyl rings in $CDCl_3$.

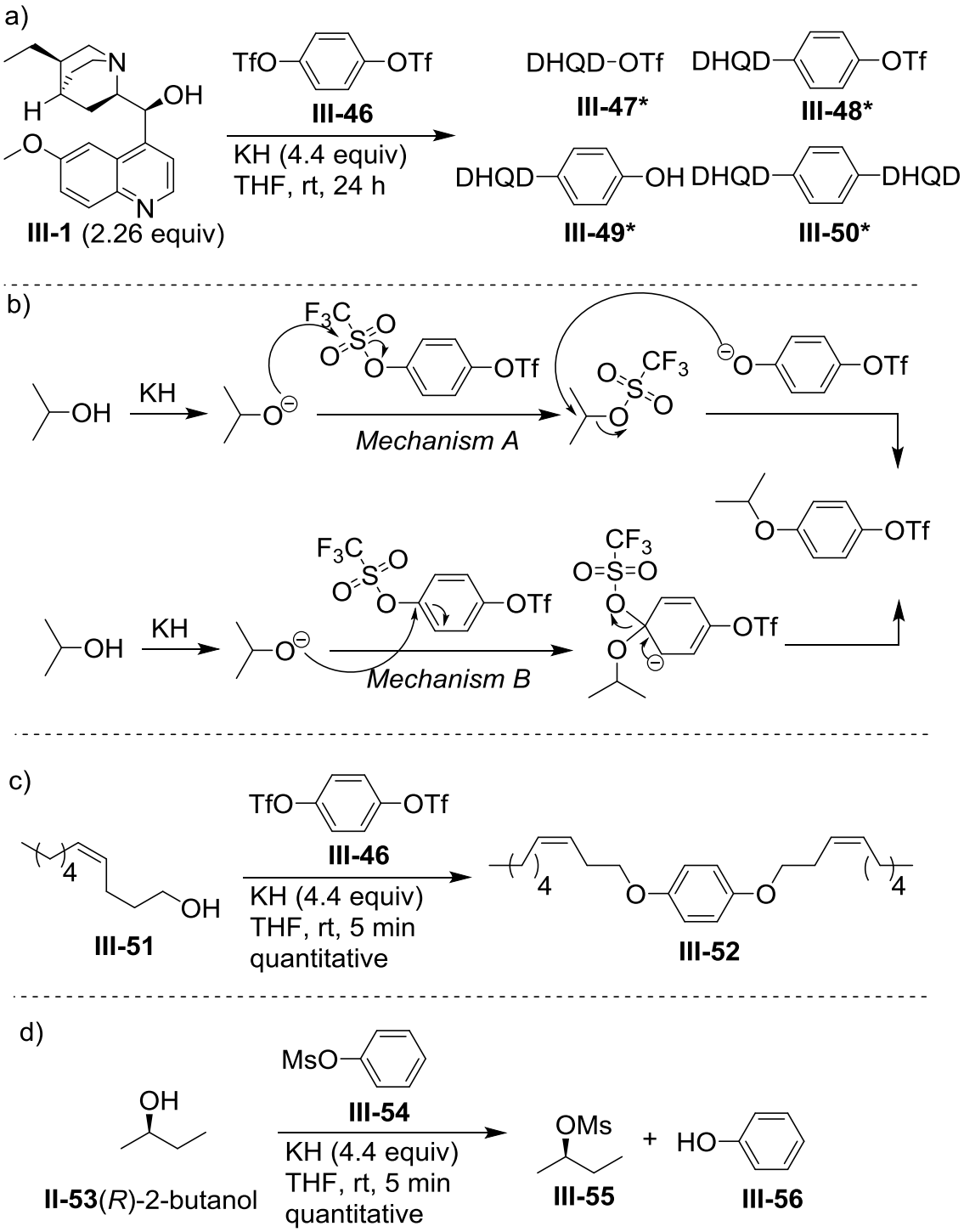
Compound	^{13}C NMR Shift
 **III-44**	132.6 ppm*
 **III-45**	133.1 ppm*
 **III-29**	139.2 ppm*
 **III-46**	148.4 ppm
 **III-7**	156.1 ppm*
 **III-22**	148.1 ppm

*Value obtained from the AIST structural database.[22]

ring. Since we knew that 2,6-dichloropyridazine dimerizes easily with base in THF at room temperature, we hypothesized that if we could make a similarly electron deficient *para*-disubstituted benzene ring, the dimerization should have a better chance of working. In efforts to quantify the electrophilicity of the carbon attached to the leaving group, we looked at the ^{13}C NMR shifts of the corresponding carbons. Table III-2

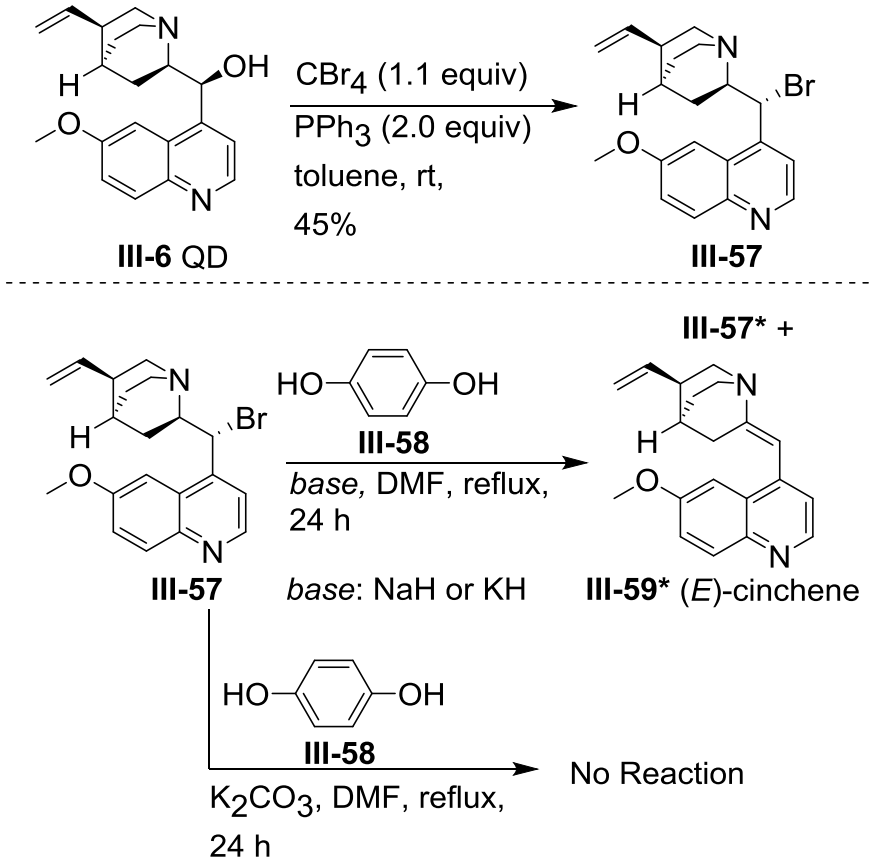
summarizes this data; with 2,6-dichloropyridazine and 1,8-dichloronaphthyridine being included since they both successfully dimerized using our developed KH / THF reaction conditions. As indicated, *para*-bistriflated hydroquinone (**III-53**) has similar ^{13}C NMR shifts at the electrophilic carbon as 1,8-dichloronaphthyridine (**III-29),** directing us to give the S_NAr with this electron deficient linker a try.

Under standard S_NAr reaction conditions (KH, THF, room temperature) the reaction of bis-triflated hydroquinone with DHQD was tried, with TLC analysis showing no starting material after 24 hours (Scheme III-13). MS analysis indicated that the reaction contained a mixture of triflated alkaloid (**III-47**), monoaddition (**III-48**), monoaddition with loss of the second sulfonyl group (**III-49**), and trace amounts of the desired dimer (**III-50**). The formation of the triflated alkaloid created an interest in the mechanism: was the triflated hydroquinone simply serving as a source of triflate for the *cinchona* alkaloid which was then undergoing S_N2 displacement with hydroquinone, or was the starting alcohol participating in an S_NAr and displacing the triflate group (Scheme III-13b)? Since the crude ^1H NMR for the reaction was messy, a simpler reaction was used to confirm that a coupled product was achieved. To do this, a primary alcohol (**III-51)** was used instead of the *cinchona* alkaloid with the bis-triflated hydroquinone. The reaction proceeded quickly (less than 5 minutes) and the crude ^1H NMR was clean indicating only the desired dimerized product (**III-52**). To probe the mechanism, a chiral secondary alcohol was reacted with sulfonated phenol, whose α_D for both enantiomers of product was reported (Scheme III-13d). The hypothesis was that by determining the α_D of the resulting product, it would be easy to understand the

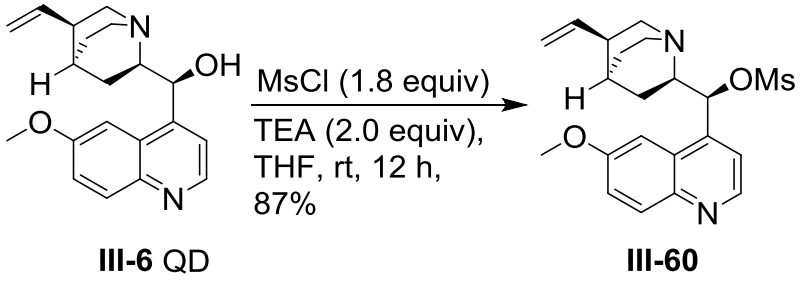


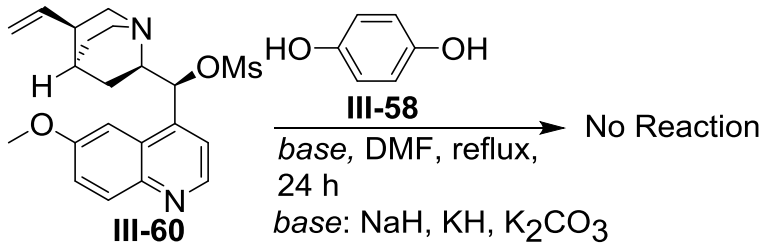
Scheme III-13. Various reactions and possible mechanisms for bis-triflated hydroquinone coupling reaction. (a) Attempt to dimerize hydroquinidine with bis-triflated hydroquininone, (b) Two possible mechanistic routes for the reaction shown in (a), (c) Simpler alcohol to prove reaction was successful, and (d) Reaction to discern the mechanism.

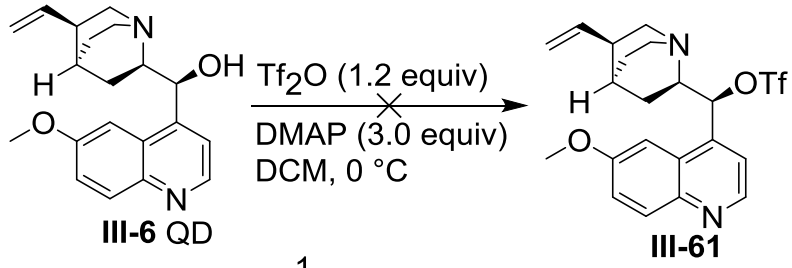
mechanism of the reaction. However, upon doing the reaction, the mechanism was uncovered without determining the α_D. Less than 5 minutes after combining the reactants, no starting alcohol was detected on TLC, so the reaction was quenched. ^{1}H NMR analysis indicated that the mesyl group had migrated to the secondary alcohol, which explains why TLC revealed its consumption. The *in situ* sulfonated secondary alcohol now underwent the S_N2 reaction much slower than the primary alcohol (**III-51**), which is why the dimer was not detected in the ^{1}H NMR. Therefore since we knew the bis-triflated hydroquinone was serving as a triflating agent in these reactions (*Mechanism B,* Scheme III-13), then perhaps directly triflating (or attaching any leaving



Scheme III-14. Synthesis and reactions of alkaloids having electrophiles attached to the C_9 center.





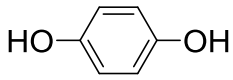


crude ^{1}H NMR was clean, but ran column to get rid of DMAP, hydrolyzed to starting material on column

One pot:

a) Tf_2O (1.2 equiv)
base (3.0 equiv)
DCM, 0 °C

→ No reaction (*cinchona* alkaloid is not triflated)

b) 

III-58

reflux, 24 h

base: K_2CO_3 or DMAP

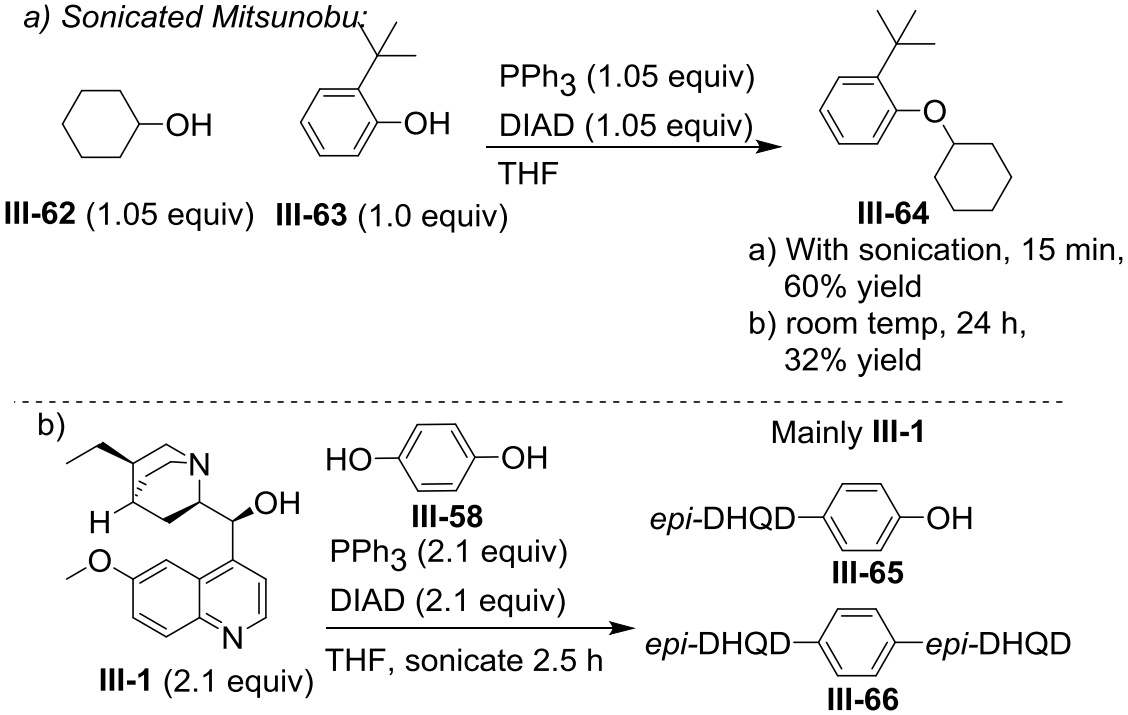
Scheme III-14 (cont'd). Synthesis and reactions of alkaloids having electrophiles attached to the C_9 center.

group to) the *cinchona* alkaloid alcohol moiety would allow for the reaction to proceed more cleanly.

Typically hydroxyls are transformed into leaving groups by substituting them with halogens or adding a sulfonyl group. Because the addition of a sulfonyl group retains the hydroxyl stereochemistry, its displacement would lead to the undesired epimer of product. Therefore a sulfonyl group would require an inversion of the C_9-hydroxyl initially before sulfonation and displacement. Since the synthesis of *epi*-bromoquinidine, does not require this additional step, this was the first electrophilic alkaloid derivative we sought (Scheme III-14).[23] Unfortunately, the stability of this compound was found to be less than ideal, with somewhat rapid elimination to (*E*)-cinchene (over hours time). With the *epi*-bromoquinidine in hand, we first tried to displace it with hydroquinone in the presence of sodium hydride or potassium hydride, which gave a mixture of starting *epi*-bromoalkaloid and (*E*)-cinchene (**III-59**). We hypothesized that the metal hydride would form the bis-alkoxide of hydroquinone which could have solubility problems, so we switched to using potassium carbonate as the base, which also proved unsuccessful, giving no reaction. We initially decided to investigate the sulfonyl leaving groups without inverting the natural stereochemistry. We began by synthesizing mesylated quinidine, which proved to be completely unreactive, with MS only indicating starting material with a variety of bases (Scheme III-14). In a final effort, the triflated alkaloid was made, whose crude ^{1}H NMR was fairly clean, however a short column was run to get rid of the DMAP, which hydrolyzed the triflated alkaloid back to quinidine. Due to this notable increase in reactivity of the triflated alkaloid, we tried to do a one pot procedure, initially

forming the triflate and then adding in the hydroquinone. First we tried to do this without adding any excess base, just using the DMAP in solution, which yielded no reaction, with the quinidine being the only observable product by MS. In a second attempt the base was changed to potassium carbonate for the entire reaction, which provided only the starting alkaloid (Scheme III-14).

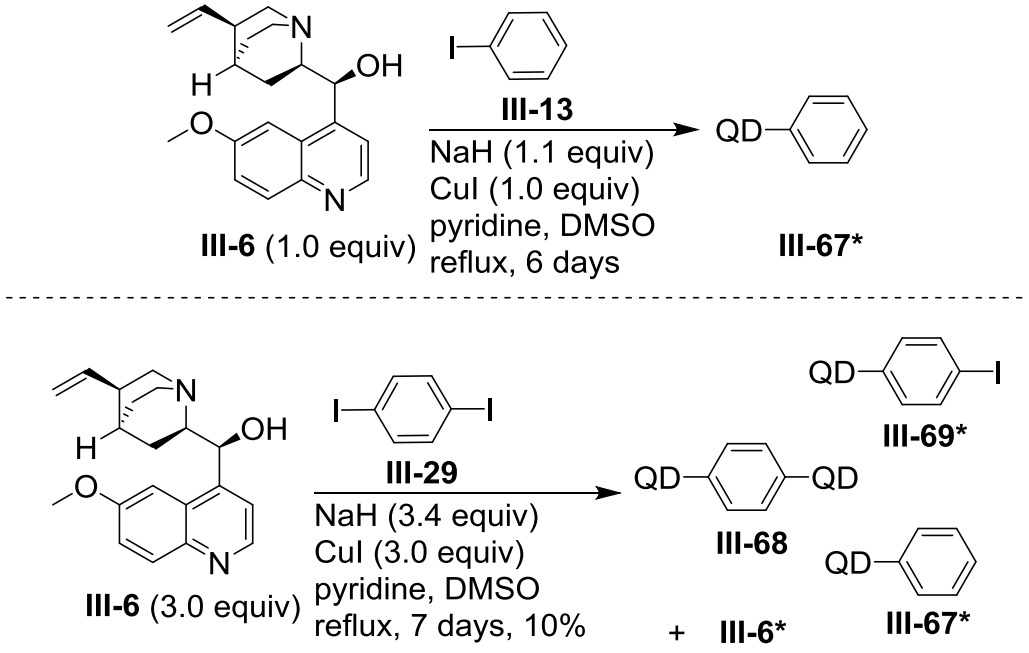
Although the nucleophilic displacement of either the *epi*-bromoquinidine or sulfonated quinidine proved fruitless, we decided to investigate a reaction with a similar mechanism, the Mitsunobu reaction. Since the Mitsunobu reaction would invert the stereochemistry of the C_9-carbinol, this would require two Mitsunobu reactions, with the first giving the unnatural epimer of the alkaloid and the dimerization regenerating the natural stereochemistry. Before putting effort into synthesizing the unnatural



Scheme III-15. (a) Literature precedent Mitusunobu for sterically hindered alcohols and (b) attempted Mitsunobu reaction with a DHQD.

monomeric epimer, we initially wanted to see if the dimerization would work. A brief literature screen of Mitsunobu's reactions with sterically hindered alcohols unveiled that sonication increased the rate and gave better yields (Scheme III-15). MS analysis of our first attempt at the Mitsunobu showed trace amounts of the monoaddition (**III-65)** and the desired dimer **(III-66)**, but mainly starting material (Scheme III-15). Unfortunately, purification of the components of this reaction mixture proved challenging, with triphenyl phosphine oxide complicating the already complex mixture. All attempts to repeat this reaction proved irreproducible.

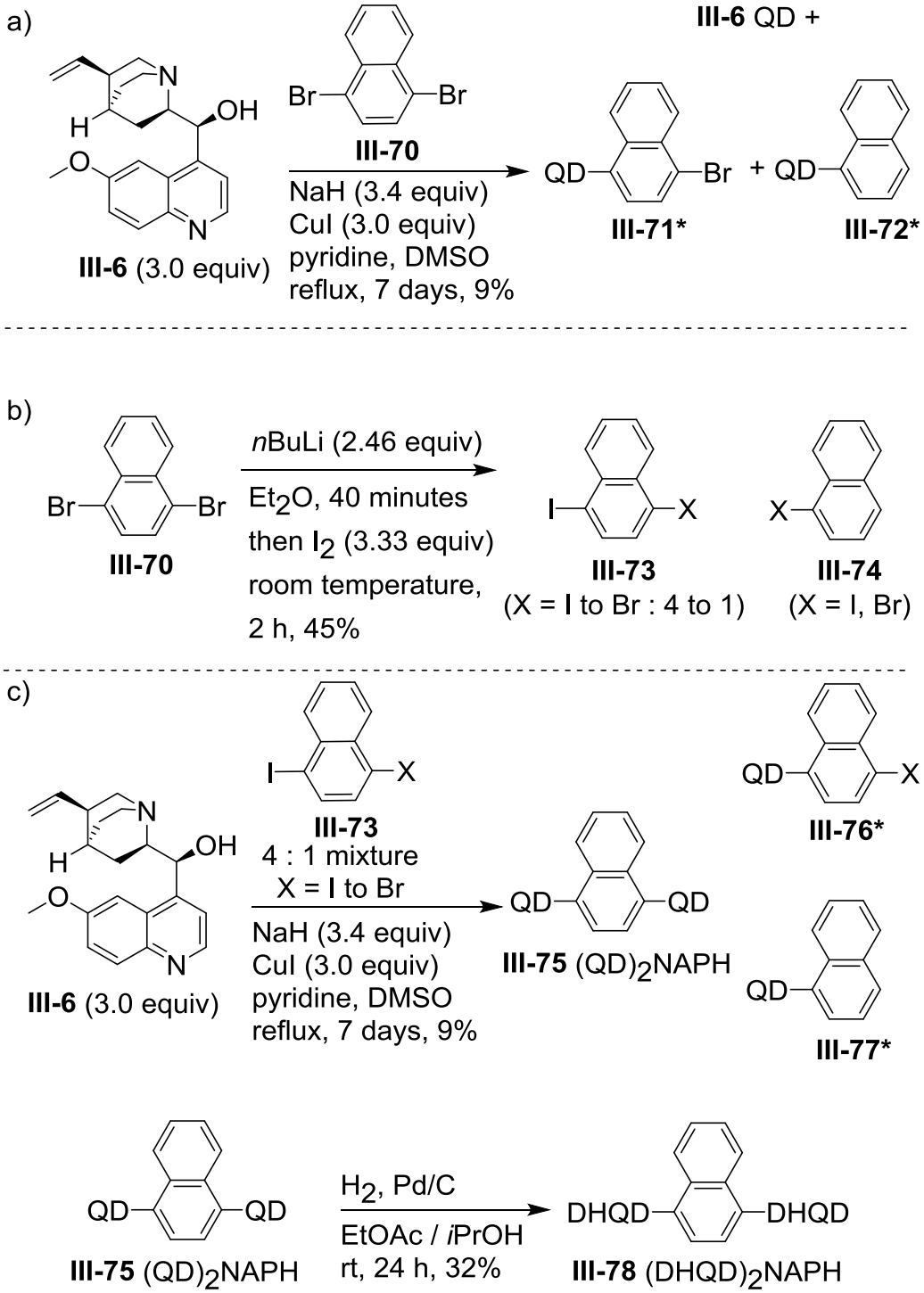
Finally after exhausting most reasonable ideas, we returned back to the unanswered question of why the Ullman reaction had failed. We decided to repeat the literature precedent reaction as a control to determine whether it was a bad reagent that caused the coupling with 1,4-diiodobenzene to fail or if it was the 1,4-diiodobenzene



Scheme III-16. Ullman coupling with iodobenzene and with 1,4-diiodobenzene.

itself. The reaction with iodobenzene was run using the same batch of copper iodide as was used the first time. This reaction did not give any product. Because copper (I) species are sensitive to oxidation, the copper iodide was freshly prepared from copper (II) sulfate and sodium iodide. This time the reaction with iodobenzene gave the desired product (Scheme III-16)! The reaction was re-run using 1,4-diiodobenzene and after one week's time, the mass of the desired dimer was observed in MS! The side products from this reaction observed in MS included a mixture of the monoaddition (**III-69)**, monoaddition followed by dehalogenation (**III-67)**, and starting material. The yield of this reaction is low because purification of this compound from all the by-products proved challenging; however because only a small quantity was needed to screen the reactions in the SER studies, optimization was not pursued.

The same procedure was applied to acquire the naphthyl linked dimeric quinidine scaffold (**III-71**), however there was one hurdle in this synthesis (Scheme III-17). The 1,4-diiodonaphthalene is not commercially available, however the 1,4-dibromonapthalene is. The Ullman coupling was tried with the dibromide **III-70**, which gave only monoaddition. Therefore the 1,4-diiodo compound **III-73** was made via a halogen – metal exchange using *n*BuLi. Unfortunately even after screening different solvents and equivalents of *n*BuLi, the reaction would not proceed to completion. The crude reaction contained a mixture of 1-bromonaphthalene, 1-iodo-naphthalene, 1-bromo-4-iodonaphthalene, and 1,4-diiodonaphthalene. Column chromatography removed the mono-halogenated naphthalenes from the dihalogenated napthalenes; and crystallization provided a 4:1 mixture of diiodonaphthalene to dibromonaphthalene (**III-**



Scheme III-17. Synthesis of naphthyl linked alkaloid dimers. (a) Attempted Ullman coupling with 1,4-dibromonaphthalene, (b) synthesis of 1,4-diiodonapthalene, (c) Ullman coupling to form naphthyl linked quinidine dimer and its hydrogenation.

73). This mixture was used in the Ullman coupling to acquire the naphthyl linked quinidine dimer **III-75.** We were able to acquire the dihydroquinidine naphthyl linked dimer via hydrogenation of **III-75** to give **III-78.**

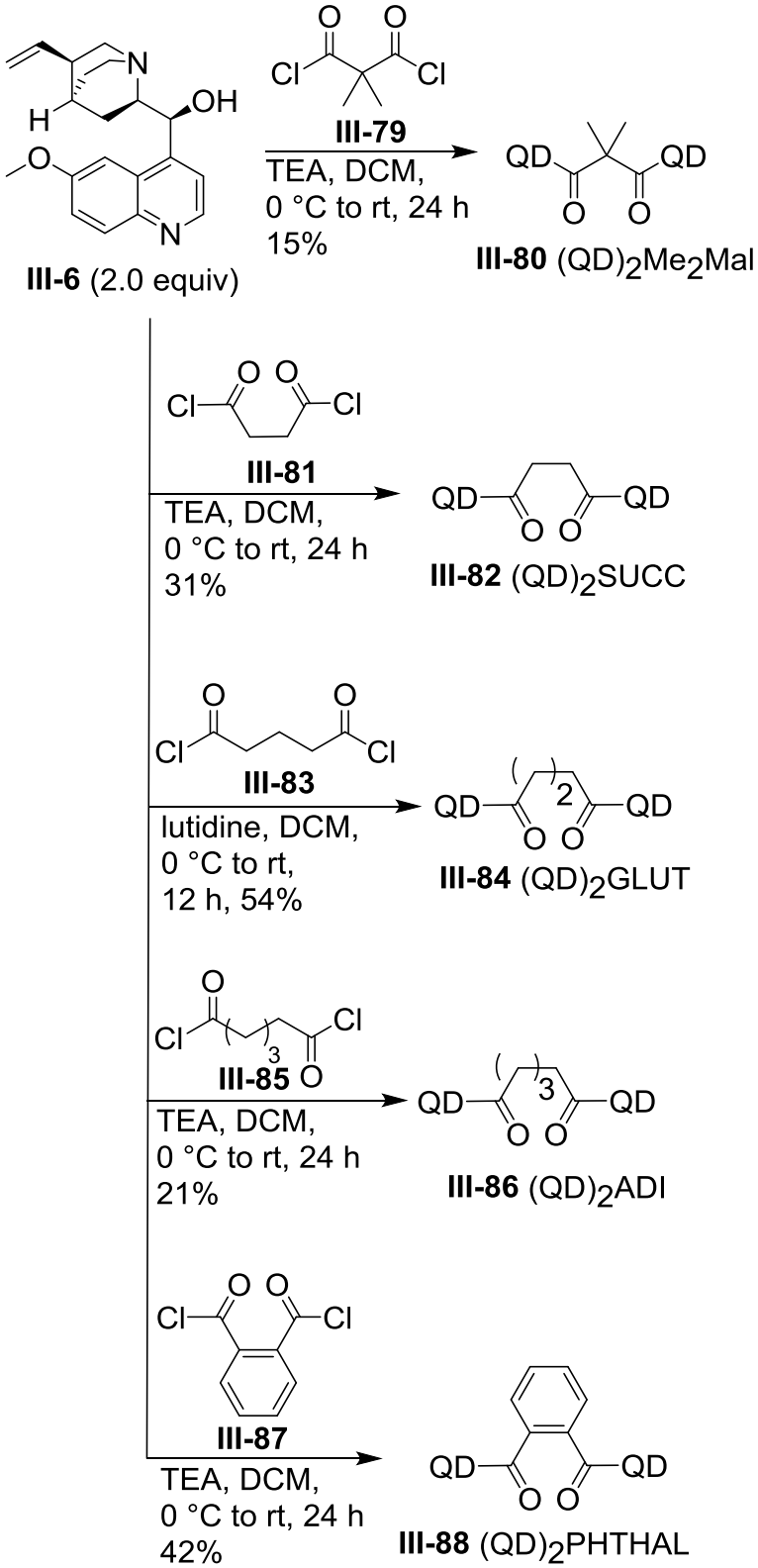
III-3 Synthesis of Catalysts with Acyl Linkers

Dimeric *cinchona* alkaloids tethered by a variety of acyl linkers have been reported in the literature.[24-28] The synthesis of most of these scaffolds uses the diacyl chloride in the presence of either triethyl amine or DMAP. We used the procedure reported by Chen[24] to synthesize a series of acyl linked dimers, 3 bearing various substituted aryl groups and 4 containing various lengths of alkyl tethers (Scheme III-18)

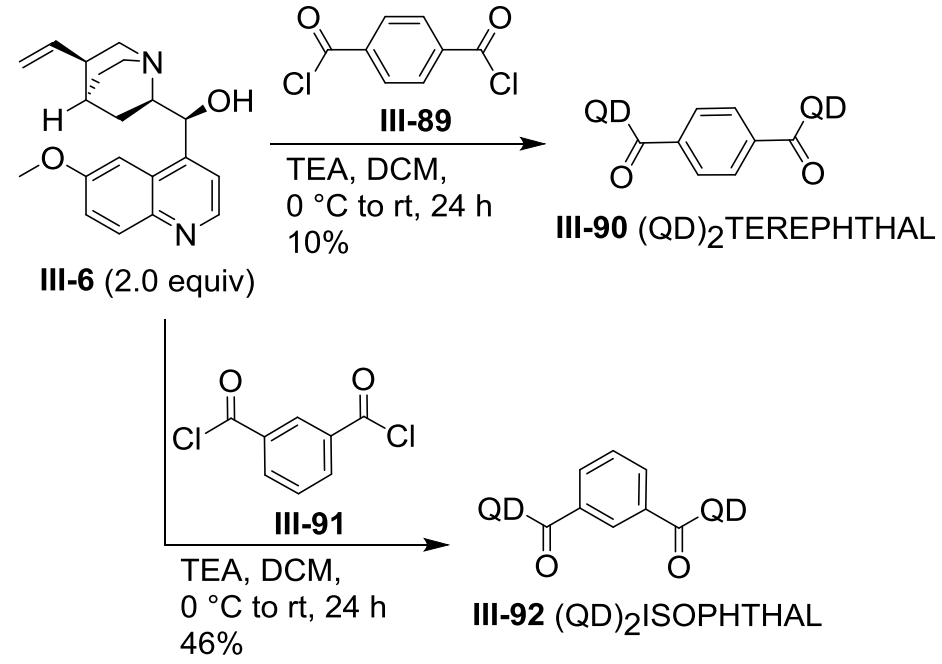
There were two acyl linked dimers that we were not able to acquire, the oxalyl and malonyl dimers. The crude ^{1}H NMR and MS of the reaction when oxalyl chloride was used showed the desired product, however after column chromatography a mixture of starting alkaloid and rearranged product **III-95** was obtained (Scheme III-18). Due to the instability of the desired dimer, its pursuit was discontinued. The other acyl catalyst that was difficult to acquire was the malonyl linked dimer. The acidity of the alpha H's in the linker most likely caused this compound to be unstable. The 2,2-dimethyl malonyl linker was used instead to eliminate these problems (Scheme III-18).

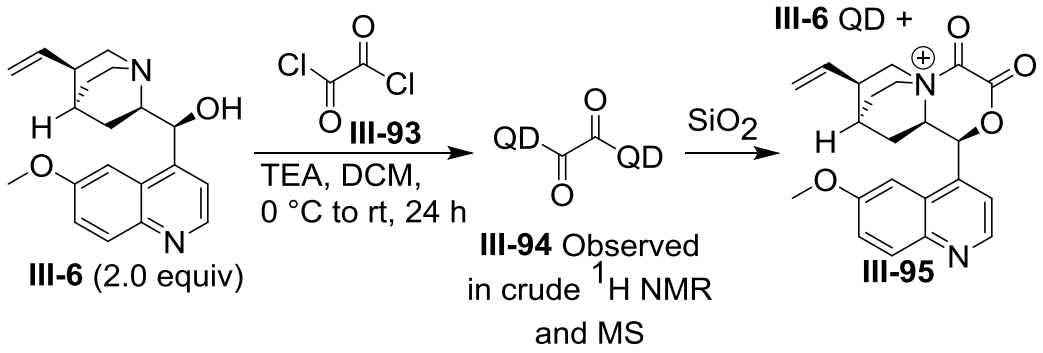
III-4 Synthesis of a Larger Quinoline Alkoxy Catalyst

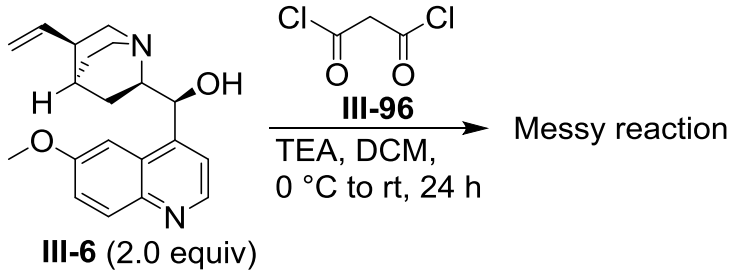
For the synthesis of the dimer containing a larger alkoxy substituent two different routes were considered. We could either demethylate the dimerized catalyst followed by alkylation of the quinoline alkoxy (Scheme III-19, *route A*) or we could demethylate the monomer, selectively alkylate the quinoline alkoxy in the presence of the alkyl



Scheme III-18. Synthesis of various acyl linked dimeric catalysts.

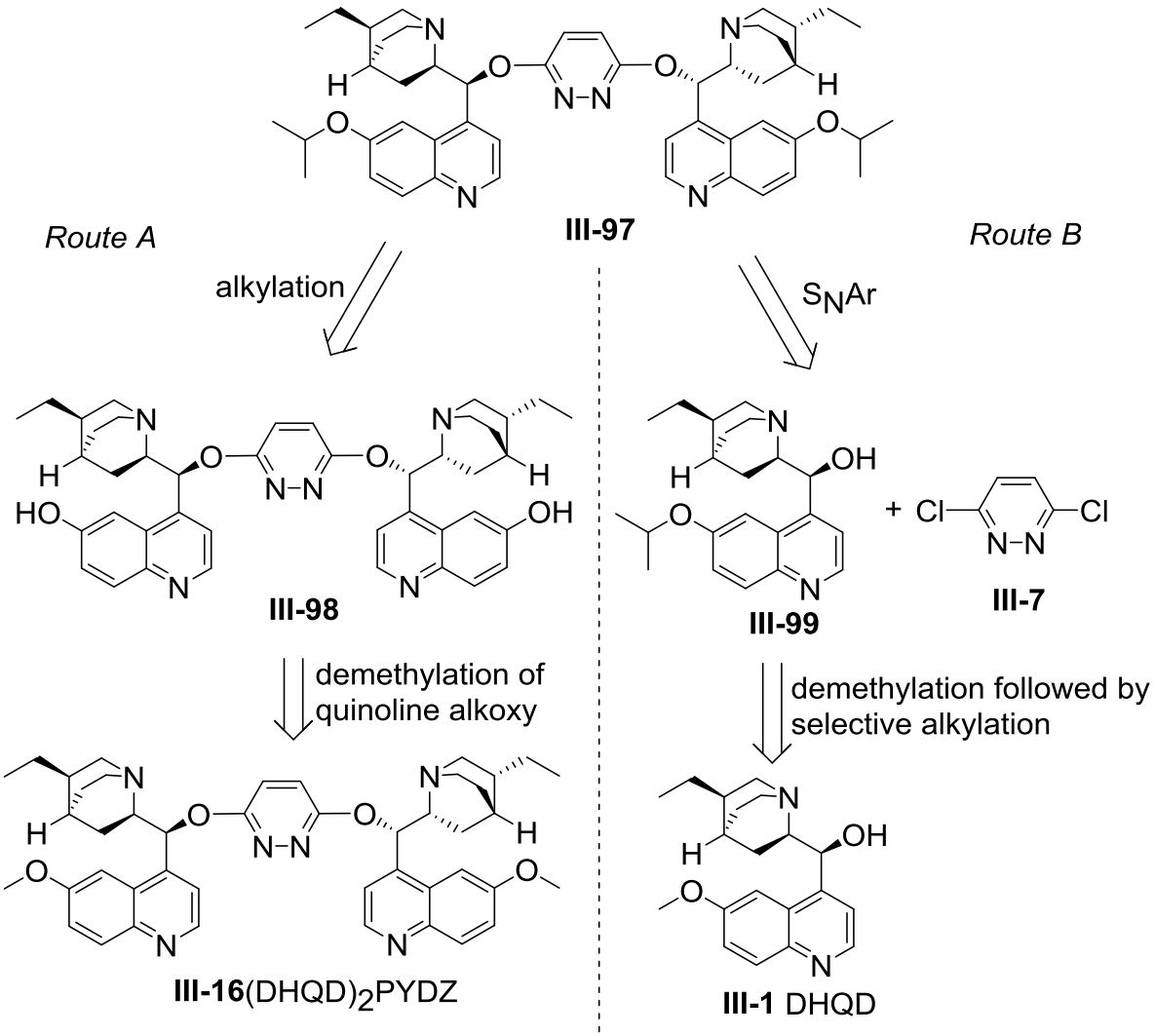






Scheme III-18 (cont'd). Synthesis of various acyl linked dimeric catalysts and failed reactions using this procedure.

alkoxy, and then dimerize (Scheme III-19, *route B*). Although the first proposal is more streamlined, the *cinchona* alkaloid – linker bond has the potential to undergo the analogous dealkylation reaction during the demethylation conditions. We hypothesized that the demethylation should occur faster than the dealkylation at the alkaloid carbinol because the attack of the nucleophile on a methyl versus secondary carbon should be much faster. Therefore, we decided to pursue route A first, since it is more streamlined and could allow us easy access to a variety of alkylated catalysts.

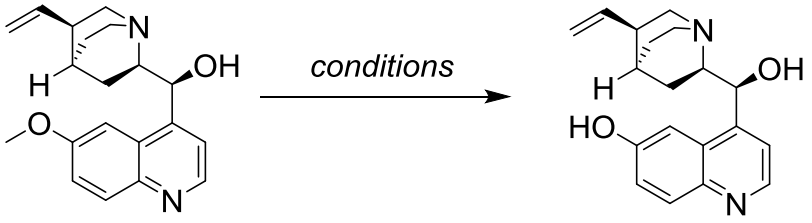


Scheme III-19. Retrosynthesis of catalyst with larger quinoline alkoxy substituent.

Both route A and B require demethylation of the quinoline methoxy group of the *cinchona* alkaloid. Three different procedures have been reported in the literature and include the use of hydrobromic acid,[29] sodium ethane thiolate,[30] or boron tribromide[31] (Table III-3). Because the yields for the three different procedures are similar and boron tribromide was available, we began our studies using this demethylation procedure.

Our synthetic efforts towards the various quinoline alkoxy catalyst began by using $(DHQD)_2PYDZ$ in the presence of BBr_3 (Scheme III-20a). This reaction gave a complex mixture of products, with none of the desired demethylated dimer of starting material being detected by MS. Therefore, we turned to route B, which began with monomer dealkylation. This reaction proceeded cleanly to give 63% yield of the desired hydroxy alkaloid **III-101.** This monomer derivative was then alkylated using 2-bromopropane and cesium carbonate to give *iPr*DHQD **III-99.** The last step was dimerization using 2,6-dichloropyridazine, which proceeded extremely slowly. Initially

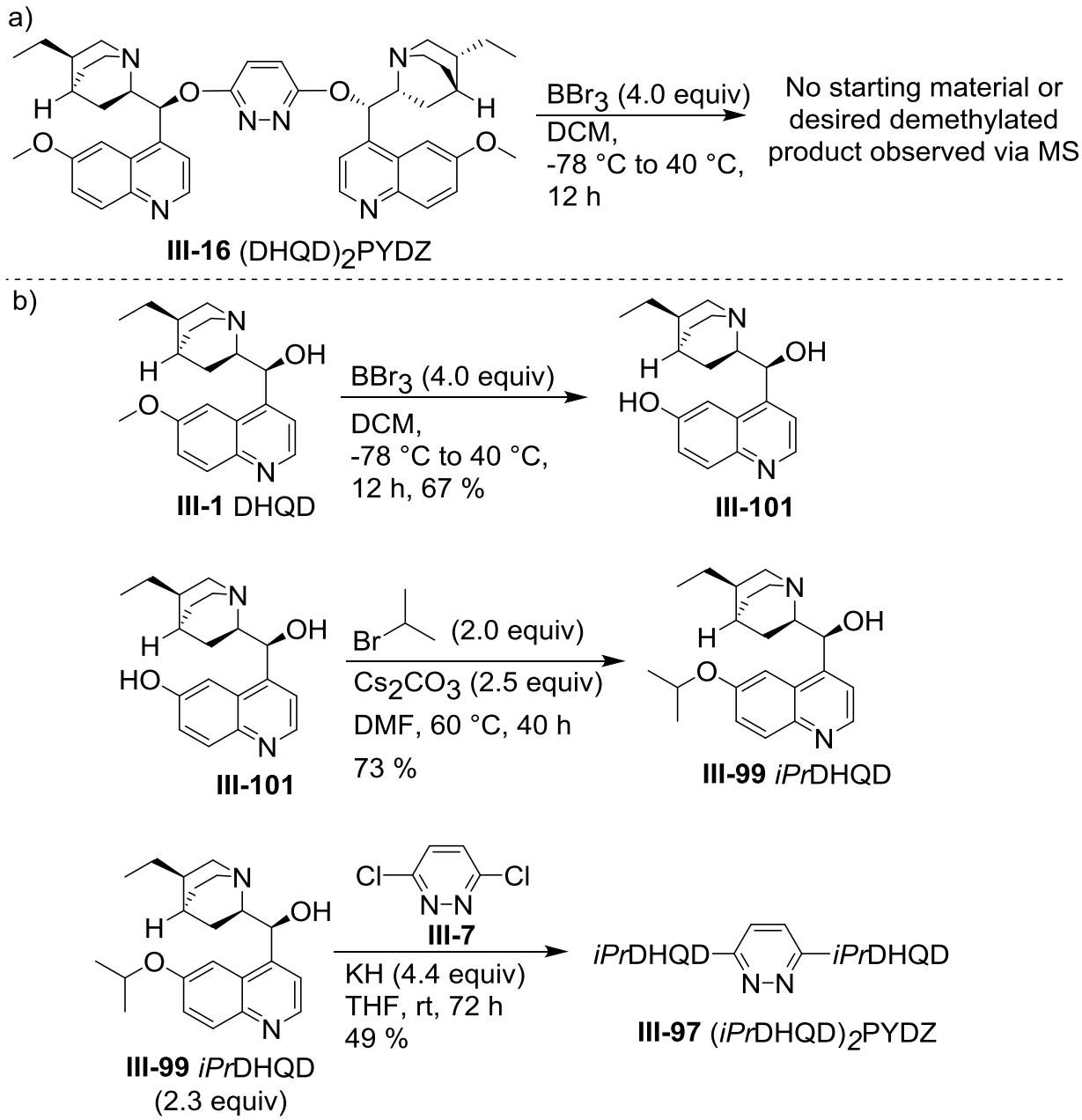
Table III-3. Literature precedent demethylation reactions for the quinoline alkoxy moiety in *cinchona* alkaloids.



III-6 QD **III-100** hydroxycinchonine

Entry	Reaction Conditions	% Yield III-95
1	HBr, H_2O, 18 h, reflux[29]	90%
2	NaSEt (4.0 equiv), DMF, 110 °C, 6 h[30]	92%
3	BBr_3 (4.0 equiv), DCM, -78 °C to 40 °C, 1 h[33]	95%

we hypothesized that there may be trace amounts of boronic acid contaminating **III-99**, but no signals were observed in boron NMR. Even after the sequence of reactions was repeated in their entirety (BBr_3 followed by alkylation), the dimerization reaction still remained extremely slow. No further investigations regarding the rate of this



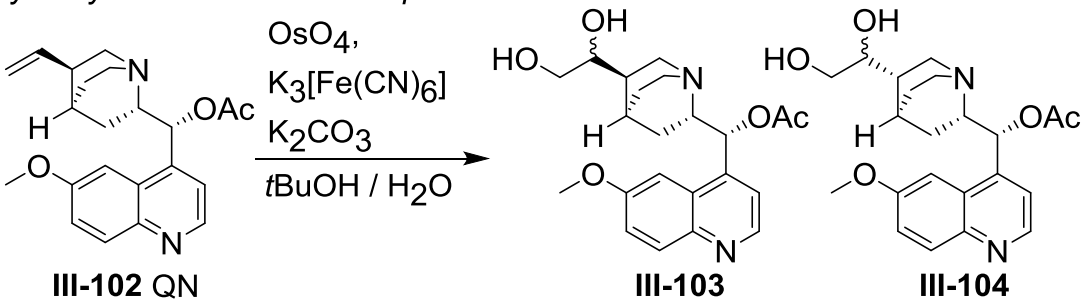
Scheme III-20. Synthesis of catalyst with larger quinoline alkoxy group. a) Synthetic attempt using *route A.* b) Synthesis using Route B.

dimerization were pursued since the desired compound was acquired.

III-5 Synthesis of Catalysts with More Sterically Encumbered Quinuclidine Substituents

The literature contains a number of modifications pertaining to the quinuclidine vinyl group; including dihydroxylations,[32] Wittig olefinations,[33] and Grubb's metatheses.[34] Our goal was to increase the sterics of the quinuclidine vinyl substituent with selectivity being a primary concern. More specifically we targeted a derivatization that would not epimerize the allylic stereocenter or generate a new chiral center. If the derivatization created a new stereocenter, this could induce even more complexity to the catalyst structure, with there being a large probability of matched / mismatched behavior. Having this in mind, we ruled out dihydroxylating the double bond. We also considered a Wittig olefination, which would require formation of an aldehyde, via a dihydroxylation / oxidation procedure. The reported procedures using sodium periodate and osmium tetroxide are inconsistent, with the original paper reporting only 5% of the epimerized product and another observing 50% of the undesired epimer (Scheme III-21).[33] One of these papers performed a number of Wittig olefinations on the acquired aldehyde alkaloid, revealing modest yields (12-80%) and poor E / Z selectivities (~1 : 2) which proved inseparable. Based on these inconsistencies and poor selectivities, we decided to do a Grubb's cross metathesis, similar to the one reported by Porco using 2-methylpropene and O-acetyl cinchonidine (Scheme III-21).[34] This procedure would not generate a new stereogenic center, even after hydrogenation of the double bond, and should not lead to allylic epimerization.

Dihydroxylation - Oxidation Sequence



III-102 QN

III-103

III-104

(1 : 1 mixture of diasteromers)

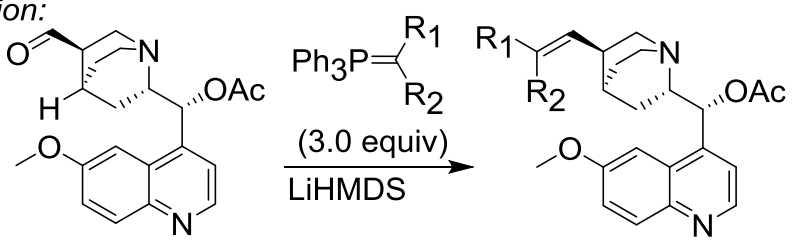
$NaIO_4$, SiO_2,H_2O,
DCM, rt, 89%

Inconsistent in literature ranging from 5 to 50% of undesired **III-106** observed (using same procedure)

III-105

III-106

Wittig Olefination:

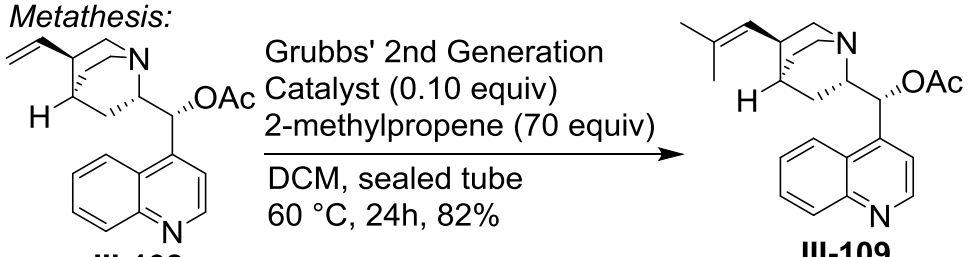


III-105

III-107

When:		Yield	*E / Z*
R_1 = Me	R_2 = H	25%	-
R_1 = Me	R_2 = Me	30%	
R_1 = H/Et	R_2 = Et/H	80%	1 : 2

Grubb's Cross Metathesis:



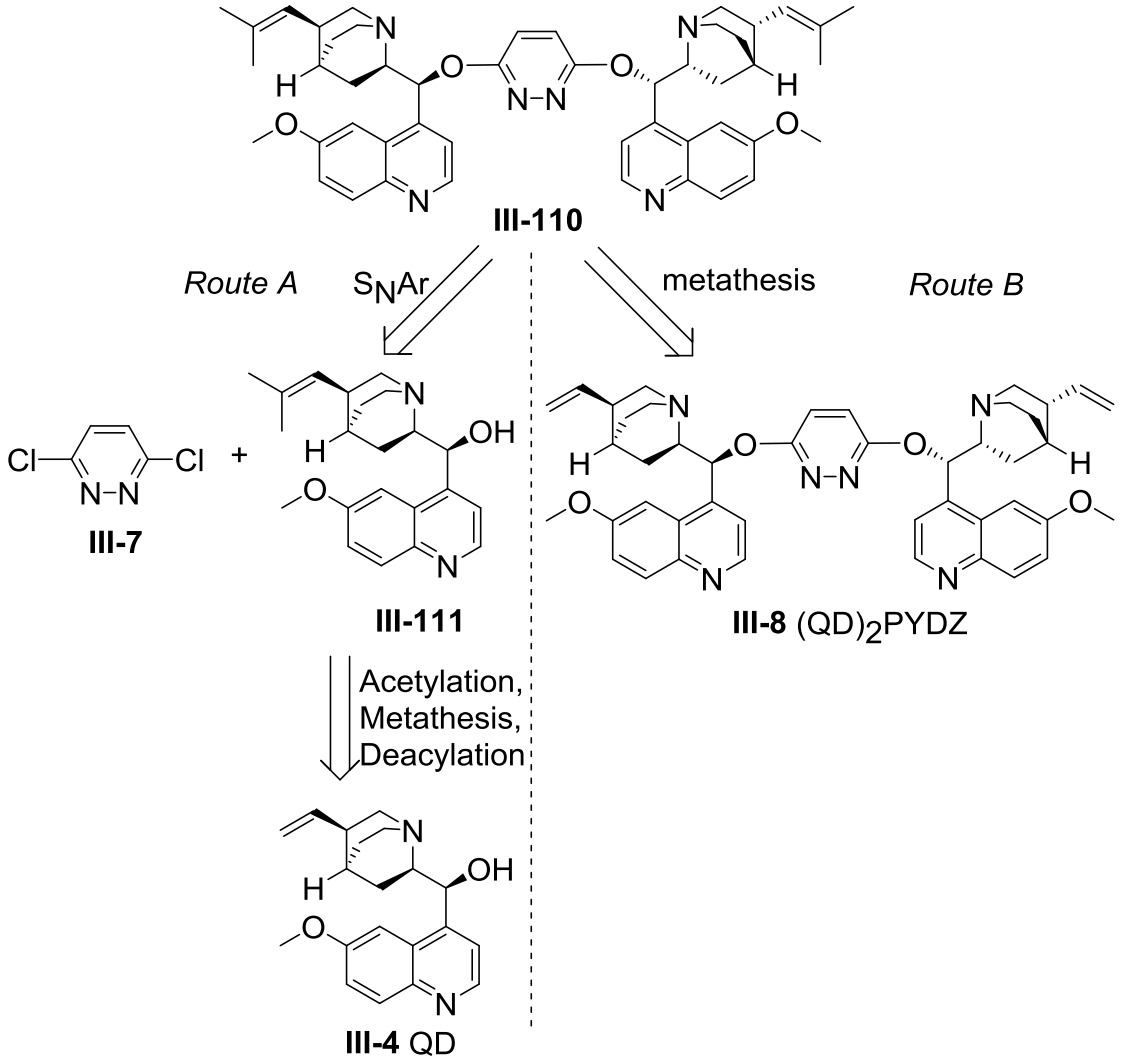
III-108

III-109

Scheme III-21. Literature precedent functionalizations of the quinuclidine vinyl group via dihydroxylation – oxidation sequence, Wittig olefination, and cross metathesis.

After a method for functionalizing the quinuclidine vinyl group had been chosen, the synthetic route was considered. Analogous to the route for the demethylation of the quinoline, the functionalization could be performed on the monomer, which could then be dimerized (Scheme III-22, route A), or the functionalization could be performed on the dimer (Scheme III-22, route B). We decided to first investigate the cross-metathesis on the monomer, since there was literature precedent.

When we started our synthetic endeavors towards a dimer with a more sterically



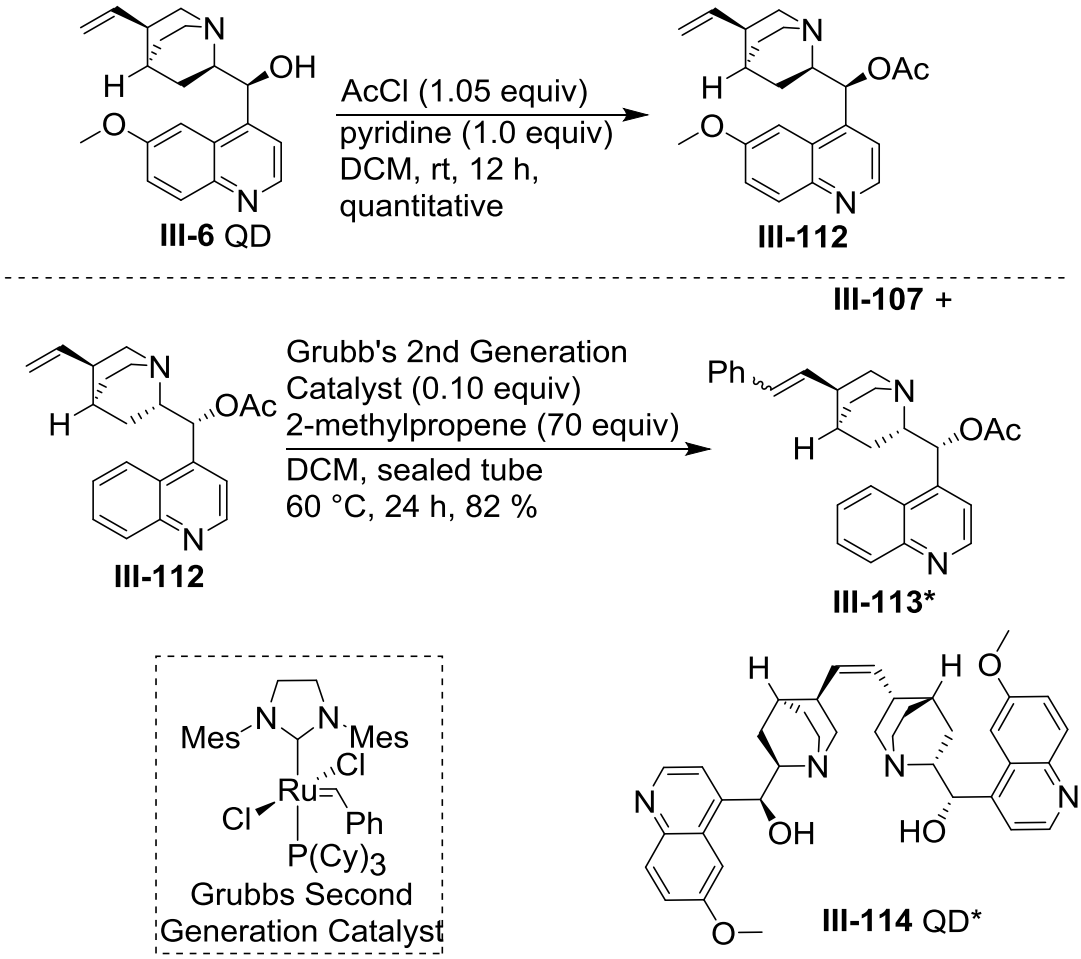
Scheme III-22. Two possible retrosyntheses of catalyst with larger quinuclidine vinyl substituent.

encumbered quinuclidine vinyl group, we substituted Porco's 2-methylbutene with styrene. We were hoping that the larger group would induce a larger effect in SER studies, with the aromatic providing an opportunity for interactions with the aryl acid substrate. We first synthesized O-acetyl-quinidine and then attempted the cross-metathesis with styrene. MS analysis indicated a mixture of homo-dimer *cinchona* alkaloid product, the desired product and starting material (Scheme III-23). Although a number of columns were run on the crude material, a clean separation was never achieved. Because it seemed that a major component of the reaction was the homo-dimer of O-acetyl quinidine, the reaction was carried out neat in styrene. This reaction returned only starting materials due to solubility problems. After numerous attempts, we decided that styrene was not an ideal candidate for this cross-metathesis and changed our focus to 2-methylpropene.

The cross metathesis between O-acetyl quinidine and 2-methylpropene had limited success (Scheme III-24). The reported procedure did lead to product formation, however it's purification from the remaining starting material proved challenging. Initially we tried to purify the product bearing the O-acetyl group, however when this was not successful, we deprotected the C_9 hydroxyl to see if it would ease the purification process. Unfortunately this proved equally challenging. Besides having to remove the residual starting material from the product, another significant hurdle was getting rid of the ruthenium after the reaction. Initially we tried to use column chromatography, which was not successful at all. We then tried charcoal,[35] which had limited success, giving the product as a brown oil in low isolated yields, even though the crude ^{1}H NMR

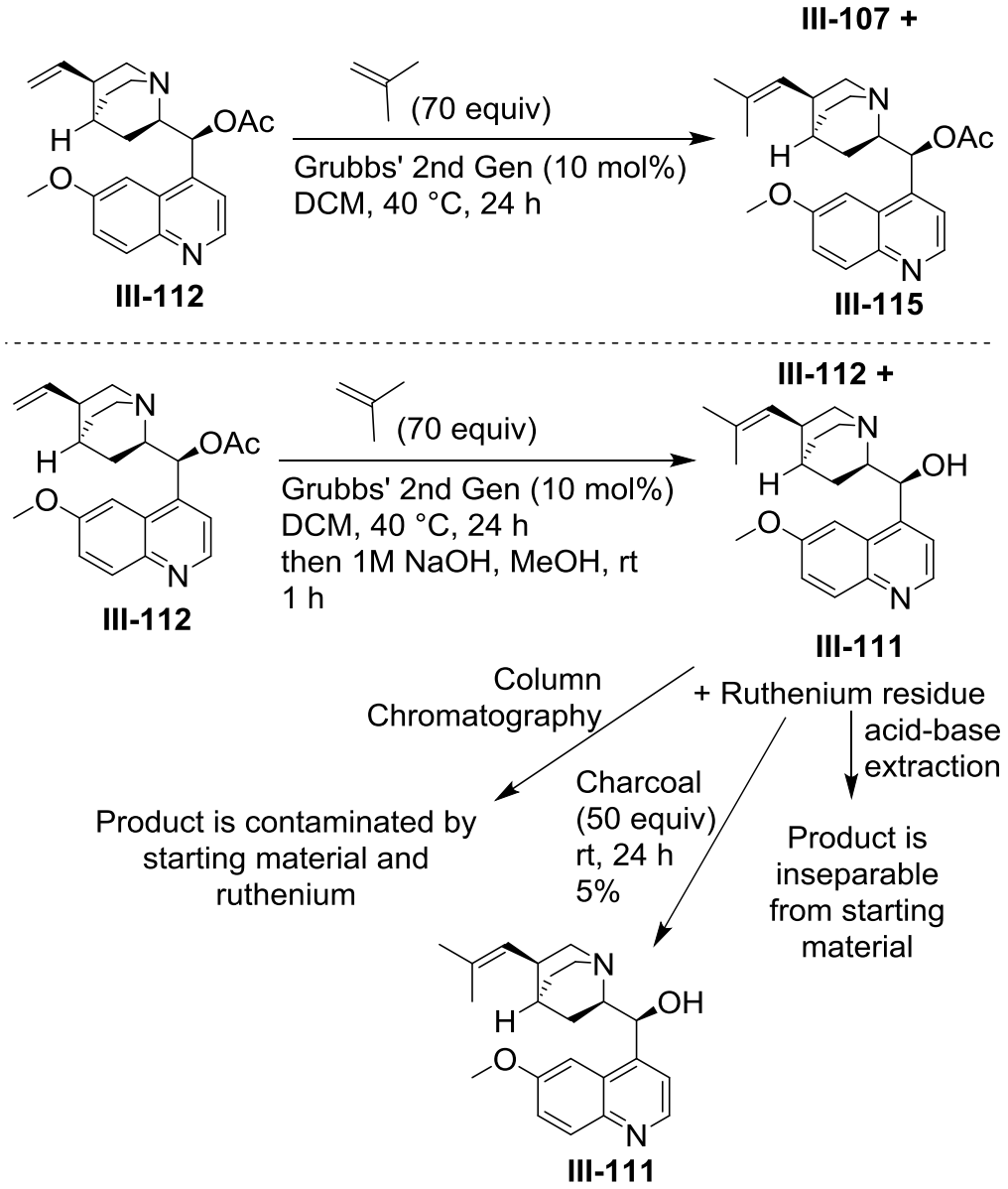
indicated nearly full conversion. Finally we found that a simple acid-base extraction worked very well to get rid of the ruthenium, however the starting material still was difficult to separate from the product. Because the cross metathesis was giving us such low yields and there was still one transformation remaining, this route seemed to be inefficient. Therefore, we decided to investigate the other synthetic route which involved the cross metathesis between $(QD)_2PYDZ$ and 2-methylpropene.

For this reaction we increased the Grubbs catalyst loadings from 10 mol% up to 35% (Scheme III-25). The reason for this is because the first time we screened the

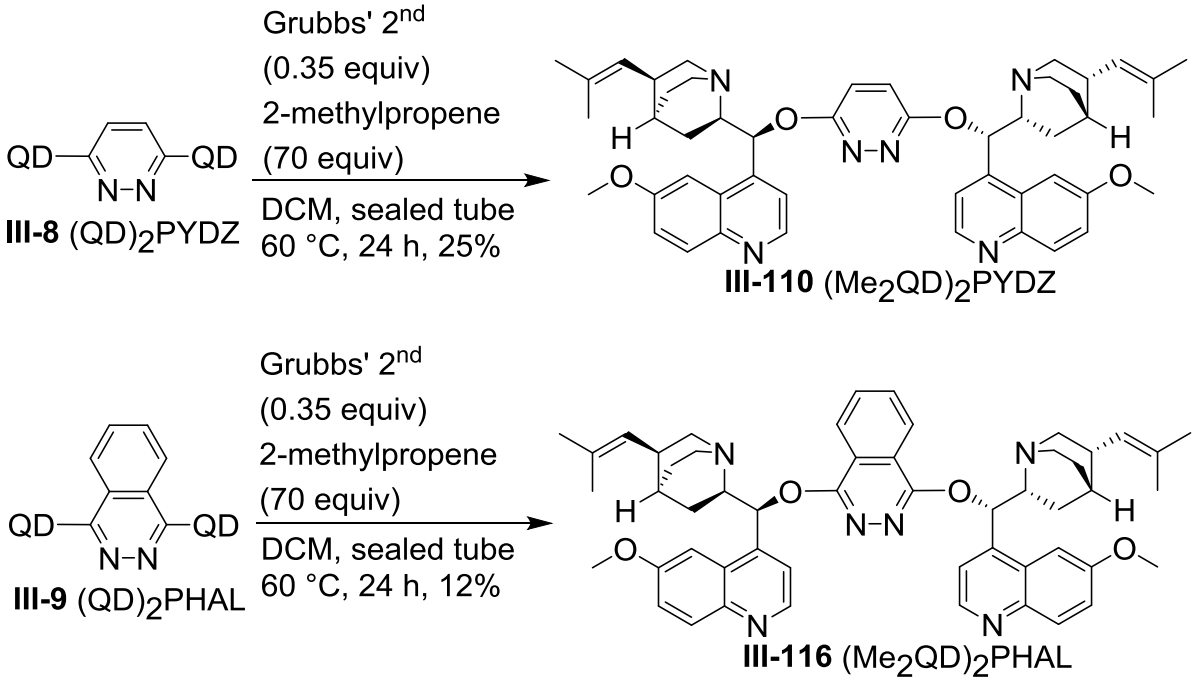


Scheme III-23. Cross metathesis attempts using styrene.
*Stereochemistry of generated olefin was not determined.

reaction, after 48 hours with 10 mol% catalyst crude ^{1}H NMR indicated approximately 30% of unreacted olefin. Since the dimer was being used, this increased the complexity of the crude product mixture by having the possibility for unreacted starting material, mono-cross-metathesis product, and bis-cross-metathesis product. To aid in purification we decided to increase the catalyst loadings to push the reaction to



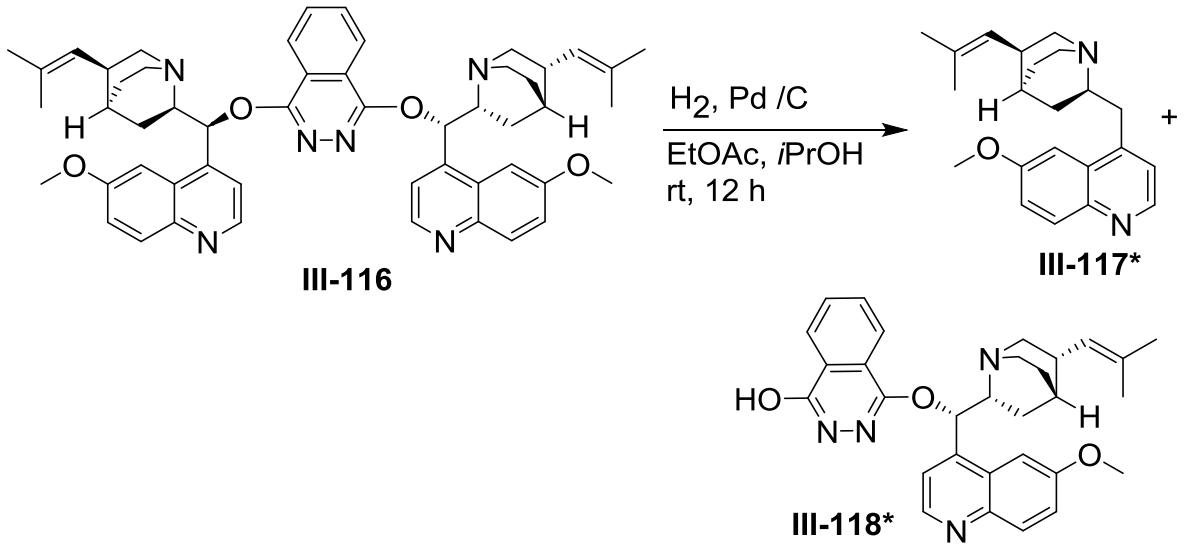
Scheme III-24. Cross metathesis attempts using 2-methylbutene and O-acetyl quinidine.



Scheme III-25. Cross metathesis using 2-methylbutene and quinidine dimers.

completion. After this small change, the reaction worked well and after the acid-base extraction to remove the ruthenium and column chromatography, the desired dimer was isolated in 25% yield. As with all of these syntheses, the yield is only based on the column fractions deemed clean via ^{1}H NMR analysis. In an analogous fashion, the dimer featuring the phthalazine linker was also synthesized.

For the SER studies, we wanted to hydrogenate the quinuclidine trisubstituted olefin in phthalazine dimer **III-116**. Typical palladium catalyzed hydrogenation conditions were used but after 24 hours, MS indicated only trace amounts of the desired hydrogenated dimer. A major product was the hydrogenation of the aryl ether bond. Notably the masses of both halves of the hydrogenated aryl ether bond products indicated that the olefin had not been hydrogenated. This is particularly interesting since the naphthyl linked dimer **III-75** was successful hydrogenated using the same

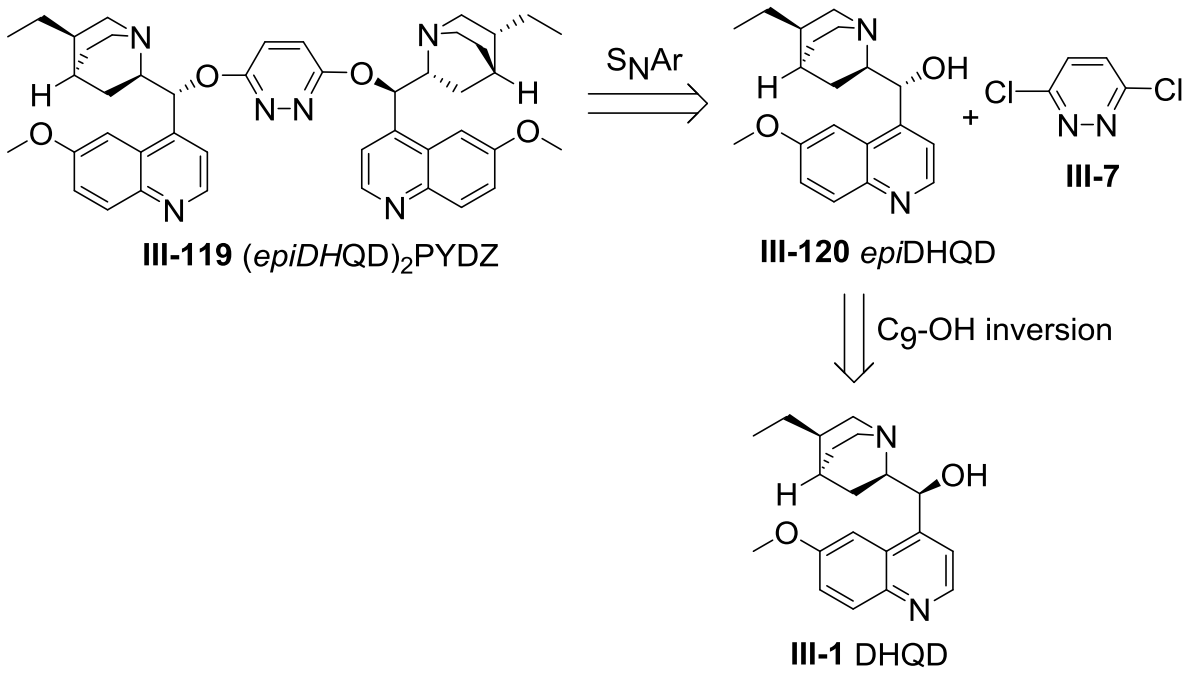


Scheme III-26. Attempt to hydrogenated $(Me_2QD)_2PHAL$ dimer.

conditions to give **III-78** (Scheme III-17). One would expect that the trisubstituted olefin should be more electron rich and thus more reactive towards hydrogenation than the mono-substituted olefin in **III-75**. It is possible that the conformation of the catalyst in **III-116** places the larger olefin in a position which shields it, making it much less reactive towards hydrogenation. Further efforts could explore the use of milder conditions, such as transfer hydrogenation to acquire this product.

III-6 Synthesis of an Epimeric *Cinchona* Alkaloid Dimer

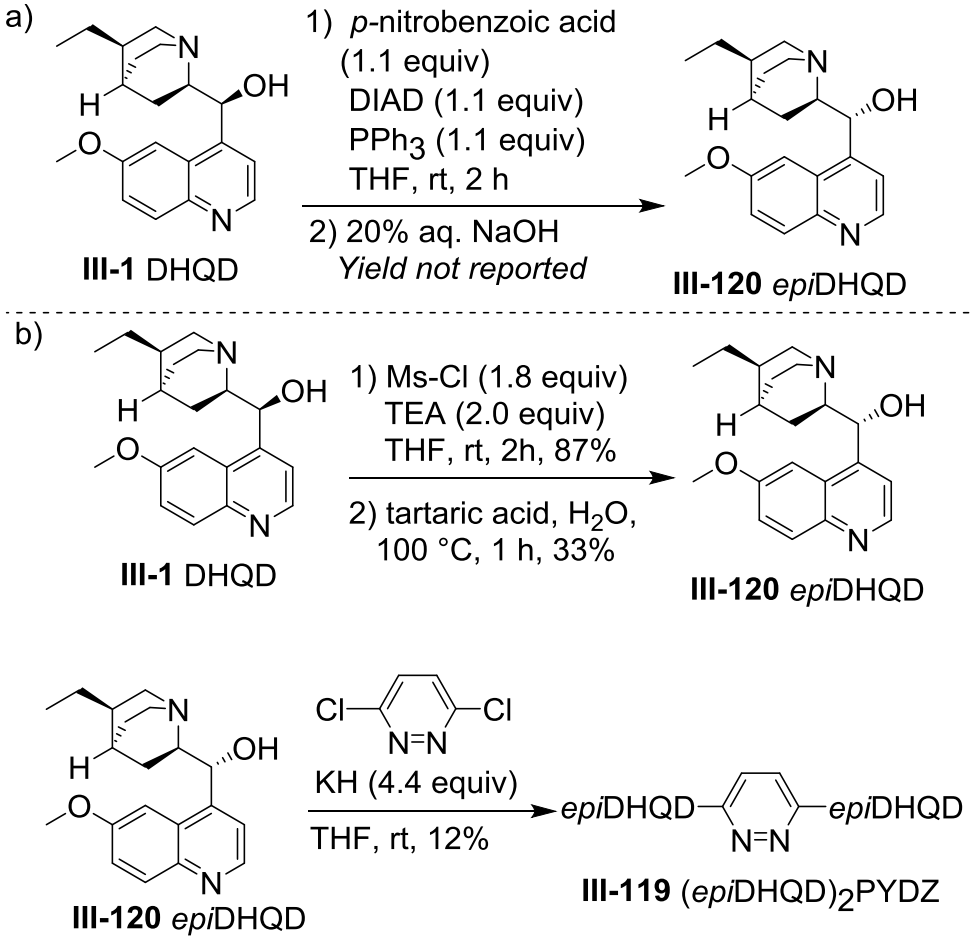
In looking at the desired epimeric dimer, there is essentially only one reasonable retrosynthesis (Scheme III-27); synthesis of the monomeric C_9-epimer and then S_NAr with 2,6-dichloropyridazine to form the dimer. The one option in the synthesis however, is the procedure used to invert the C_9 stereochemistry. One of the more well-known reactions for inverting the stereochemistry of an alcohol is the Mitsunobu reaction and since there was literature precedent for this transformation, this is where we began.[36]



Scheme III-27. Retrosynthesis of C_9-epimer of $(DHQD)_2PYDZ$.

The Mitsunobu procedure in the literature uses *p*-nitrobenzoic acid as the nucleophile to invert the C_9-stereochemistry, followed by hydrolysis (Scheme III-26a). [36] They do not report the use of column chromatography or comment on the purity or yield of the obtained material. When we carried out this reaction, we took a crude ^{1}H NMR of the intermediate nitro-benzoate ester adduct, which unveiled a complex mixture of products. We therefore decided to hydrolyze the ester, in hopes that the crude material was simply beginning to hydrolyze during workup, however this was also a mess.

We uncovered an interesting procedure in the literature which initially mesylated the dihydroquinidine alcohol and then solvolyzed the mesylate in the presence of tartaric acid, selectively generating the monomeric C_9-epimer.[23] The authors believe that the reaction proceeds via an S_N2 attack of water on the carbinol carbon whose



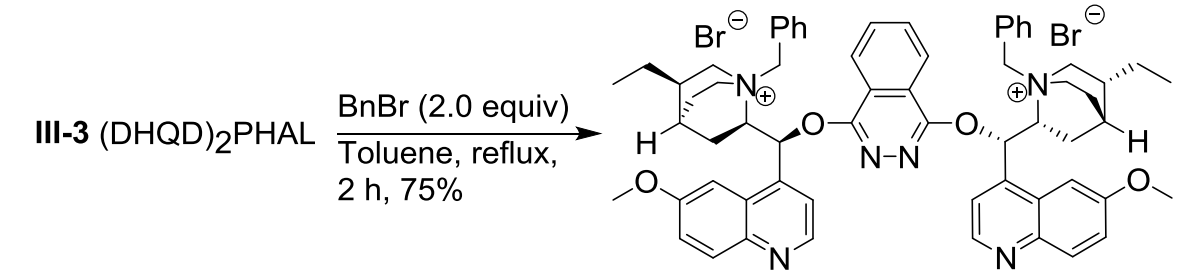
Scheme III-28. Synthesis of C_9-epimer of $(DHQD)_2PYDZ$.

conformation is rigidified by the protonated quinuclidine nitrogen forming a H-bonding bridge with the mesylate. This procedure successfully gave us the desired monomeric epimer in good diastereoselectivity, which was then dimerized with 2,6-dichloropyridazine using our developed conditions (Scheme III-26b).

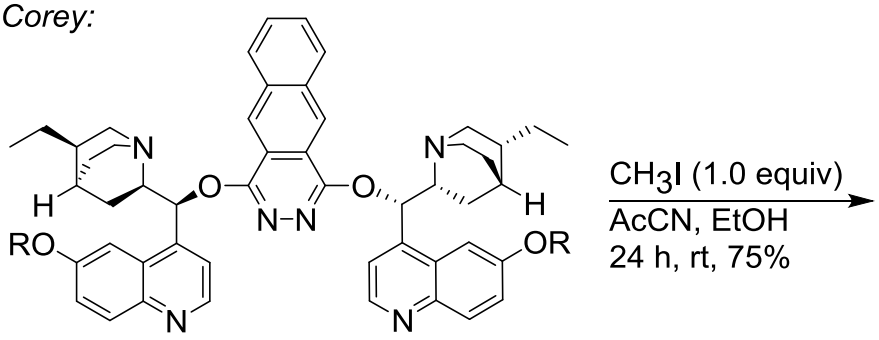
III-7 Synthesis of Alkylated $(DQHD)_2PHAL$ Catalysts

There was some literature precedent for the synthesis of mono- and dialkylated $(DHQD)_2PHAL$ catalysts, however characterization was lacking from nearly all the procedures. For dialkylation of $(DHQD)_2PHAL$ and a derivative thereof, there were two

Jeong:

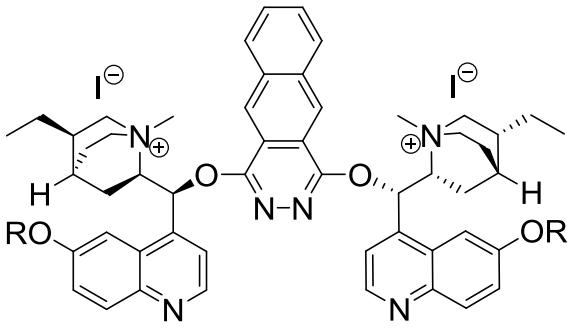


Corey:

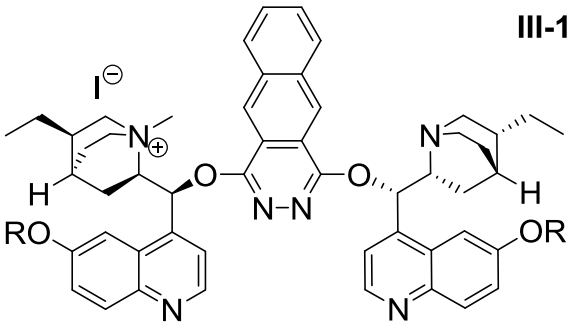


III-21 $(DHQD)_2$BENZOPHAL

Where R = $CH(CH_2CH_2CH_3)_2$



III-122 $(DHQD)_2$BENZOPHAL+ 2 MeI (18 %)



III-123 $(DHQD)_2$BENZOPHAL+ MeI (42 %)

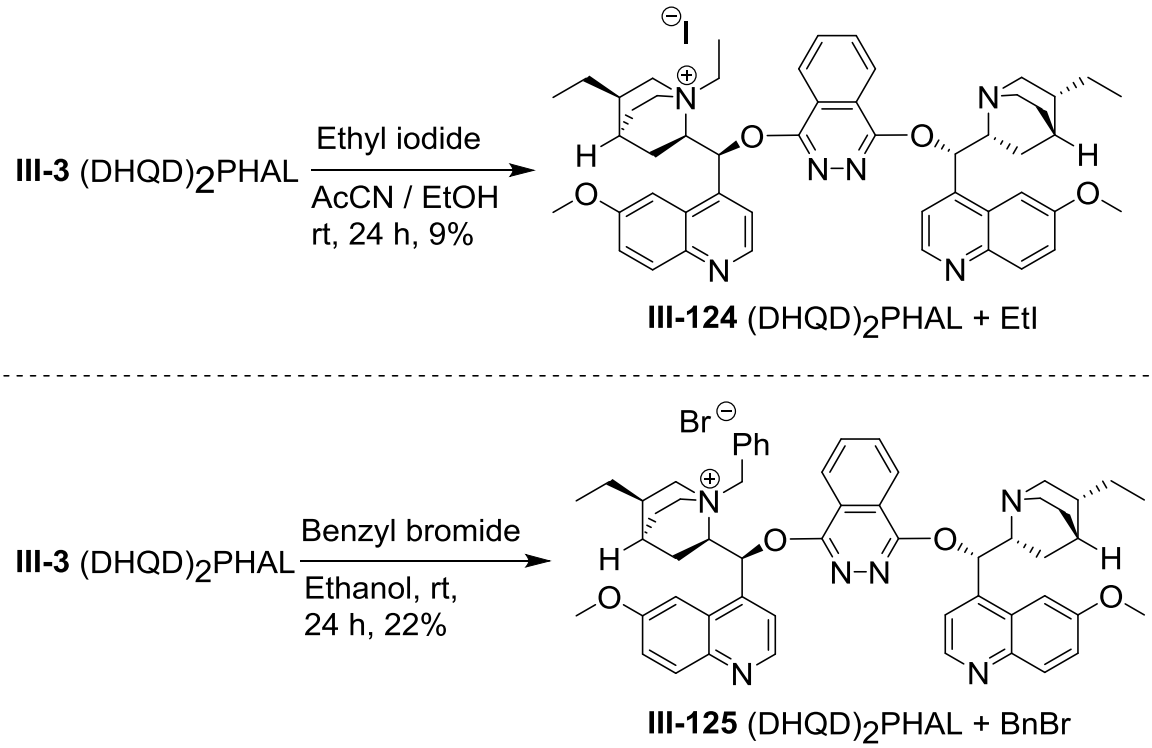
+

III-21 $(DHQD)_2$BENZOPHAL (12 %)

Scheme III-29. Reported dialkylations of $(DHQD)_2$PHAL and derivatives thereof.

reported procedures, one using methyl iodide[37] and the other benzyl bromide[38] (Scheme III-29). We attempted both of these procedures and they were successful in generating the product, the only problem was purification of the doubly charged product, from the monoalkylated and starting material. Recrystallization, silica, ion exchange and size exclusion chromatography were all tried in efforts to purify the desired compound. All of these methods failed to give the pure product and more specifically the ion exchange resin led to regeneration of the starting material. We eventually decided to forgo efforts towards these dialkylated catalysts.

We then turned to the synthesis of a monoalkylated $(DHQD)_2PHAL$ catalyst. There were a few more reported procedures for this substrate, with 3 of the 4 procedures alkylating with benzyl bromide and with allyl bromide.[17, 39-41] We chose to

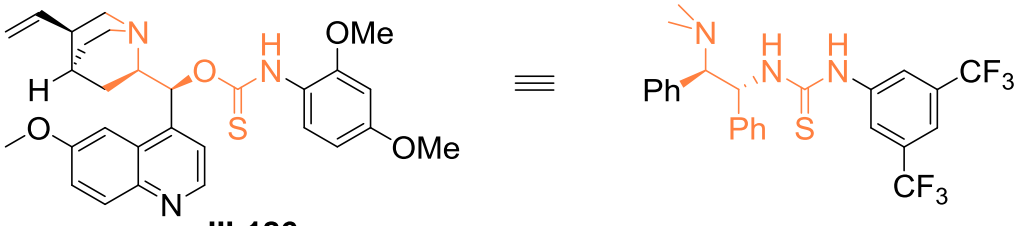


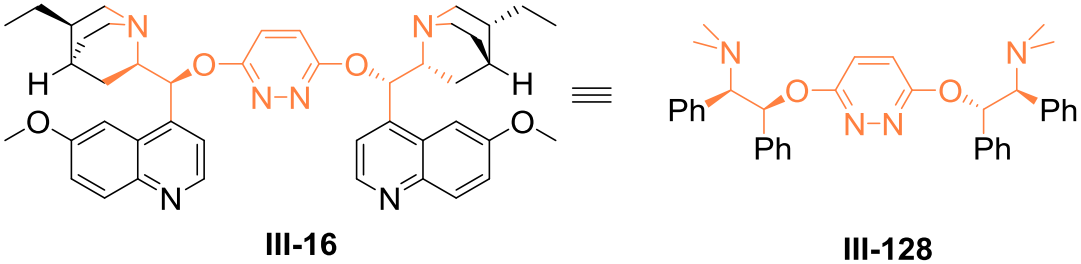
Scheme III-30. Monoalkylation of $(DHQD)_2PHAL$ using ethyl iodide and benzyl bromide.

start by alkylating with methyl iodide following the procedure reported by Corey (Scheme III-29), which again proved successful in forming the product, but proved hard to purify. We finally concluded that the methylated quinuclidine may be unstable, decomposing back to starting material or through other elimination pathways, and decided to use ethyl iodide instead since it should be less reactive (Scheme III-30). This worked well and after silica gel chromatography, the desired product was obtained. Using the same procedure the monobenzylated $(DHQD)_2PHAL$ catalyst was obtained.

III-8 Synthesis of a Truncated Catalyst

The last catalyst we set out to make was not comprised of an alkaloid, but an alkaloid mimic. The original idea for this catalyst stemmed from a paper using a scaffold (**III-127)**, which had a striking similarity to a *cinchona* alkaloid derived catalyst (**III-126**).[42, 43] Based on this observation, we wanted to use the same alkaloid "mimic"

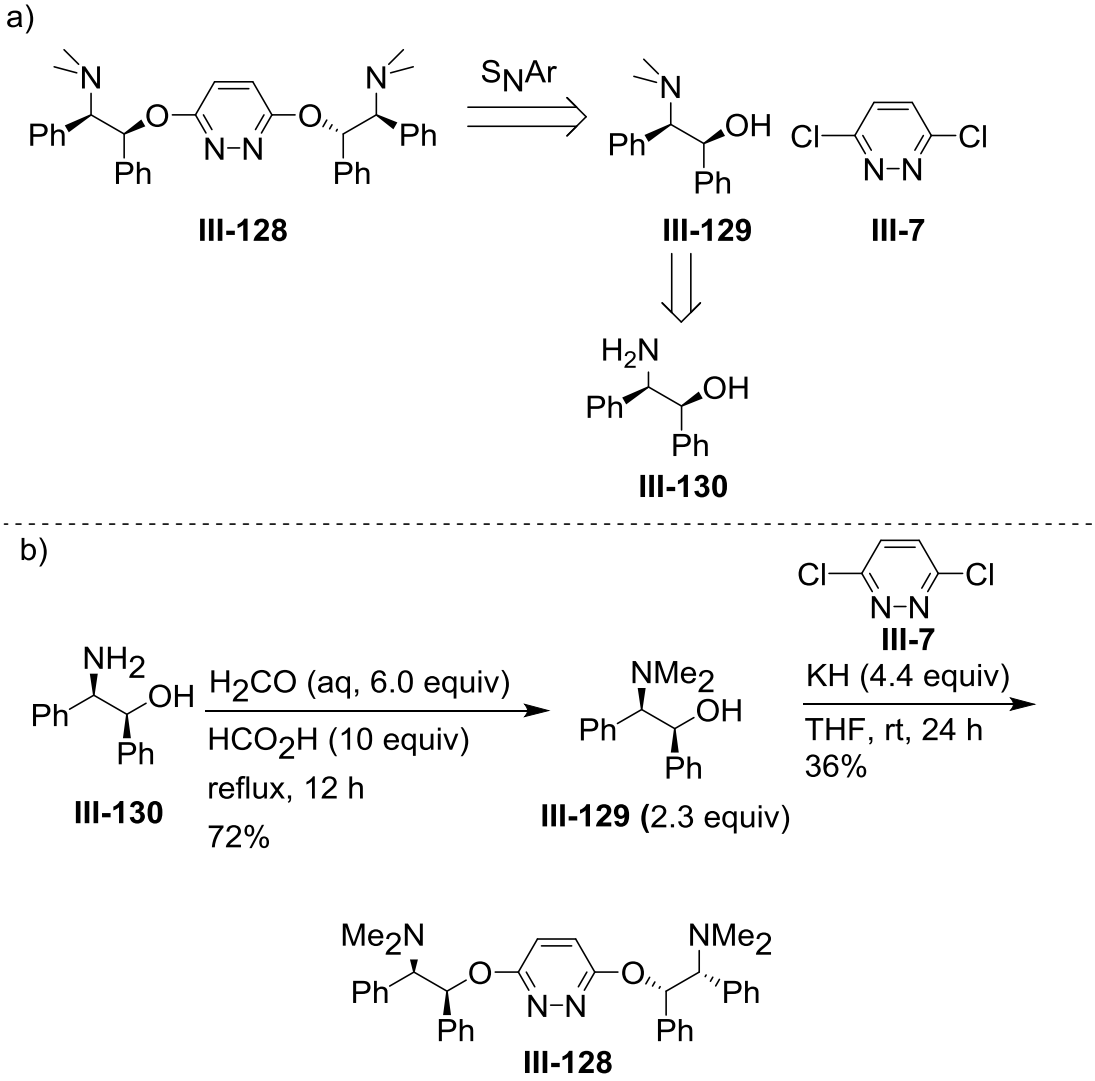




Scheme III-31. Cinchona alkaloid catalysts and their analogous mimiced derivatives.

in a pyridazine dimer (I**II-128**).

The retrosynthesis of our truncated scaffold was straight forward (Scheme III-32a). The dimer would be synthesized from the dimethylated amino alcohol monomer (**III-129**) and 2,6-dichloropyridazine and the functionalized monomer would arise from dimethylation of the commercially available amino alcohol **III-130.** Since the literature procedure to make the desired dimethylated monomer was successful, this catalyst proved easy to make.



Scheme III-32. Retrosynthesis (a) and forward synthesis (b) of truncated catalyst.

III-9 Conclusions

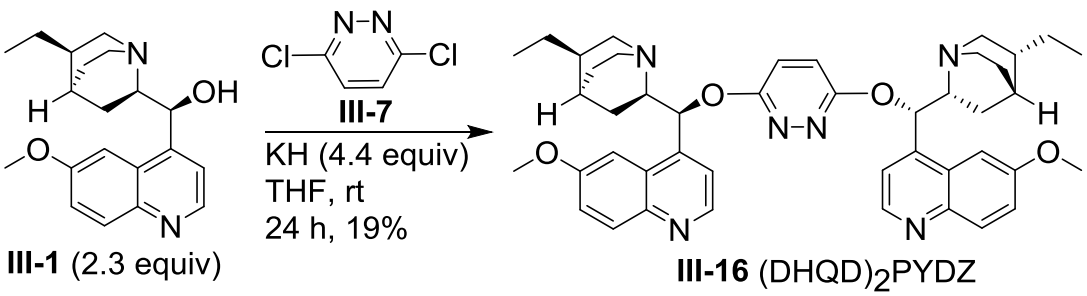
A wide variety of *cinchona* alkaloid derivatives were made for the SER studies of various asymmetric chlorocyclization reactions. Although this library of catalysts is comprehensive, one can imagine that there will always be others that can be made. As mentioned in Chapter II, the synthesis of a library of truncated analogs would be easily conceivable, offering limitless variations to the catalyst, in comparison to the alkaloid scaffold.

III-10 Experimentals

General Procedures:

All reagents were used without purification. 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. ^{1}H NMR spectra were measured at 300 or 500 MHz on a Varian Gemini-300 or a Varian VXR-500 instrument, respectively. Chemical shifts are reported relative to residual solvent (δ7.24 ppm for $CDCl_3$). 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.

(DHQD)$_2$PYDZ

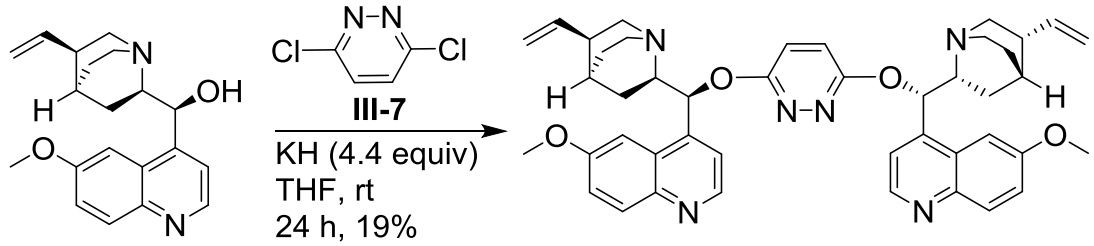


To a flame dried 100 mL round bottom flask was added KH (238 mg, 1.78 mmol, 4.36 equiv, 30% suspension in oil). The oil was removed from the potassium hydride by washing with hexanes (3 x 2 mL). THF (36 mL) was then added to the flask, followed by the addition of dihydroquinidine (302 mg, 0.925 mmol, 2.26 equiv) and 3,6-dichloropyridazine (61 mg, 0.41 mmol, 1.0 equiv). The reaction was stirred at room temperature under dry nitrogen for 24 hours, during which time the color changed from colorless to orange. At the end of 24 hours, 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 x 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 **III-16 $(DHQD)_2PYDZ$:** ^1H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, J = 4.5 Hz, 2H), 7.98 (d, J = 9.2 Hz, 2H), 7.43 (s, 2H), 7.35-7.32 (m, 4H), 6.95 (s, 2H), 6.72 (d, J = 6.2 Hz, 2H), 3.85 (s, 6H), 3.26 (dd, J = 15.8, 8.9 Hz, 2H), 2.79-2.60 (m, 8H), 1.83 (t, J = 12.3 Hz, 2H), 1.67 (s, 2H), 1.51-1.48 (m, 2H), 1.44-1.37 (m, 10H), 0.81 (t, J = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8, 157.6, 147.4, 144.7, 144.6, 131.6, 127.2, 121.7, 121.3, 118.6, 101.9, 59.9, 55.6, 50.9, 50.1, 37.4, 27.3, 26.1, 25.3, 23.2, 12.0. Expected signal for carbinol peak must be underneath $CDCl_3$ signal, so both ^1H NMR and ^{13}C NMR were run in CD_3OD to confirm carbinol signal. ^1H NMR (500 MHz, CD_3OD) δ 8.55 (d, J = 4.7 Hz, 2H), 7.88 (d, J = 9.2 Hz, 2H), 7.48 (d, J = 4.7 Hz, 2H),

7.42-7.36 (m, 4H), 7.33 (s, 2H), 6.82 (d, *J* = 4.3 Hz, 2H), 3.83 (s, 6H), 3.26 (td, *J* = 9.1, 4.4 Hz, 2H), 2.84-2.80 (m, 6H), 2.73-2.68 (m, 2H), 2.16-2.12 (m, 2H), 1.72 (s, 2H), 1.54-1.50 (m, 10H), 1.37-1.32 (m, 2H), 0.88 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (125 MHz, CD_3OD) δ 162.6, 160.1, 148.2, 146.6, 145.3, 131.7, 128.8, 124.2, 123.7, 119.9, 102.9, 77.9, 60.8, 56.7, 52.3, 51.3, 38.7, 28.1, 27.7, 26.6, 23.1, 12.6; IR (NaCl plate): v 2951, 2934, 2872, 1622, 1509, 1474, 1407, 1282, 1228, 989 cm^{-1}; HRMS (ESI) m/z calculated for $C_{44}H_{52}N_6O_4H^+$ $[M+H]^+$ 729.4128, observed 729.4144; $[\alpha]^{20}_D$ = -19.7° (*c* = 10 mg / mL, $CHCl_3$); mp = 97-99 °C.

(QD)$_2$PYDZ



III-6 QD (2.3 equiv)

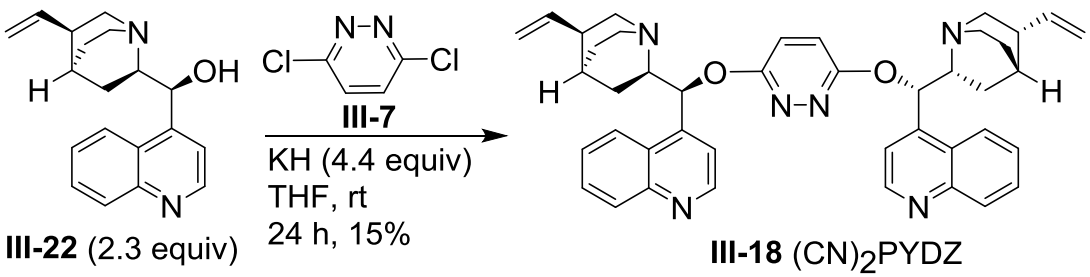
III-8 $(QD)_2PYDZ$

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 x 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, 0.41 mmol). The reaction was stirred at room temperature under dry nitrogen for 24 hours, during which time the color changed from colorless to orange. At the end of 24 hours, 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 x 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 **III-8 $(QD)_2PYDZ$:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (d, *J* = 4.5 Hz, 2H), 7.96 (d, *J* = 9.2 Hz, 2H), 7.40 (d, *J* = 2.6 Hz, 2H), 7.33-7.31 (m, 4H), 6.98 (s, 2H), 6.76 (d, *J* = 5.9 Hz, 2H), 5.96-5.89 (m, 2H), 4.98-4.94 (m, 4H), 3.83 (s, 6H), 3.26 (dd, *J* = 15.1, 8.8 Hz, 2H), 2.90-2.85 (m, 2H), 2.80-2.72 (m, 4H), 2.66-2.60 (m, 2H), 2.16 (dd, *J* = 16.5, 8.1 Hz, 2H), 1.95-1.91 (m, 2H), 1.72 (s, 2H), 1.46-1.38 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7, 157.6, 147.3, 144.6, 144.4, 140.4, 131.5, 127.1, 121.6, 121.2, 118.4, 114.5, 101.8, 76.7, 59.7, 55.5, 49.9, 49.3, 39.8, 27.9, 26.4, 23.1; IR (NaCl plate): v 2936, 1622, 1508, 1473, 1261, 1226, 1084, 1030, 991 cm^{-1}; HRMS(ESI) m/z calculated for $C_{44}H_{48}N_6O_4H^+$ $[M+H]^+$ 725.3815, observed 725.3830; $[\alpha]^{20}_D$ = -26.0° (*c* = 10 mg / mL, $CHCl_3$); mp = 103-105 °C.

$(CN)_2PYDZ$



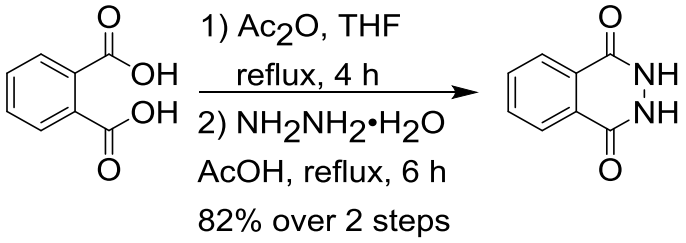
III-22 (2.3 equiv) **III-18** $(CN)_2PYDZ$

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 x 2 mL). THF (40 mL) was then added to the flask, followed by the addition of cinchonine (300 mg, 1.02 mmol, 2.26 equiv) and 3,6-dichloropyridazine (67 mg, 0.45 mmol). The reaction was stirred at room temperature under dry nitrogen for 24 hours, during which time the color changed from colorless to orange. At the end of 24 hours, 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 x 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 **III-18 $(CN)_2$PYDZ:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (d, *J* = 4.5 Hz, 2H), 8.20 (d, *J* = 8.6 Hz, 2H), 8.08 (d, *J* = 8.5 Hz, 2H), 7.68 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 2H), 7.53 (ddd, *J* = 8.3, 6.8, 1.3 Hz. 2H), 7.39 (d, *J* = 4.5 Hz, 2H), 6.97 (s, 2H), 6.82 (d, *J* = 6.3 Hz, 2H), 5.95-5.88 (m, 2H), 4.99-4.94 (m, 4H), 3.29 (dd, *J* = 15.2, 8.7 Hz, 2H), 2.90-2.86 (m, 2H), 2.80-2.70 (m, 4H), 2.66-2.59 (m, 2H), 2.17 (q, *J* = 8.4 Hz, 2H), 1.92-1.88 (m, 2H), 1.72 (s, 2H), 1.48-1.40 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8, 149.9, 148.6, 145.9, 140.5, 130.3, 129.0, 126.5, 126.2, 124.0, 121.4, 118.8, 114.6, 77.1, 60.2, 50.0, 49.3, 40.0, 28.0, 26.5, 23.3; IR (NaCl plate) v 3063, 2940, 2872, 1437, 1394, 1261, 987

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

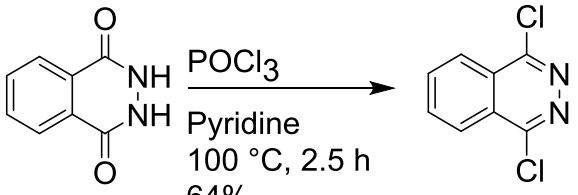
2,3-Dihydrophthalazine-1,4-dione[13]



To a flame dried 25 mL round bottom flask was added phthalic acid (1.00 g, 6.02 mmol), acetic anhydride (1.5 mL), and anhydrous THF (5.6 mL). The reaction was refluxed for 4 hours, then cooled to 40 °C, at which time the reaction flask was equipped with a short-path distillation apparatus. The solvent was distilled off, under vacuum, leaving a white solid. At this time, the reaction flask was cooled to room temperature and then the white solid was dissolved in acetic acid (25 mL). Hydrazine monohydrate (1.76 mL, 23.6 mmol, 3.92 equiv) was then slowly added to the flask. Following the addition of the hydrazine solution, the reaction became clear and was then heated to reflux. After approximately 5 minutes of heating, the solution went cloudy and then a white precipitate formed. The reaction was heated to reflux for 6 hours and was then cooled to room temperature. The white solid was filtered, washed with water, dissolved in DCM (10 mL) and concentrated. The product was dried under vacuum, giving the product as a white solid in 82% yield over 2 steps (0.80 g, 4.95 mmol).

Data for **2,3-dihydrophthalazine-1,4-dione:** ^{1}H NMR (500 MHz, DMSO-*d6*) δ 11.51 (br, 2H), 8.05 (dd, *J* = 5.7, 3.4 Hz, 2H), 7.86 (dd, *J* = 6.0, 3.4 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 155.0, 133.0, 127.6, 125.6; mp > 250 °C.

1,4-Dichlorophthalazine[14]

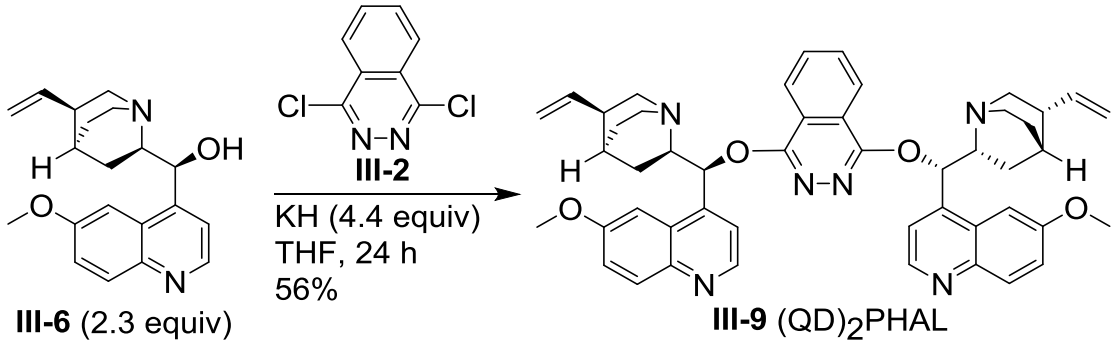


III-2

To a flame dried 25 mL round bottom flask was added 2,3-dihydrophthalazine-1,4-dione (400 mg, 2.47 mmol), phosphoryl chloride (5.25 mL), and pyridine (328 µL). The reaction was heated to reflux for 2.5 hours, 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 then 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 **III-2 1,4-dichlorophthalazine**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29-8.27 (m, 2H), 8.07-8.04 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 134.5, 127.2, 125.8; mp = 151-153 °C.

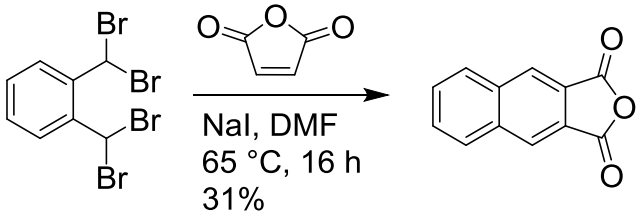
$(QD)_2PHAL$



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 three times with hexanes (3 x 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, 0.41 mmol). The reaction was stirred at room temperature under dry nitrogen for 24 hours. At the end of 24 hours, 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 x 15 mL), the combined organics were washed with water (3 x 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 **III-9 $(QD)_2PHAL$:** ^1H NMR (500 MHz, $CDCl_3$) δ 8.62 (d, *J* = 4.6 Hz, 2H), 8.32 (dd, *J* = 6.2, 3.3 Hz, 2H), 7.97 (d, *J* = 9.2 Hz, 2H), 7.90 (dd, *J* = 6.1, 3.3 Hz, 2H), 7.53 (d, *J* = 2.7 Hz, 2H), 7.40 (d, *J* = 4.6 Hz, 2H), 7.34 (dd, *J* = 9.2, 2.7 Hz, 2H), 7.02 (d, *J* = 6.0 Hz, 2H), 5.94-5.88 (m, 2H), 4.97 -4.93 (m, 4H), 3.88 (s, 6H), 3.39 (dd, *J* = 15.1, 8.9 Hz, 2H), 2.94-2.91 (m, 2H), 2.84-2.76 (m, 4H), 2.69-2.62 (m, 2H), 2.19 (q, *J* = 8.2 Hz, 2H), 2.09-2.05 (m, 2H), 1.78 (s, 2H), 1.55-1.49 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6, 156.4, 147.3, 144.9, 144.7, 140.3, 132.1, 131.5, 127.3, 123.0, 122.4, 121.8, 118.3, 114.6, 102.0, 76.1, 60.1, 55.6, 49.8, 49.5, 39.7, 27.8, 26.5, 23.2; IR (NaCl plate) v 3073, 3053, 2938, 2872, 2840, 1622, 1593, 1508, 1388, 1354, 1226, 1093, 1028, 985 cm^{-1}; HRMS (ESI) m/z calculated for $C_{48}H_{50}N_6O_4H^+$ $[M+H]^+$ 775.3972, observed 775.3976; $[\alpha]^{20}_D$ = -194.7° (*c* = 10 mg / mL, $CHCl_3$); mp = 119-120 °C.

Naphtho[2,3-c]furan-1,3-dione[15]

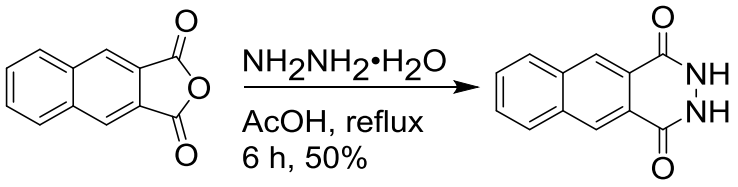


To a flame dried 100 mL round bottom flask was added α,α,α',α'-tetrabromo-*o*-xylene (7.24 g, 17.2 mmol, 1.7 equiv), maleic anhydride (0.99 g, 10.1 mmol), sodium iodide (16.1 g, 107.8 mmol, 10.6 equiv) and anhydrous DMF (40 mL). The reaction immediately turned dark brown and was heated to 65 °C for 16 hours. 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 (0.62 g, 3.1 mmol).

Data for **naphtho[2,3-c]furan-1,3-dione:** ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.79 (s, 2H), 8.36-8.33 (m, 2H), 7.89-7.86 (m, 2H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 163.4, 135.5, 130.4, 130.2, 127.4, 126.1; mp = 248-249 °C.

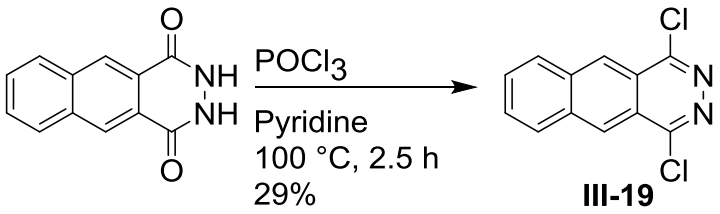
2,3-Dihydrobenzo[g]phthalazine-1,4-dione[44]



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, 1.201 mmol) 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 minutes of heating, the solution went cloudy and then a white precipitate formed. The solution was refluxed for 6 hours and was then cooled to room temperature, where it was allowed to stand overnight. The precipitate was then filtered and washed with water. The white solid was then dissolved in dichloromethane (5 mL) and concentrated. The precipitate was dried under vacuum, giving an off-white solid in 50% yield (0.128 g, 0.603 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); ^{13}C NMR (150 MHz, DMSO-d_6) δ 175.1, 137.2, 134.4, 132.2 131.6, 129.3; mp > 250 °C.

1,4-Dichlorobenzo[g]phthalazine[16]

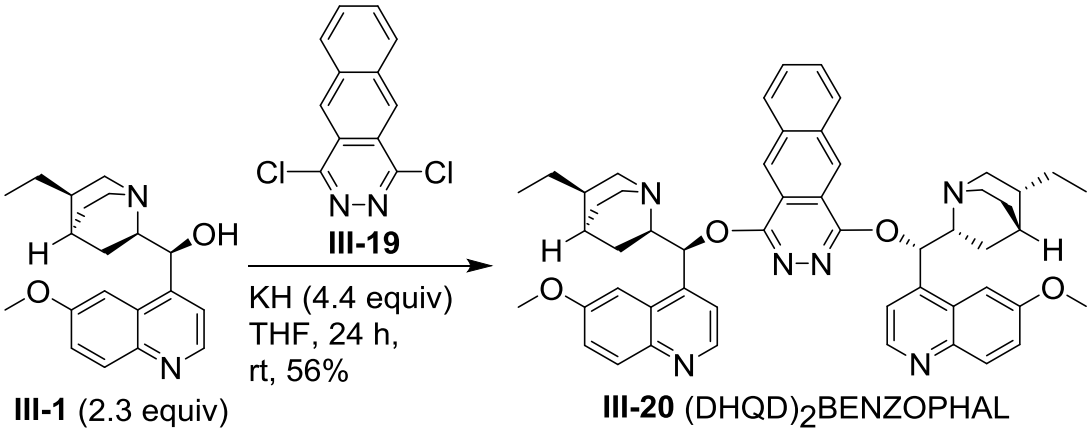


III-19

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), and pyridine (80 µL). The reaction was then heated to 100 °C for 2.5 hours, during which time the reaction changed from clear to yellow. After the 2.5 hours, 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 minutes. 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, 0.17 mmol). *The product decomposes within hours of being dissolved in DMSO-d_6.*

Data for **III-19 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); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.1, 135.3, 130.0, 129.4, 126.9, 122.7; mp = 223-225 °C.

(DHQD)$_2$BENZOPHAL

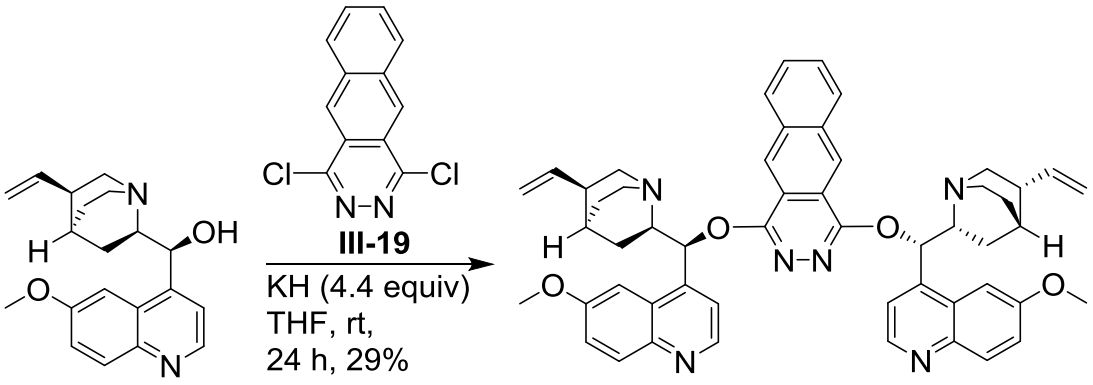


To a flame dried 100 mL round bottom flask was added KH (237 mg, 1.77 mmol, 4.36 equiv, 30% suspension in oil). The oil was removed from the potassium hydride by washing hexanes (3 x 2 mL). THF (36 mL) was then added to the flask, followed by the addition of dihydroquinidine (300 mg, 0.920 mmol, 2.26 equiv) and 1,4-dichlorobenzophthalazine (101 mg, 0.407 mmol). The reaction was stirred at room temperature under dry nitrogen for 24 hours. At the end of 24 hours, 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 x 15 mL), the combined organics were washed with water (3 x 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 **III-20 (DHQD)$_2$BENZOPHAL:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.86 (s, 2H), 8.63 (d, *J*= 4.6 Hz, 2H), 8.16 (dd, *J* = 3.3 Hz, 2H), 7.97 (d, *J* = 9.2 Hz, 2H), 7.74-7.71 (m, 2H), 7.58 (d, *J* = 2.5 Hz, 2H), 7.48 (d, *J* = 4.6 Hz, 2H), 7.34 (dd, *J* = 9.2, 2.7 Hz, 2H), 7.03 (d, *J* = 5.8 Hz, 2H), 3.89 (s, 6H), 3.44 (q, *J* = 8.9 Hz, 2H), 2.83-2.75 (m, 6H), 2.70-2.63 (m, 2H), 2.05 (t, *J* = 11.7 Hz, 2H), 1.72 (s, 2H), 1.57-1.39 (m, 12H), 0.81 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5, 156.2, 147.4, 144.8, 144.7, 134.6, 131.5, 129.0, 128.4, 127.3, 123.1, 121.8, 119.6, 118.4, 102.1, 76.3, 60.1, 55.6, 50.9, 50.0, 37.4, 27.2, 26.4, 25.4, 23.3, 11.9; IR (NaCl plate) v 3047, 2934, 2872, 1620, 1593, 1543, 1510, 1462, 1433, 1350, 1228, 1145, 1062, 846, 734 cm^{-1}; HRMS (ESI) m/z calculated for $C_{52}H_{56}N_6O_4H^+$ $[M+H]^+$ 829.4441, observed 829.4456; $[\alpha]^{20}_D$ = -312.5° (*c* = 10 mg / mL, $CHCl_3$); mp = 60-61 °C.

(QD)$_2$BENZOPHAL

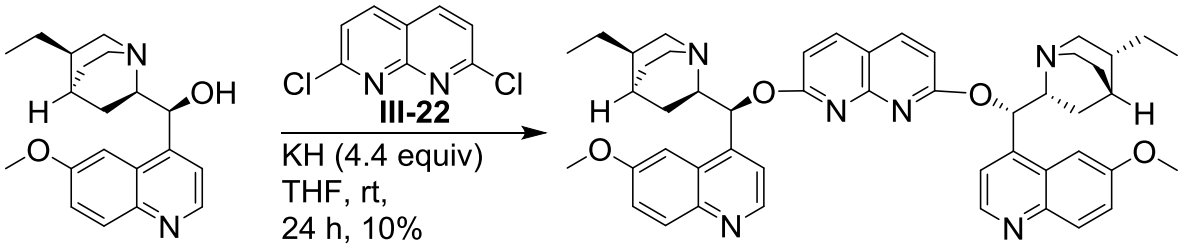


To a flame dried 100 mL round bottom flask was added KH (101 mg, 0.752 mmol, 4.36 equiv, 30% suspension in oil). The oil was removed from the potassium hydride by washing with hexanes (3 x 2 mL). THF (15 mL) was then added to the flask, followed by the addition of quinidine (126 mg, 0.390 mmol, 2.26 equiv) and 1,4-dichlorobenzophthalazine (43 mg, 0.173 mmol). The reaction was stirred at room temperature under dry nitrogen for 24 hours. At the end of 24 hours, 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 x 10 mL), the combined organics were washed with water (3 x 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 **III-21 $(DHQD)_2$BENZOPHAL:** ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.89 (s, 2H), 8.61 (d, *J* = 4.6 Hz, 2H), 8.20-8.18 (m, 2H), 7.97 (d, *J* = 9.2 Hz, 2H), 7.75-7.73 (m, 2H), 7.54 (d, *J* = 2.5 Hz, 2H), 7.46 (d, *J* = 4.6 Hz, 2H), 7.34 (dd, *J* = 9.1, 2.6 Hz, 2H), 7.11 (d, *J* = 4.7 Hz, 2H), 6.04-5.98 (m, 2H), 5.03-4.99 (m, 4H), 3.90 (s, 6H), 3.43 (dd, *J* = 14.2, 8.8 Hz, 2H), 3.06-3.02 (m, 2H), 3.86 (t, *J* = 10.4 Hz, 4H), 2.73-2.70 (m, 2H), 2.22-2.19 (m, 4H), 1.86 (s, 2H), 1.57-1.53 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 156.2, 147.4, 144.7, 140.2, 134.6, 131.6, 129.0, 128.4, 127.2, 123.6, 122.2, 119.8, 118.4, 115.0, 102.2, 76.2, 59.9, 55.7, 49.9, 49.5, 39.8, 27.9, 26.7, 23.1; IR (NaCl plate) v 3089, 3053, 2936, 2870, 1620, 1593, 1508, 1433, 1348, 1228, 1145, 1060, 985, 844 cm^{-1}; HRMS (ESI) m/z calculated for $C_{52}H_{52}N_6O_4H^+$ $[M+H]^+$ 825.4128, observed 825.4123; $[\alpha]^{20}_D$ = -266.8° (*c* = 10 mg / mL, $CHCl_3$); mp = 120 °C (decomposed).

$(DHQD)_2$NAPY



III-1 DHQD (2.3 equiv)

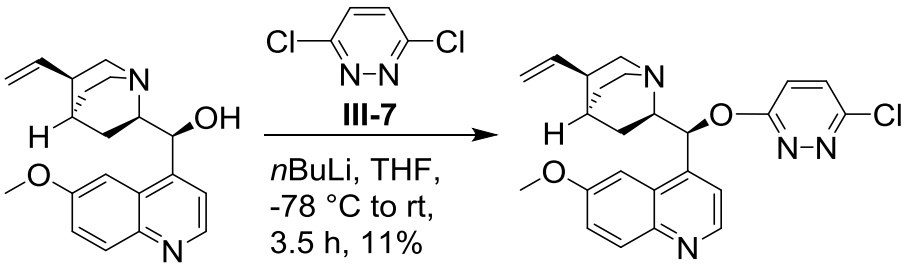
III-23 $(DHQD)_2$NAPY

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 with hexanes (3 x 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, 0.41 mmol). The reaction was stirred at room temperature under dry nitrogen for 24 hours. At the end of 24 hours, 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 then separated, the aqueous layer was washed with EtOAc (3 x 20 mL), the combined organics were washed with water (3 x 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 (32 mg, 0.041 mmol) in 10% yield.

Data for **III-23 (DHQD)$_2$NAPY:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (d, *J* = 4.5 Hz, 2H), 7.99 (d, *J* = 9.2 Hz, 2H), 7.86 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 2.5 Hz, 2H), 7.41 (d, *J* = 4.5 Hz, 2H), 7.36 (dd, *J* = 9.2, 2.5 Hz, 2H), 7.16 (d, *J* = 5.1 Hz, 2H), 6.87 (d, *J* = 8.6, 2H), 3.82 (s, 6H), 3.30 (dd, *J* = 14.0, 8.9 Hz, 2H), 2.83-2.70 (m, 4H), 2.69 (dd, *J* = 17.3, 9.7 Hz, 4H), 1.97 (t, *J* = 11.2 Hz, 2H), 1.64 (s, 2H), 1.49-1.23 (m, 12H), 0.66 (t, *J* = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.6, 157.7, 154.0, 147.4, 144.7, 139.1, 131.6, 127.2, 121.8, 118.5, 115.8, 110.8, 101.7, 75.1, 59.1, 55.8, 50.8, 50.1, 37.4, 27.3, 25.8, 25.0, 22.0, 11.9; IR (NaCl plate) v 3075, 3051, 2932, 2872, 1606, 1500, 1433, 1329, 1257, 1130, 1028, 989, 843 cm^{-1}; HRMS (ESI) m/z calculated for $C_{48}H_{54}N_6O_4H^+$ $[M+H]^+$ 779.4285, observed 779.4286. $[\alpha]^{20}_D$ = -24.5° (*c* = 10 mg / mL, $CHCl_3$); mp = 190 °C (decomposed).

(QD)PYDZ[17]



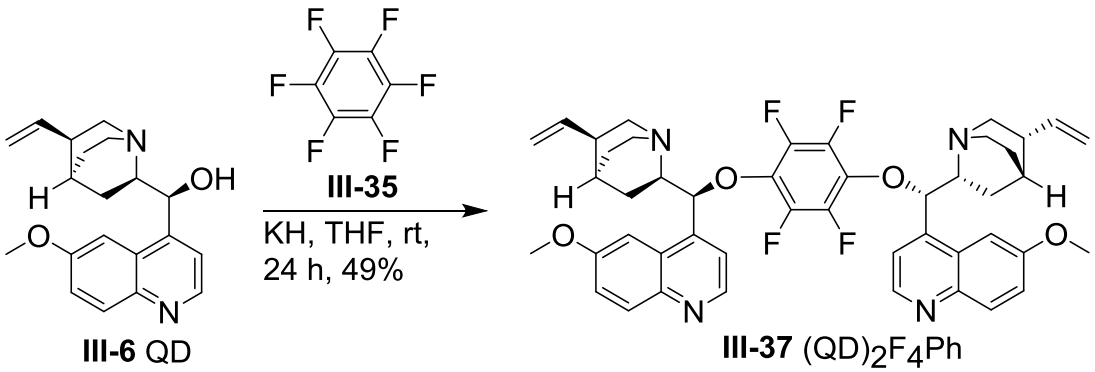
III-6 **III-28** (QD)PYDZ

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 minutes, was warmed to room temperature, and then 3,6-dichloropyridazine (149 mg, 0.999 mmol, 1.08 equiv) was then added in one portion. The reaction was stirred at room temperature for 3.5 hours 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 x 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 **III-28 (QD)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); ^{13}C 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, 77.1, 59.6, 55.2, 50.0, 49.4, 39.8, 27.9, 26.5, 23.3; HRMS (ESI) m/z calculated for $C_{24}H_{25}N_4O_2ClH^+$ $[M+H]^+$437.1744, observed 437.1737; $[\alpha]^{20}_D$ = -46.5° (*c* = 10 mg / mL, $CHCl_3$); mp = 60-62 °C.

$(QD)_2F_4Ph$

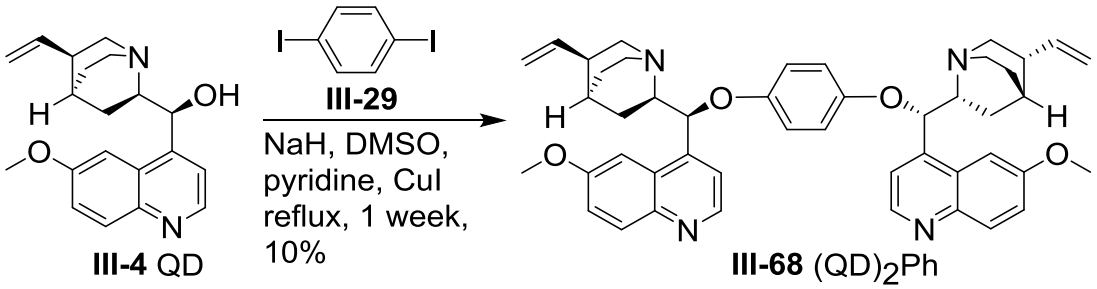


To a flame dried 100 mL round bottom flask was added KH (126 mg, 0.924 mmol, 2.0 equiv, 30% suspension in oil). The oil was removed from the potassium hydride by washing with hexanes (3 x 2 mL). THF (4.2 mL) was then added to the flask, followed by the addition of quinidine (300 mg, 0.924 mmol, 2.0 equiv) and hexafluorobenzene (54 µL, 0.462 mmol). The reaction was stirred at room temperature under dry nitrogen for 24 hours. At the end of 24 hours, 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 then separated, the aqueous layer was washed with EtOAc (3 x 20 mL), the combined organics were washed with water (3 x 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 **III-37 $(QD)_2F_4Ph$:** ^1H NMR (500 MHz, $CDCl_3$) δ 8.67 (d, *J* = 4.5 Hz, 2H), 7.95 (d, *J* = 9.2 Hz, 2H), 7.37 (s, 2H), 7.31 (dd, *J* = 9.2, 2.7 Hz, 2H), 7.21 (s, 2H), 6.02-5.96 (m, 4H), 5.06-5.02 (m, 4H), 3.85 (s, 6H), 3.25 (s, 2H), 2.95 (s, 2H), 2.85 (t, *J* = 10.1 Hz, 2H), 2.74-2.67 (m, 4H), 2.27 (q, *J* = 7.9 Hz, 2H), 2.14 (t, *J* = 10.7, 2H), 1.79 (s, 2H), 1.51 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 157.9, 147.3, 144.6, 142.5, 140.2, 131.8, 130.8, 127.0, 121.8, 119.0, 114.8, 100.7, 83.9, 60.5, 55.5, 49.9, 49.3, 39.8, 27.9, 26.4, 23.0; IR (NaCl plate) v 2085, 2047, 2939, 2874, 1622, 1593, 1499, 1475, 1227, 1032, 997, 827 cm^{-1}; HRMS (ESI) m/z calculated for $C_{46}H_{46}F_4N_4O_4H^+$ $[M+H]^+$ 795.3533, observed 795.3536; $[\alpha]^{20}_D$ = 30.0° (*c* = 10 mg / mL, $CHCl_3$); mp = 77-79 °C.

$(QD)_2Ph$



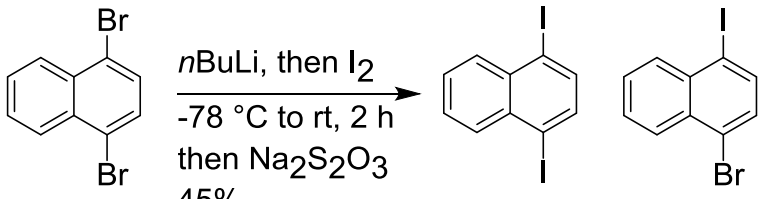
To a flame dried 3N round bottom was added quinidine (500 mg, 1.54 mmol, 3.0 equiv). The flask was then flushed with argon for 30 min. Dry DMSO (4 mL) was then added and the reaction was stirred until the solid dissolved. Sodium hydride (70 mg, 1.74 mmol, 3.39 equiv, 60% in oil) was then added in one portion and the colorless solution

became orange. The reaction was stirred for 30 minutes (until gas evolution ceased) and then dry pyridine (0.25 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 minutes, then 1,4-diiodobenzene (169 mg, 0.51 mmol) 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 minutes and then 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. Then organic layer was then 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 **III-68 $(QD)_2Ph$:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (d, *J* = 4.5 Hz, 2H), 7.99 (d, *J* = 9.4 Hz, 2H), 7.34-7.31 (m, 6H), 6.60 (s, 4H), 6.13-6.06 (m, 2H), 5.13 -5.08 (m, 4H), 3.94 (s, 6H), 3.38 (s, 2H), 3.14 (t, *J* = 8.5 Hz, 2H), 2.99 (t, *J* = 12.0 Hz, 4H), 2.82 (q, *J* = 9.4 Hz, 2H), 2.34–2.28 (m, 4H), 1.86 (s, 2H), 1.60 (s, 2H), 1.53–1.47 (m, 2H), 1.22–1.15 (m, 4H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 158.3, 151.3, 147.4, 144.5, 143.0, 139.6, 132.0, 126.2, 122.1, 118.5, 116.5, 115.3, 100.6, 78.0, 59.6, 56.1, 50.0, 49.2, 39.3, 28.0, 25.7, 20.4; IR (NaCl plate) v 3042, 2870, 1602, 1504, 1473, 1433, 1226, 1028, 977, 825 cm^{-1};

HRMS (ESI) m/z calculated for $C_{46}H_{50}N_4O_4H^+$ $[M+H]^+$ 723.3910, observed 723.3898. $[\alpha]^{20}_D$ = -92.9° (*c* = 10 mg / mL, $CHCl_3$); mp = 101-104 °C.

1,4-Diidonaphthalene



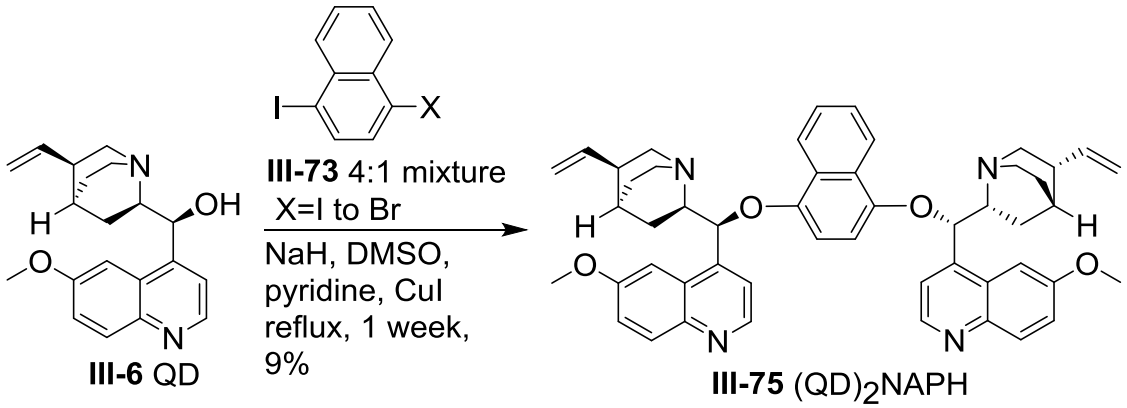
III-73 4.3 : 1

To a flame dried 100 mL round bottom flask was added 1,4-dibromonaphthalene and anhydrous THF (21 mL). The reaction was cooled to -78°C and then *n*BuLi (1.66 mL, 3.57 mmol, 2.04 equiv, 2.15 M in hexanes) was added dropwise. The reaction was stirred for 30 minutes at -78 °C and then iodine (0.994 g, 3.92 mmol, 2.24 equiv) was added in one portion. The reaction was slowly warmed to room temperature and then stirred for 2 hours. To quench the reaction, aqueous sodium thiosulfate (100 mL, 50% w/w) was added and the reaction was extracted with diethyl ether (3 x 50 mL), the combined organics were dried over anhydrous sodium sulfate, and concentrated. Two separate columns (1^{st} column: hexanes, 2^{nd} column: petroleum ether) were run to purify the desired compound, followed by recrystallization using chloroform. The product was obtained as an inseparable mixture of 1,4-diiodonaphthalene and 1-bromo-4-iodonaphthalene (4.3 : 1). The mixture was taken on to the next step (402 mg).

Data for mixture **of 1-bromo-4-iodonaphthalene and 1,4-diiodonaphthalene:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18-8.16 (m, 0.59H, *Br*), 8.07-8.05 (m, 0.59H, *Br*), 8.02-7.99

(m, 2H, *I*), 7.87 (d, *J* = 7.9 Hz, 0.59H, *Br),* 7.72 (s, 2H, *I*), 7.61-7.55 (m, 3.20H, mixture), 7.45 (d, *J* = 7.9 Hz, 0.59H, *Br*); ^{13}C NMR (175 MHz, $CDCl_3$) δ 138.0, 137.3, 135.1, 134.6, 132.9, 132.7, 132.4, 130.7, 128.5, 128.5, 128.1, 127.8, 124.1, 100.7, 99.0.

$(QD)_2$NAPH

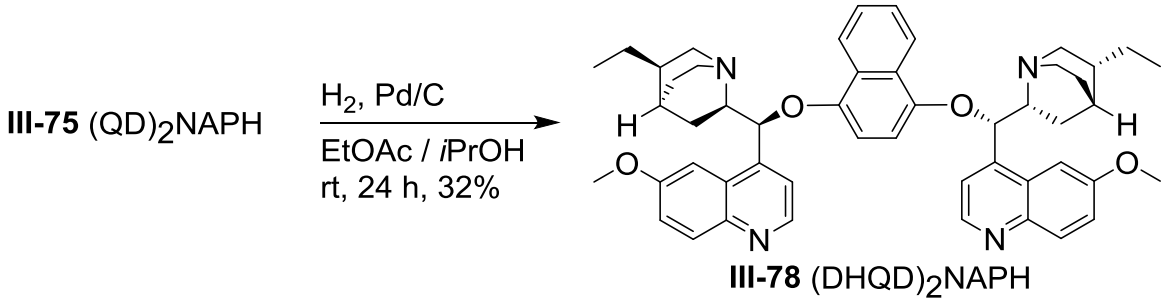


To a flame dried 3N round bottom was added quinidine (1.02 g, 3.16 mmol, 3.0 equiv). The flask was then flushed with argon for 30 min. Dry DMSO (8.2 mL) was then added and the reaction was stirred until the solid dissolved. Sodium hydride (142 mg, 3.56 mmol, 3.39 equiv, 60% in oil) was then added in one portion and the colorless solution became orange. The reaction was stirred for 30 minutes (until gas evolution ceased) and then dry pyridine (0.51 mL, 6.30 mmol, 6.0 equiv) and CuI (600 mg, 3.16 mmol, 3.0 equiv) was added; the reaction instantly turned dark brown. The reaction was stirred at room temperature for 45 minutes, then 1,4-diionaphthalene (400 mg, 1.05 mmol) 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 minutes and then

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 then dried over anhydrous sodium sulfate and concentrated. Two columns were run to purify the desired compound: 1st column ($CHCl_3$ to 5% MeOH in $CHCl_3$), 2nd column (10% MeOH in EtOAc to 40% MeOH in EtOAc). The product was obtained as a tan solid (70 mg, 0.091 mmol) in 9% yield.

Data for **III-75 $(QD)_2$NAPH:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (d, *J* = 4.6 Hz, 2H), 8.53-8.50 (m, 2H), 7.96 (d, *J* = 9.8 Hz, 2H), 7.61 (m, 2H), 7.35-7.31 (m, 6H), 6.12-6.05 (m, 2H), 5.99 (br, 4H), 5.14-5.05 (m, 4H), 3.88 (s, 6H), 3.26-3.19 (m, 4H), 2.94-2.71 (m, 6H), 2.37-2.21 (m, 4H), 1.89 (s, 2H), 1.54-1.45 (m, 6H), 1.25-1.22 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0, 147.6, 146.4, 144.6, 144.0, 140.2, 132.0, 126.7, 126.5, 126.0, 122.2, 121.8, 118.2, 114.8, 105.6, 100.8, 78.2, 60.6, 55.7, 50.0, 49.8, 39.5, 26.8, 26.4, 22.1; IR (NaCl plate) v 3080, 3005, 2934, 2872, 1622, 1597, 1508, 1464, 1271, 1240, 1082, 1026, 916, 765 cm^{-1}; HRMS (ESI) m/z calculated for $C_{50}H_{52}N_4O_4H^+$ $[M+H]^+$ calculated 773.4067, observed 773.4097; $[\alpha]^{20}_D$ = +180.5° (*c* = 10 mg / 1 mL, $CHCl_3$); mp = 85 °C (decomposed).

$(DHQD)_2NAPH$

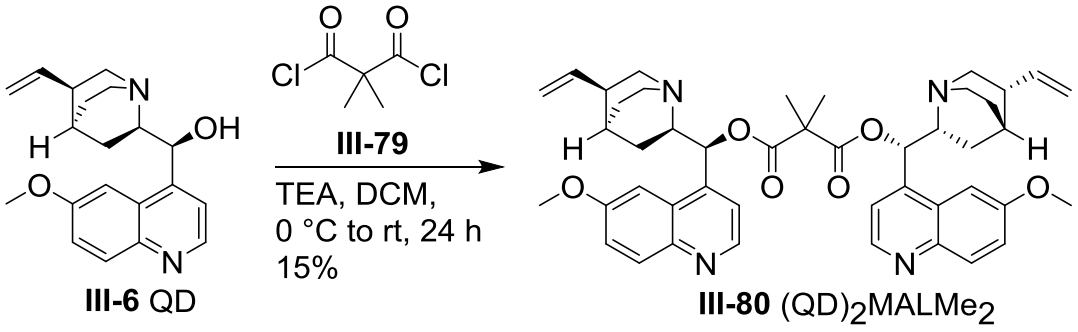


To a 25 mL round bottom flask was added $(QD)_2NAPH$ (40 mg, 0.052 mmol, sample had trace impurities), Pd/C (20 mg, 10% activated palladium on carbon), ethyl acetate (1 mL) and isopropanol (1 mL). The reaction was stirred under hydrogen for 24 hours at room temperature. The reaction was then filtered 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 in 32% yield (13 mg, 0.017 mmol).

Data for **III-78 $(DHQD)_2NAPH$:** ^1H NMR (600 MHz, $CDCl_3$) δ 8.55 (d, J = 4.5 Hz, 2H), 8.49 (dd, J = 6.4, 3.3 Hz, 2H), 8.00 (d, J = 9.2 Hz, 2H), 7.62 (dd, J= 6.3, 3.4 Hz, 2H), 7.45 (br, 2H), 7.36-7.33 (m, 4H), 6.31 (br, 2H), 6.09 (s, 2H), 3.94 (s, 6H), 3.28-3.20 (br, 4H), 2.99 (br, 4H), 2.81 (br, 2H), 2.01 (br, 2H), 1.83 (s, 2H), 1.72-1.57 (m, 10H), 1.36-1.32 (m, 2H), 0.91 (t, J = 7.3 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.7, 158.4, 147.4, 146.1, 144.6, 132.0, 126.5, 126.5, 126.1, 122.3, 121.7, 118.1, 106.1, 100.7, 76.6, 60.0, 56.1, 50.5, 49.7, 36.9, 26.5, 25.1, 22.6, 21.0, 11.8; IR (NaCl plate) v 3080, 3042, 2972, 2934, 2872, 1620, 1597, 1510 ,1462, 1433, 1390, 1267, 1240, 1078, 1026, 825,

760 cm^{-1}; HRMS (ESI) m/z calculated for $C_{50}H_{56}N_4O_4H^+$ $[M+H]^+$ calculated 777.4380, observed 777.4374; $[\alpha]^{20}_D$ = +195.6 ° (*c* = 10 mg / 1 mL, $CHCl_3$).

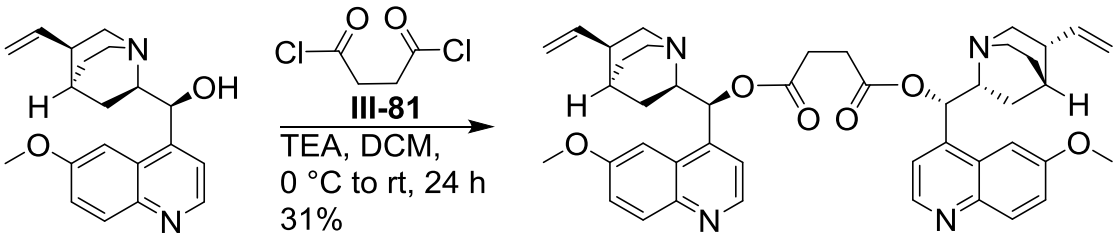
$(QD)_2MALMe_2$



To a flame dried 3N-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 (1.23 mL, 14 equiv) was added to the quinidine solution and it was subsequently cooled to 0 °C. To the addition funnel was added dimethyl malonyl chloride (61 µL, 0.46 mmol) and DCM (5 mL). The acyl chloride solution was then added dropwise to the cooled quinidine solution. Following addition, the reaction was warmed to room temperature and the reaction was stirred overnight. The reaction was quenched by adding saturated aqueous ammonium chloride (10 mL). The reaction was then extracted with DCM (3 x 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 (20% MeOH in EtOAc) giving the product as a tan solid (53 mg, 0.071 mmol) in 15% yield.

Data for **III-80 $(QD)_2$MAL-Me_2:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (d, *J* = 4.5 Hz, 2H), 7.97 (d, *J* = 9.2 Hz, 2H), 7.37 (s, 2H), 7.33 (dd, *J* = 9.2, 2.7 Hz, 2H), 7.03 (s, 2H), 6.34 (d, *J* = 8.2 Hz, 2H), 5.92-5.85 (m, 2H), 5.05-4.99 (m, 4H), 3.90 (s, 6H), 3.00 (s, 2H), 2.80-2.69 (m, 4H), 2.60-2.57 (m, 4H), 2.17 (q, *J* = 8.7 Hz, 2H), 1.74 (s, 2H), 1.50-1.23(m, 14H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 157.8, 147.3, 144.8, 143.0, 140.1, 131.9, 127.2, 121.8, 119.1, 114.9, 101.5, 77.2, 59.3, 55.5, 50.3, 49.4, 48.8, 39.7, 27.5, 26.2, 24.6, 23.0; IR (NaCl plate) v 3085, 3037, 2937, 2870, 1730, 1622, 1593, 1510, 1263, 1226, 1130, 1030, 847 cm^{-1}; HRMS (ESI) m/z calculated for $C_{45}H_{52}N_4O_6H^+$ $[M+H]^+$ 745.3965, observed 745.3973; $[\alpha]^{20}_D$ = 48.1° (*c* = 10 mg / mL, $CHCl_3$); mp = 65 °C (decomposed).

$(QD)_2$SUCC

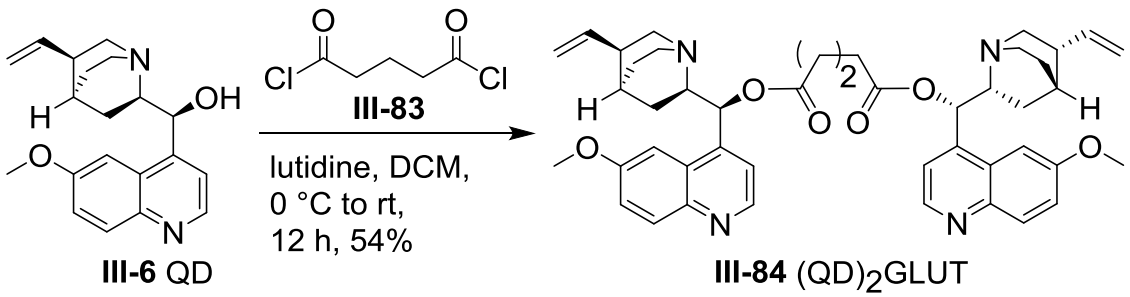


To a flame dried 3N-round bottom flask equipped with an addition funnel was added quinidine (400 mg, 1.23 mmol, 2.0 equiv) and dry DCM (6 mL). Freshly distilled triethylamine (1.23 mL, 14.3 equiv) was added to the quinidine solution and it was subsequently cooled to 0°C. To the addition funnel was added succinyl chloride (68 µL, 0.616 mmol) and DCM (5 mL). The acyl chloride solution was then added drop wise to

the cooled quinidine solution. Following addition, the reaction slowly turned dark 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 then extracted with DCM (3 x 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 **III-82 $(QD)_2$SUCC:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (d, *J* = 4.5 Hz, 2H), 7.97 (d, *J* = 10.0 Hz, 2H), 7.34-7.31 (m, 4H), 7.23 (s, 2H), 6.47 (d, *J* = 7.4 Hz, 2H), 5.98-5.91 (m, 2H), 5.06-5.01 (m, 4H), 3.87 (s, 6H), 3.17 (q, *J* =9.0 Hz, 2H), 2.84-2.82 (m, 4H), 2.71-2.61 (m, 8H), 2.19 (q, *J* = 8.2 Hz, 2H), 1.74-1.70 (m, 4H), 1.47-1.37 (m, 6H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 171.0, 157.8, 147.4, 144.7, 143.5, 140.2, 131.8, 127.0, 121.8, 118.6, 114.8, 101.3, 73.8, 59.0, 55.5, 49.7, 49.1, 39.7, 29.0, 27.7, 26.3, 23.6; IR (NaCl plate) v 3080, 2999, 2937, 2872, 1740, 1622, 1508, 1508, 1475, 1361, 1263, 1226, 1153, 1030, 989 cm^{-1}; HRMS (ESI) m/z calculated for $C_{44}H_{50}N_4O_6H^+$ $[M+H]^+$ 731.3809, observed 731.3789; $[\alpha]^{20}_D$ = +88.4° (*c* = 10 mg / mL, $CHCl_3$); mp = 68-70 °C.

(QD)$_2$GLUT

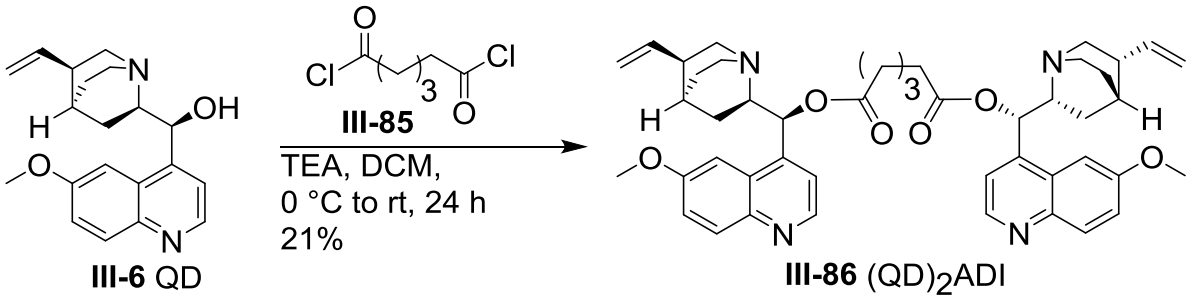


To a flame dried 3N-round bottom flask equipped with an addition funnel was added quinidine (300 mg, 0.925 mmol, 2.0 equiv) and dry DCM (6 mL). Freshly distilled lutidine (0.160 mL, 1.386 mmol, 3.0 equiv) was added to the quinidine solution and it was subsequently cooled to 0 °C. To the addition funnel was added glutaroyl chloride (60 µL, 0.463 mmol) 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 then extracted with DCM (3 x 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 (20% MeOH in EtOAc) giving the product as an off-white solid (187 mg, 0.249 mmol) in 54% yield.

Data for **III-84 (QD)$_2$GLUT:** ^{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); ^{13}C 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; IR (NaCl plate) v 3083, 3045, 2939, 2874, 1740, 1622, 1593, 1508, 1228 1165, 1030, 988, 734 cm^{-1}; HRMS (ESI) m/z calculated for $C_{45}H_{52}N_4O_6H^+$ $[M+H]^+$745.3965, observed 745.3951; $[\alpha]^{20}_D$ = 66.2° (*c* = 10 mg / mL, $CHCl_3$); mp = 53-55 °C.

$(QD)_2$ADI



III-6 QD

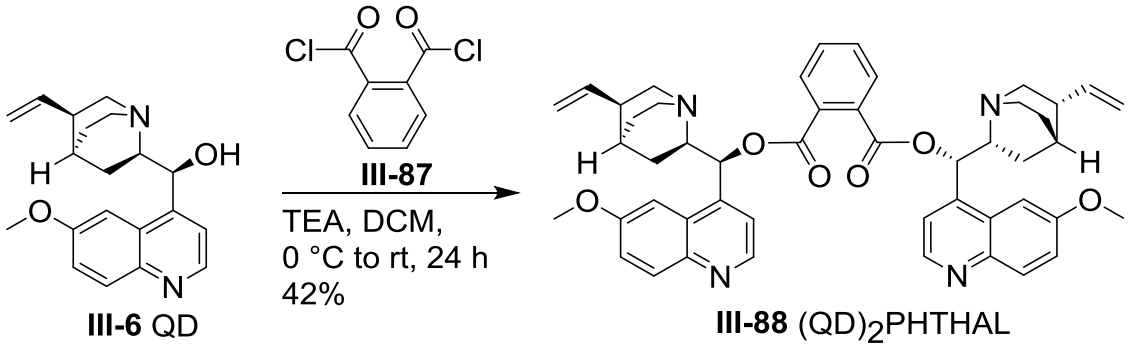
III-86 $(QD)_2$ADI

To a flame dried 3N-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 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 10 mL saturated ammonium chloride. The reaction was then extracted with DCM (3 x 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% 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 **III-86 $(QD)_2ADI$:** ^1H 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); ^{13}C 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; IR (NaCl plate) v 3092, 3040, 2937, 2872, 1740, 1022, 1500, 1473, 1361, 1228, 1167, 1030, 734 cm^{-1}; HRMS (ESI) m/z calculated for $C_{46}H_{54}N_4O_6H^+$ $[M+H]^+$759.4122, observed 759.4156; $[\alpha]^{20}_D$ = 68.4° (*c* = 10 mg / mL, $CHCl_3$); mp = 43-45 °C.

$(QD)_2$PHTHAL

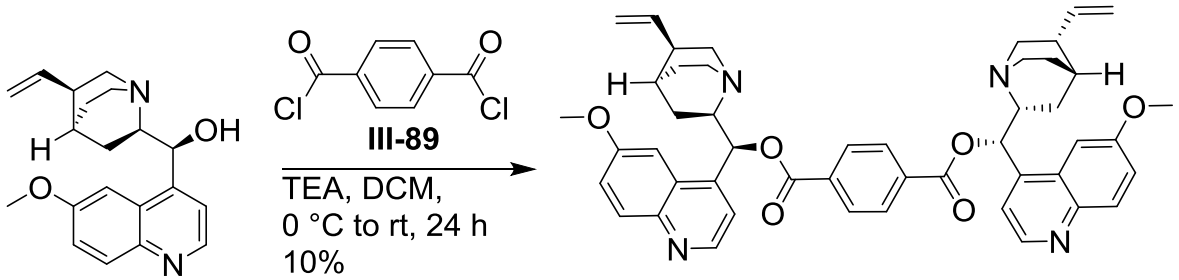


To a flame dried 3N-round bottom flask equipped with an addition funnel was added quinidine (300 mg, 0.925 mmol, 2.0 equiv) and dry DCM (6 mL). Freshly distilled triethylamine (0.925 mL, 6.61 mmol, 14.3 equiv) was added to the quinidine solution

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 then extracted with DCM (3 x 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 (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 **III-88 $(QD)_2$PHTHAL:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (d, *J* = 4.6 Hz, 2H), 7.98 (d, *J* = 9.2 Hz, 2H), 7.70-7.68 (m, 2H), 7.57-7.54 (m, 2H), 7.40 (d, *J* = 2.6 Hz, 2H), 7.33 (dd, *J* = 9.2, 2.7 Hz, 2H), 7.28 (d, *J* = 4.6 Hz, 2H), 6.56 (d, *J* = 7.9 Hz, 2H), 5.85-5.79 (m, 2H), 4.96-4.92 (m, 4H), 3.88 (s, 6H), 3.17 (q, *J* = 8.6 Hz, 2H), 2.81-2.74 (m, 4H), 2.72-2.57 (m, 4H), 2.13 (q, *J* = 8.1 Hz, 2H), 1.73 (dd, *J* = 13.5, 8.9 Hz, 2H), 1.54 (s, 2H), 1.43-1.38 (m, 4H), 1.34-1.29 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 157.8, 147.4, 144.8, 144.0, 140.2, 131.8, 131.8, 131.4, 128.8, 127.2, 121.9, 118.7, 114.6, 101.5, 74.9, 59.7, 55.5, 49.7, 49.1, 39.7, 27.6, 26.4, 24.2; IR (NaCl plate) v 3076, 3042, 3004, 2937, 2872, 1730, 1622, 1508, 1261, 1228, 1064, 916, 736 cm^{-1}; HRMS (ESI) m/z calculated for $C_{48}H_{50}N_4O_6H^+$ $[M+H]^+$ 779.3809, observed 779.3817; $[\alpha]^{20}_D$ = 45.4° (*c* = 10 mg / mL, $CHCl_3$); mp = 97-99 °C.

(QD)$_2$TEREPHTHAL



III-6 QD

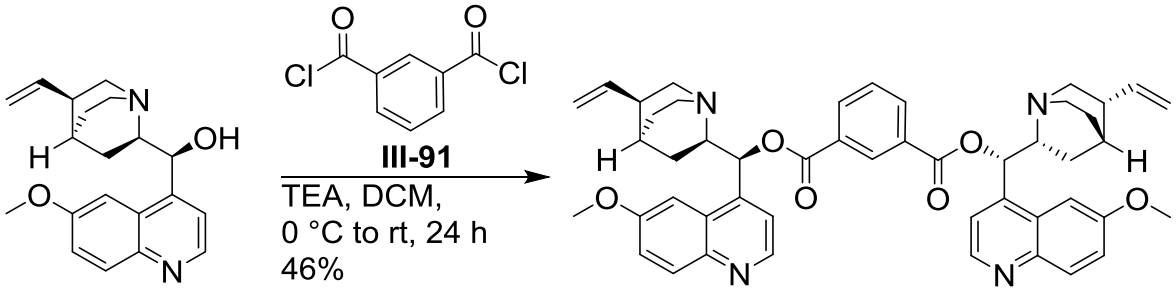
III-90 (QD)$_2$TEREPHTHAL

To a flame dried 3N-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) 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 then extracted with DCM (3 x 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 (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 **III-90(QD)$_2$TEREPHTHAL:** ^{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); ^{13}C 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; IR (NaCl plate) v 3075, 2936, 2872, 1724, 1622, 1508, 1287, 1228, 1103, 1018, 729 cm^{-1}; HRMS (ESI) m/z calculated for $C_{48}H_{50}N_4O_6H^+$ $[M+H]^+$ 779.3809, observed 779.3772; $[\alpha]^{20}_D$ = -70.5° (*c* = 10 mg / mL, $CHCl_3$); mp = 85 °C (decomposed).

(QD)$_2$ISOPHTHAL

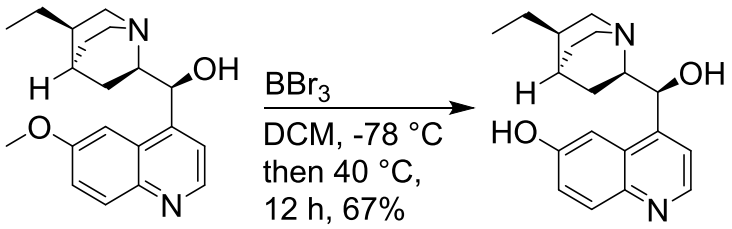


To a flame dried 3N-round bottom flask equipped with an addition funnel was added quinidine (300 mg, 0.925 mmol, 2.0 equiv) and dry DCM (6 mL). Freshly distilled triethylamine (0.925 mL, 6.61 mmol, 14.3 equiv) was added to the quinidine solution and it was subsequently cooled to 0 °C. To the addition funnel was added isophthaloyl chloride (68 µL, 0.463 mmol) and DCM (5 mL). The acyl chloride solution was 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 (15 mL). The reaction was then extracted with DCM (3 x 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 (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 **$(QD)_2$ISOPHTHAL:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (t, *J* = 1.2 Hz, 1H), 8.70 (d, *J* = 4.2 Hz, 2H), 8.28 (dt, *J* = 7.8, 1.8 Hz, 2H), 7.98 (d, *J* = 9.2 Hz, 2H), 7.55 (t, *J* = 3.9 Hz, 1H), 7.45 (d, *J* =2.6 Hz, 2H), 7.38 (d, *J* = 4.6 Hz, 4H), 6.72 (d, *J* = 7.4 Hz, 2H), 6.02-5.96 (m, 2H), 5.08-5..02 (m, 4H), 3.92 (s, 6H), 3.42 (q, *J* = 8.8 Hz, 2H), 2.93 (d, *J* = 9.0 Hz, 4H), 2.83-2.78 (m, 2H), 2.74-2.68 (m, 2H), 2.26 (q, *J* = 8.7 Hz, 2H), 1.93 (dd, *J* = 13.3, 9.0 Hz, 2H), 1.85 (s, 2H), 1.64-1.45 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 157.9, 147.4, 144.7, 143.5, 140.1, 134.1, 131.8, 131.0, 130.4, 128.9, 127.0, 121.8, 118.5, 114.9, 101.3, 74.6, 59.4, 55.5, 49.7, 49.2, 39.5, 27.6, 26.3, 23.8; IR (NaCl plate) v 3076, 2937, 2872, 1726, 1622, 1593, 1508, 1300, 1228, 1130, 1030, 731 cm^{-1}; HRMS (ESI) m/z calculated for $C_{48}H_{50}N_4O_6H^+$ $[M+H]^+$ 779.3809, observed 779.3821; $[\alpha]^{20}_D$ = -59.4° (*c* = 10 mg / mL, $CHCl_3$); mp = 78-80 °C.

6'-Hydroxy-10,11-dihydrocinchonine[45]

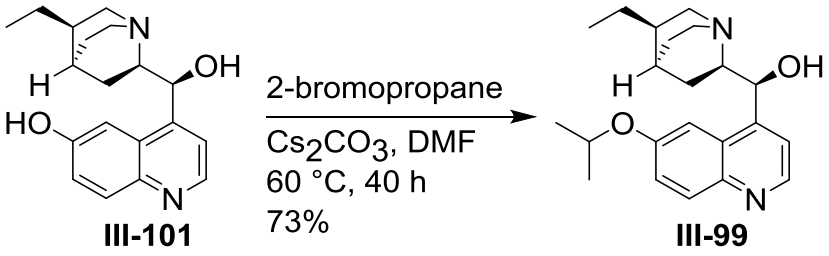


III-1 DHQD **III-101**

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 minutes and was then warmed to room temperature. The solution was refluxed for 12 hours. 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 then 10% aqueous NaOH (50 mL) was slowly added. The reaction was then poured into a separatory funnel and the organic layer was washed with aqueous 2% HCl (2 x 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 then extracted with chloroform (5 x 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 **III-101 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); ^{13}C 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; $[\alpha]^{20}_{D}$ = +230.4° (c = 10 mg / mL, MeOH); mp = 171-173°C.

6'-Isopropoxy-10,11-dihydrocinchonidine[45]

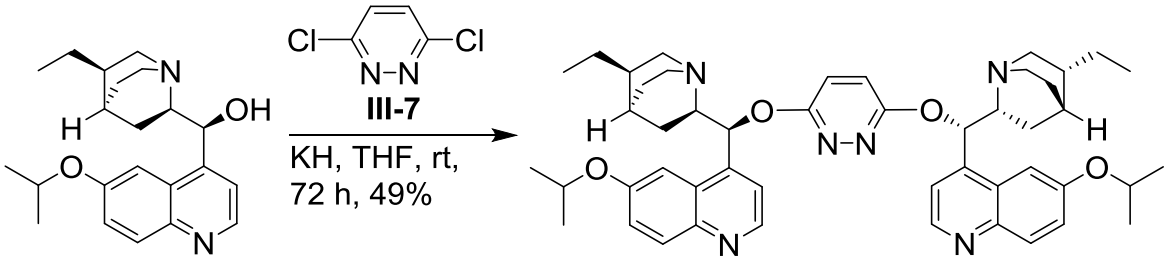


III-101 **III-99**

6'-Hydroxy-10,11-dihydrocinchonine (480 mg, 1.54 mmol) was dissolved in DMF (76 mL) in a 300 mL round bottom flask and then cesium carbonate (1.25 g, 3.85 mmol, 2.5 equiv) was added. The reaction was stirred at room temperature for 10 minutes and then 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 hours. The reaction was then 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 **III-99 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); ^{13}C 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; $[\alpha]^{20}_{D}$ = +187.5° (*c* = 20 mg / mL, EtOH); mp = 176-178 °C.

(*i*PrDHQD)$_2$PYDZ

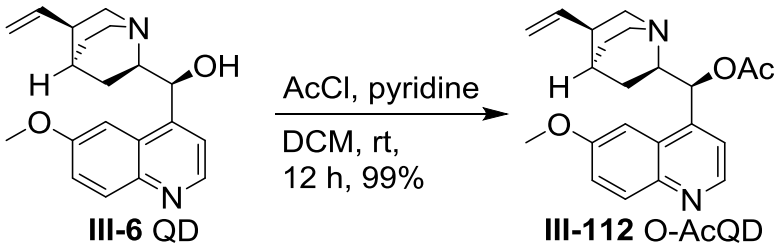


To a flame dried 100 mL round bottom flask was added KH (290 mg, 2.17 mmol, 4.36 equiv, 30% suspension in oil). The oil was removed from the potassium hydride by washing three times with 3 mL of hexanes. THF (44 mL) was then added to the flask, followed by the addition of *i*PrDHQD (400 mg, 1.12 mmol, 2.26 equiv) and 3,6-dichloropyridazine (74 mg, 0.497 mmol). The reaction was stirred at room temperature under dry nitrogen for 72 hours. At the end of 36 hours, 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 then separated, the aqueous layer was washed with EtOAc (3 x 20 mL), the combined organics were washed with water (3 x 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 an pale yellow solid (190 mg, 0.242 mmol) in 49% yield.

Data for **III-97 (*i*prDHQD)$_2$PYDZ:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (d, *J* = 4.5 Hz, 2H), 7.95 (d, *J* = 9.2 Hz, 2H), 7.43 (d, *J* = 2.2 Hz, 2H), 7.32-7.28 (m, 4H), 6.94 (s, 2H), 6.71 (d, *J* = 4.2 Hz, 2H), 4.68 (pentet, *J* = 4.9 Hz, 2H), 3.26 (dd, *J* = 15.0, 8.7 Hz, 2H), 2.79-2.62 (m, 8H), 2.29 (br, 2H), 1.87-1.83 (m, 2H), 1.66 (s, 2H), 1.49-1.43 (m, 2H), 1.40-1.23 (m, 20H), 0.84 (t, *J* = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8, 155.8, 147.2, 144.5, 144.2, 131.6, 127.1, 122.9, 121.2, 118.8, 104.2, 77.1, 70.1, 59.9, 50.8, 50.1, 37.4, 27.3, 26.1, 25.3, 23.0, 22.0, 21.7, 11.9; IR (NaCl plate) v 3047, 2934, 2872, 1618, 1506, 1435, 1260, 1224, 1113, 968 cm^{-1}; HRMS (ESI) calculated for $C_{48}H_{61}N_6O_4H^+$ $[M+H]^+$ 785.4749, observed 785.4754; $[\alpha]^{20}_D$ = -9.4° (*c* = 10 mg / mL, $CHCl_3$); mp = 94-96 °C.

O-Acetyl Quinidine[34]

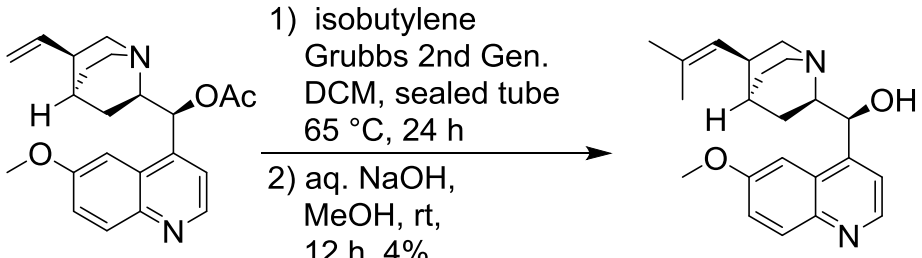


III-6 QD **III-112** O-AcQD

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 hours. Water (0.5 mL) was added and the reaction was stirred for 30 minutes. The reaction was then poured into aqueous 2M potassium carbonate (25 mL) and extracted with DCM (3 x 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 **III-112 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); ^{13}C 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; HRMS m/z calculated for $C_{22}H_{26}N_2O_3H^+$ $[M+H]^+$ 367.2022, observed 367.2036; $[\alpha]^{20}_D$ = -24.2° (*c* = 5.7 mg / 1 mL, $CHCl_3$).

Me_2QD



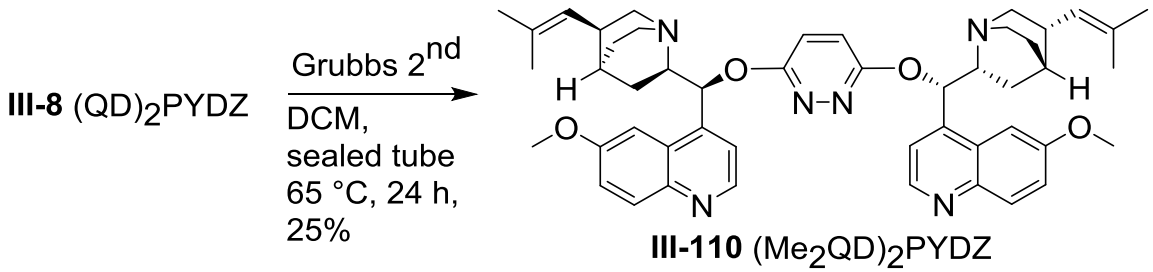
III-112 O-AcQD **III-115** Me_2QD

To a flame dried 100 mL sealed tube was added O-acetyl quinidine (500 mg, 1.36 mmol) and dry DCM (5 mL). The sealed 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 then Grubb's second generation catalyst (232 mg, 0.136 mmol, 0.20 equiv) was added in one portion. The sealed tube was then "sealed" and warmed to room temperature, followed by subsequent heating to 65 °C for 24 hours. 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 x 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 x 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 hours. The product was quenched by neutralizing the reaction by adding pH 1 HCl solution. The product was then extracted with ethyl acetate (3 x 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 **III-115 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); ^{13}C 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; IR (NaCl plate) v 3166, 3005, 2934, 2867, 2840, 1622, 1591, 1510, 1472, 1433, 1242, 1107, 1032, 831, 736 cm^{-1}; HRMS (ESI) m/z calculated for $C_{22}H_{28}N_2O_2H^+$ $[M+H]^+$ 353.2229, observed 353.2228; $[\alpha]^{20}_D$ = +149.5 ° (*c* = 10 mg / mL, $CHCl_3$); mp = 58-61 °C.

$(Me_2QD)_2PYDZ$



III-110 $(Me_2QD)_2PYDZ$

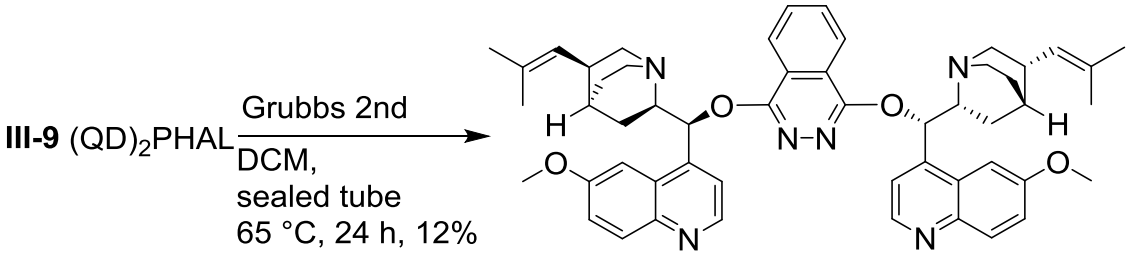
The $(QD)_2PYDZ$ used is this reaction was prepared as described above. The material was not purified via column chromatography, but simply by filtration through a pad of silica gel in a frit funnel, which was thoroughly washed with 1:10 MeOH / $CHCl_3$.

To a flame dried 100 mL sealed tube was added $(QD)_2PYDZ$ (738 mg, 1.02 mmol) and dry DCM (12 mL). The sealed 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 then Grubb's second generation catalyst (300 mg, 0.353 mmol, 0.35 equiv) was added in one portion. The sealed tube was then "sealed" and warmed to room temperature, followed by subsequent heating to 65 °C for 24 hours. 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 then extracted using 1 M HCl (3 x 50 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 x 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 **III-110 $(Me_2QD)_2PYDZ$:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (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), 6.99 (s, 2H), 6.80

(d, *J* = 5.1 Hz, 2H), 5.34 (d, *J* = 8.6 Hz, 2H), 3.85 (s, 6H), 3.29 (q, *J* = 8.8, Hz, 2H), 2.83-2.62 (m, 8H), 2.33 (q, *J* = 8.6 Hz, 2H), 1.98 (t, *J* = 12.1 Hz, 2H), 1.62-1.37 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 157.6, 147.3, 144.7, 144.3, 132.5, 131.6, 127.3, 127.1, 121.7, 121.3, 118.6, 102.0, 77.2, 59.7, 55.6, 50.8, 49.9, 34.5, 28.2, 26.6, 25.9, 23.3, 18.1; IR (NaCl plate) v 3080, 3048, 2938, 2870, 2840, 1622, 1593, 1501, 1473, 1437, 1261, 1228, 1084, 1028, 991, 846, 734 cm^{-1}; HRMS (ESI) m/z calculated for $C_{48}H_{56}N_6O_4H$ $[M+H]^+$ 781.4441, observed 781.4465; $[\alpha]^{20}_D$ = -93.3° (*c* = 10 mg / mL, $CHCl_3$); mp = 107-109 °C.

$(Me_2QD)_2PHAL$



III-116 $(Me_2QD)_2PHAL$

The $(QD)_2PHAL$ 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 / $CHCl_3$.

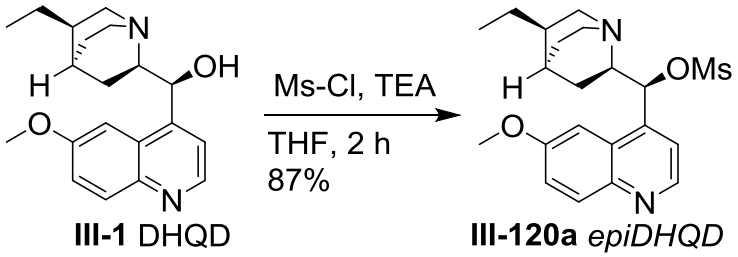
To a flame dried 100 mL sealed tube was added $(QD)_2PHAL$ (282 mg, 0.364 mmol) and dry DCM (4.5 mL). The sealed tube was sealed with a rubber septum and was subjected to three cycles of "freeze (using liquid nitrogen), pump, thaw" to degas the solution. The reaction was then cooled to -78 °C using a dry ice / acetone bath, the

reaction was cautiously opened, and condensed isobutylene (8 mL) was added. The reaction was flushed with argon and then Grubb's second generation catalyst (250 mg, 0.294 mmol, 0.81 equiv) was added in one portion. The sealed tube was then "sealed" and warmed to room temperature, followed by subsequent heating to 65 °C for 24 hours. 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 then extracted using 1 M HCl (3 x 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 x 30 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 an off-white solid in 12% yield (35 mg, 0.042 mmol).

Data for **III-116 ($Me_2QD)_2PHAL$:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (d, *J* = 4.6 Hz, 2H), 8.39 (dd, *J* = 6.1, 3.3 Hz, 2H), 7.96 (d, *J* = 9.2 Hz, 2H), 7.92 (dd, *J* = 6.1, 3.3 Hz, 2H), 7.51 (s, 2H), 7.40 (d, *J* = 4.5 Hz, 2H), 7.33 (dd, *J* = 9.2, 2.7 Hz, 2H), 7.11 (s, 2H), 5.42 (d, *J* = 8.3 Hz, 2H), 3.90 (s, 6H), 3.39 (dd, *J* =14.2, 9.0 Hz, 2H), 2.88-2.72 (m, 8H), 2.36-2.34 (m, 2H), 2.21-2.18 (m, 2H), 1.66 (s, 2H), 1.60 (s, 6H), 1.48-1.43 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 156.3, 147.3, 144.7, 144.5, 132.8, 132.1, 131.6, 127.2, 127.1, 123.0, 122.6, 121.9, 118.1, 102.0, 76.1, 49.8, 55.7, 50.8, 49.9, 34.5, 28.3, 26.5, 25.8, 22.8, 18.2; IR (NaCl plate) v 3080, 3032, 2936, 2872, 1622, 1510, 1433, 1381, 1354, 1263, 1228, 1098, 1030, 848, 733 cm^{-1}; HRMS (ESI) m/z calculated for

$C_{52}H_{58}N_6O_4H$ $[M+H]^+$ 831.4598, observed 831.4621; $[\alpha]^{20}_D$ = -117.0° (*c* = 10 mg / mL, $CHCl_3$); mp = 80 °C (decomposed).

Dihydroquindine mesylate[46]



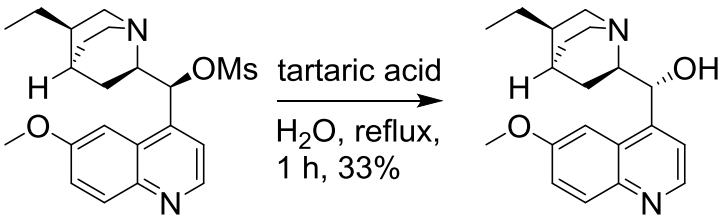
III-1 DHQD **III-120a** *epiDHQD*

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 hours. The reaction was quenched by adding saturated aqueous sodium bicarbonate (10 mL). The product was extracted with DCM (3 x 25 mL), the combined organics were washed with water (3 x 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 **III-120a 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); ^{13}C

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; $[\alpha]^{20}_D$ = +124.3° (*c* = 9.4 mg / 1 mL, DCM).

***Epi*-C9-dihydroquinidine**[44]



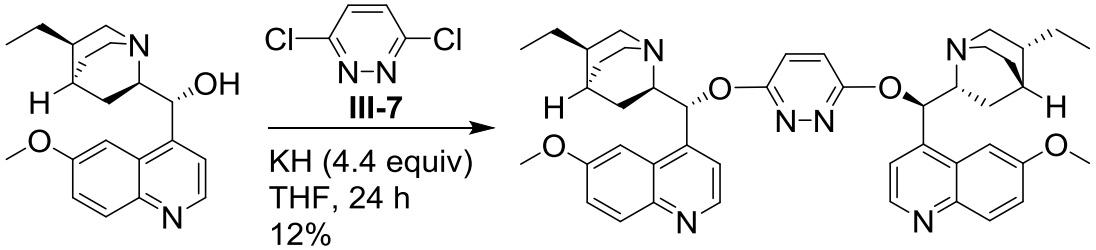
III-120a **III-120**

To a 50 mL round bottom flask was added dihydroquinidine mesylate (1.13 g, 2.79 mmol), tartaric acid (433 mg, 2.89 mmol, 1.03 equiv) and water (13 mL). The reaction was heated to 100 °C for 1 hour, during which time the reaction turned orange in color. To quench the reaction, it was cooled to room temperature and then saturated aqueous $NaHCO_3$ (30 mL) was slowly added. The product was extracted using $CHCl_3$ (3 x 50 mL), then 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 **III-120** *epi*-C9-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); ^{13}C 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; $[\alpha]^{20}_D$ = +87.8° (*c* = 5.9 mg / mL, $CHCl_3$); mp = 121-123 °C.

***(Epi*-DHQD)$_2$PYDZ**

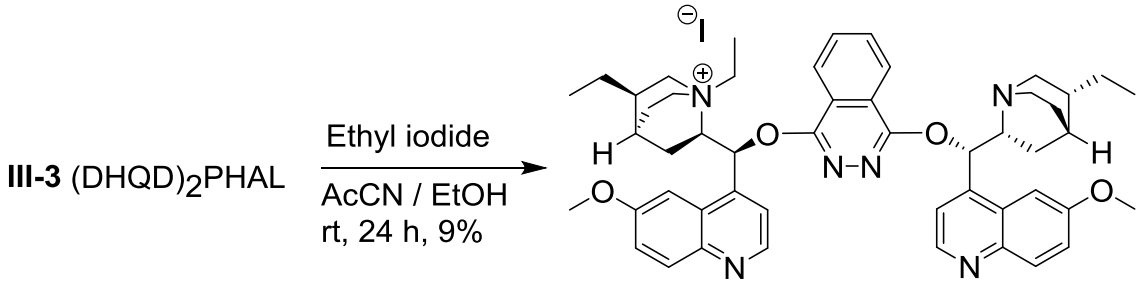


To a flame dried 100 mL round bottom flask was added KH (221 mg, 1.66 mmol, 4.36 equiv, 30% suspension in oil). The oil was removed from the potassium hydride by washing with hexanes (3 x 2 mL). THF (36 mL) was then added to the flask, followed by the addition of *epi*-C_9-dihydroquinidine (280 mg, 0.858 mmol) and 2,6-dichloropyridazine (57 mg, 0.380 mmol). The reaction was stirred at room temperature under dry nitrogen for 24 hours. At the end of 24 hours, 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 x 10 mL), the combined organics were washed with water (3 x 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 **III-119** (*epi*-**QD)$_2$PYDZ:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (d, *J* = 4.5 Hz, 2H), 7.98 (d, *J* = 9.2 Hz, 2H), 7.57 (d, *J* = 2.3 Hz, 2H), 7.43 (d, *J* = 4.6 Hz, 2H), 7.38 (dd, *J* = 2.7, 9.2 Hz, 2H), 6.88 (s, 2H), 6.49 (d, *J* = 9.8 Hz, 2H), 3.80 (s, 6H), 3.33 (q, *J* = 9.4 Hz, 2H), 2.96-2.91 (m, 2H), 2.86-2.82 (m, 4H), 2.59-2.55 (m, 2H), 1.49-1.23 (m, 14H), 1.04 (t, *J* = 9.4 Hz, 2H), 0.81 (t, *J* = 7.4 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 157.7, 147.4, 144.6, 143.9, 131.5, 128.3, 122.0, 121.4, 119.9, 101.8, 77.2, 60.3, 55.5, 49.8, 49.3, 37.4, 27.2, 25.8, 25.7, 23.7, 11.9; IR (NaCl plate) v 3075, 2932, 2872, 1622, 1508, 1435, 1259, 1226, 1035, 933, 852 cm^{-1}; HRMS (ESI) m/z calculated for $C_{44}H_{52}N_6O_4H^+$ $[M+H]^+$ 729.4128, observed 729.4150; $[\alpha]^{20}_D$ = 130.1° (*c* = 10 mg / mL, $CHCl_3$); mp = 174-176 °C.

(DHQD)$_2$PHAL + EtI

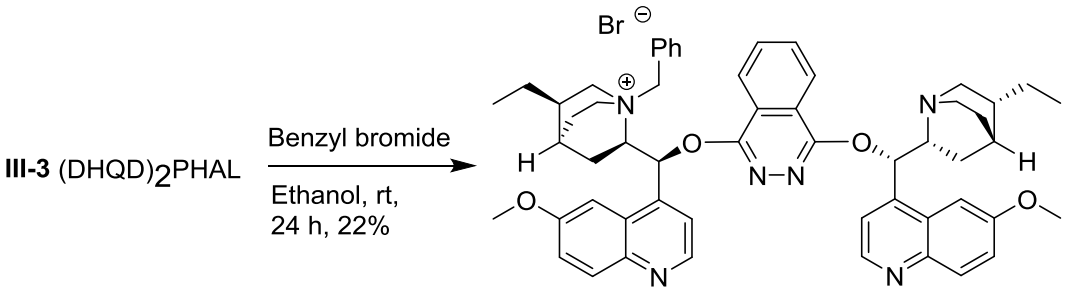


III-124 (DHQD)$_2$PHAL + EtI

$(DHQD)_2PHAL$ (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 then added in using a microsyringe and the resulting reaction was stirred at room temperature. After 24 hours, 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 **III-124 $(DHQD)_2PHAL$ + EtI:** ^1H NMR (500 MHz, $CDCl_3$ + CD_3OD) δ 8.51 (dd, *J* = 10.0, 4.8 Hz, 2H), 8.37 (dd, *J* = 6.4, 3.1 Hz, 1H), 8.23 (dd, *J* = 7.5, 3.5 Hz, 1H), 8.04 (dd, *J* = 6.1, 3.1 Hz, 2H), 7.97 (d, *J* = 9.3 Hz, 1H), 7.91 (d, *J* = 9.2 Hz, 1H), 7.66 (s, 1H), 7.42 -7.33 (m, 6H), 7.10 (d, *J* = 2.9 Hz, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.81-3.76 (m, 2H), 3.63-3.31 (m, 4H), 2.59 (t, *J* = 12.8 Hz, 1H), 2.27-2.19 (m, 4H), 1.96-1.78 (m, 2H), 1.67-1.59 (m, 4H), 1.53-1.43 (m, 6H), 1.34-1.31 (m, 2H), 1.29-1.22 (m, 5H), 0.97 (t, *J* = 7.5 Hz, 3H), 0.82 (t, *J* = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$ + CD_3OD) δ 158.8, 158.5, 156.6, 154.7, 146.7, 146.6, 143.9, 138.5, 133.6, 133.6, 131.5, 130.9, 130.8, 128.6, 126.4, 125.6, 123.0, 122.4, 122.1, 121.7, 121.7, 118.7, 117.9, 101.2, 101.0, 77.2, 69.2, 65.5, 59.4, 58.4, 56.5, 56.3, 56.2, 50.4, 49.9, 38.6, 35.2, 31.7, 29.5, 29.1, 25.7, 24.9, 24.5, 24.4, 23.7, 21.8, 11.3, 11.0, 8.9; IR (NaCl plate) v 2963, 2924, 2851, 1726, 1620, 1552, 1510, 1462, 1352, 1261, 1095, 800 cm^{-1}; HRMS (ESI) m/z calculated for $C_{50}H_{58}N_6O_4H^+$ $[M+H]^+$ 807.4598, observed 807.4604; $[\alpha]^{20}_D$ = -56.5° (*c* = 10 mg / mL, $CHCl_3$); mp = 170-174 °C.

(DHQD)$_2$PHAL + BnBr[17]



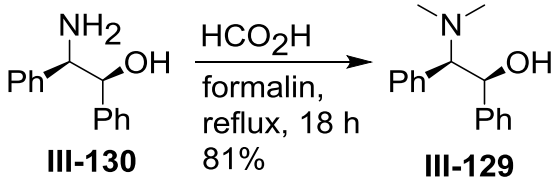
III-125 (DHQD)$_2$PHAL + BnBr

(DHQD)$_2$PHAL (300 mg, 0.385 mmol) was dissolved in anhydrous ethanol (3.6 mL) and then benzyl bromide (47 μL, 0.392 mmol) was added in, in one portion. The reaction was stirred at room temperature for 24 hours and was then 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 **III-125 (DHQD)$_2$PHAL + BnBr:** ^{1}H NMR (500 MHz, $CDCl_3$ + CD_3OD) δ 8.54 (d, *J* = 4.7 Hz, 1H), 8.46 (d, *J* = 4.6 Hz, 1H), 8.38 (dd, *J* = 9.2, 6.8 Hz, 1H), 8.29 (dd, *J* = 5.3, 2.3 Hz, 1H), 8.08-8.06 (m, 2H), 7.97 (s, 1H), 7.88 (d, *J* = 9.2 Hz, 1H), 7.83 (d, *J* = 9.2 Hz, 1H), 7.59 (d, *J* = 4.6 Hz, 1H), 7.45 (s, 1H), 7.36 (d, *J* = 4.6 Hz, 1H), 7.33-7.23 (m, 6H), 7.18 (t, *J* = 7.6 Hz, 3H), 4.89 (d, *J* = 12.1 Hz, 1H), 4.63 (d, *J* = 10.2 Hz, 1H), 4.55 (t, *J* = 11.9 Hz, 1H), 4.45 (t, *J* = 9.2 Hz, 1H), 3.95 (s, 3H), 3.84 (s, 3H), 3.60-3.53 (m, 3H), 3.32 (s, 1H), 3.20-3.12 (m, 3H), 3.02-2.86 (m, 3H), 2.68 (t, *J* = 12.1 Hz, 1H), 2.29 (s, 1H), 2.01 (s, 1H), 1.96-1.92 (m, 1H), 1.86 (s, 1H), 1.75-1.45 (m, 9H), 0.83-0.77 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$+ CD_3OD) δ 158.9, 158.6, 157.6, 155.3, 146.6,

146.5, 144.1, 139.0,133.8, 133.7, 133.4, 131.2, 131.0, 130.7, 129.3, 126.6, 126.1, 126.0 123.1, 122.9, 122.5, 122.5, 122.0, 121.9, 119.3, 117.9, 101.6, 101.4, 77.3, 70.0, 66.8, 64.0, 59.5, 57.2, 56.4, 56.2, 50.3, 49.8, 35.6, 29.6, 25.7, 25.0, 24.6, 24.5, 24.0, 22.1, 11.4, 11.1; HRMS (ESI) m/z calculated for $C_{55}H_{61}N_6O_4^+$ $[M+H]^+$ 869.4754, observed 869.4775; $[\alpha]^{20}_D$ = -165.9° (*c* = 10 mg / mL, $CHCl_3$); mp = 160 °C (decomposed).

truncated monomer ("trunc")[47]



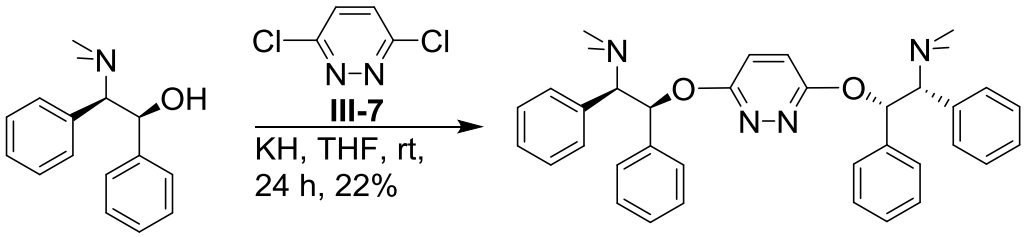
III-130 **III-129**

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 hours. The reaction was then cooled to room temperature and basified to pH 10 using 1 M aqueous sodium hydroxide. The reaction was then extracted with diethyl ether (3 x 20 mL). The combined organic fractions were then 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 **III-129 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); ^{13}C 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; $[\alpha]^{20}_D$ = +122.3° (*c* = 10 mg / mL, EtOH); mp = 91-93 °C

(Trunc)$_2$PYDZ



III-129 **III-128** (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 x 2 mL). THF (28 mL) was then 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 hours. At the end of 24 hours, 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 x 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 7.16-7.15 (m, 6H), 7.12-7.10 (m, 14H), 6.86 (d, *J* = 5.1 Hz, 2H), 6.75 (s, 2H), 3.49 (d, *J* = 5.1 Hz, 2H), 2.19 (s, 12H), 1.96 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.4, 142.0, 138.9, 132.4, 130.4, 129.9, 129.7, 129.7, 129.7, 124.6, 78.7, 78.3, 46.2; IR (NaCl plate) v 3063, 3030, 2938, 2862, 2826, 2779, 1666, 1595, 1454, 1437, 1278, 1263, 1020 cm^{-1}; HRMS (ESI) m/z calculated for $C_{36}H_{38}N_4O_2H^+$ $[M+H]^+$ 559.3073, observed 559.3088; $[\alpha]^{20}_D$ = 27.7° (*c* = 10 mg / mL, $CHCl_3$); mp = 84-85 °C.

REFERENCES

REFERENCES

1. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M., *The Journal of Organic Chemistry* **1992,** *57*, 2768-2771.

2. Amberg, W.; Bennani, Y. L.; Chadha, R. K.; Crispino, G. A.; Davis, W. D.; Hartung, J.; Jeong, K. S.; Ogino, Y.; Shibata, T.; Sharpless, K. B., *The Journal of Organic Chemistry* **1993,** *58*, 844-849.

3. Luniwal, A.; Khupse, R.; Reese, M.; Liu, J.; El-Dakdouki, M.; Malik, N.; Fang, L.; Erhardt, P., *Organic Process Research & Development* **2011,** *15*, 1149-1162.

4. Song, C. E.; Yang, J. W.; Ha, H. J.; Lee, S.-g., *Tetrahedron: Asymmetry* **1996,** *7*, 645-648.

5. Becker, H.; King, S. B.; Taniguchi, M.; Vanhessche, K. P. M.; Sharpless, K. B., *The Journal of Organic Chemistry* **1995,** *60*, 3940-3941.

6. Sun, X. L. J., Y.; He, Wei; Nan, P.J.; Zhang, S.Y. , *Bull. Korean Chem. Soc.* **2007,** *28*, 1422.

7. Liu, P.; He, W.; Zhao, Y.; Wang, P.-A.; Sun, X.-L.; Li, X.-Y.; Zhang, S.-Y., *Chirality* **2008,** *20*, 75-83.

8. Xiaoli Sun; Pingan Want, H. W., LinLin Jing, Shengyong Zhang Method for synthesizing cinchona alkaloids microwave radiation non-solvent. CN101245063 (A), 2008.

9. Wang, H. B.; Wang, P. A.; Wang, Q. J.; Sun, X. L.; Jing, L. L., *Chin. Chem. Lett.* **2008,** *19*, 1440-1444.

10. Busygin, I.; Nieminen, V.; Taskinen, A.; Sinkkonen, J.; Toukoniitty, E.; Sillanpää, R.; Murzin, D. Y.; Leino, R., *The Journal of Organic Chemistry* **2008,** *73*, 6559-6569.

11. Testaferri, L.; Tiecco, M.; Tingoli, M.; Chianelli, D.; Montanucci, M., *Tetrahedron* **1983,** *39*, 193-197.

12. Choi, W.-K.; Oh, C.-H., *Bull. Korean Chem. Soc.* **2009,** *30*, 2027-2031.

13. Cai, S. X. A., M.B; Willardsen, A.; Jiang, S.; Halter, R. J.; Slade, R.; Klimova, Y. Pharmaceutical compounds as activators of caspases and inducers of apoptosis and the use thereof July 13, 2006.

14. Sun, X.-Y.; Hu, C.; Deng, X.-Q.; Wei, C.-X.; Sun, Z.-G.; Quan, Z.-S., *European Journal of Medicinal Chemistry* **2010,** *45*, 4807-4812.

15. Patney, H. K., *The Journal of Organic Chemistry* **1988,** *53*, 6106-6109.

16. Gandolfi, C. A.; Beggiolin, G.; Menta, E.; Palumbo, M.; Sissi, C.; Spinelli, S.; Johnson, F., *J. Med. Chem.* **1995,** *38*, 526-536.

17. Kolb, H. C.; Andersson, P. G.; Bennani, Y. L.; Crispino, G. A.; Jeong, K. S.; Kwong, H. L.; Sharpless, K. B., *J. Am. Chem. Soc.* **1993,** *115*, 12226-12227.

18. Altman, R. A.; Shafir, A.; Choi, A.; Lichtor, P. A.; Buchwald, S. L., *The Journal of Organic Chemistry* **2007,** *73*, 284-286.

19. Cheong, C. L.; Wakefield, B. J., *J. Chem. Soc., Perkin Trans. 1* **1988**, 3301-3305.

20. Chambers, R. D.; Seabury, M. J.; Williams, D. L. H.; Hughes, N., *J. Chem. Soc., Perkin Trans. 1* **1988**, 255-257.

21. Lowe Iii, J. A.; DeNinno, S. L.; Coe, J. W.; Zhang, L.; Mente, S.; Hurst, R. S.; Mather, R. J.; Ward, K. M.; Shrikhande, A.; Rollema, H.; Johnson, D. E.; Horner, W.; Gorczyca, R.; Tingley Iii, F. D.; Kozak, R.; Majchrzak, M. J.; Tritto, T.; Sadlier, J.; Shaffer, C. L.; Ellerbrock, B.; Osgood, S. M.; MacDougall, M. C.; McDowell, L. L., *Bioorganic & Medicinal Chemistry Letters* **2010,** *20*, 4749-4752.

22. Technology, N. I. o. A. I. S. a. Spectral Database for Organic Compounds SDBS. http://riodb01.ibase.aist.go.jp/sdbs/cgi-bin/direct_frame_top.cgi

23. Braje, W. M.; Holzgrefe, J.; Wartchow, R.; Hoffmann, H. M. R., *Angew. Chem. Int. Ed.* **2000,** *39*, 2085-2087.

24. Chen, H.; Jin, Y.; Jiang, R.; Sun, X.-L.; Li, X.-Y.; Zhang, S.-Y., *Catal. Commun.* **2008,** *9*, 1858-1862.

25. Suzuki, H.; Mochizuki, M.; Hattori, T.; Takahashi, N.; Tajima, O.; Takiguchi, T., *Bull. Chem. Soc. Jpn.* **1988,** *61*, 1999-2005.

26. Chen, H.; Wang, Q. F.; Sun, X. L.; Luo, J.; Jiang, R., *Mendeleev Commun.* **2010,** *20*, 104-105.

27. Pires, M. M.; Emmert, D.; Hrycyna, C. A.; Chmielewski, J., *Mol. Pharmacol.* **2009,** *75*, 92-100.

28. Periasamy, M.; Ramanathan, C. R.; Kumar, N. S.; Thirumalaikumar, M., *Journal of Chemical Research (Synopses)* **2001,** *2001*, 512-513.

29. Li, F.; Li, Y.-Z.; Jia, Z.-S.; Xu, M.-H.; Tian, P.; Lin, G.-Q., *Tetrahedron* **2011,** *67*, 10186-10194.

30. Li, H.; Wang, Y.; Tang, L.; Deng, L., *J. Am. Chem. Soc.* **2004,** *126*, 9906-9907.

31. Small, L. D.; Rosenberg, H.; Nwangwu, P. U.; Holcslaw, T. L.; Stohs, S. J., *J. Med. Chem.* **1979,** *22*, 1014-1016.

32. Waddell, T. G.; Rambalakos, T.; Christie, K. R., *The Journal of Organic Chemistry* **1990,** *55*, 4765-4767.

33. Merschaert, A.; Delbeke, P.; Daloze, D.; Dive, G., *Tetrahedron Lett.* **2004,** *45*, 4697-4701.

34. Qi, J.; Beeler, A. B.; Zhang, Q.; Porco, J. J. A., *J. Am. Chem. Soc.* **2010,** *132*, 13642-13644.

35. Cho, J. H.; Kim, B. M., *Org. Lett.* **2003,** *5*, 531-533.

36. Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T., *J. Am. Chem. Soc.* **2002,** *124*, 6626-6635.

37. Corey, E. J.; Noe, M. C.; Lin, S., *Tetrahedron Lett.* **1995,** *36*, 8741-8744.

38. Lee, J.-H.; Yoo, M.-S.; Jung, J.-H.; Jew, S.-s.; Park, H.-g.; Jeong, B.-S., *Tetrahedron* **2007,** *63*, 7906-7915.

39. Choi, D. S.; Han, S. S.; Kwueon, E. K.; Choi, H. Y.; Hwang, S. H.; Park, Y. S.; Song, C. E., *Adv. Synth. Catal.* **2006,** *348*, 2560-2564.

40. Ru Jiang, Y. K., Xioali Sun, Shengyong Zhang, *Acta Chimica Slovenica* **2005,** *52*, 467-470.

41. Jiang, R.; Kuang, Y.; Sun, X.; Zhang, S., *Tetrahedron: Asymmetry* **2004,** *15*, 743-746.

42. Chen, W.-B.; Wu, Z.-J.; Hu, J.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C., *Org. Lett.* **2011,** *13*, 2472-2475.

43. Tan, C. K.; Zhou, L.; Yeung, Y.-Y., *Org. Lett.* **2011,** *13*, 2738-2741.

44. Sundermeier, U.; Döbler, C.; Mehltretter, G. M.; Baumann, W.; Beller, M., *Chirality* **2003,** *15*, 127-134.

45. Berkessel, A.; Seelig, B.; Schwengberg, S.; Hescheler, J.; Sachinidis, A., *ChemBioChem* **2010,** *11*, 208-217.

46. Zielińska-Błajet, M.; Kucharska, M.; Skarżewski, J., *Synthesis* **2006,** *2006*, 1176-1182.

47. Saigo, K.; Ogawa, S.; Kikuchi, S.; Kasahara, A.; Nohira, H., *Bull. Chem. Soc. Jpn.* **1982,** *55*, 1568-1573.

Chapter IV: Synthesis of a Class of Novel Chiral C2-Symmetric, Pyridine Scaffolds

IV-1 Introduction

In passing, Chapter II offered several glimpses into the underlying mechanism of the $(DHQD)_2PHAL$ catalyzed asymmetric chlorolactonization reaction. After a number of studies, conducted primarily by Yousefi but aided computationally by Ashketar, a calculated structural model was proposed (Figure IV-1).[1, 2] In this model, strong ionic interactions between the protonated quinuclidine nitrogen and carboxylate orient the alkenoic acid in such a way that one face of the olefin is exposed. The chlorinating agent is brought into proximity of the olefin via a hydrogen bonding interaction between the protonated quinuclidine and the more electron rich carbonyl of the hydantoin. In this highly organized intermediate the crucial element to high enantioselectivity is the orientation of the alkenoic acid in the catalyst pocket. This orientation dictates which

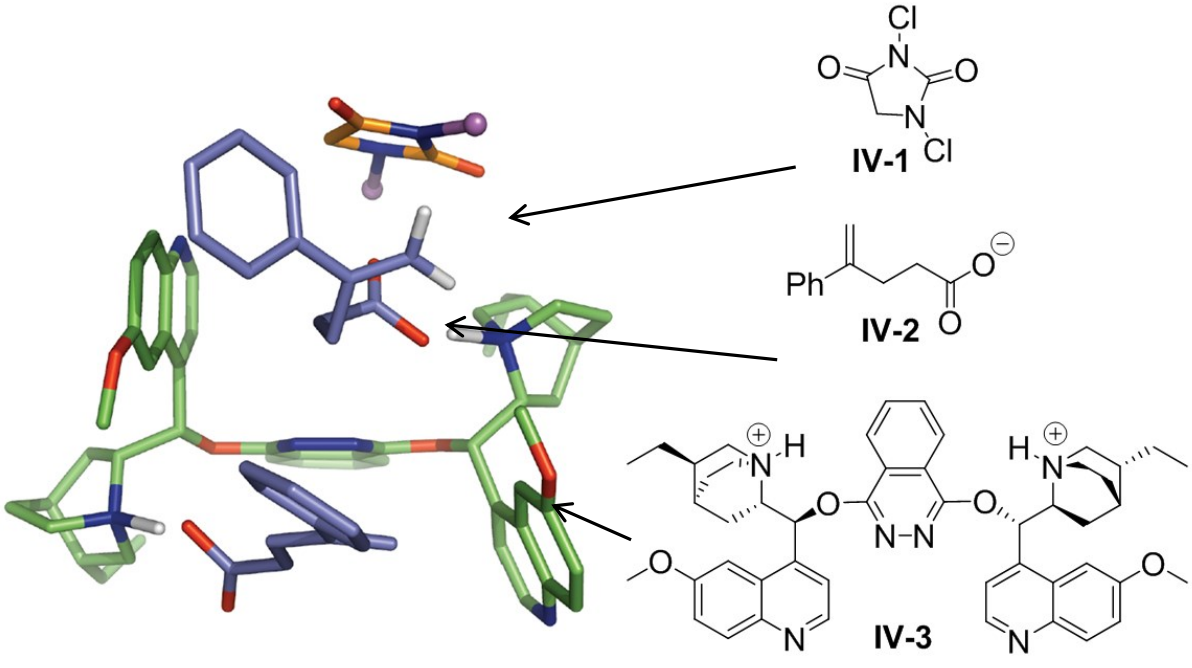


Figure IV-1. Resting state model of $(DHQD)_2PHAL$ bound to the alkenoic acid and dichlorohydantoin.

face of the olefin is chlorinated and also which face the nucleophilic carboxylate attacks. Rudimentarily, it is possible to envision simplifying this intermediate by combining the chiral motif and chlorinating agent into one scaffold. If the chloronium was engulfed in a chiral environment, templating the acid substrate should not be necessary. In this envisioned system, the scope could likely be extended to include olefin substrates lacking H-bonding or ionic functional groups, which was required in the $(DHQD)_2PHAL$ catalyzed system to tether the substrate to the catalyst. This imaginative vision is where the idea for a C_2-symmetric pyridine scaffold originated.

Out of all the nitrogen centered nucleophiles, we decided to design our

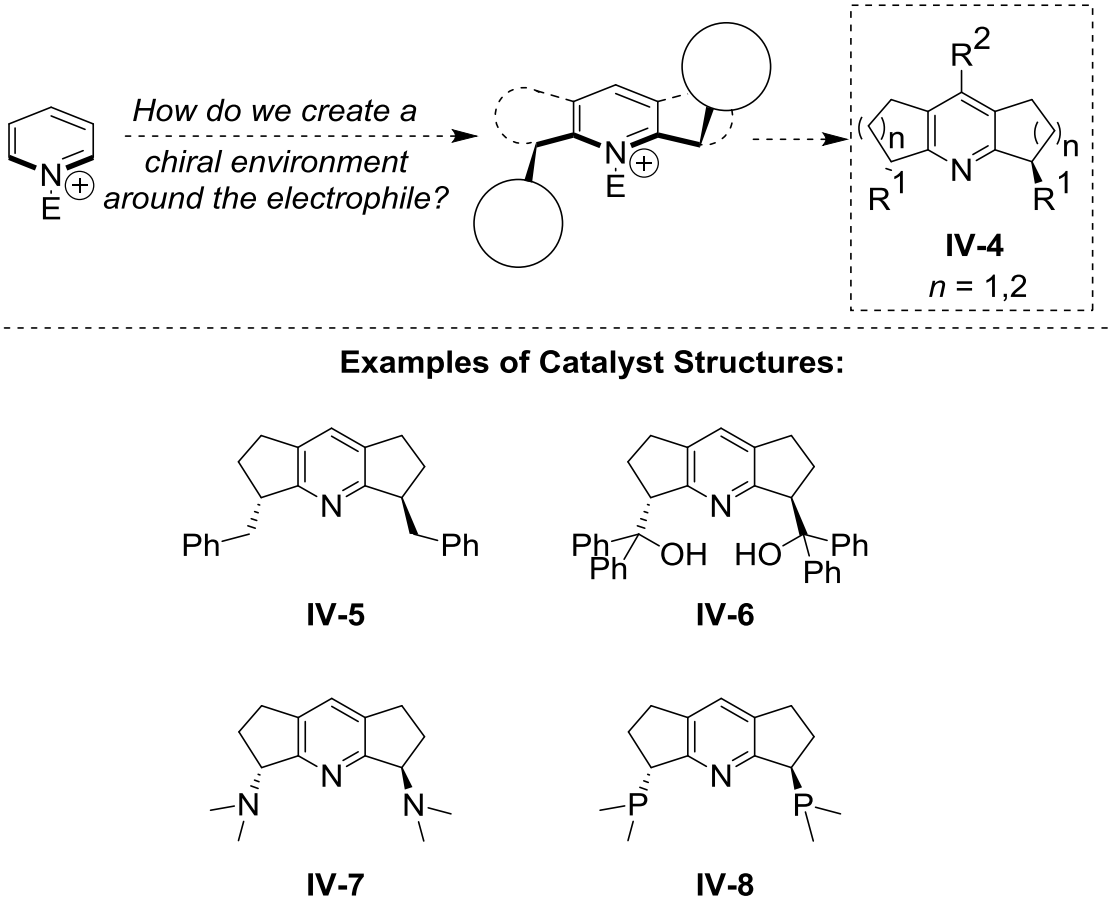


Figure IV-2. General structure of envisioned catalyst (**IV-4**) and 4 examples of catalyst structures featuring various substituents.

envisioned catalyst around a pyridine core. In contrast to most amine groups, which are conformationally flexible via bond rotations, the structure of pyridine is a rigid, planar surface. When a halogen, or any electrophile for that matter, is bound to the pyridine nitrogen, its location will be clearly understood, which makes designing a catalyst more logical. With this in mind, the next question was how do we build a chiral environment around the planar nitrogen? Clearly if an electrophile is bound to the pyridine nitrogen, then the chiral environment needs to be aimed at surrounding the electrophile. Based on this, we envisioned a general tricyclic core with two chiral centers, being *trans*-substituents, flanking the active site nitrogen (Figure IV-2). In regards to the tricyclic core, we envisioned either a 5,5- or 6,6-annelated system. Both systems were worth pursuing, with the 5,5-system being more conformationally rigid, causing the chiral substituents to be slightly angled away from the pyridine nitrogen, resulting in a marginally wider pocket. Additionally, we postulated that we could create a variety of scaffolds by varying R^1 to include alkyl, amino, alcohol, or phosphine groups, with the use of heteroatoms in these locations allowing for additional chelation to the electrophile. One last site of variation would be the substituent at R^2, which would allow

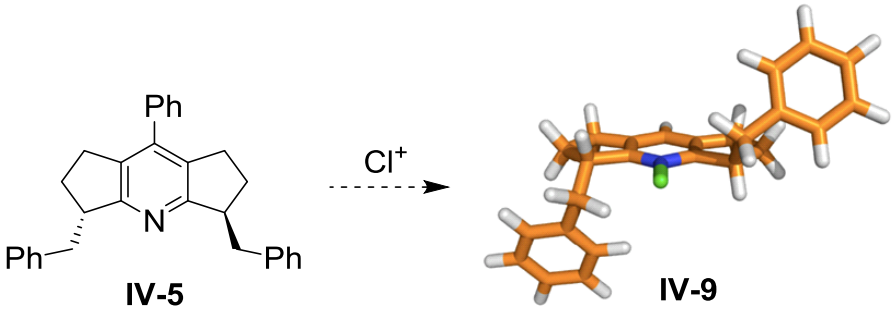


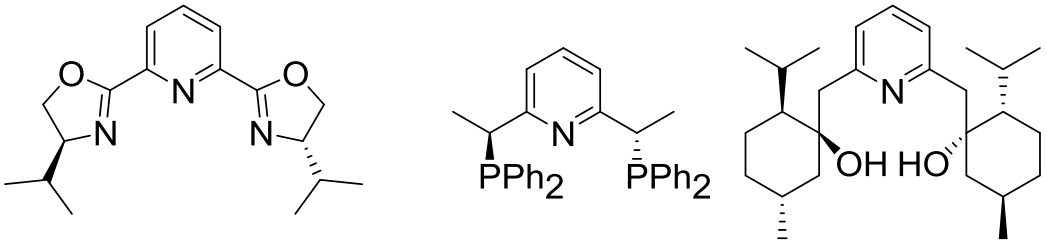
Figure IV-3. Semi-empirical energy minimization (HF 6-31G* in DCM) of **IV-5**.

us to tune the reactivity of the pyridine nitrogen.

In efforts to acquire a better understanding of the 3-dimensional shape of our proposed catalyst structure, we set out to perform energy minimization calculations. We selected **IV-5** as a preliminary target and ran an *ab initio* energy minimization calculation (HF/6-31G* in DCM) with a chlorenium in the chiral pocket (Figure IV-3). On first glance, we were happy with the shape of the catalyst, which clearly showed that when the 3-D space was split into quadrants about the plane of the active site nitrogen, two were definitively occupied. With these encouraging results in hand, we set out to search the literature for similar scaffolds.

IV-2 Review of Related Chiral Pyridine Scaffolds and Their Uses

The literature contains an assortment of chiral C_2-symmetric pyridine scaffolds, bearing various groups flanking the pyridine ring system. A few examples of these include pybox (**IV-10**);[3] diphosphino pyridine (**IV-11**),[4] and pyridine diol (**IV-12**)[5] ligands. Although these and other similar ligands have proven quite successful in a variety of applications, including chiral hydrogenations, reductions, and alkylations,[6-8] our proposed structure, which is based on the rigidified tricyclic core, has limited reports and

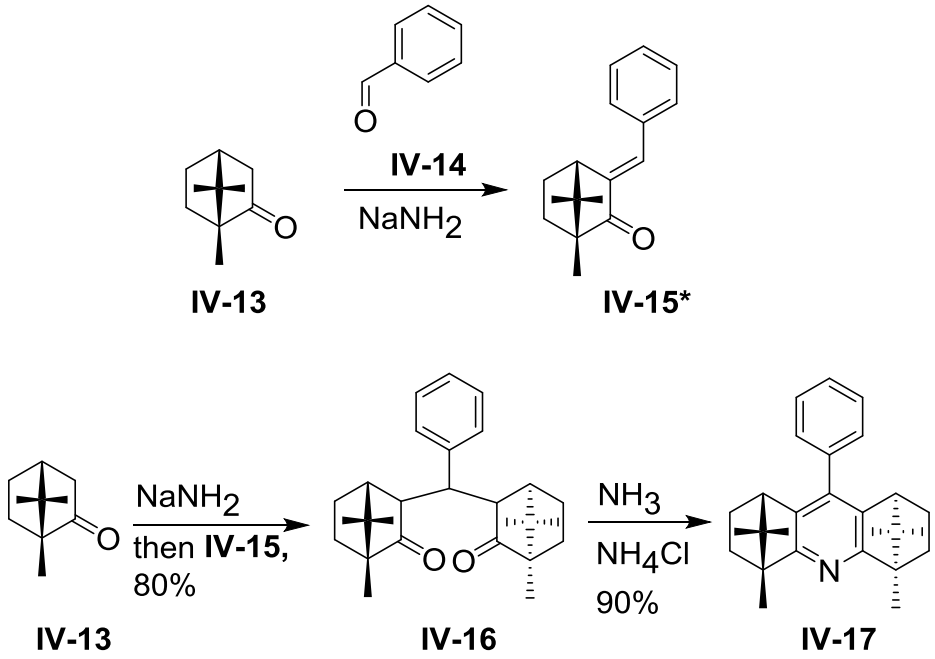


IV-10 **IV-11** **IV-12**

Figure IV-4. Examples of C_2-symmetric scaffolds.

applications in the literature. To the best of our knowledge, there are no chiral pyridine scaffolds bearing the 5,5-annelated ring system, and only a handful of catalysts based on the 6, 6-system.

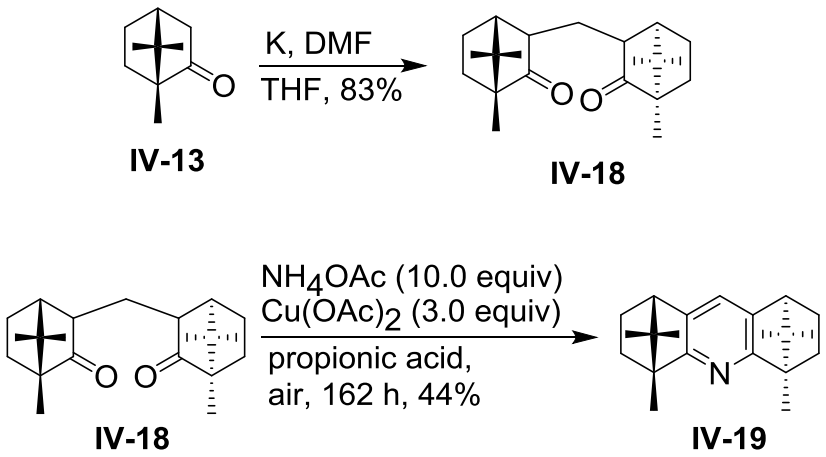
In 1987, Sotiropoulos published the synthesis of a camphor based, chiral C_2-symmetric scaffold (**IV-17**) similar to the general scaffold we envisioned (**IV-4**).[9] The target molecule was synthesized in an efficient manner, beginning with the condensation of bicylic ketone **IV-13** and benzaldehyde to give the unsaturated ketone **IV-15**. By reacting the enolate of ketone **IV-13** with the α,β-unsaturated ketone **IV-15**, the diketone **IV-16** was generated. This species was then reacted with ammonia to cyclize and oxidize yielding the desired octahydroacridine **IV-17** in good yield. The



Scheme IV-1. Sotiropoulos' synthesis of camphor based C_2-symmetric pyridine scaffold.
* Yield not reported.

authors did not report any uses of this chiral scaffold. The overall design and synthesis of this molecule is a good proof of concept, but does have limitations. Their starting ketone **IV-13** only has one set of α-protons, so how tolerable this route is to ketones with two different sets of α-protons is unclear. Also, introducing larger steric groups near the pyridine nitrogen would most likely require an entirely different starting material, since there are no obvious handles for functionalization.

In 2000, Kotsuki's group reported the synthesis of a scaffold (**IV-19**) similar to Sotiropoulos,' with the only variation being the substituent at the 9-position of octahydroacridine ring.[10] Kotsuki's catalyst, being unsubstituted at the back position used a similar route as Sotiropoulos'. Unfortunately the yields for cyclization of diketone **IV-18** were substantially lower than those reported by Sotiropoulos, even after an optimization study. Under optimal conditions, Kotsuki was only able to achieve 44% yield of **IV-19,** requiring the use of superstoichiometric copper acetate. The more



Scheme IV-2. Kotsuki's synthesis of camphor based C_2-symmetric pyridine scaffold.

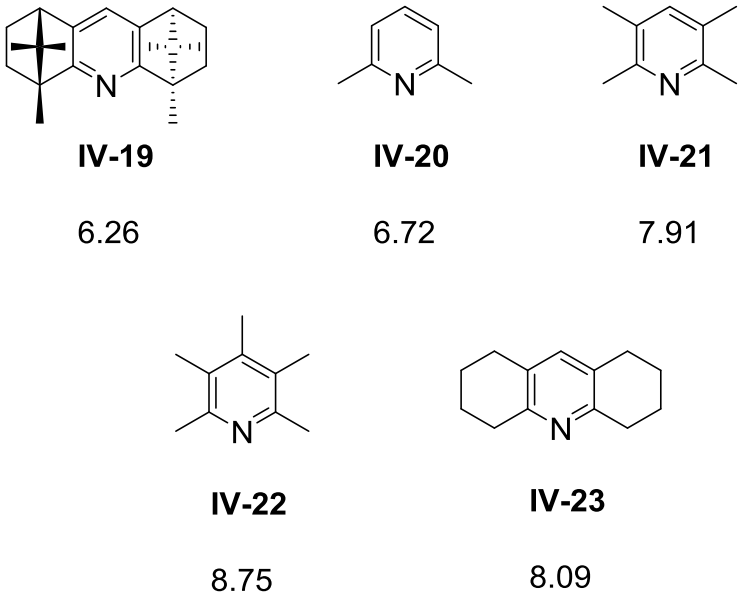
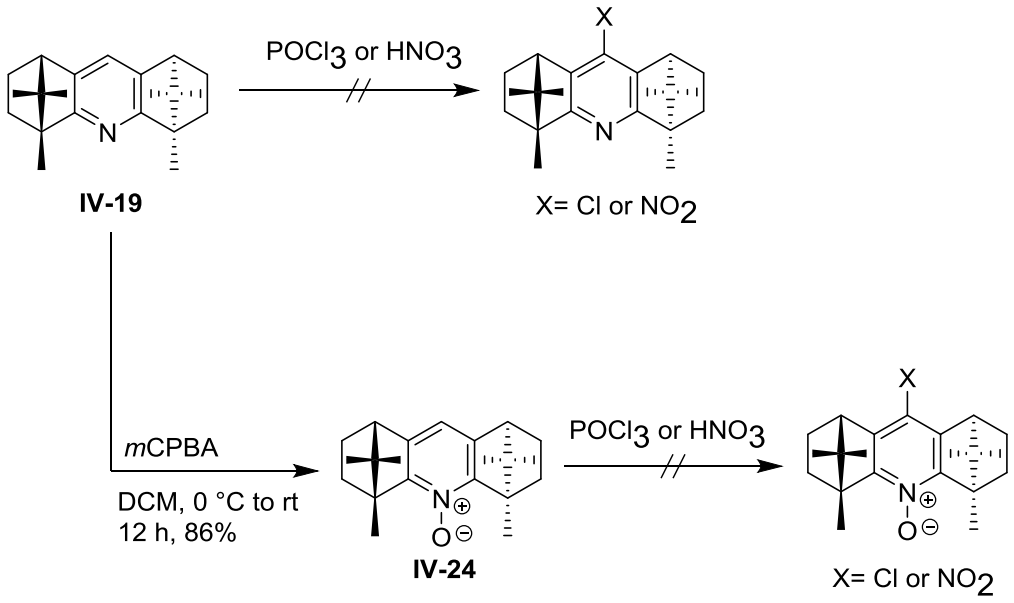


Figure IV-5. Comparison of pK_a of **IV-19** to various alkyl substituted pyridines.

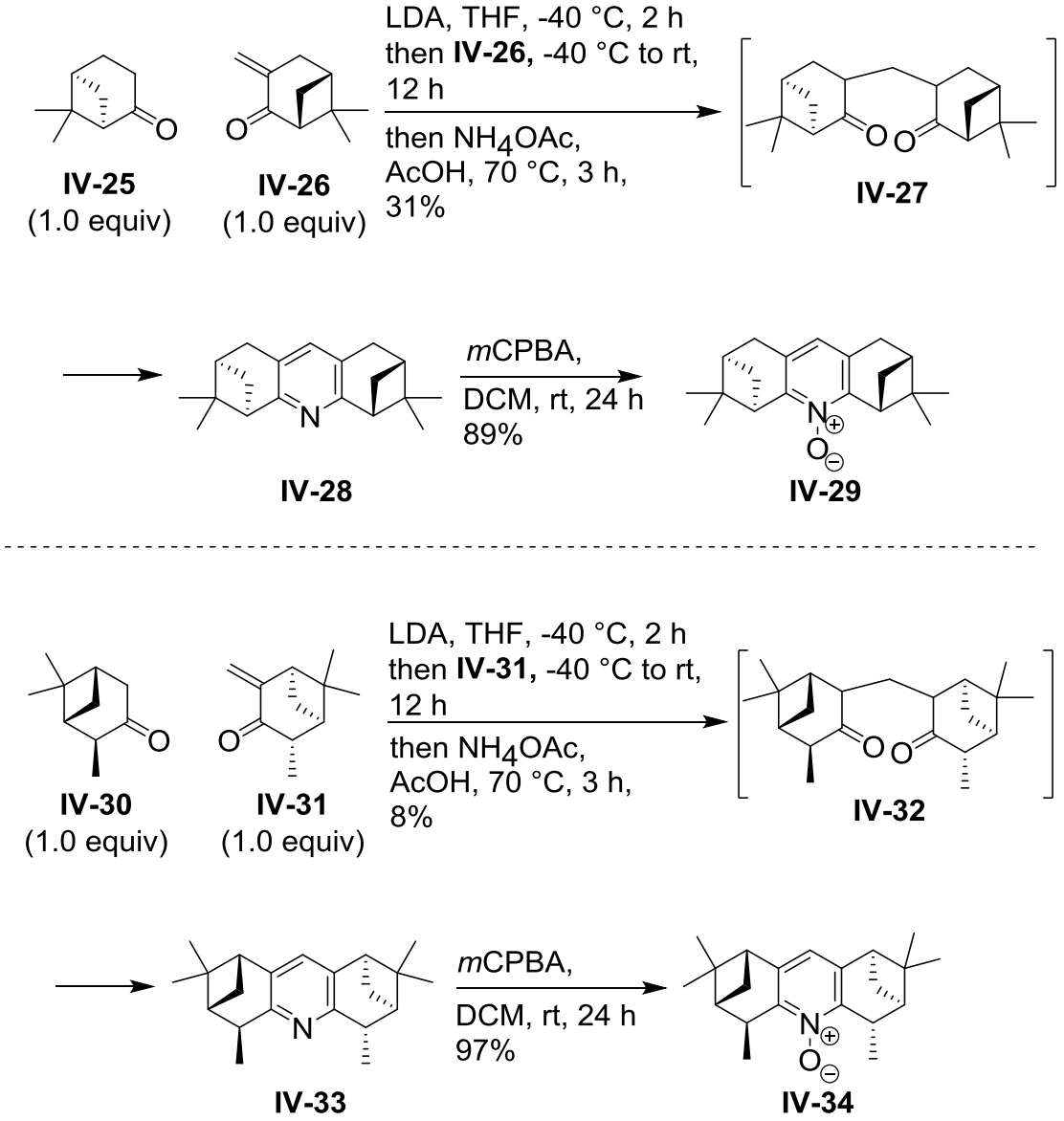
important aspect of this paper was the data regarding the reactivity of the C_2-symmetric scaffold. The pK_a of **IV-19** was determined as half-neutralization potentials by titration with 0.10 M perchloric acid in acetic acid.[11] In an analogous manner, the pK_a for a variety of methylated pyridines and octahydroacridine were determined, allowing for a direct comparison (Figure IV-5).[10] Overall, **IV-19** was found to be the weakest base, most likely attributable to the sterics around the pyridine nitrogen. The authors also examined the nucleophilicity of **IV-19** by mixing it with a variety of electrophiles including methyl iodide, acetyl chloride, acetic acid, or hydrochloric acid, however no notable reactivity was observed. Upon reacting **IV-19** with trifluoroacetic acid, crystals formed, which were characterized by X-ray crystallography .[10] Interestingly, the clefts predicted in our energy minimized structure were not as clearly defined in **IV-19**, which is most likely attributable to the rigidified structure from the bicyclic camphor starting material.



Scheme IV-3. Attempts to functionalize the 9-position of **IV-23**.

In this scaffold the chirality is focused around the aromatic ring and less around the front of the scaffold where an electrophile would be bound. Since their scaffold proved non-nucleophilic, efforts were made to introduce an electron-donating group at the 9-position. Initially simple electrophilic substitution reactions to chlorinate or nitrate the ring were tried, but both yielded no reaction (Scheme IV-3). Therefore the author's made the *N*-oxide (**IV-24**) to make the ring more electron deficient, but again the electrophilic substitution reactions were futile. To date, the authors have not published any further studies with this scaffold.[10]

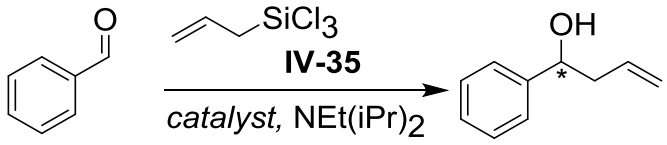
In 2008, Chelucci published two novel chiral C_2-symmetric pyridine scaffolds based on monoterpene starting materials which were used as catalysts in asymmetric allylation reactions (**IV-29** and **IV-34**).[12] This study also synthesized a variety of chiral bipyridine scaffolds which proved to be more efficient in the desired reaction, but our



Scheme IV-4. Chelucci's synthesis of C_2-symmetric pyridine scaffolds using one-pot conjugate addition – cyclization procedure.

focus will remain on the monopyridinyl derivatives. The two novel chiral catalysts were based on nopinone (**IV-25**) and isopinocampheol (**IV-30**). Although a similar synthetic strategy was used, one notable improvement over the other methods is the allowance of ketones with more than one set of α-protons. This was done by making the conjugate

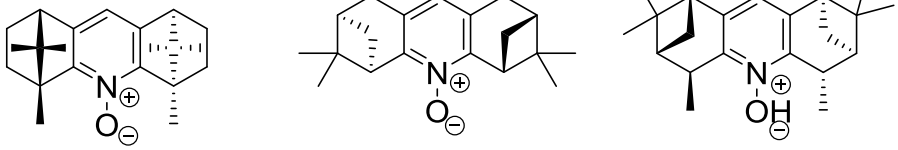
Table IV-1. Screening of C_2-symmetric pyridine scaffolds in asymmetric allylation reaction.



IV-14 **IV-36**

Entry	Catalyst	Temp (°C)	Yield (%)	*ee* (%)	Configuration
1	**IV-19**	0	n.r.	-	-
2	**IV-19**	25	65	<5	n.d.
3	**IV-29**	-40	23	42	*S*
4	**IV-29**	-40	31	48	*S*
5	**IV-29**	0	51	37	*S*
6	**IV-34**	-40	n.r.	-	-
7	**IV-34**	-40	11	15	*R*

Catalysts:



IV-19 **IV-29** **IV-34**

addition and diketone cyclization a one-pot procedure (Scheme IV-4). Although the reported yields are substantially lower (8-31%) for this method, the improvement in reaction scope permits access to a variety of scaffolds, in addition to the monoterpene based starting materials. Additionally they replicated Kotsuki's synthesis to acquire **IV-19,** for screening their desired asymmetric allylation reaction.[10] All three catalysts delivered mediocre results, with moderate to low yields and up to 48% *ee* (Table IV-1). Although these results are pedestrian, it provided us with hope that our catalyst, being of similar design, would be able to serve as a chiral scaffold for potentially a number of asymmetric transformations. We performed semi-empirical energy minimization (HF 6-

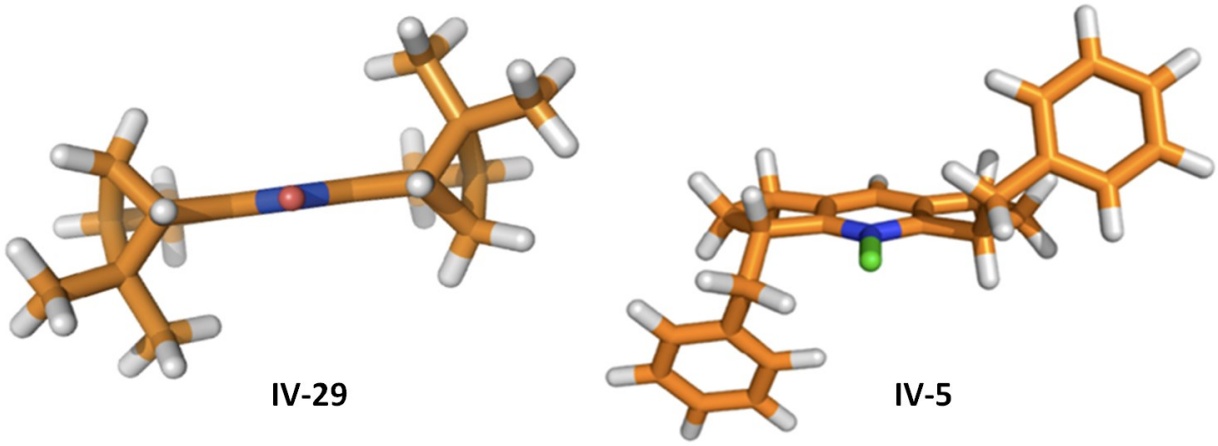
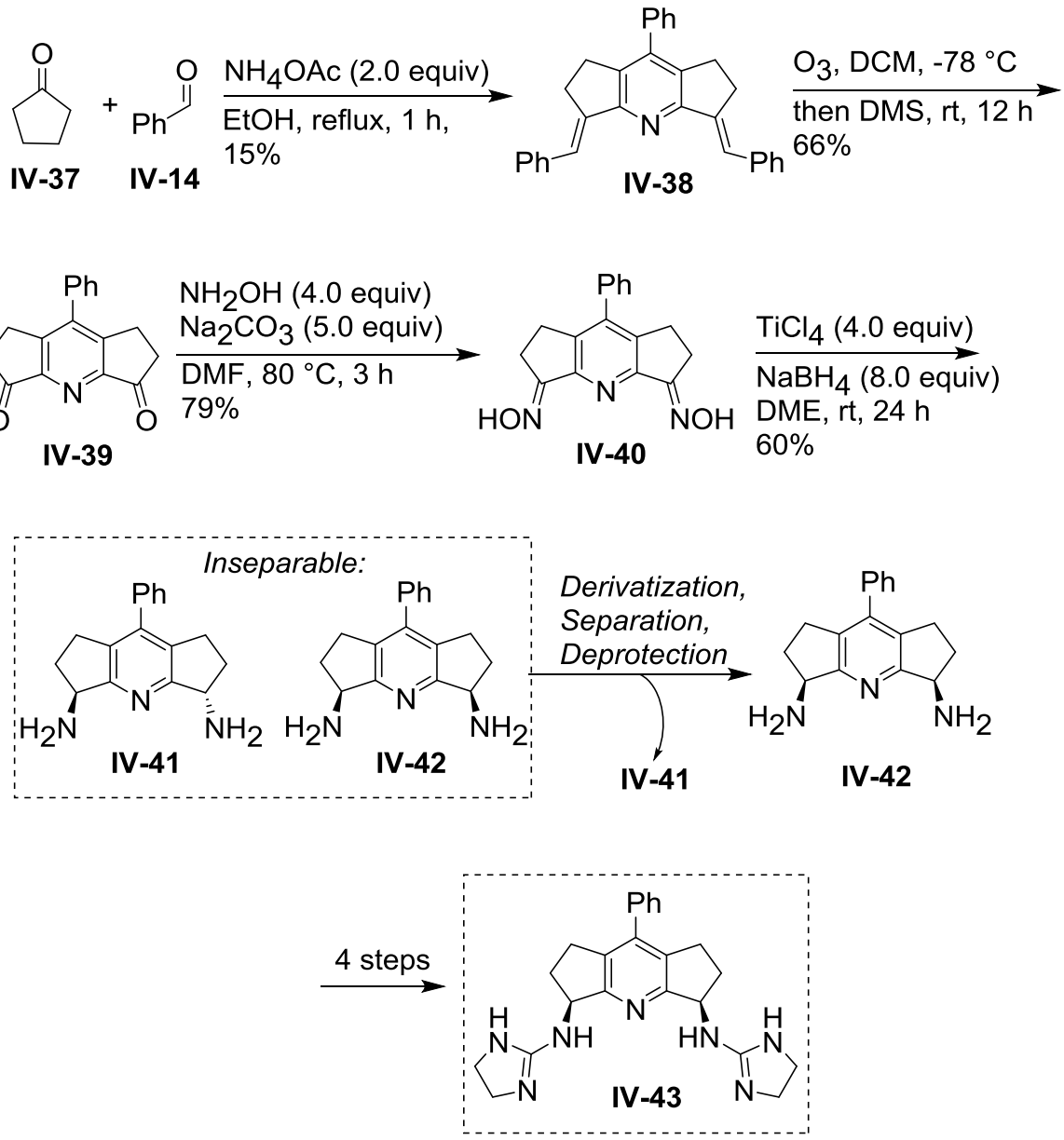


Figure IV-6. Comparison of **s**emi-empirical energy minimizations (HF 6-31G* in DCM) for **IV-29** and **IV-5.**

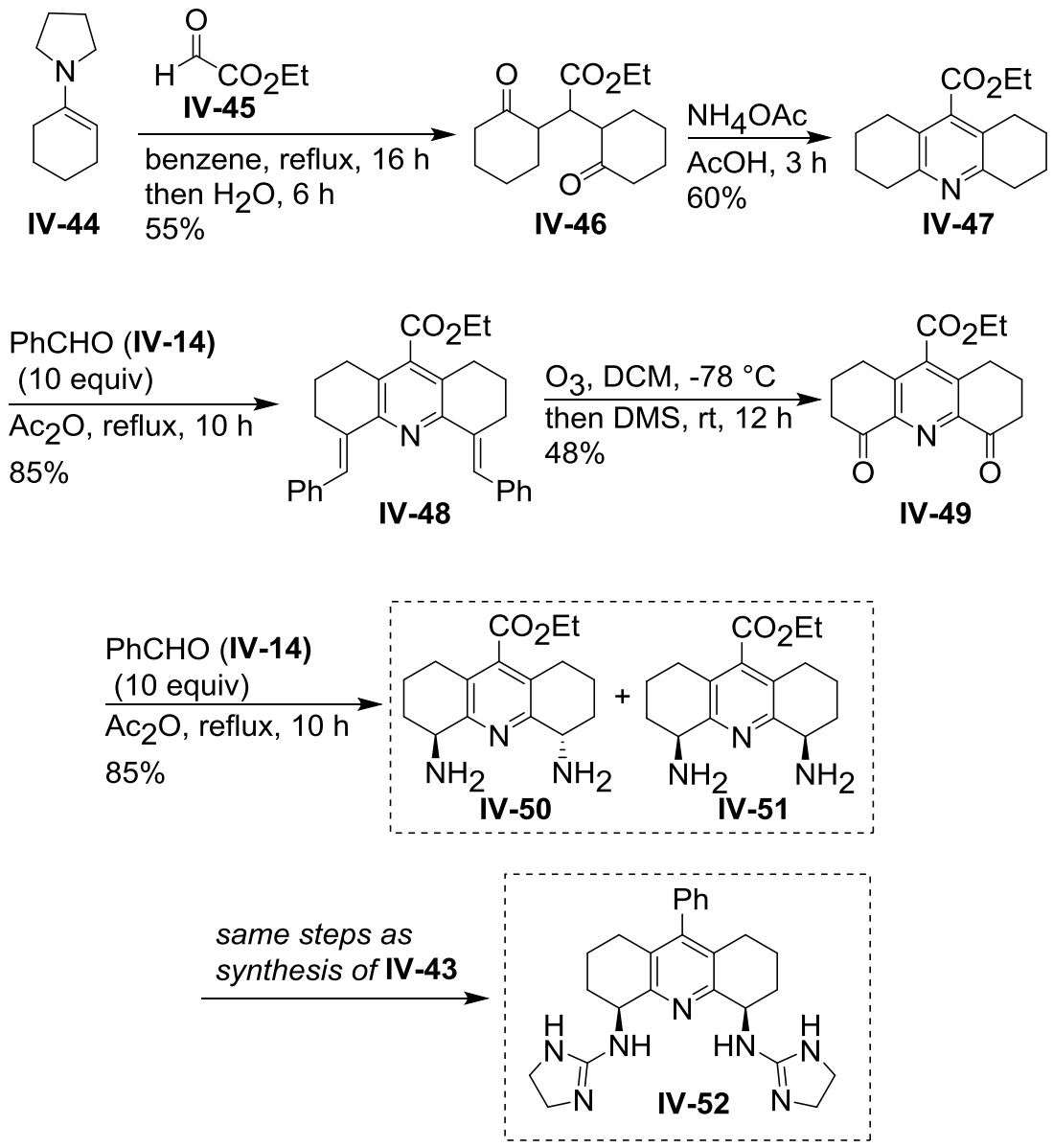
31G* in DCM) on the scaffold that gave them the best *ee*'s (**IV-29**) and found that their scaffold looked less than ideal for inducing high enantioselectivities (Scheme IV-7). The chiral bicyclic system flanking the pyridine nitrogen creates a nearly linear cleft, while the *N*-oxide places the active site further from the catalyst's chiral centers. A side-by-side comparison of their best catalyst and our proposed scaffold reveals that our chiral pocket is much more defined, with the dibenzyl substituents surrounding the bound electrophile.

Two other scaffolds worth mentioning come from Anslyn's group, which were synthesized to study their effects upon binding to phosphodiesters.[13] These scaffolds are not chiral, but have the same structural foundation as our proposed scaffold. For this study both 5,5- and 6,6-annelated systems were synthesized, having diaminoguanidinium groups flanking the pyridine nitrogen (**IV-43** and **IV-52**). The synthetic route to prepare these molecules requires several steps, but would allow a



Scheme IV-5. Anslyn's synthesis of a *meso*-5,5-annelated pyridine scaffold.

diversity oriented approach. The authors were only interested in the *cis*-diamine isomers (**IV-42 and IV-51**), but acquired the *trans*-diaminopyridine isomers (**IV-41** and **IV-50)** during the synthesis. The synthesis of the 5,5-system began with a one-pot cyclization reaction between cyclopentanone and benzaldehyde in the presence of



Scheme IV-6. Anslyn's synthesis of a *meso*-6,6-annelated pyridine scaffold.

ammonium acetate to yield bisbenzylidene **IV-38**. This substrate was subjected to ozonolysis to give diketone **IV-39**. Following this reaction, hydroxylamine was used to generate the bis-oxime **IV-40**, which then was reduced to give the diastereomeric mixture of **IV-41** and **IV-42**. The diamines were not separable at this point, so both amines were Boc protected and then separated. Following separation, the Boc groups

were removed and the desired *cis*-isomer was carried forward in the synthesis. The ratio of the isomers was not reported. For the 6,6-scaffold, enamine **IV-44** was reacted with ethyl glyoxylate, which was then hydrolyzed to give diketoester **IV-46**. This scaffold was cyclized in ammonium acetate and acetic acid to yield the octahydroacridine **IV-47**. The α-positions of the pyridine were functionalized using an acetic anhydride promoted condensation reaction with benzaldehyde to give bis-benzylidene ester **IV-48**. This was subsequently ozonolyzed to give the diketone, followed by reductive amination with ammonium acetate to yield a diasteromeric mixture of diamines, **IV-50** and **IV-51**. After the same series of steps as used in the synthesis of **IV-43,** the *cis*-bisalkylguanidium octahydroacridine scaffold was acquired. The main purpose for discussion of these syntheses was to highlight means of functionalizing the tricyclic pyridine scaffold. In this synthesis, the diketones **IV-39** and **IV-49** are valuable intermediates which can be derivatized in a variety of ways.

IV-3 Synthesis of a Novel Chiral C_2-Symmetric Pyridine Scaffold

Initially when we set out to synthesize scaffolds based on the general structure **IV-4,** we were hoping to find an approach that was diversity oriented (Figure IV-6). For the first generation catalyst, we initially chose **IV-5**. The reason for this is mainly due to the retrosynthetic analysis, which revealed a streamlined synthetic route that would easily allow analogs to be made. During the design of the retrosynthesis, we noted two hurdles that were necessary to overcome in order to acquire chiral **IV-5**: a chiral resolution and the preferential generation of the *trans*-isomer. Because chiral resolutions of pyridine compounds are literature precedent, we were optimistic that we

would be able to overcome the challenge when it came.[14-17] In regards to preferential generation of the *trans*-isomer, we hypothesized that it should be thermodynamically favored, therefore if the pK_a of the pyridine's α-protons could be lowered, then the two substituents would be easier to isomerize under basic conditions. With this in mind, we proposed that the benzyl methylene units in **IV-5** could arise from the Wolff-Kischner reduction of the diketone **IV-53**. Under basic conditions, diketone **IV-53** should equilibrate to give the desired *trans*-isomer. With the diversity oriented goal in mind, we proposed that the diketone could be achieved via α-depronation of compound **IV-54**, followed by acylation, in this case benzoylation.

With the proposed synthesis of our desired scaffold hinging on access to **IV-54,** we searched the literature to explore the available routes. There are essentially three

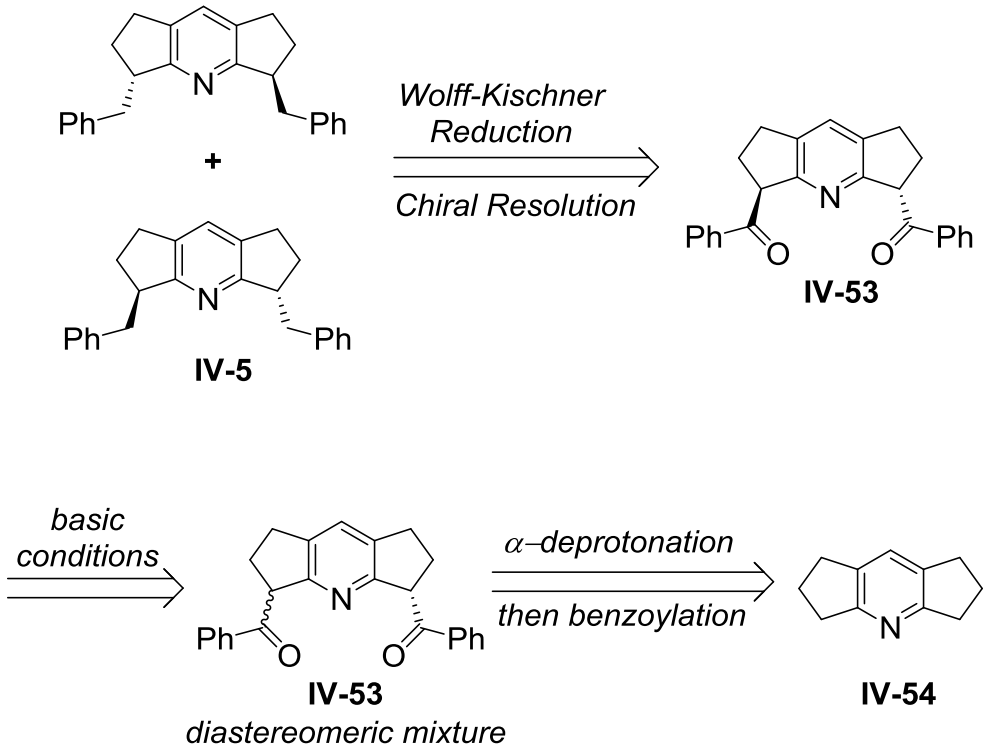
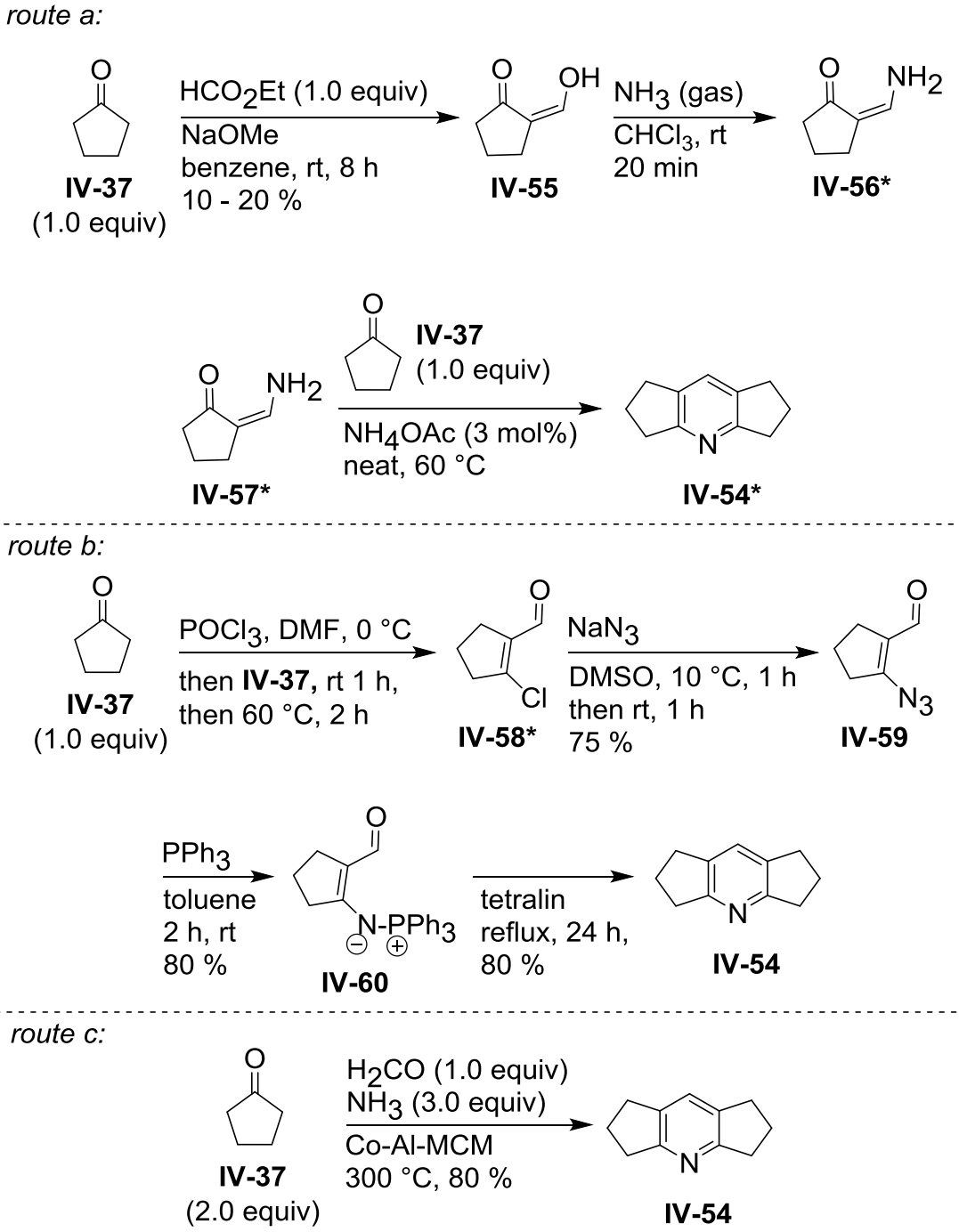


Figure IV-7. Diversity oriented retrosynthesis of **IV-1**.

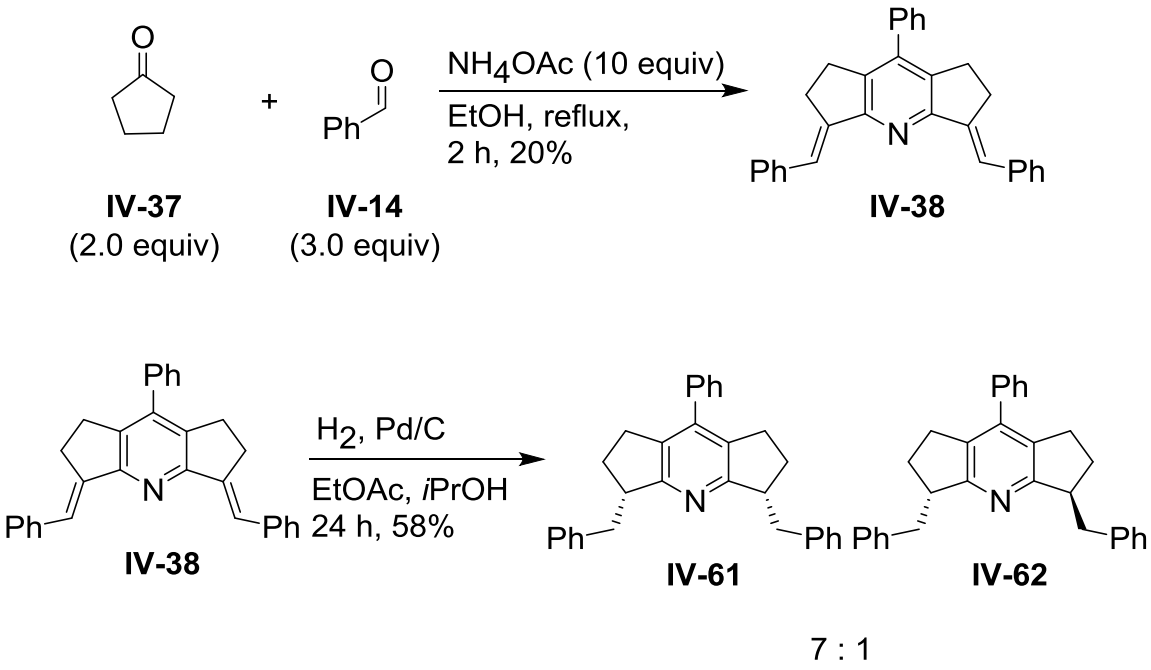


Scheme IV-7. Literature precedent procedures to make **IV-54**.
*Yield not reported.

routes (Scheme IV-7); one uses cyclopentanone and ethyl chloroformate to generate enol **IV-55**, which then is reacted with ammonia to give enamine **IV-56**. The enamine is then reacted with cyclopentanone and catalytic amounts of ammonium acetate neat to give the desired bisannelated pyridine adduct **IV-54**. We investigated this route, however the intermediates **IV-55** and **IV-56** proved unstable, decomposing within hours. This instability ultimately resulted in the formation of a complex mixture of products during the transformation of **IV-57** to **IV-54**, which proved difficult to separate.[18] Another route to access **IV-54** requires thermolysis of cycloalkenyl azide derivative **IV-60**. This synthesis begins with generation of the Vilsmeier reagent which is then reacted with cyclopentanone to give the vinyl halo-aldehyde **IV-58**. This is then reacted with sodium azide and subsequently triphenyl phosphine to generate enamine intermediate **IV-60**. Upon refluxing the cycloalkenyl amine in tetralin (~210 °C), the desired product is reported to form in 80% yield. We also tried this route, which proceeded smoothly until the key step, which turned black after 5 minutes of heating. Although the anticipated mass of the desired product was observed with MS, it was inseparable from the resulting complex, tarry mixture. It is reasonable to propose that the reactant polymerized under these harsh conditions. The last published route to acquire the product uses a variety of molecular sieve catalysts at high temperatures (+300 °C) (*route c)*.[19-23] Although the last route only requires one step and gives high yields, the molecular sieve catalysts were not readily available.

Because access to **IV-54** proved challenging and several of the intermediates in the published routes were unstable, we decided to waiver from our initial vision of the 4-

position being a simple H, and try the one pot cyclization procedure used in Ansyln's synthesis of the 5,5-dialkylguanidinium scaffold.[13] The synthetic potential of this scaffold was recognized, with hydrogenation of the benzylidene olefins offering access to a similar analog as our first proposed scaffold (**IV-5**). In fact, a 4-phenyl substituent should offer slightly increased pyridine basicity in comparison to initial target bearing a hydrogen in the 4-position. Upon screening this reaction, we were happy to find that the desired product was obtained in 20% yield (identical to the reported yield) with its purification only requiring filtration of the crude reaction mixture. The olefins were then hydrogenated, but disappointingly the *cis*-isomer (**IV-61**) was preferentially formed over the *trans*-isomer (**IV-62**), in a ratio of approximately 7 : 1. This ratio is not completely unexpected since heterogeneous palladium catalyzed hydrogenations are known to occur via *syn* addition to the least hindered face of the olefin.[24] Therefore after one



Scheme IV-8. Successful synthesis of first generation pyridine scaffold.

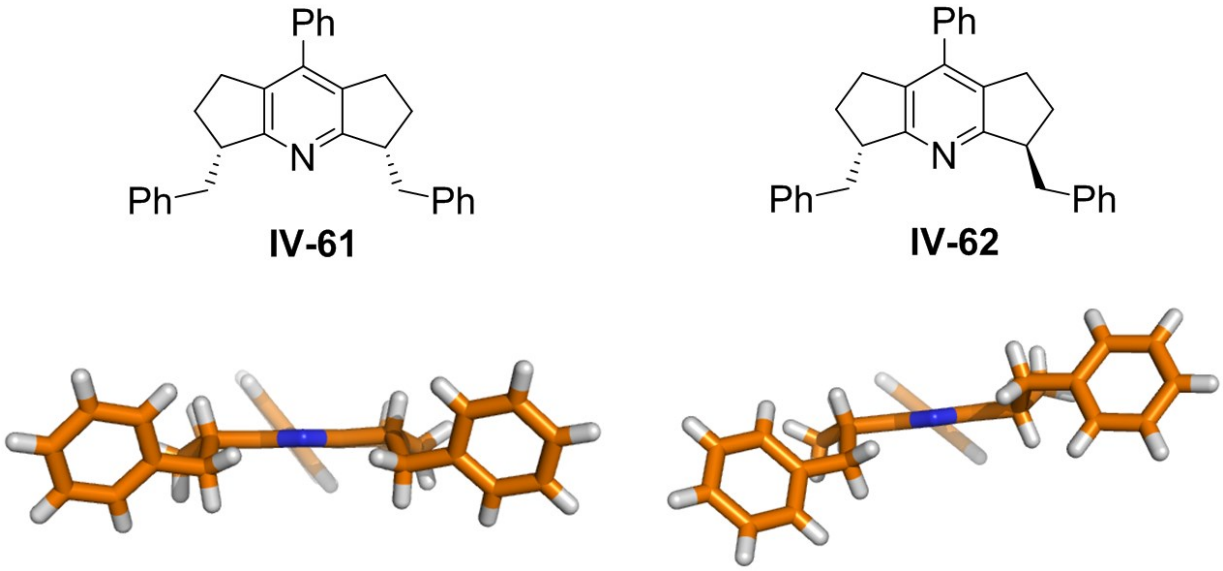
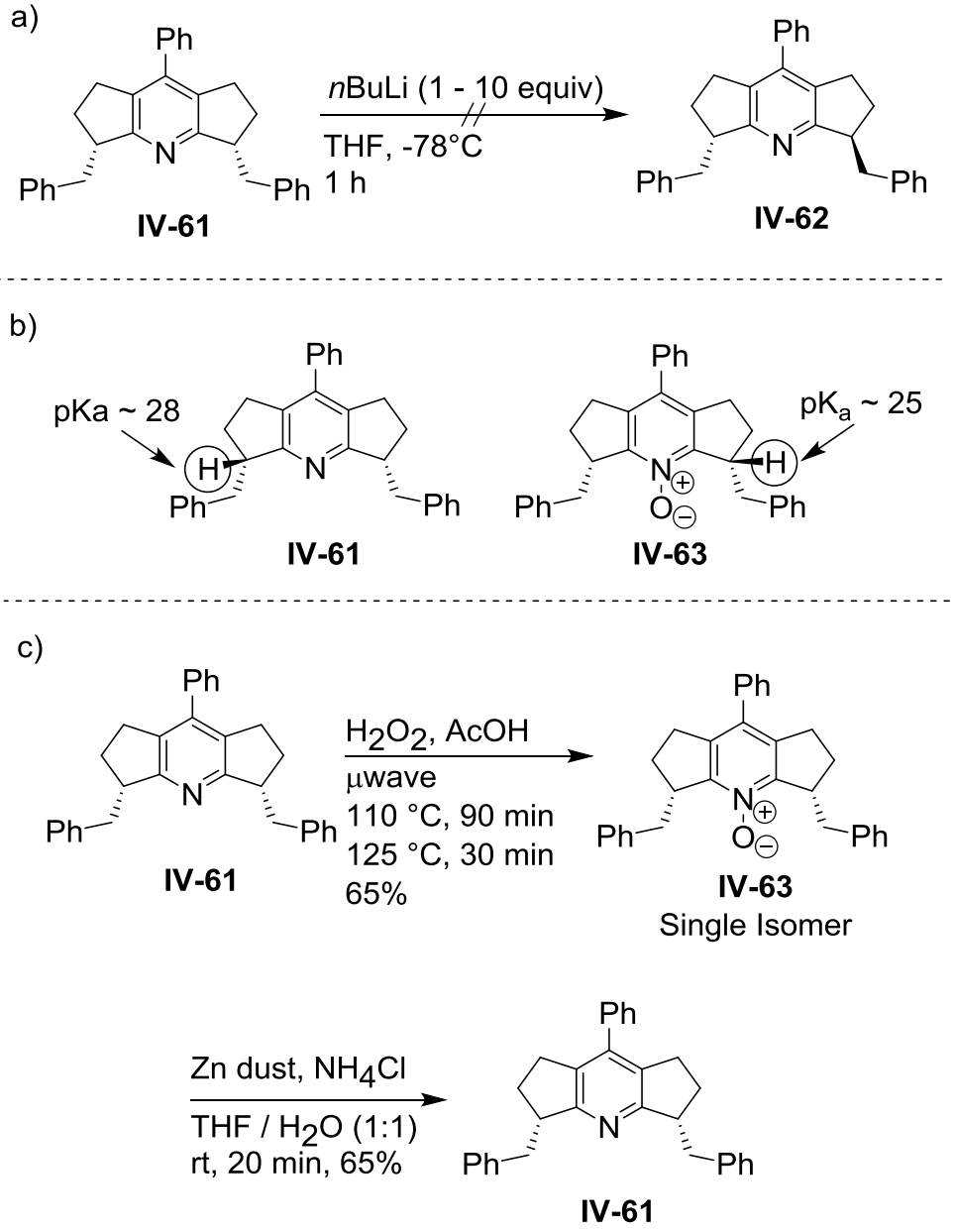


Figure IV-8. Crystal structures confirming the identity of the two isomers obtained from hydrogenation of **IV-38**.

olefin is hydrogenated in **IV-38,** the least hindered face for hydrogenation is the same face as the first. We were able to isolate both the *cis* and *trans* isomers, confirming their relative stereochemistries with X-ray crystallography (Figure IV-9). Notably, both crystal structures are of the neutral pyridine scaffolds, as compared to the chlorinated pyridinium which was used for calculations.

Although we were elated to have our first generation catalyst in hand, we knew that we would need access to decent quantities (>200 mg) of material for the chiral resolution. Since the hydrogenation reaction only gave moderate yields and the desired **IV-62** was minor, we initially tried to isomerize undesired **IV-61** with *n*BuLi (Scheme IV-9a). Even with a large excess of *n*BuLi, no isomerization was observed. Based on the literature, the expected pK_a of the indicated protons in Scheme IV-9b were estimated to be 28, which should make them the most acidic in **IV-61**. Therefore, we were uncertain

whether the isomerization was failing because the benzyl substituents were too far apart to interact with each other or if our desired and expected proton was not the most acidic in **IV-61.** As a last attempt to isomerize **IV-61** to the *trans*-isomer, we generated the *N*-



Scheme IV-9. Failed attempts to isomerize *cis* **IV-61.** a) Attempted isomerization with *n*BuLi. b) Approximate pK_a of α-protons for **IV-61** and **IV-63.** c) Attempt to isomerize via the synthesis of *N*-oxide **IV-63** and reduction back to neutral scaffold **IV-61.**

oxide **IV-63**, using *m*CPBA (Scheme IV-9c). This manipulation makes the desired protons more acidic, being approximately 3.0 pK_a units lower (Scheme IV-9b). After the somewhat harsh oxidation conditions, a single isomer was detected. The *N*-oxide was reduced back to the starting material to determine its stereochemistry, which disappointedly revealed that it had not isomerized.

We also briefly investigated other methods to acquire **IV-62**. Since palladium catalyzed hydrogenation proceeds via concerted *syn* addition, other methods proceeding via a step-wise mechanism could possibly favor the *trans* isomer. We screened **IV-38** in a variety of reductions including: TFA / triethyl silane, hydroboration-protonolysis, and hydrazine, however all of these reactions yielded only starting materials. Even by MS analysis, none of the mono-hydrogenated or dihydrogenated products were detected. We concluded that the olefins in highly conjugated **IV-38** were very unreactive.

Since all attempts to acquire the desired **IV-41** in good yield and selectivity had failed, we reevaluated our target structure. We began by looking at the crystal structure of the *trans*-isomer **IV-62** (Figure IV-9). Upon reexamination, we were somewhat disappointed that the cleft created by the two benzyl substituents was not as open as we envisioned and we also recognized that benzyl groups may not be the best substituents. This decision was based on the realization that with benzyl substituents, the rotation about the indicated bond in Figure IV-10 (**IV-62**) induces different steric environments. Therefore we decided to investigate the use of *tert*-butyl groups instead,

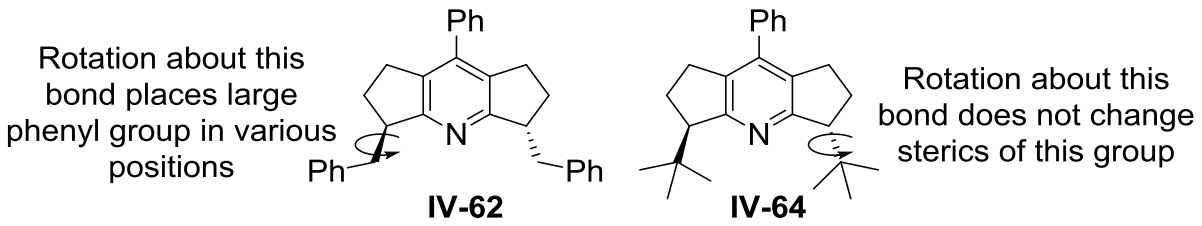


Figure IV-9. Reason for changing catalyst substituents from benzyl to *tert*-butyl groups.

since rotation about the analogous bond does not lead to drastic changes in the steric environment (**IV-64**).

We began by performing energy minimization calculations (HF 6-31G* in dichloromethane) for chlorinated **IV-64** (Figure IV-11). We were pleased with the *pseudo*-diaxial relationship between the *tert*-butyl groups and set out to synthesize the desired scaffold. The retrosynthetic analysis (Figure IV-10) of **IV-64** commences with deoxygenation of diol **IV-66**, which we propose could occur via an acid catalyzed silane reduction or single electron transfer process. Formation of diol **IV-66** should be accessible by bis-Grignard addition to diketone **IV-39**, which we predicted should occur in a predominantly *trans*-fashion since it should be a stepwise process. The diketone **IV-67** is a known compound, arising from the ozonolysis of **IV-38.**[13]

With **IV-38** in hand, we initiated our synthesis by ozonolyzing the benzylidene olefins (Scheme IV-10a). Although this reaction remained colorless during the course of the reaction, it became a dark black color while warming to room temperature after being quenched with dimethyl sulfide. Even after column chromatography, the product was isolated as a dark green / black solid in low yield. Upon adding this solid to dichloromethane, the color became even darker over the course of a few minutes. The

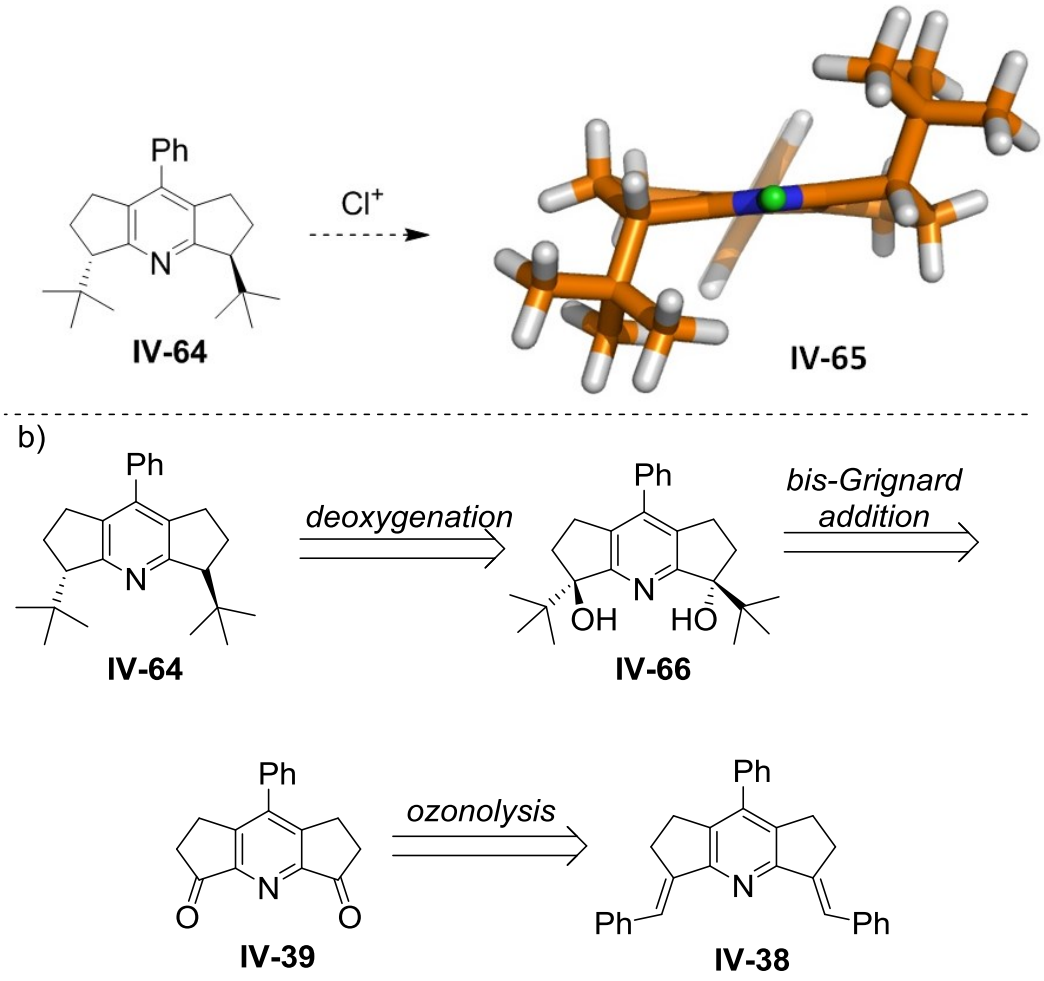
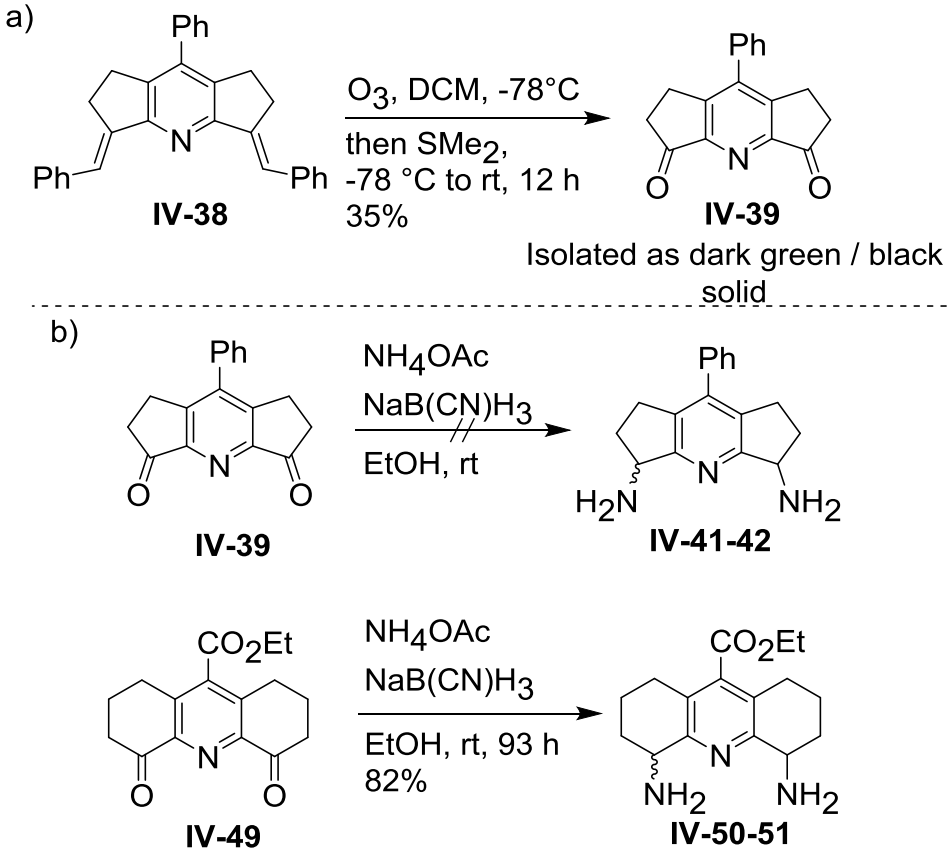


Figure IV-10. a) *Ab initio* energy minimization (Hartree Fock 6-31G* in dichloromethane) of **IV-65** and b) retrosynthetic analysis of **IV-64**.

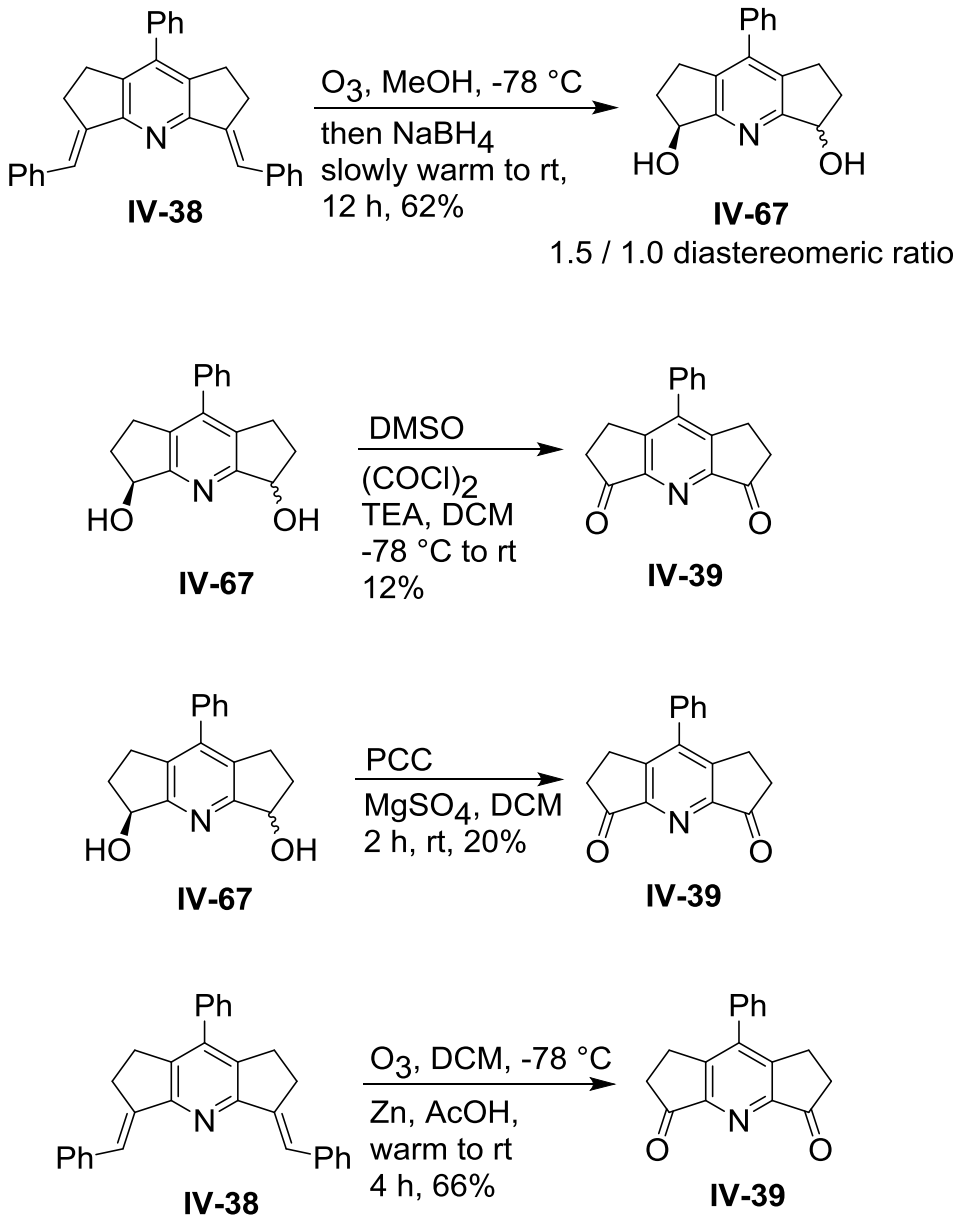
published ozonolysis procedure, reported by Anslyn's group, also commented on the strange reactivity of **IV-39**, stating that under reductive amination conditions (ammonium acetate and sodium cyanoborohydride), the reaction with diketone **IV-39** immediately turns black, and none of the desired product can be isolated.[13] This is even more intriguing, since the same authors report that with a similar 6,6-annelated pyridine system, reductive amination conditions give the desired product in high yield (Scheme IV-10b). Although it is reasonable to hypothesize that under the strongly oxidizing



Scheme IV-10. a) Our ozonolysis reaction result and b) Published reaction of diketone **IV-39,** exhibiting strange reactivity in comparison to a related substrate **IV-49.**

ozonlysis conditions, side reactions leading degradation are possible; the observed instability from the published procedure during reductive amination eludes limited stability of diketone **IV-39**. To test this, we set out to screen other synthetic methods which would allow us to reach the same diketone scaffold to see if the decomposition could be slowed and the product could be obtained in higher yields.

The first method we decided to screen used ozonolysis as well, but the ozonide was reduced to the diol by quenching with sodium borohydride. This reaction cleanly gave a mixture of diasteromers as a stable, white solid (Scheme IV-11). From this



Scheme IV-11. Screening of various reactions to synthesize diketone **IV-39.**

result, we ruled out that decomposition was linked to ozonolysis, therefore indicating that degradation was most likely linked to the stability of the product. With the diol in hand, we screened oxidation procedures, including PCC and Swern. Full conversions were observed via TLC for both Swern and PCC, however both reactions gave low

yields and the same dark colored product. Notably, the Swern reaction was colorless until the triethylamine was added, causing the reaction to turn black almost immediately. Although this might suggest that basic conditions accelerate decomposition, Anslyn observed decomposition during the slightly acidic reductive amination conditions. At this point we were certain that the product was reacting with itself, with the mechanism and identity of the degradation product(s) being unclear. In looking at the structure of **IV-39**, the most reactive functionalities are the ketones and pyridine nitrogen. We therefore hypothesized we could mask the nucleophilicity of the pyridine nitrogen by quenching the ozonolysis reaction with acetic acid and zinc, known reductive work up conditions. Under these conditions, the pyridine nitrogen should be protonated which may inhibit degradation while the ozonide is quenched. These conditions worked well, preventing formation of dark solution and delivering the product in significantly improved yields.

With diketone **IV-39** in hand, the next step was to add the two *tert*-butyl groups via a Grignard reagent. We were quite disappointed to find that the diketone was not soluble in diethyl ether or THF, two solvents commonly used in these reactions. In conjunction with this, upon addition of the Grignard reagent to the reaction, we found the reaction immediately turned black. MS analysis clearly indicated that the desired product was formed, however its purification proved challenging. The product was always obtained as a dark colored solid in low quantities; therefore it is not possible to report a yield accurately.

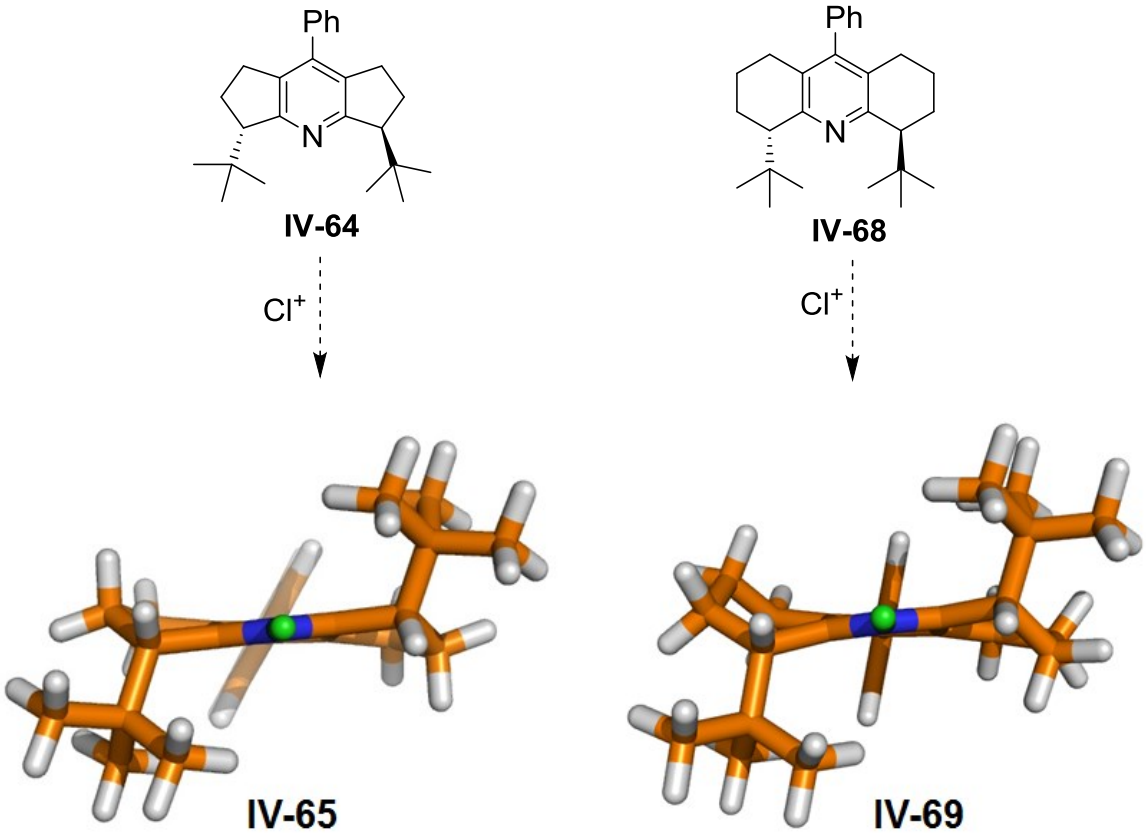


Figure IV-11. Comparison of semi-empirical minimization calculations (HF 6-31G*) for the chlorinated 5,5- versus 6,6-annelated pyridine scaffolds.

Based on the challenges in this synthetic route, with a central focus revolving around the stability of diketone **IV-39,** we ultimately decided to change the core to an octahydroacridine scaffold. Because Anslyn's results showed that the 6,6-annelated pyridine scaffold behaved as expected under reductive amination conditions (Scheme IV-10b),[13] we were hopeful that it would prove more stable. With all other aspects of the catalyst remaining the same, we performed a semi-empirical energy minimization (HF 6-31G*) on the chlorinated analog of the newly envisioned motif (**IV-49**). A

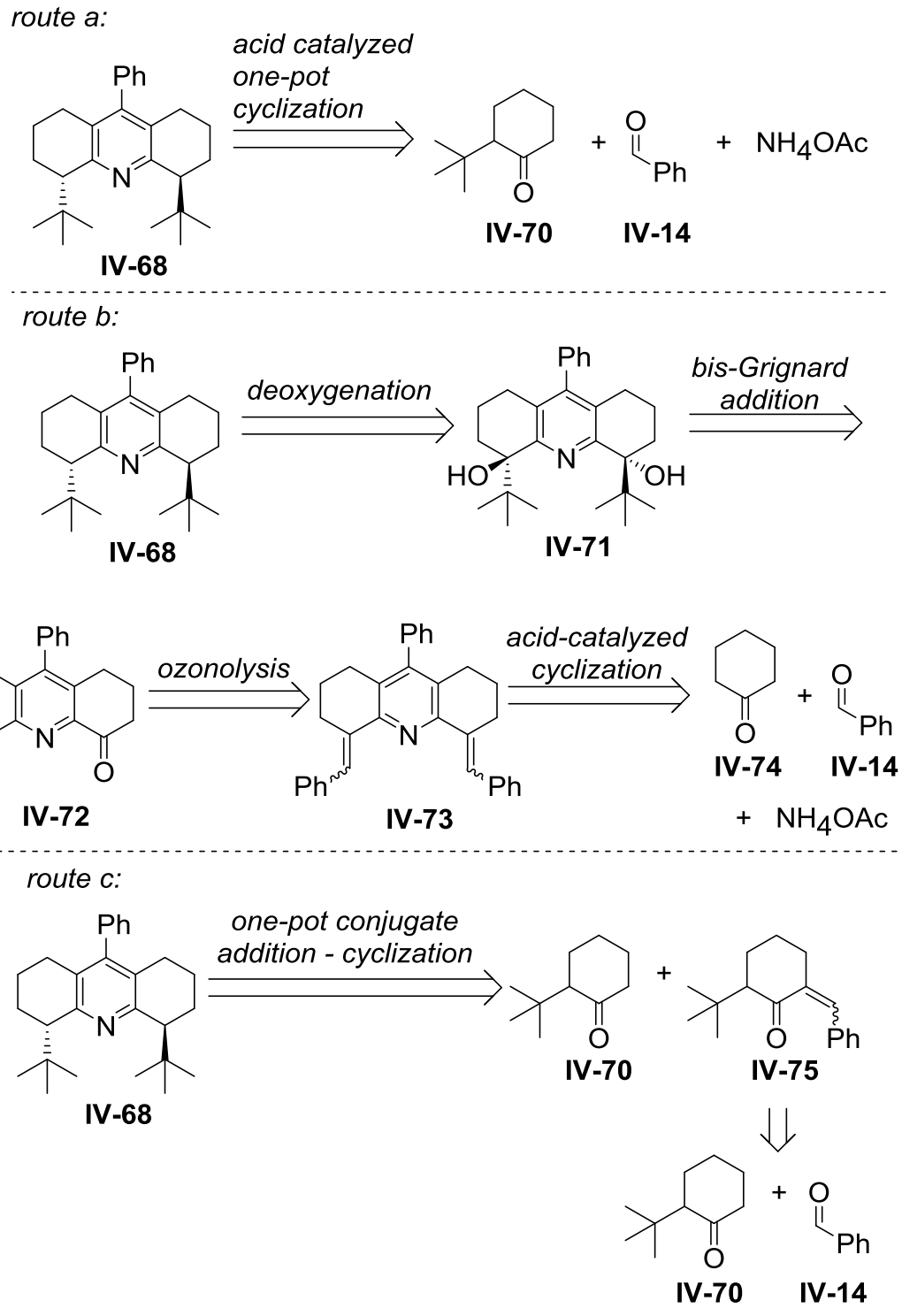


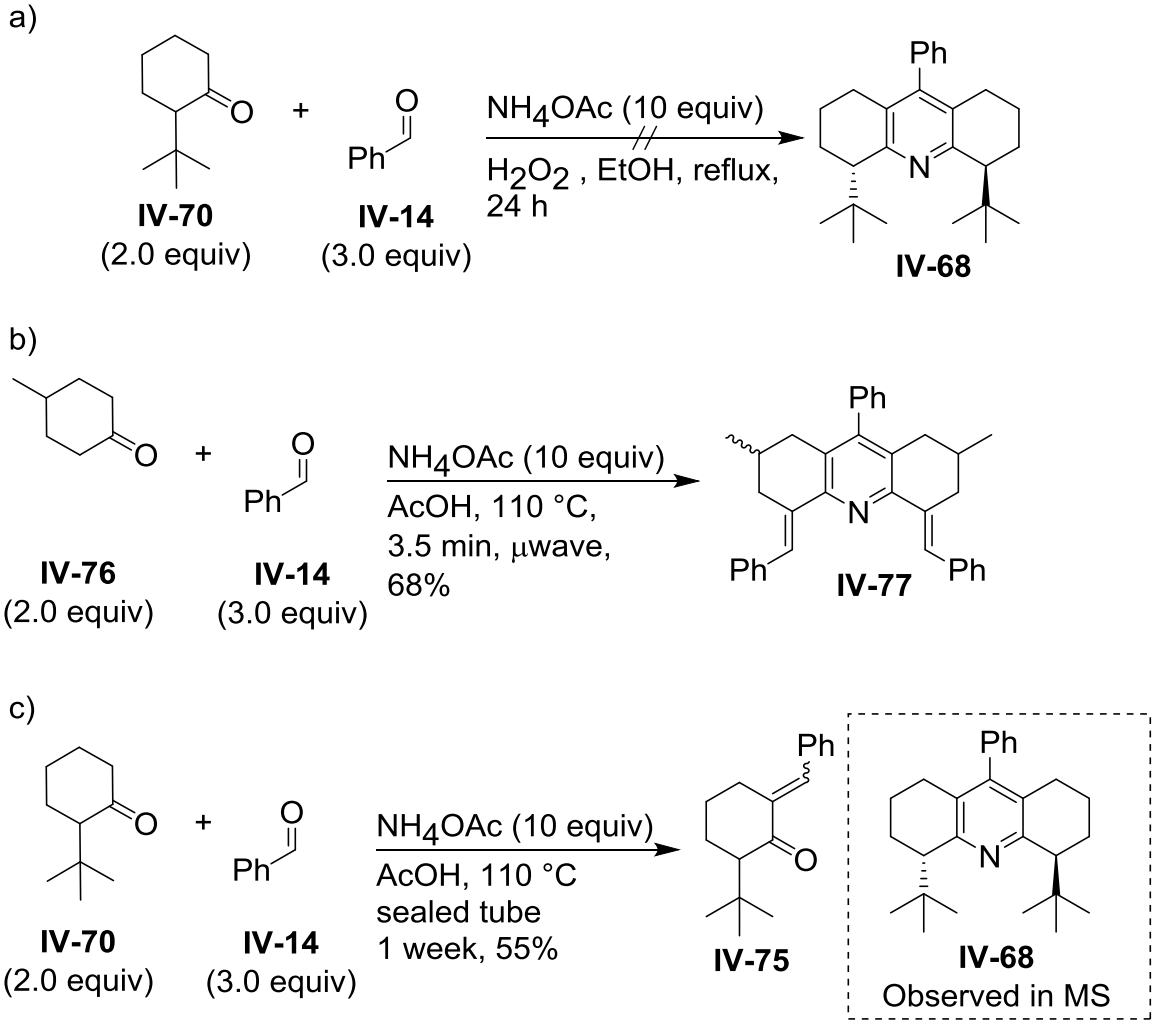
Figure IV-12. Three possible retrosyntheses for **IV-68.**

comparison of the two calculated structures can be seen in Figure IV-12. Overall the chlorinated 5,5- and 6,6-annelated pyridine scaffolds look very similar.

To access racemic **IV-68,** we proposed three possible retrosyntheses. The most convenient of the three, is based on a one-pot cyclization reaction, analogous to the one used to form **IV-38** (Figure IV-13). In place of cyclopentanone, racemic 2-*tert*-butyl cyclohexanone would be used, which could deliver **IV-68** in one-pot (Figure IV-13, *route a*). The second procedure, based on the same one-pot acid catalyzed cyclization would use cyclohexanone to form the bis-benzylidene scaffold **IV-73,** which would then require the same transformations as the 5,5-annelated system; ozonolysis to give the diketone **IV-72**, followed by Grignard addition, followed by deoxygenation (Figure IV-12, *route b*). Based on our problems with this route in the 5,5-system and the number of steps, we reserved this route as a last resort. The third retrosynthesis would utilize the same synthetic method as Chelucci reported to access C_2-symmetric scaffolds (Section IV-4),[12] with 2-*tert*-butyl cyclohexanone as the starting ketone (Figure IV-13, *route c*). This would require the synthesis of the unconjugated ketone **IV-75**, followed by the one pot conjugate addition – cyclization procedure.

We initially began by trying *route a,* since it would prove the most expedient. If successful, we would be able to easily access a variety of scaffolds by changing the α-substituent on the cyclohexanone. Using the same conditions as we used in the synthesis of **IV-38**, we disappointing found that none of the desired product could be detected by MS (Scheme IV-12a). We therefore looked in the literature and found a one pot cyclization procedure to form an octahydroacridine core with a variety of 4-

substituted cyclohexanones with acetic acid as a solvent and a microwave reactor (Scheme IV-12b).[25, 26] During the time of this research, we did not have access to a microwave, so we did the reaction in a sealed tube at the same temperature. After 24 hours, the anticipated mass of the desired product was observed in LC-MS, but only in trace amounts; with the major product being the α,β-unsaturated ketone **IV-75** (Scheme IV-12c). Even after heating the reaction for 1 week, the reaction did not show a

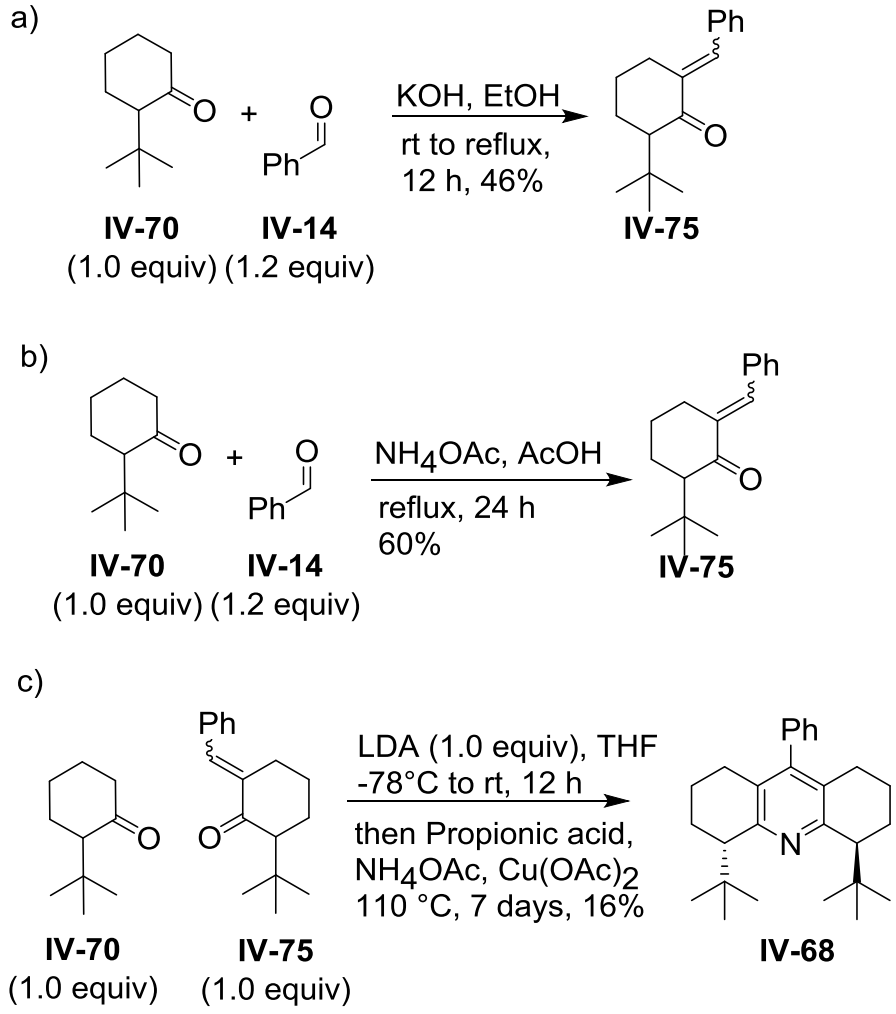


Scheme IV-12. Attempted one pot syntheses of octahydroacridine scaffold. a) Same conditions used to access 5,5-annelated scaffold; b) Published procedure to make octahydroacridine scaffold; c) Attempt to use published procedure with 2-*tert*-butylcyclohexanone.

significant amount of progress. Because the conjugated ketone was the major product, it seemed that the conjugate-addition was slow under acidic conditions. We therefore proposed that we could favor the formation of the product by formally generating the kinetic enolate of **IV-70**, using the two-step method published by Chelucci *et al* in the synthesis of camphor based C_2-symmetric pyridine scaffolds (**IV-29** and **IV-34**).[12] This method would first require synthesis of the conjugated ketone and then a one pot conjugate addition - cyclization procedure (Figure IV-13, *route c*).

Most of the procedures in the literature use basic conditions to promote the condensation reaction between an aldehyde and cyclohexanone. We initially tried these conditions, but found that it gave us a dark colored mixture, containing several side products and low yields.[27] Recall that the use of ammonium acetate in acetic acid cleanly gave **IV-75** as the major product (Scheme IV-12c). In efforts to make this reaction more efficient, we decreased the number of equivalents of benzaldehyde, affording **IV-75** in moderate yields. With the conjugated ketone in hand, we tried the one-pot conjugate addition – cyclization reaction, beginning with formation of the kinetic enolate of 2-*tert*-butyl cyclohexanone via LDA. After 12 hours, the reaction was quenched by adding propionic acid and ammonium acetate, followed by distillation of the THF. After 1 week of heating at 110 °C, we were elated to find that this reaction gave the desired product, albeit in long reaction times and somewhat low yields (Scheme IV-13c). We noted that our cyclization was much slower than the Chelucci's reported time (3 hours), which most likely is due to the sterics of the *tert*-butyl substituents. When we first isolated the product, we were unsure of the relative

stereochemistry of the *tert*-butyl groups. The crude ^{1}H NMR showed only one triplet in the 2.80-2.90 range, indicating the formation of a single diastereomer. Because the cyclization reaction required such long reaction times, we hypothesized that the stereochemistry of the *tert*-butyl groups most likely isomerized during the course of the reaction and the final closure may not be favored until the thermodynamically favored *trans* relationship is achieved. By forming the TFA salt of **IV-68**, we were able to use X-ray crystallography to confirm that the relationship between the two substituents was



Scheme IV-13. Synthesis of unsaturated ketone **IV-75** and one-pot conjugate addition – cyclization procedure to give desired **IV-68.**

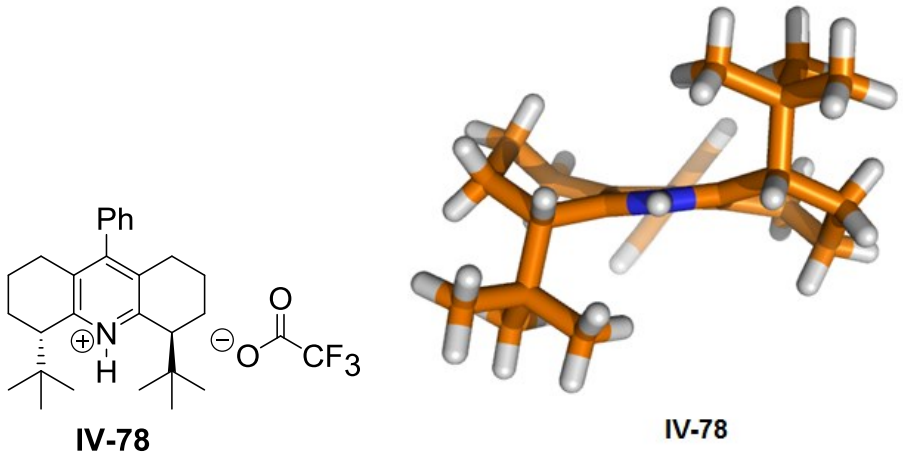


Figure IV-13. Crystal structure of **IV-58,** proving *trans*-relationship between the *tert*-butyl groups.

*The TFA counterion was omitted from the crystal structure for clarity.

trans (Figure IV-14). Because the preparation of **IV-68** could be easily done in 2 steps, we were able to access large quantities of the scaffold quite rapidly. Therefore we moved onto the next challenge, performing a chiral resolution.

Chiral resolutions on pyridine scaffolds are fairly common in the literature. Since most resolutions are trial and error, we began by using tartaric acid in acetonitrile, conditions published for resolution of a different monopyridinyl scaffold.[16] After dissolving the tartaric acid in boiling acetonitrile, **IV-68** was added and the flask was

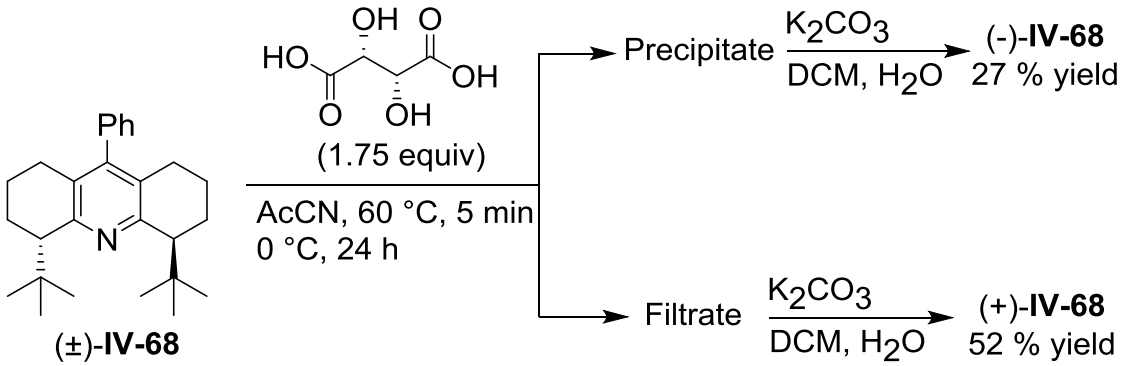
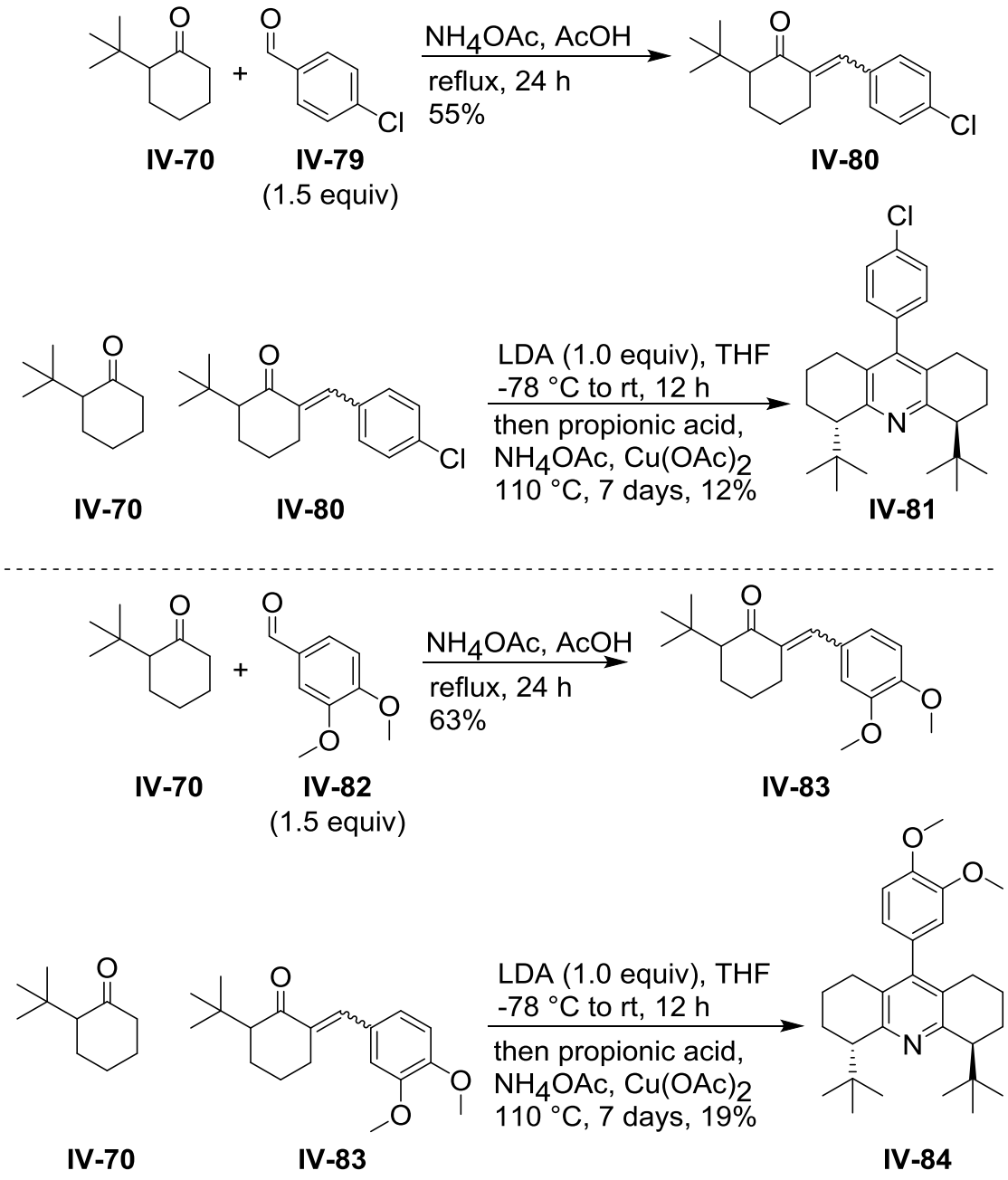


Figure IV-14. Fractional crystallization of (±)-**IV-49** with tartaric acid.

placed in the freezer for 24 hours. After this time, a white precipitate had formed which was filtered and neutralized. The precipitate was found to have a negative optical rotation, while the filtrate was found to have a positive optical rotation. We were pleased that on our first attempt, we had successfully separated the enantiomers, at least to some extent. Unfortunately we were not able to determine how efficient the resolution had been because the nonpolarity of **IV-68** made it difficult to separate the enantiomers by chiral HPLC or GC. Since **IV-68** was so non-polar, this proved very difficult. We screened all the chiral HPLC and GC columns in our laboratory, with no signs of separation. Because of this, we decided to synthesize two other analogs of **IV-81,** bearing a 4-chlorophenyl and 3,4-dimethoxyphenyl substituent at the 4-position of the pyridine ring (**IV-84**). The 4-chlorophenyl group was mainly chosen to serve as a heavy atom, which would allow the determination of absolute stereochemistry after resolution by X-ray crystallography; as for the 3,4-dimethoxyphenyl group, we were hoping that it would make the pyridine scaffold more polar so we would be able to separate the enantiomers by chiral HPLC or GC-MS.

After synthesizing **IV-81** and **IV-84**, we found that we were unable to use chiral HPLC or GC to resolve **IV-81**, but were happy to find that chiral HPLC easily separated the enantiomers of **IV-84**. Unfortunately we were surprised to find that under the same resolution conditions that worked for **IV-68**, no resolution was achieved with either of the new pyridinyl scaffolds. We screened approximately 50 different conditions to resolve **IV-84**, since we could separate by HPLC, but even after screening a variety of solvents, temperatures, and equivalencies of tartaric acid, no resolution was observed.



Scheme IV-14. Synthesis of various 4-substituted C_2-symmetric pyridine scaffolds.

Additionally we screened other chiral carboxylic acids including mandellic and lactic acid; but none of these conditions gave any resolution as judged by polarimetry. We began to wonder if we had isolated the *cis*-isomer of product, but X-ray crystallography confirmed that **IV-84** was *trans* (Figure IV-16).

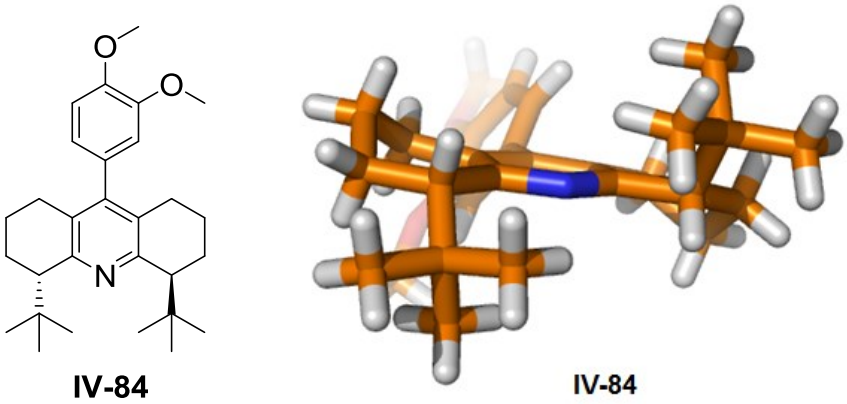
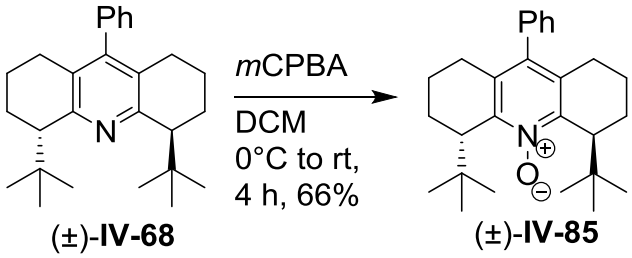


Figure IV-15. Crystal structure of **IV-84**, proving *trans*-relationship between the *tert*-butyl groups.

We were frustrated at this point, that with the **IV-84**, we were able to use chiral HPLC to separate the enantiomers, but could not resolve the enantiomers via fractional crystallization; and with **IV-68** we could resolve the enantiomers to some extent by fractional crystallization, but could not separate the enantiomers via chiral HPLC or GC. Since increasing the polarity of the pyridine compound proved to aid in the separation of the enantiomers on HPLC as demonstrated with **IV-84**, we considered ways to make **IV-68** more polar. We realized that one way to increase the polarity of this scaffold would be to synthesize the *N*-oxide. We were able to easily carry out this transformation and during the first run on chiral HPLC, we were able to successfully resolve the enantiomers (Scheme IV-15). We therefore oxidized our samples from the earlier



Scheme IV-15. Synthesis of *N*-oxide to increase polarity of **IV-49.**

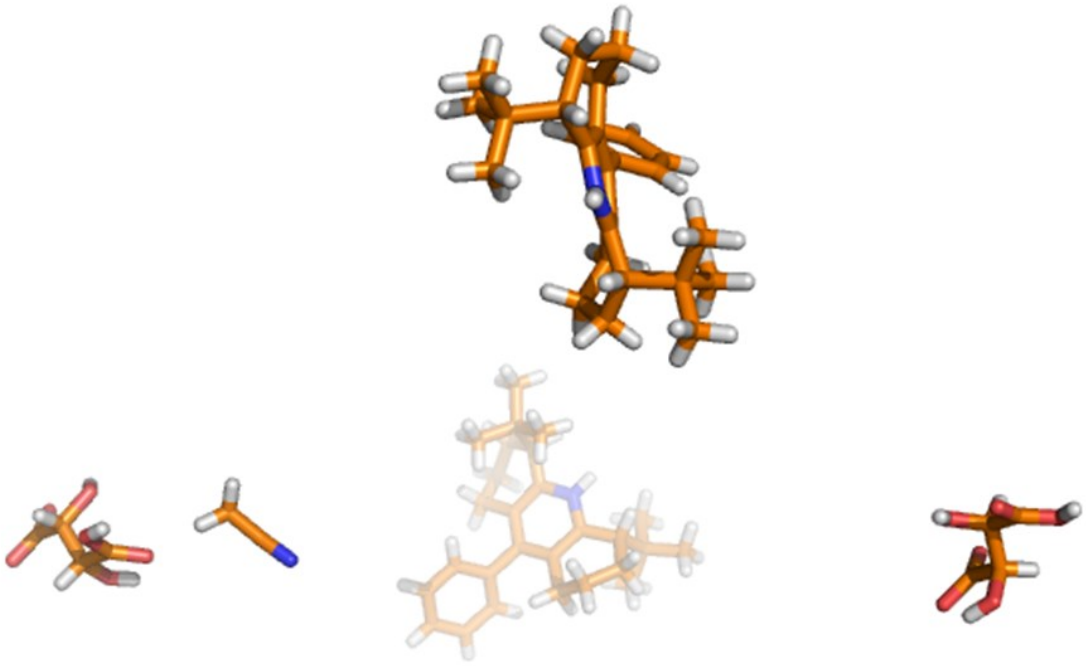


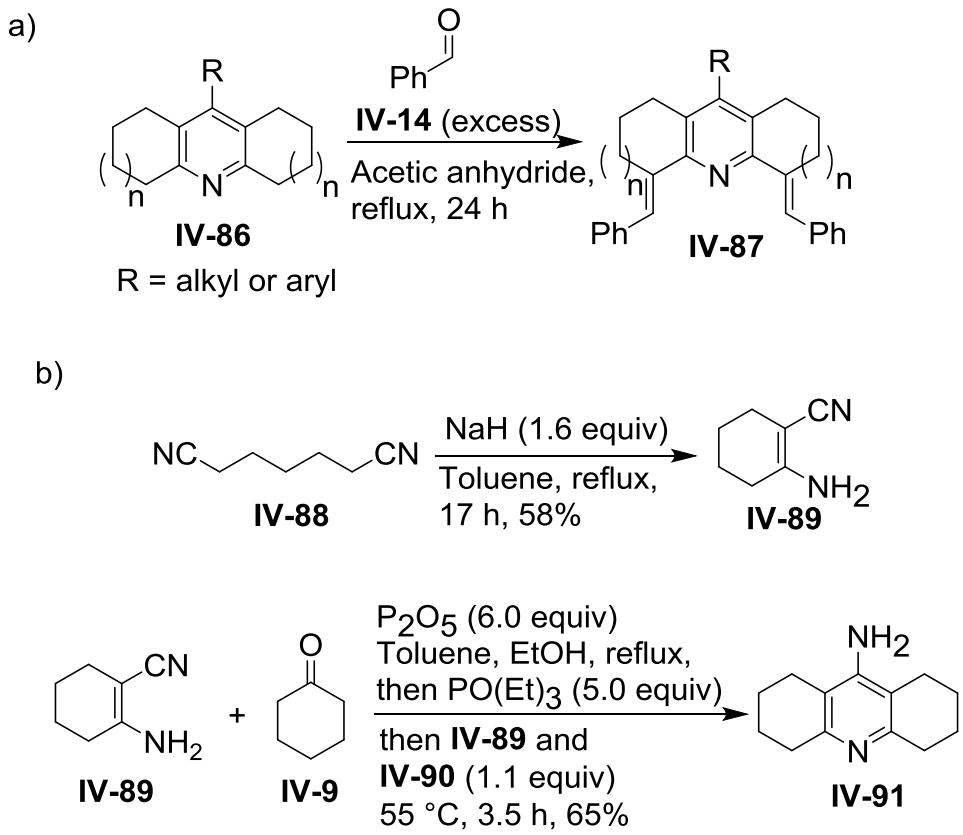
Figure IV-16. Crystal structure of **IV-68** and (L)-tartaric acid (and one molecular of acetonitrile), proving that the absolute stereochemistry of the pyridine in the crystals has the (*S*,*S*)-configuration.

fractional crystallization and were delighted to find that the *ee* of the crystals was 94%, while the filtrate was 60% enriched. During the scale up of this procedure, we were able to acquire higher quality crystals during the fractional crystallization. By using X-ray crystallography, we were able to determine that the absolute stereochemistry of the scaffold in this precipitate had the (*S,S*)-configuration (Figure IV-17).

After successfully acquiring a novel, chiral C_2-symmetric pyridine scaffold, we contemplated screening reactions to see if the new scaffold would induce enantioselectivity. At the same time, we developed an idea for the synthesis of a morenucleophilic C_2-symmetric scaffold. Due to time limitations, we decided that the synthesis would be a more practical project.

IV-4 Synthetic Efforts Towards a Novel, Chiral C_2-Symmetric 4-Amino Pyridine Catalyst

With the knowledge base of common transformations for both the 5,5- and 6,6-annelated pyridine scaffolds in hand, we considered synthetic routes to develop a much more nucleophilic 4-amino pyridine catalyst scaffold. Several approaches to access this motif were contemplated during the time of the project, however finally a reasonable one was envisioned. This route was based on a functionalization commonly observed with bis-annelated pyridine scaffolds, a bis-condensation reaction using benzaldehyde in refluxing acetic anhydride to form the bis-benzylidene adduct **IV-87** (Scheme IV-16a). With this transformation in mind, we researched whether the simple 9-aminooctaahydrocridine scaffold (**IV-91**) was easily accessible. We were encouraged when we found that this compound could be accessed in 2 steps from commercially available reagents (Scheme IV-16b). With access to **IV-91,** we envisioned two different catalyst targets, shown in Figure IV-18. One of these would utilize a similar retrosynthesis as one we had tried previously, with **IV-92** coming from the deoxgenation of diol **IV-93**. This diol could arise from the bis-Grignard addition to diketone **IV-94** which would arise from ozonolysis of bis-benzylidene **IV-96**, which comes from alkylation of known compound **IV-91.** The other target, I**V-96,** featuring the diamino groups flanking the pyridine nitrogen, could be accessed via reductive amination of **V-94**. This motif could potentially chelate an electrophile with the pyridine nitrogen and two amino groups.



Scheme IV-16. Literature precedent procedures. a) Condensation reaction to generate bis-benzylidene scaffold **IV-87.** b) Procedure to access target I**V-91.**

Following the reported procedures, we were able to access large quantities of **IV-91** (>10 g). We initially tried to alkylate the amino group, to give the dialkylamino substituent using reductive amination conditions. We found that this reaction was slow, only giving trace amounts of product after 3 days, with either sodium cyanoborohydride or Eschenmoser conditions (Scheme IV-17a-b). We also tried a reported procedure for reductive amination with 2,5-dimethoxytetrahydrofuran using sodium borohydride, as the reducing agent, but this gave no reaction after several days (Scheme V-17c). Since all reductive aminations had failed, we turned to simple alkylation procedures, using basic conditions with either ethyl bromide or 1,4-diiodobutane. With ethyl bromide, no

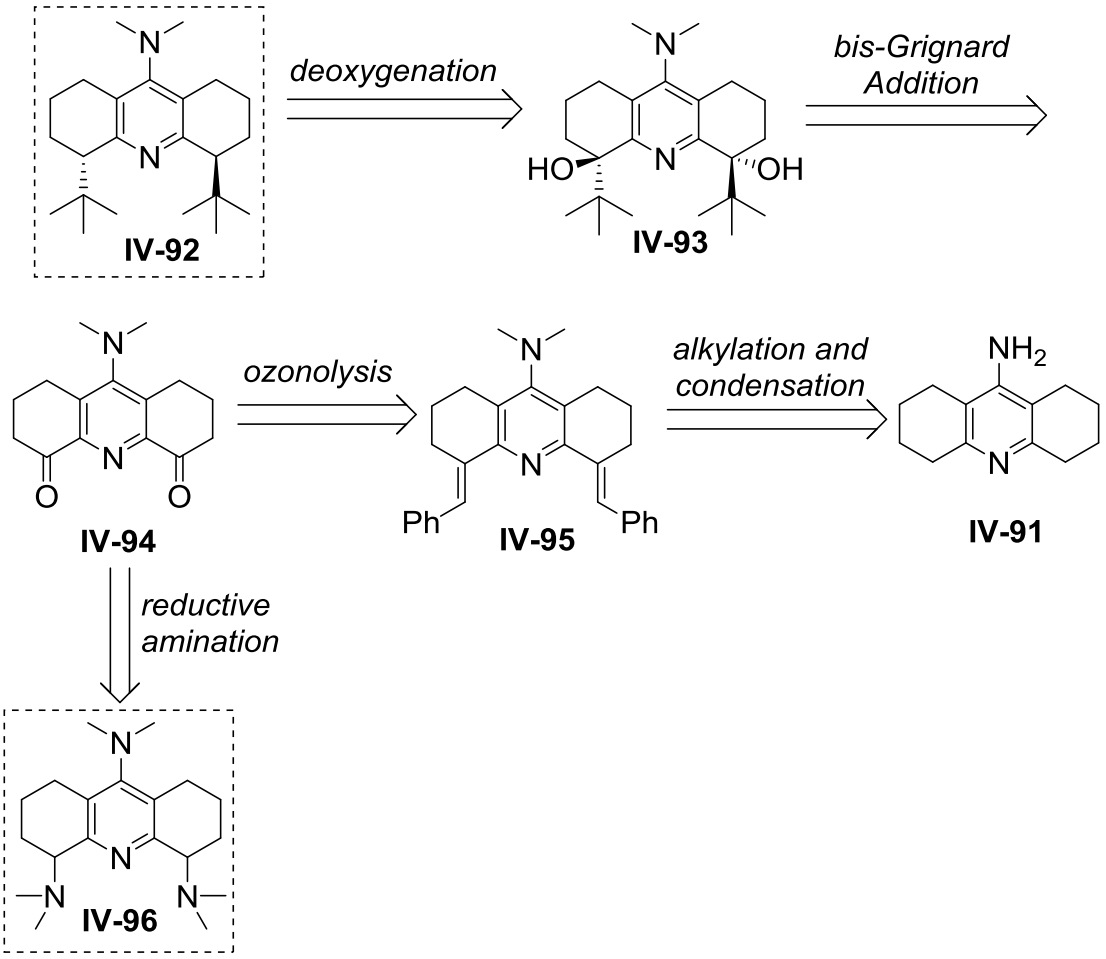
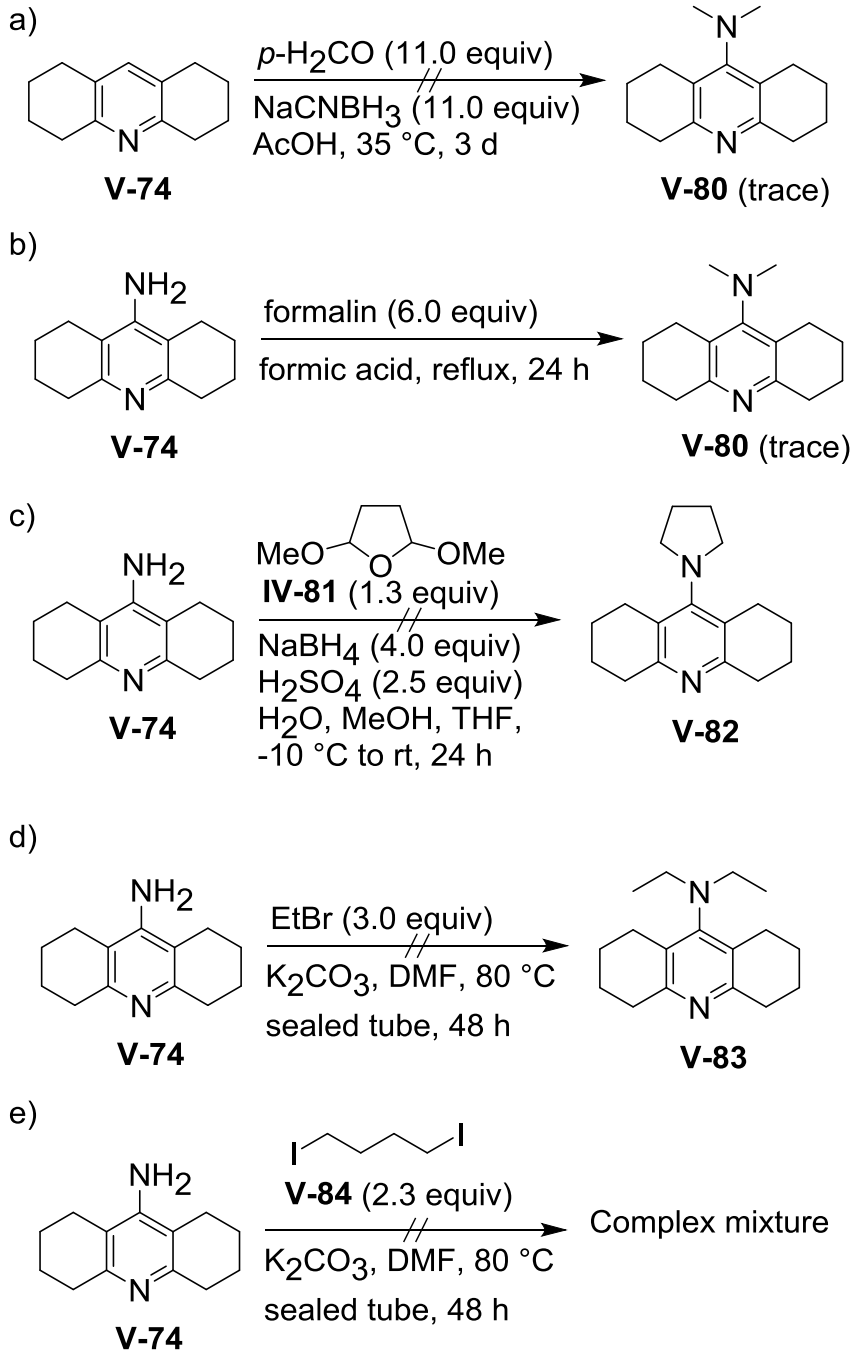


Figure IV-17. Retrosynthetic analysis for 9-amino-octahydroacridine catalysts **IV-93** and **IV-97.**

reaction was observed even after days of heating in a sealed tube. With 1,4-diiodobutane, a complex mixture was obtained which proved challenging to purify. The mixture contained the alkylated pyridine nitrogen, mono alkylated, mono-alkylated with elimination, desired product, and alkylated desired product. After these fruitless attempts, we decided that alkylation of the pyridine nitrogen may not be necessary, since it was proving to be unreactive.

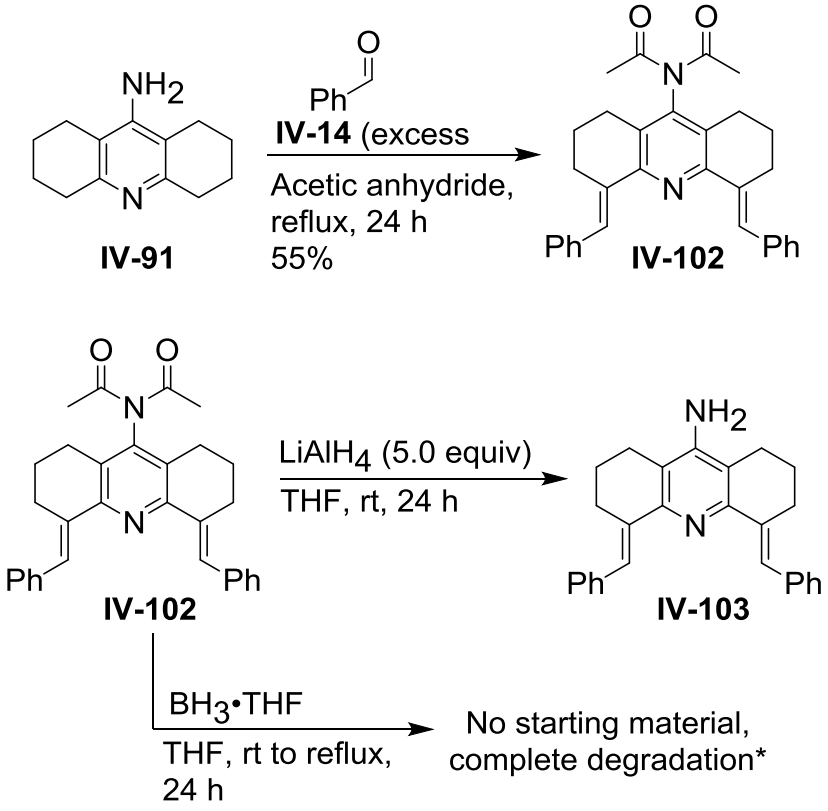
Next, we decided to follow the literature precedent condensation reaction between **IV-91** and benzaldehyde in acetic anhydride.[13, 28, 29] It is important to note



Scheme IV-17. Attempts to alkylated the 9-amino-substituent.

that all the reported scaffolds in the literature have alkyl substituents in the 9-position. We were surprised to find that in addition to the benzylidenes at the α-positions of the pyridine scaffold, the amino group had also been bis-acetylated. With this in hand, we decided to investigate whether the acetyl group could be reduced to give the dialkyl amine. Initially we tried lithium aluminum hydride, which cleanly removed the acetyl groups, giving **IV-103.** We also tried a borane reduction, which gave a number of degradation products, whose masses were unidentifiable by MS.

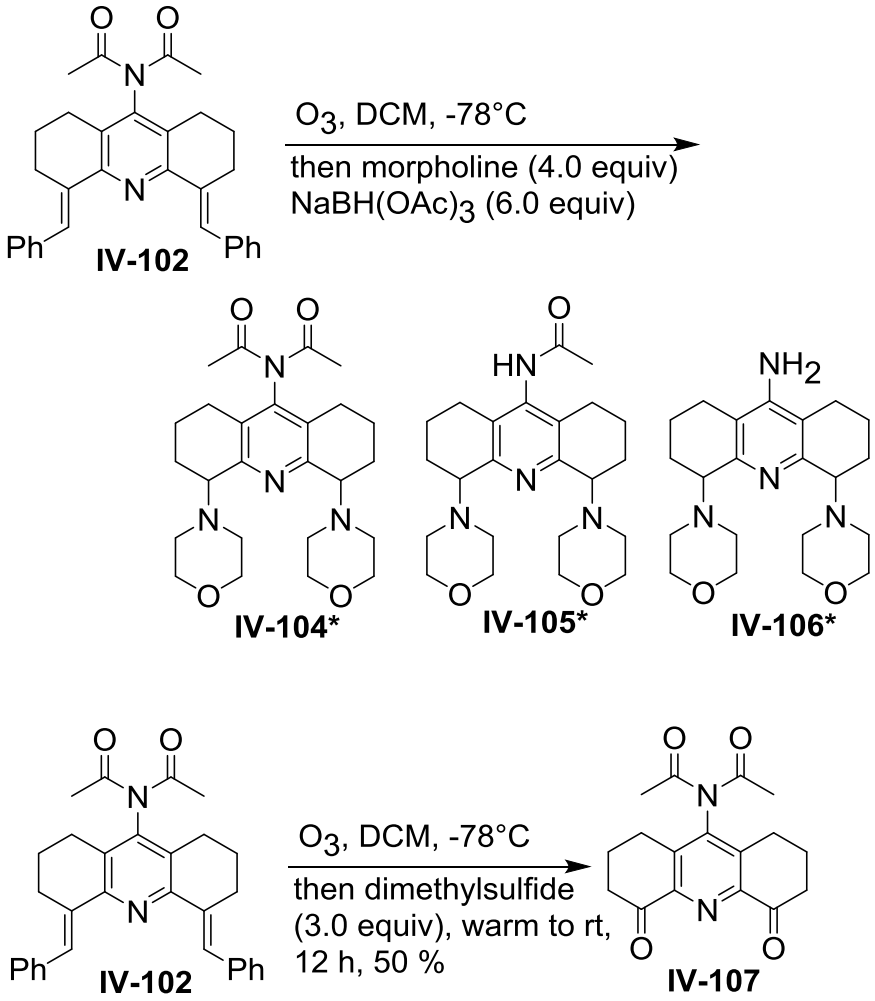
The last transformation we carried out was the ozonolysis of the benzylidene olefins. We were initially hoping that we would be able to carry out a one-pot ozonolysis



Scheme IV-18. Condensation between **IV-91** and benzaldehyde to generate bis-benzylidene I**V-102**. Attempted reductions of N,N-diacetyl pyridine **IV-102.**

*Observed by MS

- reductive amination reaction sequence, but during the first attempt, this reaction gave



Scheme IV-19. Ozonolysis reactions of bis-benzylidene **IV-102.**

a mixture of products including the mono-acetylated and un-acetylated amino groups. Since we were overzealous in our attempt to make this reaction one pot, we then decided to carry out the simple ozonolysis transformation followed by quenching with dimethyl sulfide. This successfully generated diketone **IV-107**, but unfortunately due to timing, that is the current state of the project.

IV-5 Conclusions and Future Work

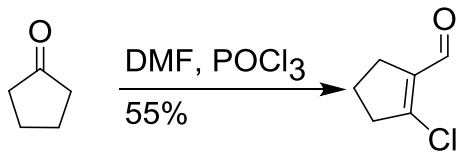
A rigid chiral, C_2-symmetric pyridine was successfully synthesized in an efficient manner, followed by separation of the enantiomers via resolution. Additionally, the ground work for a more nucleophilic chiral C_2 symmetric 4-aminopyridine scaffold has been laid, with two possible routes of functionalization to explore. This project remains in its infancy, with these chiral scaffolds having a variety of applications to asymmetric catalysis. Although the design for the ligand originated as a chiral environment to bind to a halenium, a number of other potential applications include use as a chiral proton source, ionic liquid, or Bronsted base.

IV-6 Experimentals

General Procedures:

All reagents were used without purification. 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. ^{1}H NMR spectra were measured at 300 or 500 MHz on a Varian Gemini-300 or a Varian VXR-500 instrument, respectively. Chemical shifts are reported relative to residual solvent (δ7.24 ppm for $CDCl_3$). 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.

2-chlorocyclopent-1-enecarbaldehyde[28]

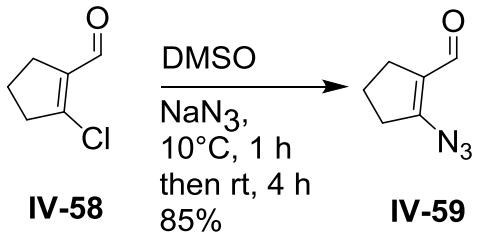


IV-37 **IV-58**

Anhydrous DMF (4.6 mL, 59.4 mmol, 2.0 equiv) was added to a flame-dried 50 mL round bottom flask and was subsequently cooled to 0 °C. $POCl_3$ (4.4 mL, 59.4 mmol, 1.6 equiv) was then slowly added to the flask, resulting in the formation of an orange colored solution, which was stirred for 8 minutes at 0 °C. After this, the reaction was warmed to room temperature using a room temperature water bath, for 7 minutes, favoring formation of the Vilsmeier-Haack reagent. The reaction was then cooled back down to 0 °C and cyclopentanone (2.6 mL, 29.7 mmol) was added dropwise. The solution was stirred at 0 °C for 15 minutes and then at room temperature for 15 minutes. The reaction was quenched by pouring over ice (50 g), and careful neutralization with $NaHCO_3$ (which was added until gas evolution ceased). The product was extracted using diethyl ether (3 x 20 mL), the combined organics were dried over anhydrous sodium sulfate and concentrated. The product was acquired in 55% yield (2.13 g, 16.3 mmol) as a pale yellow oil.

Data for **IV-58 2-chlorocyclopent-1-enecarbaldehyde:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.99 (s, 1H), 2.81-2.78 (m, 2H), 2.59-2.55 (m, 2H), 2.01 (pent, J = 7.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.7, 151.2, 137.3, 40.3, 28.7, 20.5.

2-azidocyclopent-1-enecarbaldehyde[30]

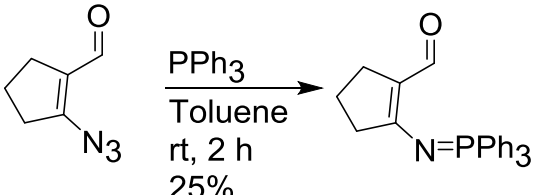


IV-58 **IV-59**

Sodium azide (0.98 g, 16.31 mmol) was dissolved in anhydrous DMSO and was cooled in a 10 °C bath (water with a little ice, monitored by thermometer). A solution of 2-chlorocyclopent-1-enecarbaldehyde (2.13 g, 16.31 mmol) in anhydrous DMSO (8 mL) was slowly added to the azide solution (if the solution froze, it was thawed and then re-cooled, before addition was continued). Following addition of the substrate, the reaction was stirred for 1 hour at 10 °C and then for 4 hours at room temperature. To quench the reaction, water (0.30 mL) was added and the product was extracted with diethyl ether (3 x 25 mL). The combined organics were washed with water (25 mL), brine (25 mL), dried over anhydrous sodium sulfate, and concentrated. The product was purified using column chromatography (10% EtOAc in hexanes to 25% EtOAc in hexanes) giving the product as a yellow oil in 85% yield (1.90 g, 13.9 mmol). *The product was not very stable and was quickly taken on to the next step.*

Data for **IV-59 2-azidocyclopent-1-enecarbaldehyde:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.84 (s, 1H), 2.82-2.77 (m, 2H), 2.59-2.55 (m, 2H), 2.00 (pent, J = 3.4 Hz, 2H).

2-aminocyclopent-1-enecarbaldehyde[30]



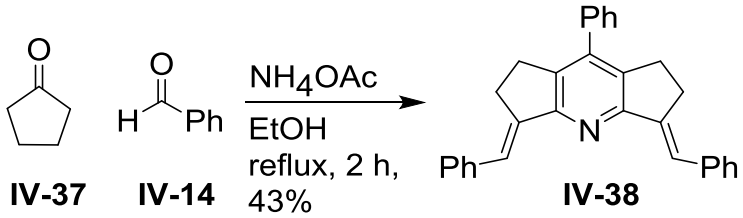
IV-59 **IV-60**

To a flame dried 300-mL round bottom was added 2-azidocyclopent-1-enecarbaldehyde (3.32 g, 24.2 mmol) and dry toluene (70 mL). In a 50 mL flame dried round bottom,

triphenyl phosphine (7.62 g, 29.1 mmol) was dissolved in toluene (58 mL), was then added dropwise to the reaction flask containing the azido substrate. The reaction was stirred at room temperature for 2 hours, during which time a white precipitate began to form. The reaction was placed in the freezer for 30 minutes, then the solid was filtered and recrystallized using DCM and hexanes. The product was obtained as a white solid in 25% yield (2.23 g, 6.01 mmol).

Data for **IV-60 2-aminocyclopent-1-enecarbaldehyde:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.26 (s, 1H), 7.72-768 (m, 6H), 7.52 (td, *J* = 7.1, 1.4 Hz, 3H), 7.48 (td, *J* = 7.9, 3.1 Hz, 6H), 2.48 (t, *J* = 7.2 Hz, 2H), 1.97 (t, *J* = 7.7 Hz, 2H), 1.66 (pent, *J* = *7.6* Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.2, 132.8, 132.7, 132.6, 132.6, 129.2, 129.1, 39.4, 29.2, 21.6.

(3E,5E)-3,5-dibenzylidene-8-phenyl-1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridine[13]



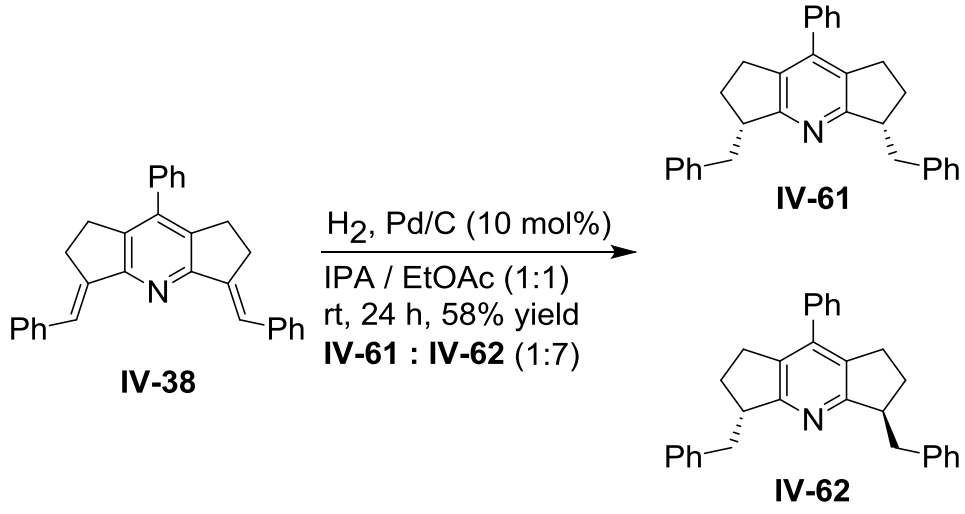
IV-37 **IV-14** **IV-38**

To a flame dried 500 mL round bottom was added benzaldehyde (5.1 mL, 50.1 mmol, 2.0 equiv), cyclopentanone (2.21 mL, 25.0 mmol, 1.0 equiv), ammonium acetate (19.3 g, 249.7 mmol, 5.0 equiv), and ethanol (125 mL). The reaction was refluxed for 2 hours, during which time it turned to a dark brown solution with yellow precipitate. The reaction

was then cooled to room temperature and the yellow precipitate was filtered and thoroughly rinsed with acetone, until the orange color had dissipated. The product was obtained as a pale yellow solid in 43% yield (2.24 g, 5.44 mmol).

Data for **IV-38 (3E,5E)-3,5-dibenzylidene-8-phenyl-1,2,3,5,6,7-hexa-hydrodicyclopenta [b,e] pyridine:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (t, J = 2.6 Hz, 2H), 7.58 (d, J = 7.8 Hz, 4 H), 7.46 (t, J = 7.8 Hz, 2H), 7.41-7.34 (m, 7H), 7.24 (t, J = 7.8 Hz, 2H), 3.17 (td, J = 6.7, 3.6 Hz, 4H), 2.96 (dd, J = 6.7, 3.6 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 143.8, 141.8, 138.1, 137.4, 136.9, 129.2, 128.7, 128.5, 128.2, 128.1, 126.8, 122.1, 29.5, 27.8; mp = 214-216 °C.

***trans*-3,5-dibenzyl-8-phenyl-1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridine**



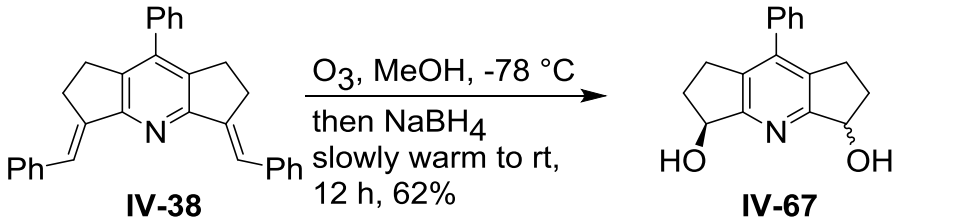
To a flame dried 500 mL round bottom flask was added 2-aminocyclopent-1-enecarbaldehyde, palladium on carbon (0.5 g, 0.71 mmol, 0.12 equiv, 15% w/w palladium on carbon), ethyl acetate (50 mL), and isopropanol (50 mL). The reaction

was vigorously stirred under hydrogen for 24 hours. The reaction was monitored by TLC (4% diethyl ether in hexanes) and when complete, was filtered through a pad of celite, which was thoroughly washed with chloroform. The filtrate was concentrated and was purified via column chromatography (4% diethyl ether in hexanes). The two isomers were acquired in 58% combined yield (1.31 g, 3.15 mmol), in a 1:7 mixture (*trans* / *cis*). (The trans isomer is the less polar compound.)

Data for **IV-61 *cis*-3,5-dibenzyl-8-phenyl-1,2,3,5,6,7-hexahydrodicyclopenta[b,e] pyridine:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.15 (m, 15H), 3.53-3.47 (m, 4H), 2.76-2.62 (m, 6H), 2.08 (tt, *J* = 13.8, 7.5 Hz, 2H), 1.78 (dt, *J* = 13.8, 7.5Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 140.7, 137.6, 133.1, 129.9, 129.3, 128.3, 128.2, 128.2, 127.7, 125.8, 47.0, 40.2, 29.5, 28.1; IR (NaCl plate) v 3061, 3026, 2926, 2851, 1718, 1579, 1496, 1453, 1377 cm^{-1}; HRMS m/z calculated for $C_{31}H_{30}NH^{+}$ $[M+H]^{+}$ 416.2378, observed 416.2377; mp = 115-117 °C.

Data for **IV-62 *trans*-3,5-dibenzyl-8-phenyl-1,2,3,5,6,7-hexahydrodicyclopenta [b,e]pyridine:** ^{1}H NMR (500 MHz, $CDCl_3$) δ7.41-7.38 (m, 2H), 7.34-7.32 (m, 1H), 7.29-7.23 (m, 10H), 7.21-7.18 (m, 2H), 3.59-3.49 (m, 4H), 2.68-2.60 (m, 6H), 2.15-2.08 (m, 2H), 1.76 (td, *J* = 14.5, 7.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 142.7, 141.3, 138.0, 133.1, 129.5, 128.6, 128.6, 128.5, 128.0, 126.1, 47.5, 40.5, 30.2, 28.4; IR (NaCl plate) v 3051, 2918, 2851, 1724, 1664, 1653, 1558, 1494, 1455 cm^{-1}; HRMS m/z calculated for $C_{31}H_{30}NH^{+}$ $[M+H]^{+}$ 416.2378, observed 416.2381; mp= 105-108 °C.

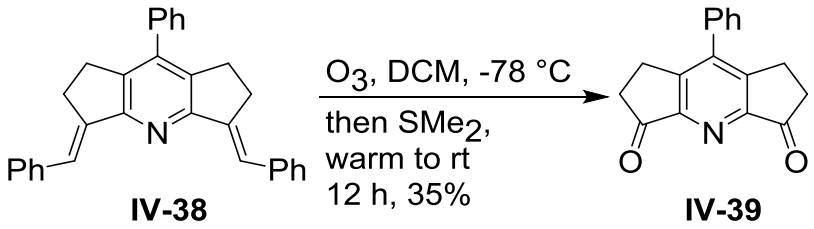
8-phenyl-1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridine-3,5-diol:



To a flame dried 100 mL round bottom flask was added (3E,5E)-3,5-dibenzylidene-8-phenyl-1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridine (1.0 g, 2.43 mmol) and MeOH (12 mL). The yellow reaction contents were cooled to -78 °C using a dry ice / acetone bath and then ozone was bubbled into the reaction until it turned blue in color. Nitrogen gas was then bubbled into the reaction while maintaining the -78 °C temperature to eradicate the remaining ozone. Sodium borohydride (736 mg, 19.5 mmol, 8.0 equiv) was added to the reaction in one portion and the reaction was slowly allowed to warm to room temperature in the cooling bath (~12 hours). The reaction was then cautiously quenched using concentrated HCl to pH = 3. The reaction was filtered through celite, extracted using ethyl acetate (3 x 25 mL), dried over anhydrous sodium sulfate, and concentrated. Column chromatography (75% ethyl acetate in hexanes to 100% ethyl acetate) was used to purify the product which was obtained as a white solid in 62% yield (403 mg, 1.51 mmol). The product was obtained as diastereomeric mixture in a 1.5/1.0 ratio. The identity of the major diastereomer was not confirmed.

Data for **IV-67 8-phenyl-1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridine-3,5-diol (mixture of diasteromers):** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46-7.43 (m, 2H), 7.40-7.37 (m, 1H), 7.31-7.28 (m, 2H), 5.36 (t, *J* = 7.5 Hz, 1.20 H), 5.31 (t, *J* = 6.0 Hz, 0.80 H), 2.97 (ddd, *J* = 13.1, 8.6, 4.1 Hz, 1H), 2.88-2.69 (m, 3H), 2.62-2.55 (m, 1H), 2.54-2.47 (m, 1H), 2.10-1.97 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3, 164.2, 144.7, 144.7, 134.3, 134.0, 128.5, 128.3, 128.2, 128.2, 74.2, 74.1, 32.9, 32.8, 26.9, 26.7; HRMS m/z calculated for $C_{17}H_{17}NO_2H^+$ $[M+H]^+$ 268.1338, observed 268.1337; mp = 160 °C (decomposed).

8-phenyl-1,2,6,7-tetrahydrodicyclopenta[b,e]pyridine-3,5-dione[13]



IV-38 **IV-39**

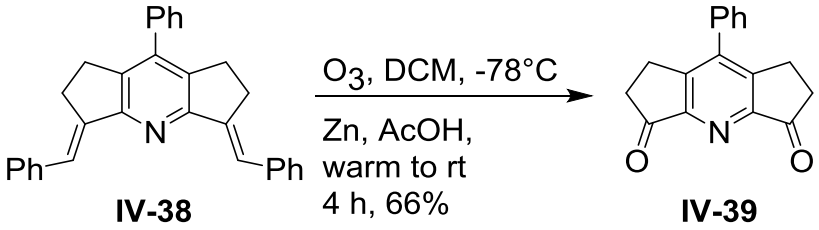
Procedure A:

To a flame dried 100 mL round bottom flask was added (3E,5E)-3,5-dibenzylidene-8-phenyl-1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridine (150 mg, 0.365 mmol) and anhydrous DCM (45 mL). The yellow reaction contents were cooled to -78 °C using a dry ice /acetone bath, and then ozone was bubbled into the reaction until it turned blue

in color. Nitrogen gas was then bubbled into the reaction while maintaining the -78 °C temperature to eradicate remaining ozone and then dimethyl sulfide (78 µL, 1.06 mmol, 2.91 equiv) was added. The reaction was allowed to warm to room temperature and was stirred under nitrogen gas for 12 hours. The reaction was then concentrated and column chromatography (50% EtOAc in hexanes, crude material absorbed on silica gel) gave the product in 35% yield (34 mg, 128 mmol). *This product is not stable, it rapidly turns black if the ozonolysis reaction is more concentrated or if the product is dissolved in DCM.*

Data for **IV-39 8-phenyl-1,2,6,7-tetrahydrodicyclopenta[b,e]pyridine-3,5-dione:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57-7.37 (m, 5H), 3.11-3.09 (m, 4H), 2.81-2.79 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) 203.9, 155.8, 150.4, 148.2, 133.4, 129.4, 129.3, 127.8, 35.7, 23.1; mp = 216-218 °C.

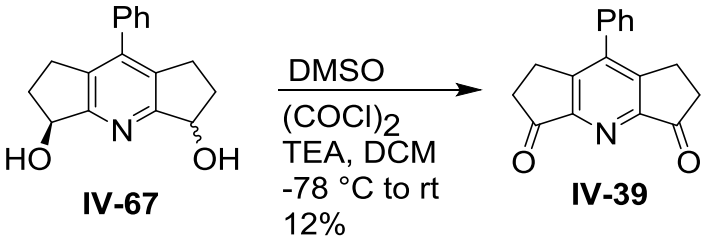
Procedure B:



To a flame dried 500 mL round bottom flask was add (3E,5E)-3,5-dibenzylidene-8-phenyl-1,2,3,4,5,6-hexhydrodicyclopenta[b,e]pyridine (5.2 g, 12.6 mmol) and anhydrous DCM (200 mL). The yellow reaction contents were cooled to -78 °C using a dry ice/ acetone bath and then ozone was bubbled into the reaction until it turned blue in color.

Nitrogen gas was then bubbled into the reaction, while maintaining the –78 °C temperature, to eradicate remaining ozone and then zinc dust (4.91 g, 75.6 mmol, 6.0 equiv) and a solution of 1:1 acetic acid / water (250 mL) were used to quench the reaction. Following their addition at -78 °C, the reaction was slowly allowed to warm to room temperature. After stirring for 4 hours, the reaction was filtered through a pad of celite and the filtrate was carefully neutralized with sodium bicarbonate. The filtrate was then extracted using ethyl acetate (3 x 50 mL), the combined organics were washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated. Column chromatography (50% EtoAc in hexanes, crude material absorbed on silica gel) was used to purify the product, giving it as an off-white solid in 66% yield (2.18 g, 8.30 mmol). *For characterization data, see Procedure A.*

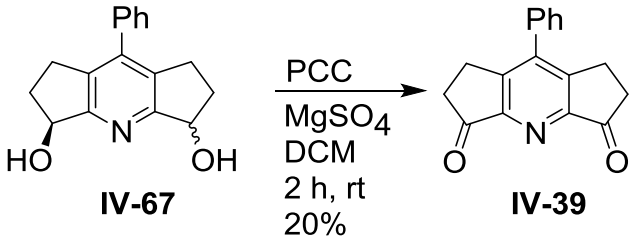
Procedure C:



To a flame dried 500 mL round bottom flask was added anhydrous DMSO (6.18 mL, 87.1 mmol, 4.5 equiv) and oxalyl chloride (3.74 mL, 43.6 mmol, 2.25 equiv). The contents of this flask were cooled to -78 °C using a dry ice / acetone bath. In a separate flame-dried 25 mL round bottom, was added 8-phenyl-1,2,3,5,6,7-

hexahydrodicyclopenta[b,e]pyridine-3,5-diol (5.19 g, 19.4 mmol) and anhydrous DCM (5 mL). This solution was added dropwise to the oxalyl chloride / DMSO solution using a cannula. Following the addition, the reaction was stirred for 10 minutes at -78 °C. Then triethylamine (24.2 mL, 173.8 mmol, 9 equiv) was added and the reaction was slowly warmed to room temperature. Upon warming the reaction, it changed from pale yellow to dark brown in color. The reaction was then diluted with diethyl ether (200 mL) and washed with brine (3 x 50 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated. Column chromatography (50% EtOAc in hexanes) gave the product as a white-solid in 12% yield (612 mg, 2.33 mmol). *For characterization data, see Procedure A.*

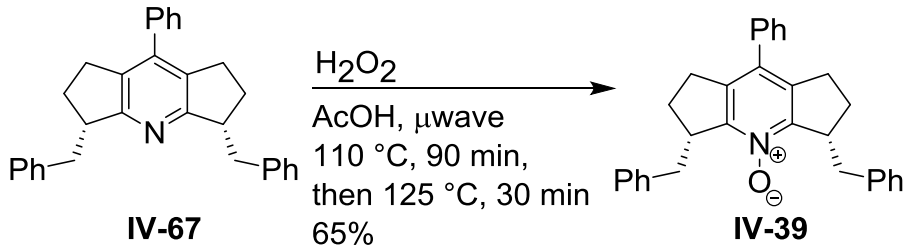
Procedure D:



To a flame dried 100 mL round bottom was added PCC (0.319 mg, 1.48 mmol, 4.39 equiv) and anhydrous magnesium sulfate (1.59 g). Anhydrous DCM (25 mL) was added, creating an orange slurry, which was vigorously stirred. In one portion, 8-phenyl-1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridine-3,5-diol (90 mg, 0.337 mmol) was added to the reaction, and it quickly turned dark brown in color. The reaction was

quenched after 2 hours by adding anhydrous diethyl ether (25 mL) to precipitate the PCC. After 2 minutes of vigorous stirring, the reaction was filtered through a pad of celite, rinsing repeatedly with DCM (100 mL). The filtrate was concentrated and a short column (50% EtOAc in hexanes) was used to obtain the product which was a white solid in 20% yield (18 mg, 0.067 mmol). *For characterization data, see Procedure A.*

***cis*-3,5-dibenzyl-8-phenyl-1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridine 4-oxide**

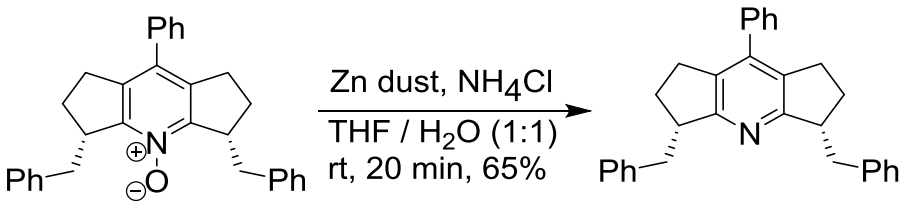


To a 10 mL microwave vial was added a *cis*-3,5-dibenzyl-8-phenyl-1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridine (50 mg, 0.121 mmol), acetic acid (0.5 mL), and hydrogen peroxide (0.25 mL, 30% aqueous solution). The vial was sealed and was heated in the microwave to 110 °C for 90 minutes and 125 °C for 30 minutes. The reaction was concentrated and then extracted using chloroform (3 x 10 mL), the combined organics were dried over anhydrous sodium sulfate, and concentrated. Column chromatography (4% diethyl ether in hexanes) gave the product as a yellow oil in 65% yield (34 mg, 0.079 mmol).

Data for **IV-39 *cis*-3,5-dibenzyl-8-phenyl-1,2,3,5,6,7-hexahydrodicyclopenta[b,e] pyridine 4-oxide:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.33 (m, 2H), 7.31-7.26 (m, 4H), 7.22-7.17 (m, 4H), 7.20-7.17 (m, 2H), 7.09-7.06 (m, 2H), 3.92 (t, *J* = 8.7 Hz, 2H), 3.55

(dd, *J* = 13.3, 3.5 Hz, 2H), 2.94 (dd, *J* = 13.3, 8.8 Hz, 2H), 2.59-2.52 (m, 4H), 2.13-2.06 (m, 2H), 1.98-1.93 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 153.0, 140.0, 138.7, 136.5, 129.4, 128.5, 128.4, 128.3, 128.2, 128.1, 126.1, 43.7, 36.1, 29.1, 27.9; IR (NaCl plate) v 3088, 1063, 3027, 2926, 2854, 1726, 1497, 1454, 1426, 1282, 1169, 1047 cm^{-1}, HRMS m/z calculated for $C_{31}H_{29}NOH^+$ $[M+H]^+$ 432.2327, observed 423.2342.

***cis* -3,5-dibenzyl-8-phenyl-1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridine**

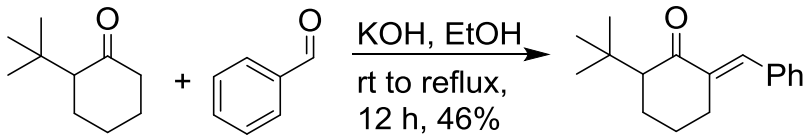


IV-63 **IV-61**

To a 5 mL round bottom was added *cis*-3,5-dibenzyl-8-phenyl-1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridine 4-oxide (28 mg, 0.065 mmol) and THF (1 mL). Ammonium chloride (0.3 g, 0.006 mmol) dissolved in water (1 mL) was then added to the reaction followed by zinc dust (19 mg, 0.291 mmol, 4.5 equiv). The reaction was stirred at room temperature for 20 minutes. The reaction was monitored by TLC (4% diethyl ether in hexanes). The reaction was quenched by filtration on Celite which was with diethyl ether (50 mL). The organic layer was then separated and the aqueous layer was washed with diethyl ether (3 x 25 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The product was purified using column chromatography (4% diethyl ether in hexanes) giving the product as an off-white solid in 65% yield (18 mg, 0.042 mmol).

For characterization data, see above.

(E)-2-benzylidene-6-(tert-butyl)cyclohexanone[31]

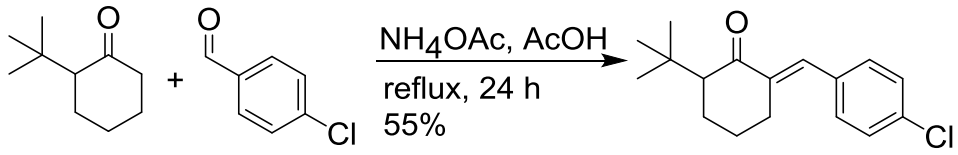


IV-70 **IV-14** **IV-75**

Procedure A: To a 50 mL round bottom flask was added KOH (1.30 g, 23.2 mmol, 2 equiv), ethanol (13.5 mL) and water (2.5 mL). 2-tert-Butylcyclohexanone (2.0 mL, 11.6 mmol) was added in one portion and the reaction was stirred at room temperature for 10 minutes. The reaction was then heated to reflux for 12 hours. To quench the reaction, it was cooled to room temperature and was then neutralized using 1N HCl. The product was extracted using dichloromethane (3 x 25 mL), the combined organics were dried over anhydrous sodium sulfate, and concentrated. Column chromatography (hexanes) was used to obtain the product as a yellow oil in 46% yield (1.29 g, 5.33 mmol).

Data for **IV-75 (Z)-2-benzylidene-6-(tert-butyl)cyclohexanone:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.34 (m, 4H), 7.28 (ddd, *J* = 8.8, 6.4, 1.7 Hz, 1H), 7.22 (t, *J* = 2.3 Hz, 1H), 2.93-2.87 (m, 1H), 2.71-2.64 (m, 1H), 2.27-2.24 (m, 1H), 2.10-2.06 (m, 1H), 1.91-1.85 (m, 1H), 1.70-1.62 (m, 1H), 1.57-1.48 (m, 1H), 1.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) 204.9, 139.9, 136.1, 133.2, 130.1, 128.3, 128.2, 57.5, 33.9, 29.0, 28.1, 25.5, 22.7.

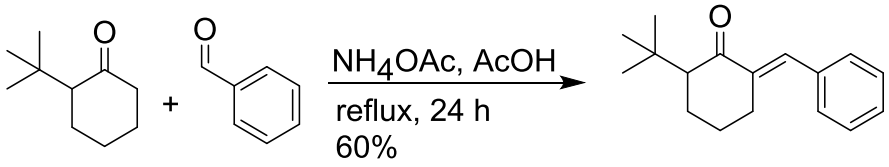
Procedure B:



IV-70 **IV-79** **IV-80**

To a flame dried 500 mL round bottom flask was added 2-tert-butylcyclohexanone (15 mL, 87.1 mmol), benzaldehyde (13.3 mL, 130.5 mmol), ammonium acetate (150 g), and acetic acid (105 mL). The reaction was heated to reflux for 24 hours. The reaction was then cooled to room temperature and extracted with chloroform (3 x 100 mL). The combined organics were then washed with water (3 x 200 mL), dried over anhydrous sodium sulfate, and concentrated. The crude residue was purified via column chromatography (hexanes) or by vacuum distillation. The product was obtained as a yellow oil in 60% yield (12.7 g, 52.3 mmol). *For characterization data, see Procedure A.*

(E)-2-(tert-butyl)-6-(4-chlorobenzylidene)cyclohexanone



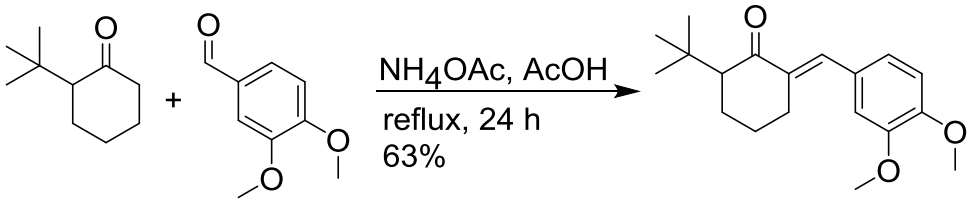
IV-70 **IV-14** **IV-75**

This substrate was synthesized using Procedure B. The crude yellow solution was purified using column chromatography (hexanes). After the column, traces of both the ketone and aldehyde were found to be contaminates in the product, so vacuum

distillation was used to eliminate them from the product. The product was given as a yellow oil in 55% yield.

Data for **IV-80 (E)-2-(tert-butyl)-6-(4-chlorobenzylidene)cyclohexanone:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.34 (m, 4H), 7.20-7.19 (t, *J* = 2.3 Hz, 1H), 2.92-2.87 (m, 1H), 2.72-2.68 (m, 1H), 2.30 (dd, *J* = 10.9, 7.2 Hz, 1H), 2.15-2.11 (m, 1H), 1.96-1.91 (m, 1H), 1.74-1.67 (m, 1H), 1.63-1.53 (m, 1H), 1.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7, 140.4, 134.5, 134.1, 131.9, 131.3, 128.6, 57.5, 33.9, 29.1, 28.1, 25.5, 22.7; IR (NaCl plate) v 2955, 2868, 1678, 1599, 1491, 1258, 1145, 1093, 1012, 831 cm^{-1}; HRMS m/z calculated for $C_{17}H_{22}OCl^{+}$ $[M+H]^{+}$ 277.1359, observed 277.1360.

(E)-2-(tert-butyl)-6-(3,4-dimethoxybenzylidene)cyclohexanone



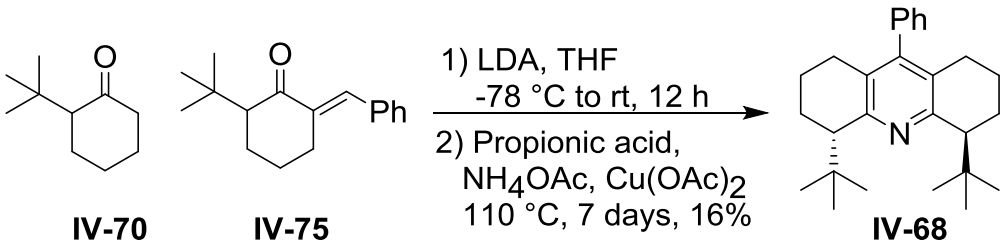
IV-70 **IV-82** **IV-83**

This substrate was synthesized using Procedure B. The substrate was purified using column chromatography (5% ethyl acetate in hexanes). The product was obtained in 63% yield as a yellow oil.

Data for **IV-83 (E)-2-(tert-butyl)-6-(3,4-dimethoxybenzylidene)cyclohexanone:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (t, *J* = 1.9 Hz, 1H), 7.00 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.92 (d, *J* = 1.9 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 2.91-2.86 (m, 1H), 2.70-2.63 (m, 1H), 2.22 (dd, *J* = 10.9, 7.3 Hz, 1H), 2.05-2.02 (m, 1H), 1.90-1.85

(m, 1H), 1.65-1.61 (m, 1H), 1.53-1.47 (m, 1H), 0.98 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) 205.0, 149.5, 148.8, 138.1, 133.7, 129.2, 123.8, 113.7, 111.1, 57.5, 56.1, 56.1, 34.3, 29.4, 28.3, 25.7, 22.9; IR (NaCl plate) v 3004, 2953, 2867, 2825, 1672, 1593, 1510, 1464, 1253, 1143, 1026 cm^{-1}; HRMS m/z calculated for $C_{19}H_{27}O_3H^+$ $[M+H]^+$ 303.1960, observed 303.1953.

4,5-di-tert-butyl-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridine



IV-70 **IV-75** **IV-68**

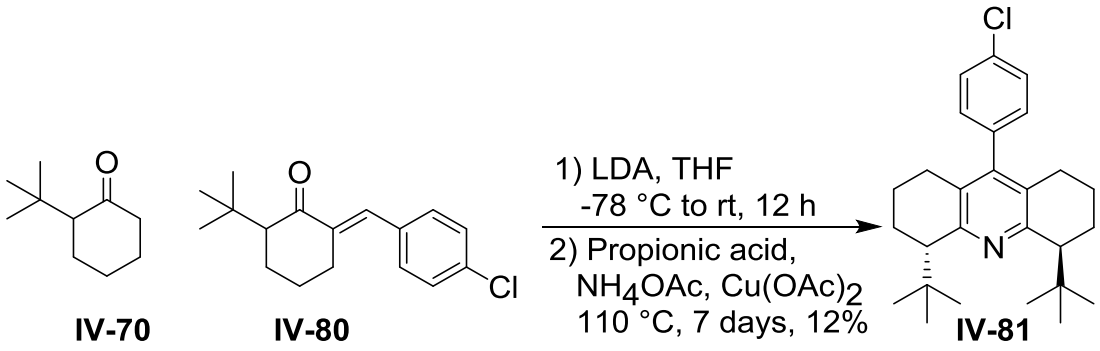
To a flame dried 1000 mL round bottom flask was added freshly distilled diisopropyl amine (5.6 mL, 39.8 mmol, 1.2 equiv) and anhydrous THF (164 mL). The solution was cooled to -78 °C using a dry ice / acetone bath and then *n*BuLi (24.0 mL, 33.1 mmol, 1.0 equiv, 1.38 M in hexanes) was added dropwise. The reaction was then stirred at -78 °C for 10 minutes, it was then warmed to 0 °C using an ice bath for 15 minutes, and then cooled back down to -78 °C. Next, 2-tert-butylcyclohexanone (5.71 mL, 33.1 mmol) was dissolved in anhydrous THF (11 mL) and was added dropwise to the LDA solution at -78 °C. Following the addition of the substrate, the reaction was allowed to stir at -78 °C for 2 hours. (E)-2-Benzylidene-6-(tert-butyl)cyclohexanone (8.03 g, 33.1 mmol) was then dissolved in anhydrous THF (11 mL), and was added dropwise to the enolate

solution. Following the addition of the benzylidene substrate, the reaction was stirred at -78 °C for 10 minutes, and then was slowly warmed to room temperature. The reaction was stirred at room temperature for 18 hours, at which time TLC analysis (4% EtOAc in hexanes, $KMnO_4$ burn) indicated the reaction was complete. The reaction was quenched by slowly adding propionic acid (102 mL), ammonium acetate (25 g, 324 mmol, 9.8 equiv), and copper acetate (19.8 g, 109 mmol, 3.3 equiv). The THF was then distilled from the reaction, followed by heating the reaction to 110 °C for 7 days. Notes: *The reaction is most efficiently monitored by ^{1}H NMR analysis, because the propionic acid makes TLC analysis difficult, in addition to the complicated mixture of compounds formed during the reaction. Additionally, it was found that heating above 110 °C leads to decomposition of the ammonium acetate and shuts down the reaction completely. The addition of excess ammonium acetate throughout the reaction is beneficial.* After one week's time, the reaction is cooled to room temperature and 250 mL of water is added. The reaction mixture is extracted with ammonium hydroxide (5 x 100 mL) until the aqueous layer does not acquire a blue hue. The organic layer is then dried over anhydrous sodium sulfate and concentrated. Two separate columns (first: 100% hexanes, second: 100% petroleum ether) are used to purify the product, which is obtained as a yellow solid in 16% yield (2.01 g, 5.30 mmol).

Data for **IV-68 4,5-di-tert-butyl-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridine:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (t, J = 7.2 Hz, 2H), 7.33-7.31 (m, 1H), 7.09-7.08 (m, 2H), 2.85 (t, J = 8.2 Hz, 2H), 2.27 (ddd, J = 16.0, 10.8, 4.8 Hz, 2H), 2.16-2.10 (m, 2H), 1.99-1.95 (m, 2H), 1.79-1.74 (m, 2H), 1.68-1.58 (m, 2H), 1.34-1.25 (m, 2H), 0.99 (s, 18H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 154.9, 146.1, 139.4, 129.0, 128.3, 126.9, 49.5, 35.5, 28.9, 28.3, 26.6, 22.8; IR (NaCl plate) v 3069, 3032, 2953, 2872, 1724, 1399, 1363, 1226, 1128, 1072, 702 cm^{-1}; HRMS m/z calculated for $C_{27}H_{37}NH^+$ $[M+H]^+$ 376.3004, observed 376.3004; mp = 54-56 °C. (Relative stereochemistry confirmed via X-ray crystallography.)

4,5-di-tert-butyl-9-(4-chlorophenyl)-1,2,3,4,5,6,7,8-octahydroacridine



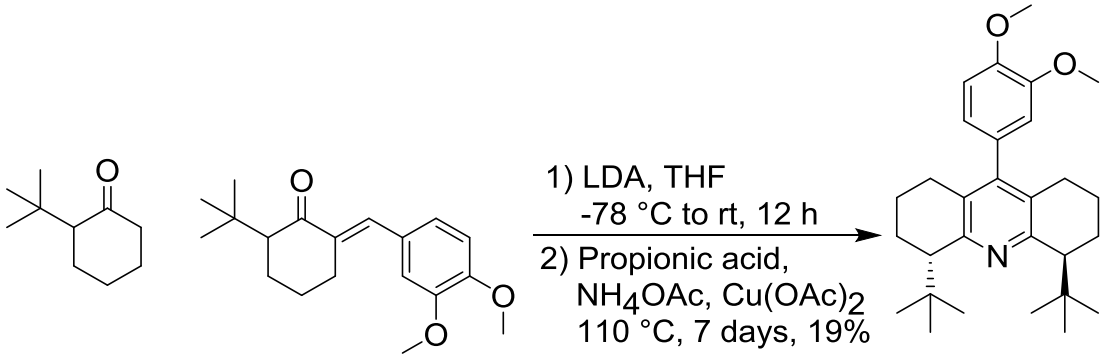
IV-70 **IV-80** **IV-81**

This substrate was synthesized using the same procedure as was used to make 4,5-di-tert-butyl-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridine. This compound is a yellow solid which was obtained in 12% yield.

Data for **IV-81 4,5-di-tert-butyl-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridine:** ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (d *J* = 6.4 Hz, 2H), 7.02 (d, *J* = 8.3 Hz, 2H), 2.84 (t, *J* = 8.3 Hz, 2H), 2.27-2.21 (m, 2H), 2.10-2.06 (m, 2H), 1.97-1.95 (m, 2H), 1.78-1.76 (m, 2H), 1.63-1.54 (m, 2H), 1.31-1.27 (m, 2H), 0.97 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) 155.1, 145.8, 137.7, 132.8, 130.5, 128.6, 128.2, 49.4, 35.5, 28.8, 28.3, 26.5, 22.8; IR (NaCl

plate) v 3063, 2948, 2864, 1726, 1597, 1556, 1491, 1392, 1363, 1089, 1016, 835 cm^{-1}; HRMS m/z calculated for $C_{27}H_{36}NClH^+$ $[M+H]^+$ 410.2615, observed 410.2622; mp = 89-90 °C.

4,5-di-tert-butyl-9-(3,4-dimethoxyphenyl)-1,2,3,4,5,6,7,8-octahydroacridine



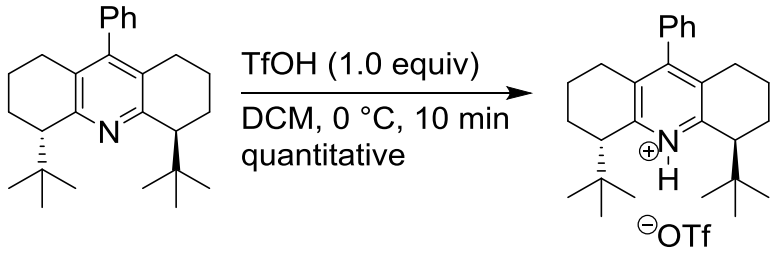
IV-70 **IV-80** **IV-84**

This substrate was synthesized using the same procedure as was used to make 4,5-di-tert-butyl-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridine. This compound is a yellow solid obtained in 19% yield.

Data for **IV-84 4,5-di-tert-butyl-9-(3,4-dimethoxyphenyl)-1,2,3,4,5,6,7,8-octahydro acridine:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (d, *J* = 8.2 Hz, 1H), 6.62-6.58 (m, 2H), 3.90 (s, 3H), 3.84 (s, 3H), 2.83 (t, *J* = 8.2 Hz, 2H), 2.32-2.25 (m, 2H), 2.18-2.14 (m, 2H), 1.98-1.95 (m, 2H), 1.79-1.75 (m, 2H), 1.66-1.61 (m, 2H), 1.29 (q, *J* = 11.8 Hz, 2H), 1.00 (s, 9H), 0.94 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) 154.9, 154.99, 148.7, 148.8, 146.8, 131.9, 128.6, 128.5, 121.3, 112.3, 110.9, 56.0, 55.8, 50.9, 49.5, 49.4, 35.5, 35.5, 28.9, 28.8, 28.3, 28.3, 28.3, 26.6, 26.6, 22.9; IR (NaCl plate) v 3063, 2950, 2869, 1732, 1514, 1394, 1250, 1232, 1136, 1030 cm^{-1}; HRMS m/z calculated for $C_{29}H_{41}NO_2H^+$ $[M+H]^+$

436.3216, observed 436.3199; mp = 52-54 °C. (Relative stereochemistry confirmed via X-ray crystallography.)

4,5-di-tert-butyl-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridin-10-ium



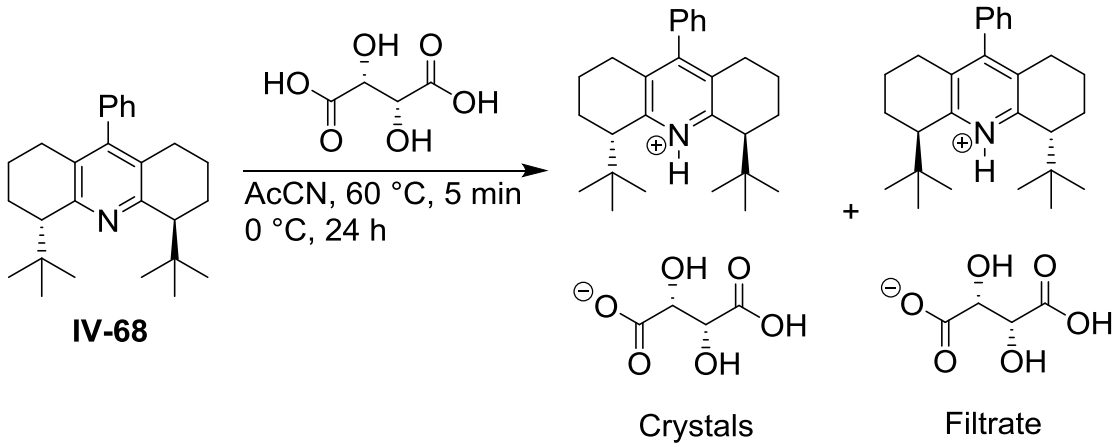
IV-68 **IV-78**

To a flame dried 25 mL round bottom flask was added 4,5-di-tert-butyl-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridine (50 mg, 0.132 mmol). The contents of the flask were cooled to 0 °C using an ice bath and then a solution of triflic acid (12 µL, 0.132 mmol, 1.0 equiv) in anhydrous diethyl ether (3 mL) was added dropwise. The reaction was stirred at 0 °C for 10 minutes and then was concentrated, giving the product as a yellow solid. The yellow solid was recrystallized from methanol to give the product as yellow crystals in quantitative yield (69 mg, 0.132 mmol).

Data for **IV-78 4,5-di-tert-butyl-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridin-10-ium:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53-7.49 (m, 3H), 7.13 (d, J = 6.4 Hz, 2H), 3.58 (dd, J = 7.7, 2.1 Hz, 2H), 2.55-2.50 (m 2H), 2.32-2.31 (m, 2H), 2.12-2.09 (m, 2H), 1.98-1.93 (m, 4H), 1.29-1.24 (m, 2H), 0.89 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0 (q), 157.8,

155.7, 138.8, 137.2, 132.2, 131.8, 131.0, 47.6, 40.6, 30.4, 30.1, 25.8, 24.6; IR (NaCl plate) 3245, 3067, 3030, 2959, 2876, 2720, 1773, 1734, 1668, 1481, 1178, 1030, 798 cm^{-1}.

Resolution of **4,5-di-tert-butyl-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridine**



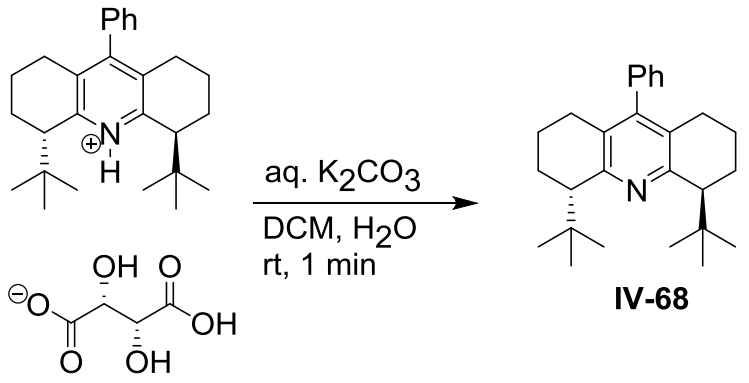
To a 100 mL round bottom flask was added L-tartaric acid (0.701 g, 4.67 mmol, 1.75 equiv) and acetonitrile (35 mL). The contents of the round bottom were heated using a heat gun until the tartaric acid dissolved. 4,5-Di-tert-butyl-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridine (1.00 g, 2.66 mmol) was then added in, and the contents of the round bottom were heated once again to reflux using a heat gun for 5 minutes. After heating, the flask was slowly cooled to room temperature and then a closed with a rubber septum. The rubber septum was equipped with a pink needle to allow for ventilation and then the flask was placed in the freezer for 24 hours. After 24 hours, the colorless crystals (399 mg) were filtered and washed with cold acetonitrile (25 mL). The filtrate was concentrated (632 mg) giving a yellow oil. Both diastereomers were characterized

without further purification. *Note: The higher observed optical rotation of the filtrate is most likely attributable to the presence of excess tartaric acid.*

Data for **(4S,5S)-4,5-di-tert-butyl-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridin-10-ium (2R,3R)-3-carboxy-2,3-dihydroxypropanoate** (crystals): ^{1}H NMR (500 MHz, CD_3CN) δ 7.46-7.40 (m, 3H), 7.13-7.11 (m, 2H), 5.35 (br, 16H), 4.35 (s, 6H), 3.10 (dd, *J* = 11.5, 7.9 Hz, 2H), 2.42-2.35 (m, 2H), 2.16-2.11 (m, 2H), 1.97-1.94 (m, 2H), 1.85-1.82 (m, 6H), 0.91 (s, 18H); ^{13}C NMR (125 MHz, CD_3CN) δ 174.0, 153.4, 136.5, 135.8, 129.9, 129.8, 129.5, 72.8, 47.6, 37.8, 28.4, 28.3, 24.9, 22.6; IR (NaCl plate) 3158, 2950, 2867, 2657, 1736, 1617, 1366, 1300, 1246, 1211, 1138, 1078, 997, 855 cm^{-1}; $[\alpha]^{20}_{D}$ = -18.2 ° (*c* = 10 mg / mL, MeOH); mp = 151-154 °C. (Absolute stereochemistry determined via X-ray crystallography.)

Data for **(4R,5R)-4,5-di-tert-butyl-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridin-10-ium (2R,3R)-3-carboxy-2,3-dihydroxypropanoate** (filtrate): ^{1}H NMR (500 MHz, CD_3CN) δ ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 172.8, 153.3, 153.3, 141.6, 133.7, 129.0, 128.9, 128.7, 72.1, 47.4, 36.7, 27.8, 27.7, 24.7, 22.1; IR (NaCl plate) 3154, 2939, 2872, 1718, 1561, 1442, 1361, 1261, 1211, 1140, 1083 cm^{-1}; $[\alpha]^{20}_{D}$ = + 32.7 ° (*c* = 10 mg / mL, MeOH).

Neutralization of **(4S,5S)-4,5-di-tert-butyl-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridin-10-ium (2R,3R)-3-carboxy-2,3-dihydroxypropanoate (crystals)**

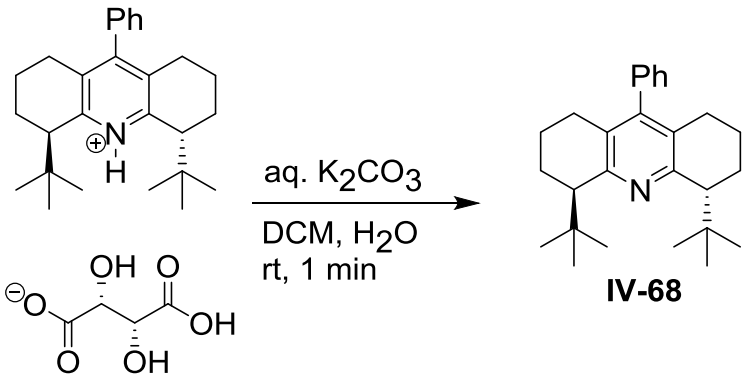


IV-68

(4S,5S)-4,5-Di-tert-butyl-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridin-10-ium (2R,3R)-3-carboxy-2,3-dihydroxypropanoate (399 mg, 0.759 mmol) was added to a 60 mL separatory funnel along with saturated aqueous potassium carbonate (20 mL) and dichloromethane (20 mL). After being shaken, the aqueous layer was removed. The organic layer was washed with water (2 x 10 mL), dried over anhydrous sodium sulfate, and concentrated. The crude material was a white solid obtained in 27% yield (275 mg, 0.732 mmol). The product was characterized with no further purification.

Data for **(4S,5S)- 4,5-di-tert-butyl-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridine** (crystals): *For full characterization data, see rac-4,5-di-tert-butyl-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridine;* $[\alpha]^{20}_{D}$ = -117.4 ° (*c* = 10 mg / mL, $CHCl_3$).

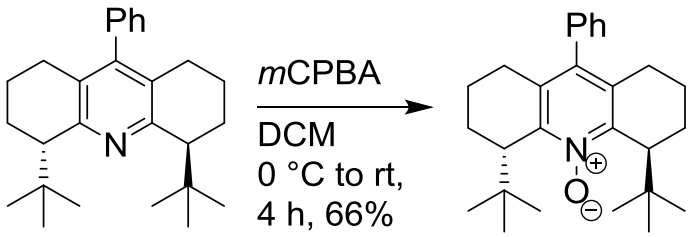
Neutralization of **(4R,5R)-4,5-di-tert-butyl-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridin-10-ium (2R,3R)-3-carboxy-2,3-dihydroxypropanoate (filtrate)**



(4R,5R)-4,5-Di-tert-butyl-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridin-10-ium (2R,3R)-3-carboxy-2,3-dihydroxypropanoate (399 mg, 0.759 mmol) was added to a 60 mL separatory funnel along with saturated aqueous potassium carbonate (40 mL) and dichloromethane (35 mL). After being shaken, the aqueous layer was removed. The organic layer was washed with water (2 x 20 mL), dried over anhydrous sodium sulfate, and concentrated. The crude material was a white solid obtained in 52% yield (525 mg, 1.40 mmol). The product was characterized with no further purification.

Data for **IV-68 (4R,5R)- 4,5-di-tert-butyl-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridine** (filtrate): *For full characterization data, see rac-4,5-di-tert-butyl-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridine*; $[\alpha]^{20}_{D}$ = +61.7 ° (*c* = 10 mg / mL, $CHCl_3$).

Determination of enantiopurity from resolution via synthesis of **(4S,5S)-4,5-di-tert-butyl-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridine 10-oxide**



IV-68 **IV-85**

To a flame dried 25 mL round bottom flask was added 4,5-di-tert-butyl-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridine (50 mg, 0.132 mmol) and anhydrous dichloromethane (4 mL). The reaction was cooled to 0 °C using an ice bath and then the *m*CPBA (90 mg, 0.40 mmol, 77% w/w) was added in in one portion. The reaction was then warmed to room temperature and stirred for 4 hours. The reaction was quenched by adding 40% aqueous sodium thiosulfate (1 mL) and the reaction was extracted with dichloromethane (3 x 10 mL). The combined organics were dried over anhydrous sodium sulfate and concentrated. Column chromatography (10% EtOAc in hexanes) gave the product as a white solid in 66% yield (34 mg, 0.087 mmol).

Data for **(*rac)*-4,5-di-tert-butyl-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridine 10-oxide:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (t, *J* = 7.1 Hz, 2H), 7.35 (t, *J* = 5.2 Hz, 1H), 7.14 (d, *J* = 6.5 Hz, 2H), 4.14 (dd, *J* = 7.3, 5.8 Hz, 2H), 2.45-2.38 (m, 2H), 2.20-2.15 (m, 2H), 1.90-1.87 (m, 4H), 1.82-1.77 (m, 2H), 1.17-1.13 (m, 2h), 0.95 (s, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.4, 137.5, 136.2, 133.7, 129.9, 128.4, 127.6, 39.8, 39.0, 28.7, 27.8, 23.9, 21.9; HRMS m/z calculated for $C_{31}H_{29}NO^+$ $[M+H]^+$ 432.2327, observed 432.2342; IR

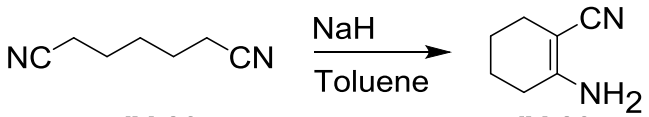
(NaCl plate) 3078, 2953, 2878, 1701, 1576, 1418, 1306, 1264, 1072, 899 cm^{-1}; mp = 144-146 °C.

Resolution of enantiomers: CHIRALCEL AD-H, 1% IPA-hexane, 0.3 mL/min, 254 nm, RT1 = 15.06 min (*S,S*-enantiomer), RT2 = 16.71 min (*R,R*-enantiomer).

Data for **(4S,5S)-4,5-di-tert-butyl-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridine 10-oxide:** $[\alpha]^{20}_D$ = -163.4° (*c* = 10 mg / mL, $CHCl_3$); HPLC analysis found this sample to be 91% *ee.*.

Data for **(4R,5R)-4,5-di-tert-butyl-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridine 10-oxide:** $[\alpha]^{20}_D$ = +100.1° (*c* = 10 mg / mL, $CHCl_3$); HPLC analysis found this sample to be 60% *ee.*.

2-aminocyclohex-1-enecarbonitrile[32]



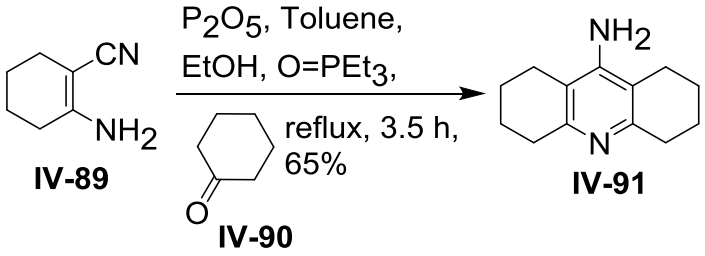
IV-89 **IV-89**

Sodium hydride (4.9 g, 122.5 mmol, 1.6 equiv, 60% in oil) and distilled toluene (130 mL) was added to a flame dried 500 mL round bottom flask. 1,5-Dicyanopentane (10 mL, 77.84 mmol) was then added dropwise to the reaction. The reaction was then heated to reflux for 16 hours. The reaction was monitored by TLC (30% EtoAc in hexanes, $KMnO_4$ charred). The reaction is quenched at reflux temperature by slowly adding ethanol (7 mL), water (33 mL), and acetic acid (5 mL). The reaction was then cooled to room temperature and the aqueous layer was removed. The organic layer was dried

over anhydrous sodium sulfate and concentrated to approximately 75 mL. While the product solution is warm (from rotovap-bath), petroleum ether was added (250 mL). A white precipitate quickly formed, which was filtered immediately, giving 4.42 g of the product. The filtrate was recrystallized in the same fashion, giving 1.13 g of product. The product is a white solid which was given in 58% yield (5.55 g, 45.4 mmol).

Data for **IV-89 2-aminocyclohex-1-enecarbonitrile:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.22 (br, 2H), 2.15-2.09 (m, 4H), 1.65-1.53 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) 156.0, 120.8, 74.2, 28.1, 24.2, 21.9, 21.5; mp = 79-81 °C.

1,2,3,4,5,6,7,8-octahydroacridin-9-amine

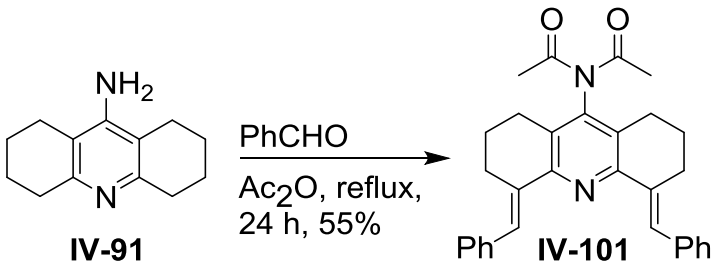


To a flame dried 500 mL round bottom flask was added phosphorus pentoxide (38.65 g, 272.4 mmol, 6.0 equiv) and anhydrous toluene (50 mL). This solution was heated to 55 °C using an oil bath. Triethyl phosphate (38.6 mL, 22.7 mmol, 5.0 equiv) was then added dropwise to the reaction, followed by the addition of anhydrous ethanol (3.92 mL, 68.1 mmol, 1.5 equiv). The reaction was then stirred for 30 minutes at 55°C. The reaction was then cooled to room temperature and for 2-aminocyclohex-1-enecarbonitrile (5.55g, 45.4 mmol, 1.0 equiv) and cyclohexanone (4.9 mL, 47.7 mmol,

1.05 equiv) were added in one portion. The reaction was then heated to 55 °C for 3.5 hours. During this time the reaction changed from colorless to bright orange. The reaction was then cooled to 0°C using an ice bath and then a thermometer was placed in the reaction flask. Water (100 mL) was slowly added, keeping the reaction temperature less than 40 °C. Following the addition of water, the reaction was heated to 55 °C for 30 minutes. The reaction was then cooled to room temperature and the aqueous layer was separated from the organic. The organic layer was washed with water (100 mL) and the combined aqueous layers were then added dropwise into 30% aqueous ammonium hydroxide (200 mL). The resulting mixture was then extracted using a solution of 10:1 chloroform-methanol (5 x 100 mL). The combined organics were dried over anhydrous sodium sulfate and concentrated. The product was purified via recrystallization from acetone-petroleum ether (repeated twice: 1st crystallization obtained 5.10 g, 2nd crystallization obtained 3.81 g), giving the product as a white solid in 65% yield (8.91 g, 44.0 mmol).

Data for **1,2,3,4,5,6,7,8-octahydroacridin-9-amine:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.93 (br, 2H), 2.78 (t, *J* = 6.2 Hz, 4H), 2.40 (t, *J* = 5.7 Hz, 4H), 1.86-1.79 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.4, 148.5, 112.7, 32.7, 23.1, 22.9, 22.7; IR (NaCl plate) 3389, 3149, 296, 2932, 2857, 1730, 1641, 1576, 1437, 1130, 1071 cm^{-1}; HRMS (ESI) m/z calculated for $C_{13}H_{19}N_2^+$ $[M+H]^+$ 203.1548, observed 203.1548; mp = 217-219 °C.

N-acetyl-N-((4E,5E)-4,5-dibenzylidene-1,2,3,4,5,6,7,8-octahydroacridin-9-yl)acetamide



To a 50 mL round bottom flask was added 1,2,3,4,5,6,7,8-octahydroacridin-9-amine (4.622 g, 22.85 mmol), benzaldehyde (21 mL, 205.8 mmol, 9.0 equiv) and acetic anhydride (20 mL). The mixture was refluxed for 24 hours. The reaction was then cooled to room temperature and methanol (25 mL) was added. The reaction was placed in the freezer for 12 hours. After 12 hours, the yellow solid was filtered and washed with cold methanol (15 mL). The solid was dried under vacuum, giving the product as a bright yellow solid in 55% yield (5.8 g, 12.6 mmol).

Data for **IV-101 N-acetyl-N-((4E,5E)-4,5-dibenzylidene-1,2,3,4,5,6,7,8-octahydro acridin-9-yl)acetamide:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 2H), 7.42 (d, *J* = 7.2 Hz, 4H), 7.37 (t, *J* = 7.5 Hz, 4H), 7.25 (t, *J* = 7.3 Hz, 2H), 2.88 (td, *J* = 6.6, 1.6 Hz, 4H), 2.56 (t, *J* = 6.2 Hz, 4H), 2.28 (s, 6H), 1.84-1.82 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 151.9, 145.0, 137.8, 135.1, 129.7, 128.4, 128.2, 127.8, 126.9, 27.5, 26.1, 25.0, 22.2; IR (NaCl plate) 3449, 3401, 3032, 2941, 2869, 2844, 1716, 1543, 1394, 1367, 1265, 1234, 1132, 1072 cm^{-1}; HRMS (ESI) m/z calculated for $C_{31}H_{30}N_2O_2H^+$ $[M+H]^+$ 463.2386, observed 463.2391; mp = 194-196 °C.

REFERENCES

REFERENCES

1. Yousefi, R. A., K.D.; Whitehead, D.C.; Jackson, J.E.; Borhan, B., *Submitted.* **2012**.

2. Yousefi, R. Michigan State University, East Lansing, MI, 2012.

3. Nishiyama, H.; Sakaguchi, H.; Nakamura, T.; Horihata, M.; Kondo, M.; Itoh, K., *Organometallics* **1989,** *8*, 846-848.

4. Jiang, Q.; Van Plew, D.; Murtuza, S.; Zhang, X., *Tetrahedron Lett.* **1996,** *37*, 797-800.

5. Le Goanvic, D.; Holler, M.; Pale, P., *Tetrahedron: Asymmetry* **2002,** *13*, 119-121.

6. Chelucci, G., *Chem. Soc. Rev.* **2006,** *35*, 1230-1243.

7. Wurz, R. P., *Chem. Rev.* **2007,** *107*, 5570-5595.

8. Kwong, H.-L.; Yeung, H.-L.; Yeung, C.-T.; Lee, W.-S.; Lee, C.-S.; Wong, W.-L., *Coord. Chem. Rev.* **2007,** *251*, 2188-2222.

9. Sotiropoulos, J.; El Batouti, N.; Lamazouère, A.-M., *J. Heterocycl. Chem.* **1987,** *24*, 907-912.

10. Kotuski, H.; Sakai, H.; Jun, J.-G.; Shiro, M., *Heterocycles* **2000,** *52*, 661.

11. Markgraf, J. H.; Katt, R. J., *The Journal of Organic Chemistry* **1972,** *37*, 717-718.

12. Chelucci, G.; Baldino, S.; Pinna, G. A.; Benaglia, M.; Buffa, L.; Guizzetti, S., *Tetrahedron* **2008,** *64*, 7574-7582.

13. Kneeland, D. M.; Ariga, K.; Lynch, V. M.; Huang, C. Y.; Anslyn, E. V., *J. Am. Chem. Soc.* **1993,** *115*, 10042-10055.

14. Kozma, D., *Optical Resolutions via Diastereomeric Salt Formation*. London, 2002.

15. Nohira, H. S., K., Optical Resolution by Means of Crystallization. In *Enantiomer Separation, Fundamental and Practical Method*, Toda, F., Ed. Kluwer Academic: Netherlands, 2005; pp 165-191.

16. Gnanamani, E.; Ramanathan, C. R., *Tetrahedron: Asymmetry* **2009,** *20*, 2211-2215.

17. Jacques, J. C., A.; Wilen, S.H., *Enantiomers, Racemates, and Resolutions*. Wiley-InterScience: 1981.

18. Thummel, R. P.; Kohli, D. K., *The Journal of Organic Chemistry* **1977,** *42*, 2742-2747.

19. Kulkarni, S. J. R., K.V.; Rani, V.R.; Srinivas, N. A process for the preparation of biscycloalkylpyridine derivatives using a zeolite catalyst. March 30, 2001, 2001.

20. Kulkarni, S. J.; Krishna, M. K. V. V.; Radha, R.; V; Narender, N.; Raghavan, K. V., Synthesis of heterocyclic three-fused ring compounds using molecular sieve catalysts. In *Stud. Surf. Sci. Catal.*, E. van Steen, M. C.; Callanan, L. H., Eds. Elsevier: 2004; Vol. Volume 154, Part C, pp 2781-2787.

21. Kulkarni, S. J.; Raghavan, K. V.; Vippagunta, R. R.; Nagabandi, S. A process for the synthesis of an annulated pyridine base. 2002.

22. Krishna Mohan, K. V. V.; Narender, N.; Kulkarni, S. J., *Microporous Mesoporous Mater.* **2007,** *106*, 229-235.

23. Ratnamala, A.; Durgakumari, V.; Lalitha, K.; Subrahmanyam, M., *Catal. Commun.* **2007,** *8*, 267-274.

24. Clayden, J.; Greeves, N.; Warren, S.; Wothers, P., *Organic Chemistry*. Oxford University Press: Oxford, 2007.

25. Wu, P.; Cai, X.-M.; Wang, Q.-F.; Yan, C.-G., *Synth. Commun.* **2011,** *41*, 841-850.

26. Wang, Q.-F.; Yan, C.-G., *Central European Journal of Chemistry* **2008,** *6*, 404-409.

27. Thanigaimalai, P.; Lee, K.-C.; Sharma, V. K.; Rao, E. V.; Roh, E.; Kim, Y.; Jung, S.-H., *Bioorganic & Medicinal Chemistry Letters* **2011,** *21*, 1922-1925.

28. Shaffer, A. R.; Schmidt, J. A. R., *Organometallics* **2008,** *27*, 1259-1266.

29. Bell, T. W.; Firestone, A., *J. Am. Chem. Soc.* **1986,** *108*, 8109-11.

30. Tabyaoui, B.; Aubert, T.; Farnier, M.; Guilard, R., *Synth. Commun.* **1988,** *18*, 1475-1482.

31. Sanz, M. J. A., V.; Moran, J. R.; Anaya, J., *An. Quim.* **1992,** *88*, 596-600

32. Ma, M.; Hou, G.; Wang, J.; Zhang, X., *Tetrahedron: Asymmetry* **2011,** *22*, 506-511.