1. REINVESTIGATION OF A CATALYTIC, ENANTIOSELECTIVE ALKENE DIBROMINATION AND CHLOROHYDROXYLATION
2. DOUBLE CROSS-COUPLING REACTIONS OF SILOXABOROLATES
3. THE ENANTIOSELECTIVE SYNTHESIS OF 3-SUBSTITUTED MORPHOLINES USING COMPUTER-GUIDED CATALYST DESIGN

BY

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THESIS

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ABSTRACT

In Chapter 1, attempts to reproduce eight, putative, enantioselective dibromination and chlorohydroxylation reactions from oft-cited literature studies are described. The reactions were performed with full fidelity to the original report wherever possible. Analysis of the enantiomeric composition was performed by CSP-HPLC or CSP-SFC, as opposed to the original report, which used chiral shift reagent NMR spectroscopy. After careful study, the reported levels of enantioselectivity were found to be incorrect. Possible explanations for the false positive results are discussed.

Chapter 2 moves to a completely different area of chemistry, in the Nobel Prizewinning field of cross-coupling. A bench-stable, crystalline siloxaborolate is described, capable of double cross-coupling reactions to form *ortho*-teraryls. The initial Suzuki reaction proceeded with high yields but the second, Hiyama-Denmark reaction proved troublesome for coupling with electron-rich aryl bromides, providing only low yields of the desired teraryls. A four-factor DoE study was undertaken to attempt to identify conditions to allow a more general scope for teraryl synthesis, however, these could not be identified in the study.

Chapter 3 involves, again, a project very distinct from the other two. This took the form of synthesis and validation of a large, multipurpose set of diverse bisoxazolines of computationally-aided design. This ligand set was tasked with the enantioselective synthesis of *C*-substituted morpholines, for which a general and highly-selective cyclization has not yet been discovered. A number of ligands were tested for the cyclization of SnAP imines to this purpose, this being a highly general method for morpholine synthesis that previously lacked excellent enantioselectivity, and a broad spread of data was achieved for the purposes of computational modeling.

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"Not knowing the literature is a sin; knowing it is a virtue.
But who has only virtues?" – Albert Eschenmoser

"I thought people in my field – physics – were crazy,
but then I heard about organic chemists" – Unknown, Quality Bar, Champaign, 2015

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CHAPTER 3

CHAPTER 1 REINVESTIGATION OF A CATALYTIC, ENANTIOSELECTIVE ALKENE DIBROMINATION AND CHLOROHYDROXYLATION[†]

"To kill an error is as good a service as, and sometimes even better than, the establishing of a new truth or fact" – Charles Darwin

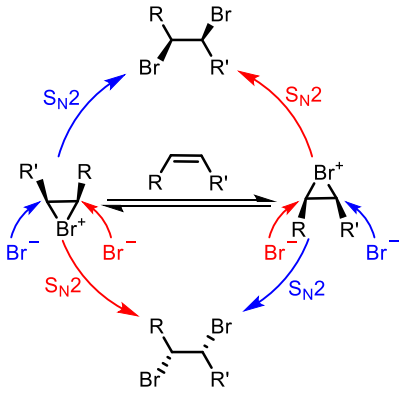
1. INTRODUCTION

The halofunctionalization of alkenes with electrophilic halogenating agents has long been a staple of stereoselective synthesis, prized for its predictable constitutional selectivity and relative stereochemical course.[2–4] However, catalytic dihalogenation methods, in which the absolute configuration of the products is controlled from an achiral starting material, have proved elusive until recently.[5–8] Enantioselective bromination is of particular interest due to the ability of bromide to act as a leaving group in stereospecific substitution reactions. Additionally, over 3800 organobromine compounds are known in nature, the majority isolated from marine organisms.[9–11]

In the reactions of olefins with Br_2, vicinal dibromides are formed *via* bromide ion attack on either an alkene−Br_2 π-complex or a bromiranium ion, resulting in *anti*-stereospecific addition of Br_2 across the double bond.[12–14] However, strategies for enantioselectivity may be thwarted in a number of ways: (1) A racemic background reaction may occur from the formation of molecular bromine (or its equivalent) when both electrophilic and nucleophilic bromine sources are present; (2) facial selectivity must also be controlled to produce an enantioenriched alkene-Br_2 π-complex or bromiranium ion intermediate; (3) bromiranium ions are configurationally unstable in the presence of excess olefin, *via* an alkene-to-alkene transfer pathway;[15] and (4) the regioselectivity of bromide addition must also be controlled, since attack on either carbon atom of a non-C_2-symmetric bromiranium ion intermediate yields enantiomeric products (Scheme 1).

[†] Results and conclusions of this chapter are outlined in a report published in *Organic Letters*.[1]

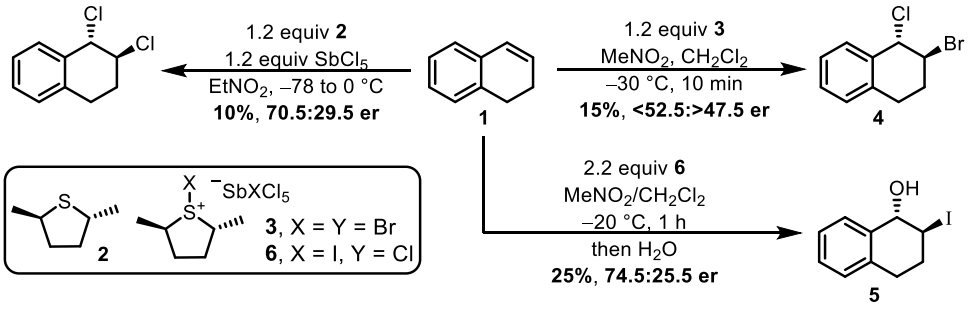
Scheme 1. Addition of Bromine Equivalents to Alkenes



2. BACKGROUND

Despite the extensive history of dihalogenation and other halofunctionalization reactions of alkenes, methods to form stereodefined, dihalogenated products from olefins are rare. Chiral, enantiopure chloro- and iodosulfonium reagents have been used to effect the enantioselective *anti*-dichlorination and interhalogenation of 1,2-dihydronaphthalene **1**, albeit with compromise between moderate enantiomeric ratio and low yield (Scheme 2).[16] In the case of the dichlorination, the chlorosulfonium reagent was generated *in situ* from chiral sulfide **2** and $SbCl_5$. Bromochlorination proved unsuccessful, the bromochloride **4** apparently being unstable, and close to racemic. Chloroiodination was also attempted, but the product was unstable on silica gel, resulting in several decomposition products. When the chloroiodination reaction was quenched with H_2O, *anti*-iodohydrin **5** was formed in 25% yield and 74.5:25.5 er.

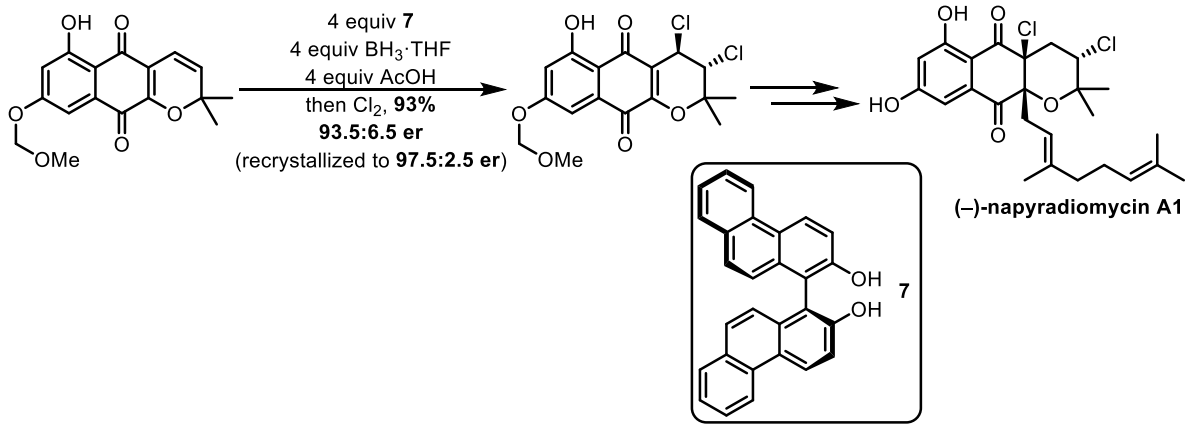
Scheme 2. Enantioselective *Anti*-Dihalogenation of 1,2-Dihydronaphthalene



The same group also employed an enantioselective dichlorination in the total synthesis of the estrogen antagonist (−)-napyradiomycin A1 (Scheme 3).[17] Enantioselectivity was controlled by a large excess of axially chiral diol additive **7**, apparently by π-stacking with the substrate. The

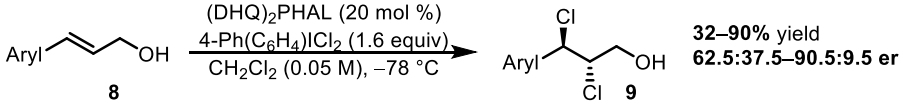
stereochemistry of the C–Cl bond that does not appear in the natural product was exploited by a regioselective, retentive substitution by acetate in the following step.

Scheme 3. Enantioselective Dichlorination in the Total Synthesis of (−)-Napyradiomycin A1



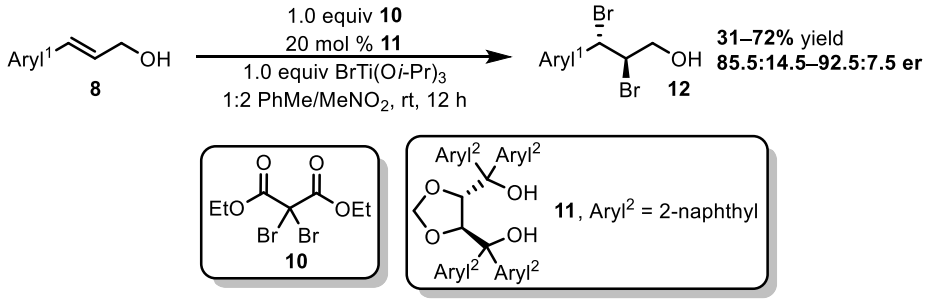
In 2011, Nicolaou and coworkers reported an *anti*-dichlorination reaction of cinnamyl alcohols **8** using $(DHQ)_2PHAL$ as the catalyst and an aryl dichloroiodane as the chlorinating agent (Scheme 4).[18] Dichloride products **9** were formed from electronically-diverse cinnamyl alcohols, in a wide range of selectivities (62.5:37.5–90.5:9.5 er). Monobenzylated (*E*)- and (*Z*)-but-2-ene-1,4-diol were also viable substrates, although the dichlorinated products were obtained in only 71.5:28.5 and 77:23 er, respectively.

Scheme 4. Enantioselective *Anti*-Dichlorination of Allylic Alcohols



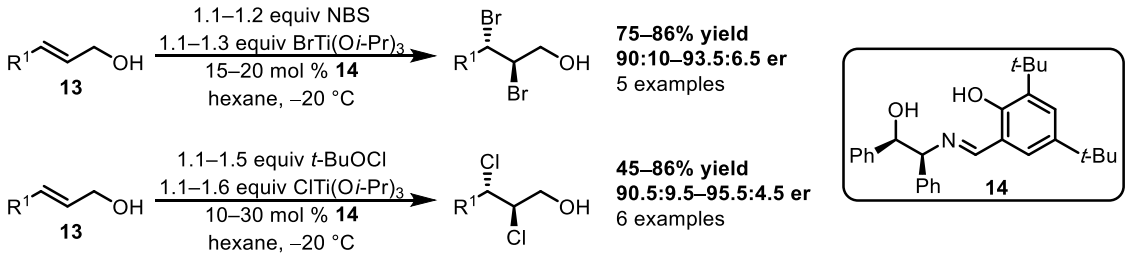
More recently, Burns and coworkers developed an enantioselective dibromination of cinnamyl alcohols **8** using dibromomalonate **10** as an electrophilic bromine source and $BrTi(O\textit{i}\text{-}Pr)_3$ as a nucleophilic bromine source, with TADDOL-derived catalyst **11** (Scheme 5).[19] The dibromide products **12** were formed with good enantioselectivities (85.5:14.5−92.5:7.5 er). This work was later extended to enantioselective bromochlorination of allylic alcohols with constitutional site selectivities of 6:1−>20:1 and enantioselectivities of 89:11− 98.5:1.5 er.[20]

Scheme 5. *Anti*-Dibromination of Allylic Alcohols

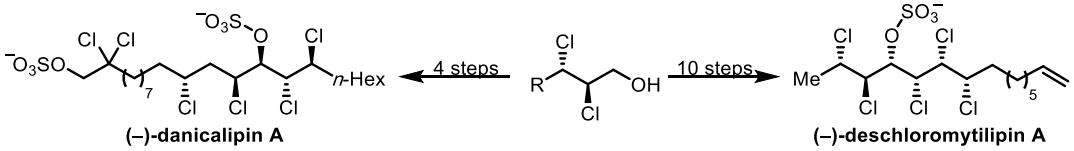


Most recently, allylic alcohols **13** have also been used as substrates for enantioselective *anti*-dihalogenation, without the need for aryl groups enforcing regioselective attack on a benzylic haliranium intermediate (Scheme 6).[21] In the case of dibromination, NBS and BrTi(O*i*-Pr)$_3$ were used as bromine sources, and enantiomeric ratios of 90:10–93.5:6.5 were obtained. For dichlorination, *t*-BuOCl and ClTi(O*i*-Pr)$_3$ afforded enantiomeric ratios of 90.5:9.5–95.5:4.5. Imino diol **14** was used in both cases as chiral catalyst. However, neither protocol has yet been shown to be compatible with any heteroatomic functionality. Burns was also able to apply the enantioselective dichlorination methodology to the syntheses of the unnatural enantiomers of natural polychlorosulfolipids danicalipin A and deschloromytilipin A, the rest of the stereodefined chlorine atoms being installed *via* diastereoselective reactions (Scheme 7).

Scheme 6. Enantioselective Dihalogenation of Allylic Alcohols



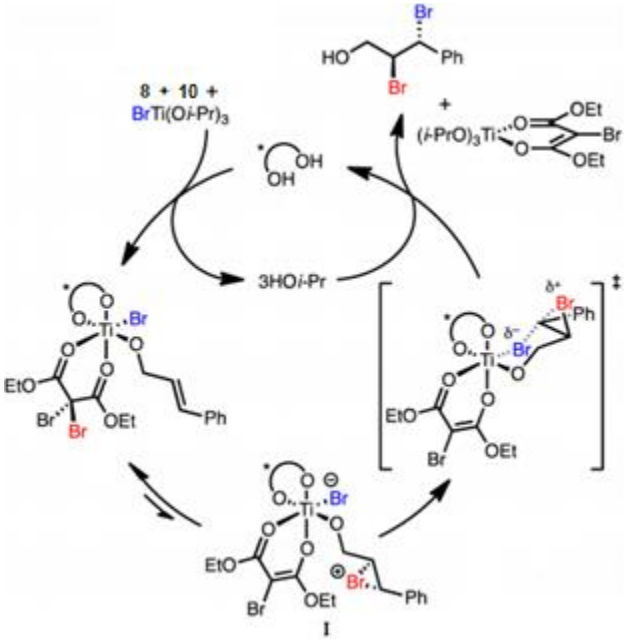
Scheme 7. Synthesis of (−)-Danicalipin A and (−)-Deschloromytilipin A from a Common Motif



The proposed catalytic cycle throughout Burns's work involves a haliranium ion **I** that may be captured quickly by intramolecular halide delivery from the coordination sphere of Ti (Scheme 8). This process avoids both a racemic background reaction and the rapid racemization of

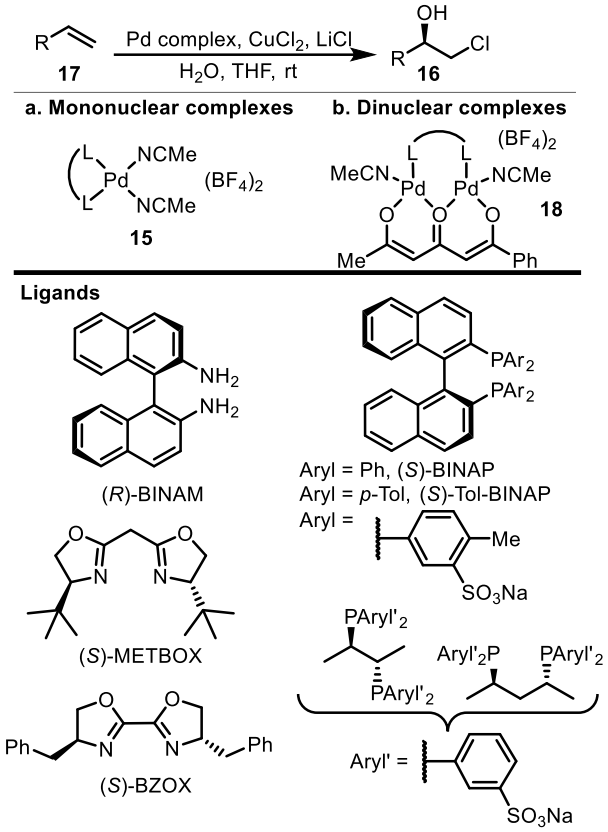
enantioenriched bromiranium (and by extension, chloriranium) ions in the presence of free alkene. Despite its high reactivity leading to a facile background reaction, *t*-BuOCl gave the highest selectivities in a screen of multiple electrophilic chlorine sources, possibly due to its Lewis basic nature allowing it to bind to the chiral Ti adduct.

Scheme 8. Burns's Proposed Dihalogenation Catalytic Cycle using Diol Ligands. Adapted with permission from *J. Am. Chem. Soc.*, **2013**, *135*, 12960–12963, © 2013 American Chemical Society



The Wacker oxidation has also been modified for halofunctionalization of alkenes. The use of high chloride ion concentrations under Wacker-type conditions results in the conversion of ethylene to ethylene chlorohydrin, instead of the expected acetaldehyde product.[22] An enantioselective variant of this reaction was subsequently reported by Henry and coworkers, using chiral, nonracemic palladium(II) bisphosphine catalysts **15** to achieve the enantioselective generation of chlorohydrins **16** from terminal alkenes **17** (Scheme 9).[23] The possibility of a facile background reaction stemming from dihalogen formation was reduced by the use of chloride as the sole halogen source. A limited number of chlorohydrins were produced, with constitutional site selectivities of 5.5:1−>95:1, and reported enantioselectivities of 64:36−91:9 er (Scheme 9a). In all cases, yields were reported based solely on O_2 uptake.

Scheme 9. Henry's Wacker-type Chlorohydrin Synthesis



Enantioselectivity was reportedly improved in later work by Henry and co-workers, by the use of dinuclear palladium(II) complexes **18** with bridging triketone ligands, although no direct comparisons to the mononuclear catalysts were made (Scheme 9b).[24–26] Terminal olefins **17** were converted to chlorohydrins **16** with constitutional site selectivities of 2.3:1−>95:1 and enantioselectivities of 57.5:42.5−97:3 er.

Henry and co-workers later reported an extension of this work to the enantioselective dibromination of olefins, using similar Wacker-type conditions with 2.5−17.7 mol % (per Pd atom) palladium(II) catalyst **15** or **18** (Table 1).[27] The reactions were performed in aqueous THF solutions of varying composition, containing copper(II) bromide (~2 M) and lithium bromide (0.13−0.29 M). The concentration of alkene substrate **19** varied between 0.06 and 0.47 M. Since these reaction conditions (i.e., concentrations of LiBr, $CuBr_2$, catalyst, and alkene, and solvent THF/H_2O ratio) varied incoherently for each substrate, attempt at direct comparison is of limited value. The higher intrinsic nucleophilicity of bromide ion compared to H_2O, coupled with the high

bromide ion concentrations employed, led to the formation of vicinal dibromides **20** rather than bromohydrins as the major products. Yields of dibromides reported were highly variable (31−95%), and one was indecipherable – a yield of 80%, based on O_2 uptake, is reported for the dibromination of methyl crotonate, but 30% of the starting material was also recovered (Table 1, entry 6). Good to excellent enantioselectivities were claimed (90:10−98.5:1.5 er), apart from the case of methyl (*E*)-cinnamate (Table 1, entry 9; 57:43 er). Enantiomeric ratios were determined by ^{1}H NMR spectroscopic analysis using chiral shift reagent Eu(hfc)$_3$, although neither spectra nor details of concentrations were given. Optical rotation data were provided for only two of the nine dibromide products.

Henry and coworkers claimed the rate does not decrease during the reaction, i.e. it was overall zeroth order. Qaseer, a coauthor on the original dibromination paper, later reported a similar system using Wacker-type conditions and a racemic dinuclear Pd^{II} catalyst **18a** to generate vicinal dibromides, and reported a zeroth order rate of O_2 uptake (Scheme 10).[28] However, measurement of O_2 uptake is insufficient to substantiate claims related to the rate of product formation. For example, the yield for the dibromination of methyl crotonate (catalysed by a mononuclear palladium(II) bisoxazoline complex) is reported as 80% based on O_2 uptake. However, the amount of recovered starting material is 30% by mass. This inconsistency exemplifies that O_2 uptake is not a reliable method for monitoring product formation.

Scheme 10. Qaseer's Racemic Alkene Dibromination

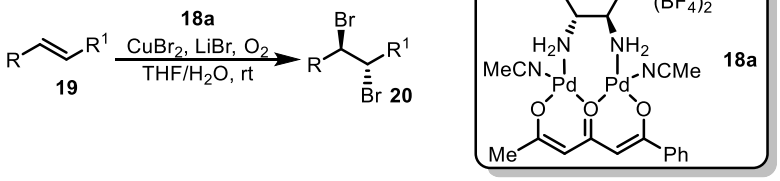
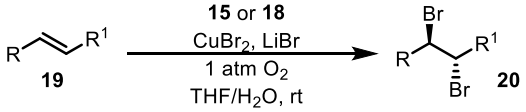
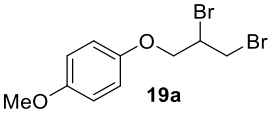
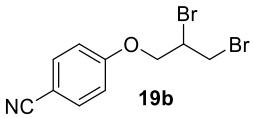
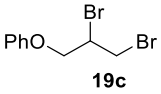
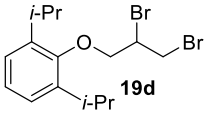
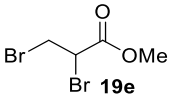
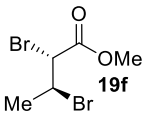
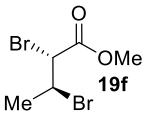
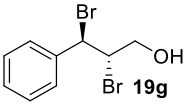
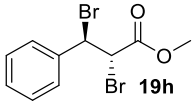
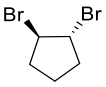


Table 1. Henry's Reported Enantioselective Dibromination Results



Entry	Product[a]	Nuclearity of catalyst	Ligand	Recovered alkene	Dibromide yield, %[b]	er[c]
1	 **19a**	*Ambiguous in original text*	(*S*)-BINAP	NR	95	98:2
2	 **19b**	2	(*S*)-Tol-BINAP	NR	95	98.5:1.5
3	 **19c**	2	(*S*)-BINAP	NR	95	97.5:2.5
4	 **19d**	1	(*S*)-BINAP	NR	95	97:3
5	 **19e**	2	(*S*)-METBOX	63%	31	97:3
6	 **19f**	1	(*S*)-BZOX	30%	80[d]	92:8
7	 **19f**	2	(*S*)-METBOX	21%	70	91:9
8	 **19g**	2	(*R*)-BINAM	24%	77	90:10
9	 **19h**	2	(*R*)-BINAM	12%	83	57:43
10	 **19i**	2	(*S*)-Tol-BINAP	NR	85[e]	-

NR = not reported. [a] Absolute configuration not determined. [b] Isolated yield. Yields differ from the values in the original paper since they are based on olefin substrate rather than recovered starting material, where this information is available. [c] er of dibromide products determined by ^{1}H chiral shift reagent NMR. [d] Yield calculated from oxygen uptake. [e] An unnamed side-product was formed in approximately 14% yield by GC analysis.

3. RESULTS

3.1 Enantioselective Dibromination of Alkenes

Four reactions in the original report from Henry and coworkers (Table 2, entries 1−7) were replicated. The allylic ether dibromination procedures were repeated as rigorously as the described procedures allow, albeit on a smaller scale (0.25 mmol versus 2.8−3.7 mmol allylic ether in the original work). To confirm that scale was not a critical factor, one trial was performed on the original scale (3.0 mmol) and was let run for the original reaction time of 6 days (Table 2, entry 3). Although dibromides **20** revert to the corresponding allylic ethers **19a**–**d** over several weeks in light, running reactions and isolating products in the dark affected neither the yields nor enantioenrichment of products. Workup and chromatographic isolation of products was performed immediately and identically to the original protocol to obviate any possibility of epimerization over time.

The catalyst used in Table 2, entry 1 was produced by replication of Henry's described method with as complete fidelity as possible. This procedure afforded a mixture of compounds, as determined by ^{31}P NMR spectroscopy. The dinuclear palladium complexes used in Table 2, entries 2, 5, and 6 were synthesized by a modification of Henry's method, in which NaH rather than Et_3N was used as a Brønsted base. Although in one procedure, the authors describe the addition of Me_3N, it appears Et_3N was actually used.[24,25] This procedure afforded compounds that appeared to be pure by ^{31}P NMR spectroscopy and circumvented the laborious separation of triethylammonium tetrafluoroborate from the complex. The pure complexes were stored in a glovebox and were found to decompose over time in solution, and *in vacuo*, with decomposition observable by NMR spectroscopy after just a few minutes *in vacuo*. It is likely that vacuum promotes loss of the labile MeCN ligands. The complexes were therefore characterized and used immediately after purification. The decomposition product (readily visible as a multiplet exhibiting P-P coupling by ^{31}P NMR spectroscopy) could be removed by extensive washing of the solid with anhydrous, degassed toluene under an Ar atmosphere. Nonetheless, the method of preparation of the dinuclear complex had no impact on the reaction outcome (Table 2, entries 1−2). For operational simplicity, the mononuclear Pd^{II} bisphosphine complexes **15** used in entries 3−4 were generated *in situ* from $Pd(MeCN)_4(BF_4)_2$ and the requisite chiral bisphosphine.[29] The

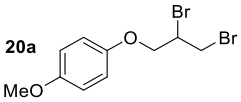
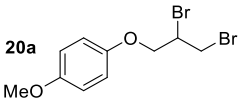
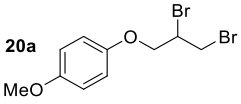
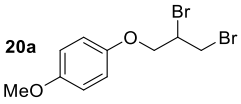
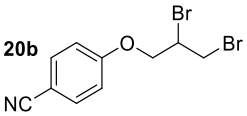
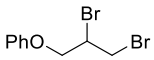
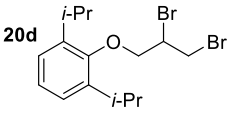
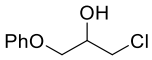
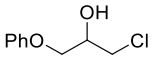
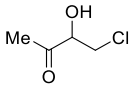
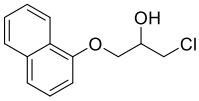
mononuclear catalyst used in Table 2, entry 7 was prepared under Ar and found to be stable in the absence of air and moisture.[30] All reactions were run under positive pressure from an O_2 manifold.

Moderate to high yields of dibrominated products **20** were obtained, with small amounts of side products observable in the ^{1}H NMR spectra. Both the crude product mixtures and the chromatographically pure dibromides were analysed by CSP-HPLC or CSP-SFC to assess enantioenrichment. In every case examined, the vicinal dibromides were racemic (Table 2). It is notable that, in our hands, the complete conversion of starting material was achieved in significantly shorter times than those quoted in the original work: 24 or 28 h versus 4−7 days. It is possible that the original reactions were monitored by O_2 uptake whereas our experiments were monitored by TLC conversion. A repeat of the dibromination of allyl 4-methoxyphenyl ether **19a** was arbitrarily stopped after 6 h (Table 2, entry 4) to determine whether an initial enantioselective process may occur, only to be compromised by epimerization under the reaction conditions. In this case as well the product was racemic.

In light of these results, four chlorohydroxylation reactions from Henry and co-workers' earlier reports were also investigated (Table 2, entries 8−11).[23] These experiments were performed on a 0.5−1.0 mmol scale (original scale: 3.7−6.5 mmol where reported). However, analysis by CSP-SFC and CSP-GC again revealed that all chlorohydrin products **16** were racemic.

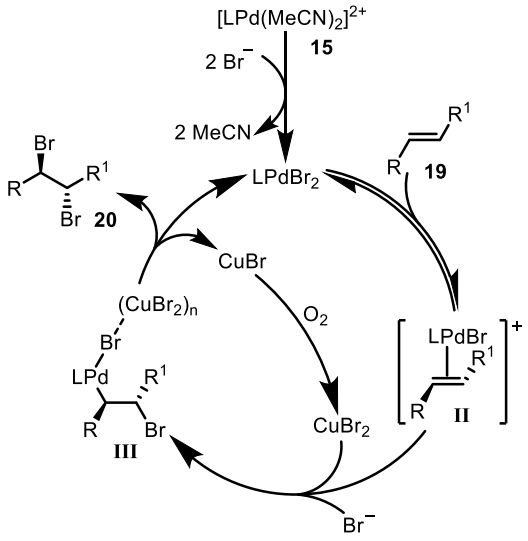
In their original report, Henry and coworkers proposed a mechanism that bypasses a bromiranium ion intermediate, instead suggesting that the palladium complex (shown as mononuclear with a chiral ligand abbreviated as L) coordinates olefin **19** (Scheme 11). Free bromide then attacks the activated olefin **II** from the opposite face, yielding an alkylpalladium(II) complex **III**. Cu^{II} may stereoretentively oxidize the C−Pd^{II} bond to form the alkyl bromide without overall oxidation state change at Pd.[31] This putative bromide may be derived from either the coordination sphere of Pd or that of Cu in complex **II**.

Table 2. Comparison of Results for the Dibromination and Chlorohydroxylation of Several Substrates

Run	Ligand	Nuclearity of complex	Time, days	Product	Yield, %	er	Lit. yield, %	Lit. er
1	(*R*)-BINAP[a,e]	2[b]	1.17	**20a** 	86[d]	50:50	95	98:2
2	(*R*)-BINAP[a]	2[b]	1.17	**20a** 	86[d]	50:50	95	98:2
3	(*R*)-BINAP[a]	1[b]	6	**20a** 	78[c]	50:50	95	98:2
4	(*R*)-BINAP[a]	1[b]	0.25	**20a** 	65[d]	50:50	-	-
5	(*R*)-Tol-BINAP[a]	2	1	**20b** 	85[d]	50:50	95	98.5:1.5
6	(*R*)-BINAP[a]	2	1	**20c** 	69[d]	50:50	95	97.5:2.5
7	(*R*)-BINAP[a]	1	1	**20d** 	90[d]	50:50	95	97:3
8	(*R*)-Tol-BINAP	1	14	**16a** 	14	50:50	NR	90:10
9	(*R*)-BINAP[a,e]	2	5	**16a** 	40	50:50	92	96.5:3.5
10	(*R*)-Tol-BINAP	1	10	**16b** 	33[f]	50:50	NR	91:9
11	(*R*)-BINAP[a,e]	2	10	**16c** 	29	50:50	95[g]	90:10

NR = not reported. [a] The (*S*)-enantiomer of the ligands was used in the original work. [b] The nuclearity of the catalyst used is ambiguous in the original text. [c] 3.0 mmol scale. [d] The yield is the average of two runs, each within 2% of the average. [e] The dinuclear catalyst was produced exactly according to Henry's procedure. [f] 1.0 mmol scale. [g] The product was mischaracterized in the original work.

Scheme 11. Putative Catalytic Cycle for Dibromide Formation



No side-products were reported in many reactions; others contained a small amount of undesired bromohydrin. Qaseer's later report claims 10–25% ketone and/or bromohydrin side-products are present in all crude reaction mixtures.[14] In our hands, tiny amounts of organic side-products were observable by ^{1}H NMR in all reactions.

4. DISCUSSION

The ability to reproduce the formation of the dibromides **20** and chlorohydrins **16** from multiple substrates following the original procedure, but to obtain uniformly racemic products, presents a quandary. The possibility that important details are missing for preparing the catalysts or executing the reactions cannot be excluded. Certainly many possibilities exist for generating Br_2 under the reaction conditions, and indeed, $CuBr_2$ itself is also capable of effecting the dibromination of alkenes at room temperature.[32,33] However, in our opinion, the more likely explanation for the disparity is the authors' use of chiral shift reagent NMR analysis to determine the enantiomeric composition of the dibromide products. Unfortunately, the spectral data are not provided. Our own attempt to observe signal separation in a racemic sample of allyl 4-methoxyphenyl ether **19a** using $Eu(hfc)_3$ was inconclusive. After portionwise addition of 4 equiv of the chiral shift reagent, some degree of signal separation was observed, showing roughly equal quantities of each enantiomer. However, the level of signal broadening precluded any quantitative determination of enantiomeric ratio.

5. CONCLUSIONS

In conclusion, four dibromination and four chlorohydroxylation reactions of allylic ethers catalysed by chiral mono- or dinuclear palladium(II) complexes reported by Henry and coworkers were repeated. Although the reaction yields were reproduced, the dibromide and chlorohydrin products were generated in racemic form.

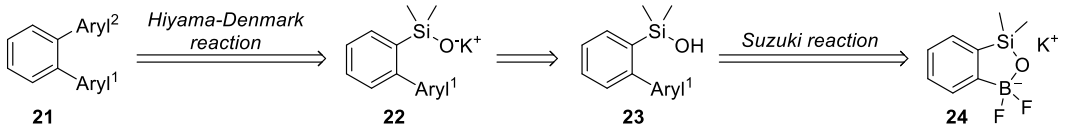
CHAPTER 2 DOUBLE CROSS-COUPLING REACTIONS OF SILOXABOROLATES

1. INTRODUCTION

Palladium-catalysed cross-coupling is a pillar of organic synthesis, ubiquitous in industrial and academic settings, for synthetic and medicinal chemistry, and materials applications. This versatile, Nobel Prizewinning method is most prevalently used to forge sp^2-sp^2 bonds, to make flat moieties commonly found in drug molecules.[34–37]

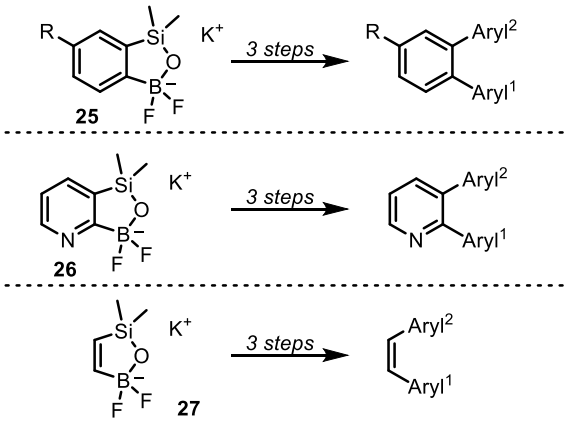
Recently, a stable, crystalline siloxaborolate has been developed in these laboratories. This dual-functionalized molecule is firstly reactive in Suzuki couplings with a range of organohalides to yield an *ortho*-substituted arylsilanol after aqueous workup, which may then be deprotonated to an arylsilanolate (Scheme 12). This anionic species is then primed for a Hiyama-Denmark cross-coupling, which permits the use of inexpensive, non-toxic silicon reagents in bond formation without need for an external activator.

Scheme 12. Formation of Teraryls by Double Cross-Coupling from Siloxaborolate **24**



This double, sequential C–C bond formation could allow a wide variety of *ortho*-teraryls **21** and other *ortho*-disubstituted arenes. Other siloxaborolates could potentially be developed to further expand this process to the synthesis of, for example, further substituted arenes, vicinally-disubstituted unsaturated heterocycles, or (*Z*)-disubstituted alkenes from siloxaborates **25**–**27**, respectively (Scheme 13).

Scheme 13. Double Cross-Coupling Reactions of Other Siloxaborates



Additionally, since the immediate product of the initial Suzuki reaction prior to workup in a silanolate, the double coupling process could potentially be improved to a one-pot procedure without isolation and separate deprotonation of the monocoupled silanol.

2. BACKGROUND

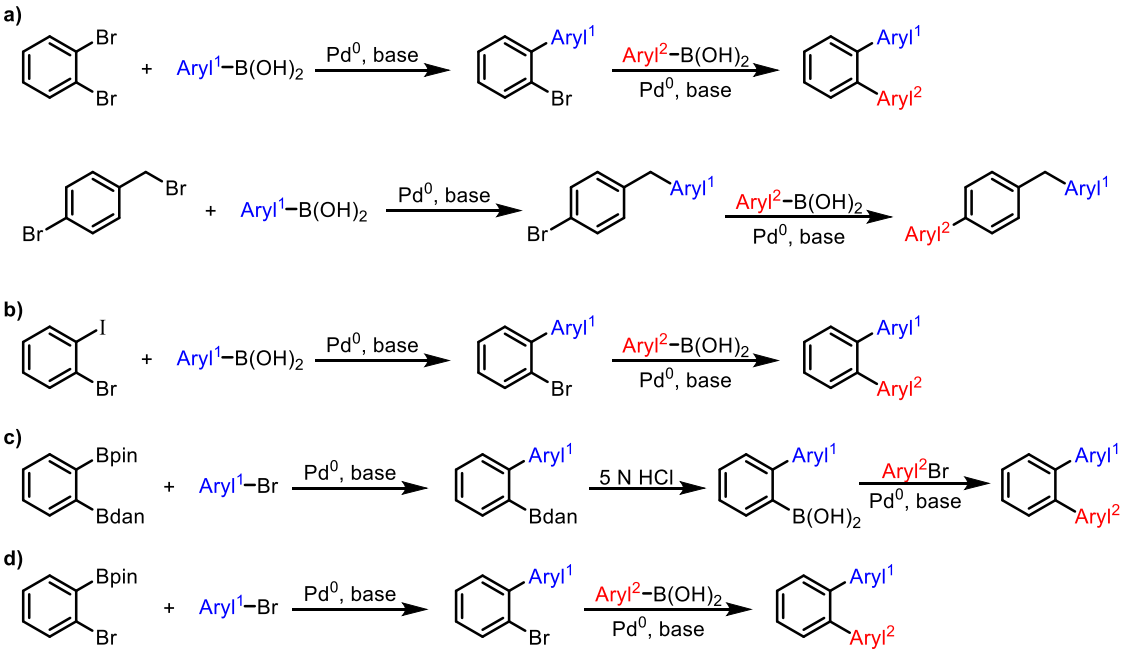
The Suzuki cross-coupling between arylboron species and aryl halides or triflates is one of the most widely-developed cross-coupling methods.[38–44] The range of functional group compatibility is very high, and boron byproducts are readily removed during workup procedures. Boronic acids remain the most popular boron reagents, although their use may result in protiodeborated or homocoupled side-products during the coupling process.[45,46] Additionally, many boronic acids are prone to dehydrative trimerization to boroxines, resulting in their use in excess due to uncertainties in stoichiometry. This problem may be resolved by using boronate esters, although their use can complicate purification steps. To mitigate these concerns, aryltrifluoroborate salts are increasing in usage. These are generally indefinitely air- and water-stable, readily-prepared, and often commercially-available.[46–51] The inorganic borate side-products are readily separated from the desired products. Importantly, protiodeboration is inhibited in these systems.

Cross-coupling of easily-accessible silanol and silanolate donors (the Hiyama-Denmark reaction) is a versatile method, offering a wide range of functional group compatibility.[52] Organosilanols are air- and moisture-stable, and readily-synthesized *via* diverse methods. These features particularly stand out in contrast to organosilanes, the first Si cross-coupling reagents to

be used (the Hiyama reaction), in addition to their ability to avoid fluoride activation of the silane.[53–57] Thus far, (hetero)aryl-,[58–60] alkenyl-,[61–64] and allylsilanolates[65–67] have been used as coupling donors. The dominant transmetalation pathway in these systems is by silanolate assistance, where a second silanolate molecule is required to activate the Si atom in the Si–O–Pd linkage of the pre-transmetalation intermediate.

Sequential, double cross-coupling methods are known, typically by use of a homobifunctional dielectrophile or organodimetallic reagent that may be selected for in turn either by intrinsic selectivity differences or by iterative coupling of symmetrical substrates, exploiting reactivity differences between the starting material and monocoupled product (Scheme 14a).[68–71] Substrates containing two functional groups of differing reactivity (eg: 1-chloro-2-iodobenzene and its derivatives allow the generation of products with unsymmetrical substitution on the initial coupling partner (Scheme 14b)).[72–75] Likewise, one functional group may be masked initially, and unmasked for a second coupling (Scheme 14c).[76–78] Lastly, functionalized organometallics may be used firstly as cross-coupling donors and then as electrophiles in a second cross-coupling reaction, so long as homocoupling is minimal (Scheme 14d).[79–81] These strategies allow selectivity of mono- over dicoupled products in the initial step, leaving a single functional handle for a second reaction with a different coupling partner.

Scheme 14. Double Suzuki Cross-Coupling Strategies to form *Ortho*-Disubstituted Arenes



Alternative strategies for the formation of teraryls or other *ortho*-diorganyl arenes include (directed) C–H activation strategies,[82,83] or cyclization to form one or more arene rings.[84]

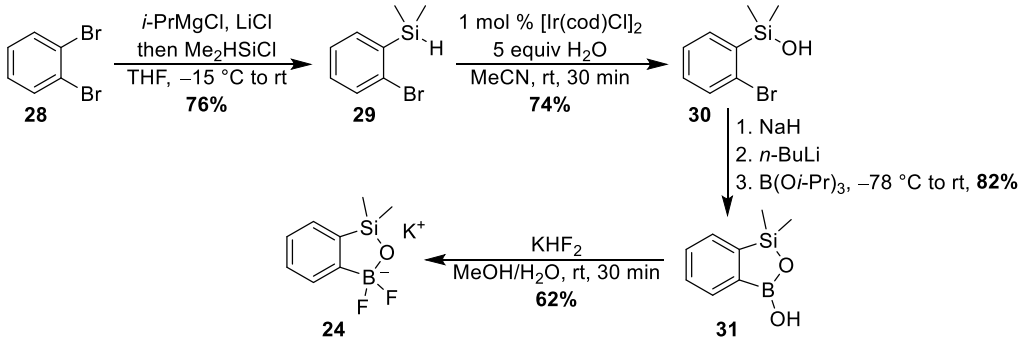
3. Research Objectives

The object of this project was to effect double cross-coupling from siloxaborolate **24**. Firstly, a Suzuki coupling is performed. Although the immediate product of this reaction is the respective silanolate, aqueous workup and isolation of the silanol will be performed, followed by its deprotonation to the silanolate. This allows pure silanolate to be used for the initial screening. The Hiyama-Denmark coupling will then be performed. Yields of both cross-couplings will be optimized, with a view to creating a general procedure for the synthesis of many 1,2-disubstituted compounds, including *ortho*-teraryls **21**.

4. Synthetic Strategies

Siloxaborolate **24** was synthesized in four steps from 1,2-dibromobenzene **28** (Scheme 3). Firstly, a Knochel Grignard lithium-bromine exchange generated the aryl Grignard reagent *in situ*, with subsequent displacement of chloride from chlorodimethylsilane to form aryl silane **29**. This silane was oxidized using H_2O with 1 mol % $[Ir(cod)Cl]_2$ to form silanol **30**, which may then be deprotonated, lithiated and borylated to siloxaborolol **31**. Treatment of this boronate semiester with potassium bifluoride in aqueous methanol yielded **24** in 62% yield.

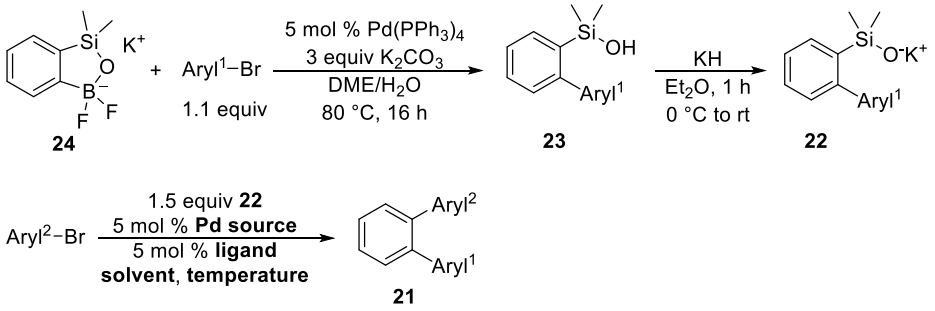
Scheme 15. Synthesis of Siloxaborolate **24**. cod = 1,5-cyclooctadiene



Siloxaborolate **24** can undergo Suzuki reactions with aryl bromides *via* the borate functional group to yield 2-biphenylsilanol derivatives **23** (Scheme 4). The products can then be deprotonated with potassium hydride to form potassium 2-biarylsilanolates **22**, which may

undergo a Hiyama-Denmark reaction with an aryl bromide *via* the silanolate functional group to yield the desired *ortho*-terphenyl product **21**.

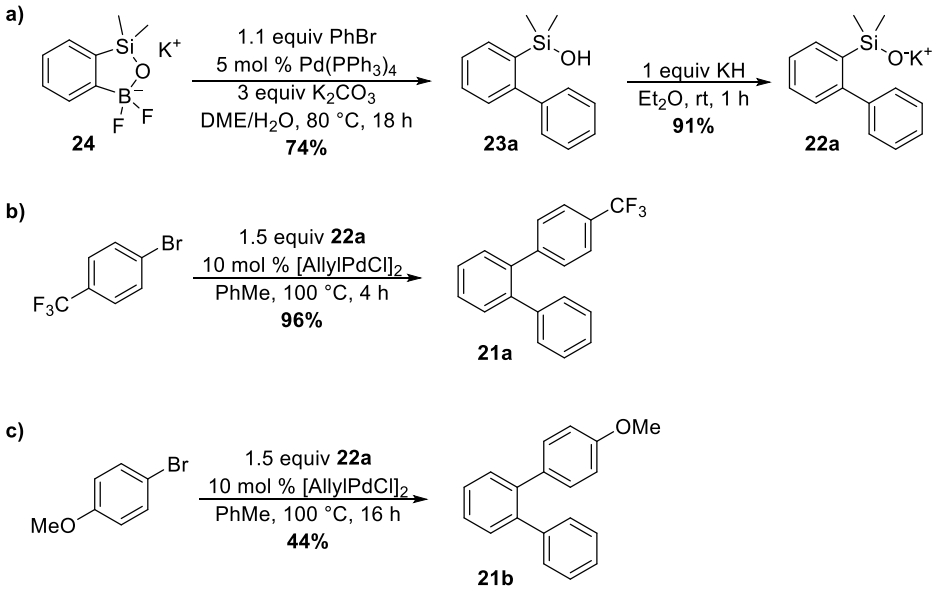
Scheme 16. Iterative Suzuki and Hiyama-Denmark Cross-Coupling Reactions of Siloxaborolate **24**



5. INITIAL STUDIES

Early work on this project was performed by Dr Brian Casey. (2-Biphenyl)dimethylsilanol **23a** could be formed from bromobenzene in 74% yield and deprotonated with KH to silanolate **22a** (Scheme 17a). This silanolate was used as a test substrate for optimization of the Hiyama-Denmark coupling step. Initial studies showed that using $[AllylPdCl]_2$ as the palladium source in the absence of external ligands at 100 °C, teraryl **21a** could be formed in 96% yield after 4 h from 4-bromobenzotrifluoride (Scheme 17b). However, reaction under the same conditions with electron-rich anisoyl bromide produced teraryl **21b** in only 44% yield after 16 h (Scheme 17c).

Scheme 17. Initial Studies of the Hiyama-Denmark Reaction with Electron-Deficient and Electron-Rich Aryl Bromides



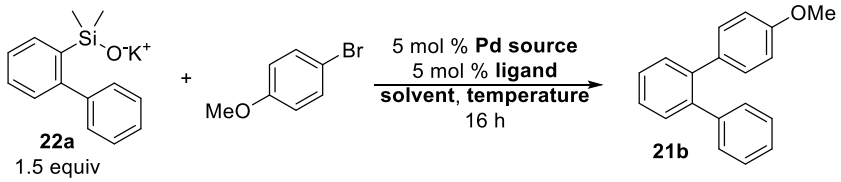
Since coupling of electron-rich aryl bromides to the hindered *ortho*-substituted biphenyl silanolate proved troublesome, a Design of Experiment (DoE) study was planned, based on factors (aka: variables) of solvent, temperature, ligand, and palladium source. This was designed to allow rapid optimization of conditions for the Hiyama-Denmark cross-coupling.

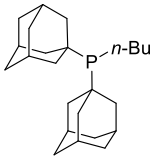
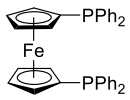
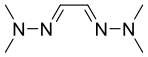
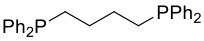
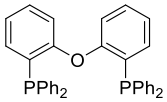
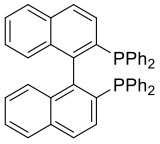
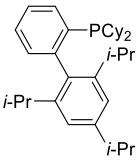
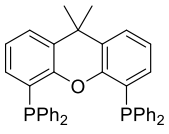
It was hypothesized that oxidative addition of the aryl bromide to the palladium center, being more difficult for electron-rich aryl groups, is the limiting step for this reaction. Strategies to counter slow oxidative addition have historically included the use of strongly σ-donating ligands, particularly phosphines, and the use of bulky ligands to favor ligation of only one phosphine ligand to Pd.[85] However, all external ligands tested within these laboratories thus far show less reactivity than allylpalladium(II) chloride dimer alone.[86] This may be an indication of the necessity of sterically unencumbered ligands to facilitate transmetalation. These competing effects imply that an electron-rich ligand with intermediate steric bulk may be ideal to achieve high yields. XPhos **L11** (Chart 1) and other 2-biphenylphosphine derivatives have been found to be effective for Suzuki couplings of bulky, electron-rich aryl chlorides, which are also known to have a low aptitude for oxidative addition.[87]

These features informed the choice of levels (predefined values for each factor), with a D-optimal design involving 98 reactions to explore the chemical space in the four factors

(Chart 1). Each reaction was run for 16 h. A range of temperatures from 80–140 °C was explored, along with solvent selections of DME, 1,4-dioxane, toluene, and *p*-cymene. Combinations of solvents and temperature which would raise the solvent above its standard boiling point were discarded from the experimental design. Palladium sources employed, in 5 mol % per Pd atom, were $Pd_2(dba)_3$, allylpalladium(II) chloride dimer, palladium(II) acetate, and bisbenzonitrilepalladium(II) chloride. Eleven structurally- and functionally-diverse ligands were also entered into the screen.

Chart 1. Factor levels for DoE study



Solvents					
DME	1,4-dioxane	Toluene	*p*-Cymene		
Pd sources					
$Pd_2(dba)_3$	$[allylPdCl]_2$	$Pd(OAc)_2$	$(PhCN)_2PdCl_2$		
Ligands					
					
L1	**L2**	**L3** (dppf)	**L4**	**L5**	**L6** (dppb)
					
L7 (DPEPhos)	**L8**	**L9** (BINAP)	**L10**	**L11** (XPhos)	**L12** (Xantphos)

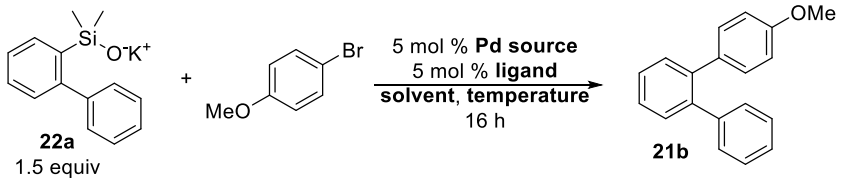
6. Results and Discussion

Each DoE screening reaction was run for 16 h, then immediately worked up. *n*-Tetradecane (100 μmol) was added to each reaction as an internal standard, to allow calculation of yields of product and recovered starting materials (anisoyl bromide, and (2-biphenyl)dimethylsilanol **23a**, produced from the silanolate during aqueous workup). Since protiodesilylation of silanolates during cross-coupling is known, yields of biphenyl were also calculated. The results of the DoE screen are shown in Table 3.

No DoE screen reaction could significantly outperform the results obtained with 'ligandless' APC. It appears that the hindered steric environment around Si disfavors the approach of a second silanolate to activate the species for transmetalation, allowing side-reactions such as protiodesilylation to occur.

Although this second, Hiyama-Denmark reaction proceeded favorably for electron-poor aryl bromides, it remains a challenging procedure for electron-rich aryl bromides such as anisoyl bromide.

Table 3. Results of DoE Screen



Run	Solvent	Temp, °C	Pd source	Ligand	Recovered ArylBr	Biphenyl yield	Recovered silanol	Yield
1	cymene	100	$(PhCN)_2PdCl_2$	Xantphos	55%	28%	0%	3%
2	dioxane	100	$[AllylPdCl]_2$	*n*-Bu_3P	37%	10%	7%	0%
3	toluene	80	$Pd(OAc)_2$	Xantphos	68%	20%	2%	2%
4	cymene	80	$[AllylPdCl]_2$	BINAP	48%	14%	2%	4%
5	dioxane	100	$Pd(OAc)_2$	PPh_3	37%	n.d.	0%	4%
6	toluene	80	$Pd_2(dba)_3$	$AsPh_3$	39%	2%	31%	0%
7	cymene	100	$Pd_2(dba)_3$	PPh_3	9%	8%	1%	1%
8	cymene	140	$Pd(OAc)_2$	XPhos	n.d.	37%	0%	4%

Table 3 (cont.). Results of DoE Screen

Run	Solvent	Temp, °C	Pd source	Ligand	Recovered ArylBr	Biphenyl yield	Recovered silanol	Yield
9	DME	80	$Pd(OAc)_2$	$AsPh_3$	8%	n.d.	0%	16 %
11	DME	80	$[AllylPdCl]_2$	dppb	0%	9%	21%	0%
12	toluene	100	$Pd(OAc)_2$	*bis*-hydrazone	68%	16%	3%	8%
13	cymene	80	$[AllylPdCl]_2$	$AsPh_3$	64%	10%	6%	11%
14	cymene	100	$Pd(OAc)_2$	*n*-Bu_3P	37%	7%	0%	13%
15	DME	80	$Pd_2(dba)_3$	dppf	0%	n.d.	0%	2%
16	dioxane	80	$Pd(OAc)_2$	BINAP	70%	n.d.	3%	3%
17	cymene	100	$[AllylPdCl]_2$	$POPh_3$	18%	10%	11%	22%
18	cymene	140	$Pd(OAc)_2$	*n*-$BuPAd_2$	72%	15%	0%	7%
19	toluene	100	$Pd_2(dba)_3$	dppb	65%	26%	1%	2%
20	DME	80	$(PhCN)_2PdCl_2$	Xantphos	75%	n.d.	0%	0%
21	dioxane	100	$Pd(OAc)_2$	XPhos	25%	n.d.	0%	3%
22	DME	80	$Pd_2(dba)_3$	BINAP	0%	24%	0%	4%
23	toluene	80	$Pd(OAc)_2$	dppf	41%	21%	0%	20%
24	cymene	100	$Pd_2(dba)_3$	dppf	0%	6%	3%	5%
26	cymene	100	$(PhCN)_2PdCl_2$	*n*-$BuPAd_2$	15%	3%	9%	7%
27	dioxane	100	$(PhCN)_2PdCl_2$	$POPh_3$	81%	n.d.	0%	0%
28	toluene	80	$[AllylPdCl]_2$	*bis*-hydrazone	10%	0%	5%	45%
29	dioxane	80	$Pd_2(dba)_3$	dppb	n.d.	n.d.	0%	0%
30	toluene	80	$Pd_2(dba)_3$	$POPh_3$	n.d.	3%	76%	1%
31	dioxane	100	$Pd_2(dba)_3$	Xantphos	54%	34%	2%	0%
32	dioxane	80	$Pd(OAc)_2$	DPEPhos	n.d.	34%	1%	0%
33	cymene	140	$(PhCN)_2PdCl_2$	*bis*-hydrazone	0%	13%	0%	0%
34	toluene	100	$Pd(OAc)_2$	$POPh_3$	0%	10%	0%	13%
37	DME	80	$[AllylPdCl]_2$	$POPh_3$	0%	45%	0%	0%

Table 3 (cont.). Results of DoE Screen

Run	Solvent	Temp, °C	Pd source	Ligand	Recovered ArylBr	Biphenyl yield	Recovered silanol	Yield
39	toluene	80	$Pd(OAc)_2$	XPhos	n.d.	5%	62%	2%
40	cymene	80	$Pd(OAc)_2$	*bis*-hydrazone	n.d.	6%	26%	2%
42	cymene	140	$Pd(OAc)_2$	PPh_3	72%	10%	1%	9%
43	DME	80	$Pd_2(dba)_3$	DPEPhos	83%	n.d.	3%	2%
44	cymene	80	$(PhCN)_2PdCl_2$	PPh_3	77%	8%	12%	0%
45	dioxane	100	$Pd(OAc)_2$	*n*-BuPAd$_2$	0%	51%	0%	4%
46	dioxane	100	$Pd(OAc)_2$	dppf	44%	n.d.	0%	12%
47	toluene	100	$[AllylPdCl]_2$	$AsPh_3$	0%	4%	7%	49%
48	cymene	80	$[AllylPdCl]_2$	DPEPhos	38%	19%	10%	1%
49	toluene	100	$[AllylPdCl]_2$	Xantphos	0%	6%	1%	22%
51	dioxane	80	$(PhCN)_2PdCl_2$	*n*-Bu_3P	44%	n.d.	8%	1%
52	dioxane	100	$Pd_2(dba)_3$	$AsPh_3$	79%	n.d.	4%	1%
53	cymene	80	$Pd_2(dba)_3$	*n*-Bu_3P	n.d.	13%	55%	0%
54	cymene	80	$(PhCN)_2PdCl_2$	dppb	74%	13%	13%	0%
55	toluene	80	$(PhCN)_2PdCl_2$	DPEPhos	n.d.	6%	66%	1%
56	toluene	80	$(PhCN)_2PdCl_2$	BINAP	n.d.	13%	50%	0%
57	cymene	80	$[AllylPdCl]_2$	XPhos	54%	18%	1%	6%
61	cymene	80	$Pd(OAc)_2$	$POPh_3$	84%	7%	n.d.	3%
62	dioxane	100	$Pd_2(dba)_3$	BINAP	n.d.	84%	0%	0%
63	dioxane	80	$Pd_2(dba)_3$	*bis*-hydrazone	70%	n.d.	7%	3%
67	DME	80	$(PhCN)_2PdCl_2$	*bis*-hydrazone	0%	96%	0%	0%
68	toluene	80	$Pd(OAc)_2$	dppb	n.d.	14%	32%	3%
69	DME	80	$Pd(OAc)_2$	PPh_3	n.d.	91%	0%	0%
70	dioxane	80	$[AllylPdCl]_2$	Xantphos	0%	13%	2%	6%
72	cymene	80	$Pd_2(dba)_3$	Xantphos	49%	17%	7%	0%

Table 3 (cont.). Results of DoE Screen

Run	Solvent	Temp, °C	Pd source	Ligand	Recovered ArylBr	Biphenyl yield	Recovered silanol	Yield
73	cymene	100	$Pd(OAc)_2$	$AsPh_3$	58%	6%	1%	3%
74	toluene	100	$(PhCN)_2PdCl_2$	XPhos	56%	5%	36%	4%
75	toluene	100	$Pd(OAc)_2$	BINAP	0%	5%	2%	33%
76	cymene	100	$(PhCN)_2PdCl_2$	DPEPhos	72%	n.d.	0%	0%
78	toluene	80	$Pd(OAc)_2$	*n*-BuPAd$_2$	73%	3%	15%	4%
79	dioxane	80	$(PhCN)_2PdCl_2$	$AsPh_3$	n.d.	55%	25%	2%
80	dioxane	80	$[AllylPdCl]_2$	dppf	0%	17%	2%	22%
82	cymene	100	$[AllylPdCl]_2$	*bis*-hydrazone	61%	0%	18%	10%
83	toluene	100	$[AllylPdCl]_2$	dppf	0%	0%	4%	32%
84	dioxane	100	$[AllylPdCl]_2$	DPEPhos	7%	4%	3%	26%
85	dioxane	100	$(PhCN)_2PdCl_2$	dppb	100%	0%	0%	0%
88	cymene	140	$Pd(OAc)_2$	dppf	71%	7%	9%	2%
90	cymene	80	$Pd_2(dba)_3$	*n*-BuPAd$_2$	43%	11%	5%	4%
91	dioxane	80	$Pd_2(dba)_3$	PPh_3	50%	n.d.	8%	3%
94	dioxane	100	$(PhCN)_2PdCl_2$	*bis*-hydrazone	50%	42%	0%	0%
95	cymene	100	$[AllylPdCl]_2$	dppb	0%	15%	1%	15%
96	toluene	80	$[AllylPdCl]_2$	PPh_3	21%	13%	0%	20%
97	cymene	80	$(PhCN)_2PdCl_2$	dppf	74%	14%	1%	1%

bis-Hydrazone = **L5**. n.d. = not determined due to overlap on chromatogram. Run numbers refer to randomization numbers generated by the DoE software. Not all integers from 1–98 are represented due to incompatibility between solvent and temperature at standard pressure.

7. FUTURE WORK

It is possible that combinations of temperature, solvent, Pd source, and ligand are not sufficient to raise the yields of this reaction with electron-rich aryl bromides to synthetically useful standards. It appears that the low reactivity is a result of steric obstruction around the Si atom. Use

of cesium rather than potassium silanolates may favor transmetalation, due to their higher nucleophilicity.

If it is possible to increase the yields to a useful level, other analogs of **24** may be produced, to yield other 1,2-disubstituted products, including 1,2-disubstituted heterocycles, or (*Z*)-alkenes.

The immediate product of the initial Suzuki reaction prior to workup is a silanolate. Therefore, the optimized double cross-coupling reaction could potentially be expanded to a one-pot process without the requirement of isolation and separate deprotonation of the monocoupled silanol.

8. Conclusions

A bench-stable, crystalline oxasilaborolate capable of double cross-coupling reactions to form *ortho*-terphenyls has been synthesized. The initial Suzuki reaction gave high yields. However, after a four-factor DoE study, conditions were not identified to allow synthetically useful Hiyama-Denmark couplings of electron-rich aryl bromides, and the project was not continued. This contrasts with electron-poor aryl bromides, which could be coupled in excellent yield.

CHAPTER 3 THE ENANTIOSELECTIVE SYNTHESIS OF 3-SUBSTITUTED MORPHOLINES USING COMPUTER-GUIDED CATALYST DESIGN

1. INTRODUCTION

Enantioselective methods for the synthesis of substituted morpholines are sought after due to their paucity. Many pharmaceuticals and natural products contain *C*-substituted morpholines, including the appetite suppressant phendimetrazine, the antidepressant reboxetine, and the plant alkaloid polygonapholine, a component of a tonic used in traditional Taiwanese medicine (Figure 1).[88–92] Additionally, bupropion, an anti-depressant and smoking cessation aid, undergoes metabolic oxidation and ring closure to form the active morpholine compound **33** (Scheme 18).[93] Chiral, enantioenriched acylmorpholines have been used as a subunit of peptides and peptidomimics, where conformation is controlled by the six-membered morpholine ring.[94,95]

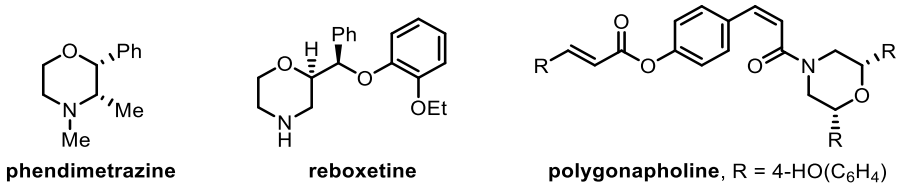
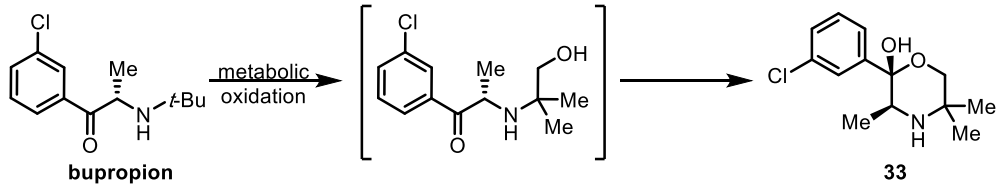


Figure 1. *C*-Substituted Morpholines of Interest

Scheme 18. Conversion of Bupropion to Active Metabolite **33**



Chiral, enantioenriched, *C*-substituted morpholines are also useful tools in synthetic chemistry. They may behave as enantioselective organocatalysts for aldol,[96,97] Michael,[96,98] and aziridination[99] reactions, and dialkylzinc addition to aldehydes.[100] These cyclic compounds are also useful as chiral auxiliaries for the diastereoselective synthesis of propargylamines[101] and tetrahydropyridines.[102] The diversity of morpholines that have been used for these purposes is limited only to a few, readily-available compounds, synthesized from a few chiral pool α-amino acids. Morpholines may also be used as precursors to enantioenriched α-amino acids[103] and 1,2-amino alcohols.[104]

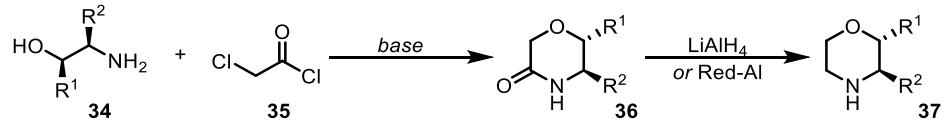
2. BACKGROUND

2.1 The Enantioselective Synthesis of Morpholines

2.1.1 Prior Art

The preparation of enantioenriched, *C*-substituted morpholines has traditionally depended on the stepwise annulation of two C2 units with preinstalled, stereogenic centers.[105–111] Most commonly, a chiral, enantioenriched amino alcohol **34** is coupled with a bis-electrophile such as α-chloro acetyl chloride **35**, followed by reduction of the resultant morpholinone **36** to yield morpholine **37** (Scheme 19). Diastereoselection may also occur in the case of a chiral electrophile.[112] Overall, this and similar approaches require several steps, are plagued by low yields, and often necessitate protecting group strategies.[113–116]

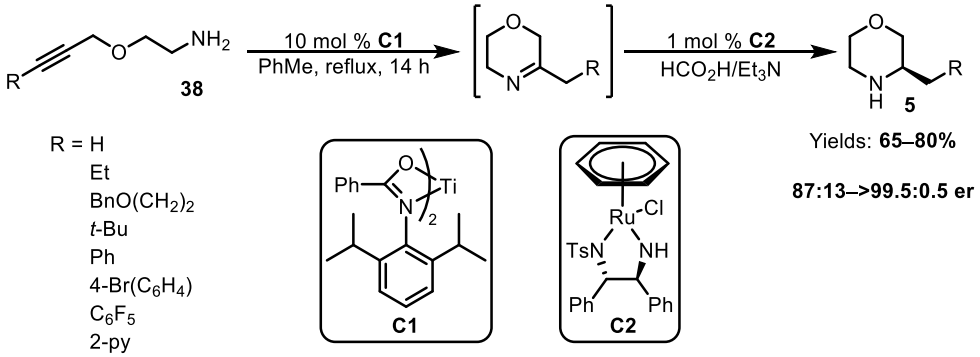
Scheme 19. Synthesis of Morpholines from Enantioenriched Amino Alcohols



An alternative strategy has been to resolve the enantiomers of racemic morpholines by chiral stationary phase chromatography, by formation of diastereomeric derivatives and their separation, or by kinetic resolution.[117–119]

A more enticing possibility is one-step enantioselective cyclization to the morpholine. Schafer has reported a one-pot alkyne hydroamination and enantioselective imine reduction of amino propargyl ethers **38**, using sequential Ti catalysis and Ru catalysis to form 3-substituted morpholines enantioselectively (Scheme 20).[120] Although product enantiomeric ratios were generally in excess of 98.5:1.5, little functional group compatibility was demonstrated.

Scheme 20. Schafer's Hydroamination-Reduction to form Enantioenriched Morpholines

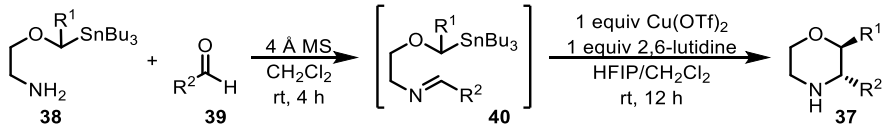


2.1.2 SnAP Morpholine Synthesis

Most recently, Bode and coworkers have developed a morpholine synthesis based on SnAP (the stannyl amine protocol). SnAP chemistry offers an air- and moisture-tolerant, one-pot synthesis of many nitrogen heterocycles, such as piperazines and morpholines, without the use of protecting groups.[121–124] A wide range of pendant moieties derived from alkyl and (hetero)aryl aldehydes may be incorporated, and the method is compatible with diverse functional groups. Pendant (alkyl or aryl) halides, phenols, ethers, aldehydes, esters, tertiary amines, amides, carbamates, pinacolboronates, nitriles, and nitro groups have all shown compatibility with the reaction conditions. Many SnAP reagents are commercially available,[125] and can be made on multi-gram scale.

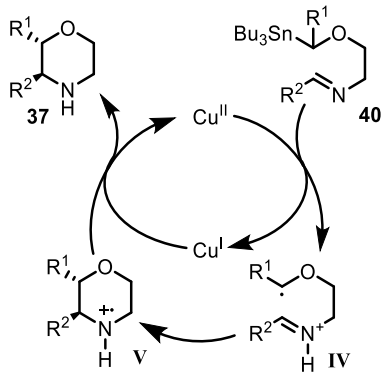
An initial report by Bode and coworkers detailed the synthesis of 3-substituted morpholines **37** from SnAP M **38a** (R^1 = H) with aliphatic or (hetero)aryl aldehydes or glyoxals **39** (Scheme 21).[126] SnAP M may be made in four steps from commercially-available tributyl(iodomethyl)stannane and ethylene glycol.

Scheme 21. Stoichiometric SnAP Morpholine Synthesis



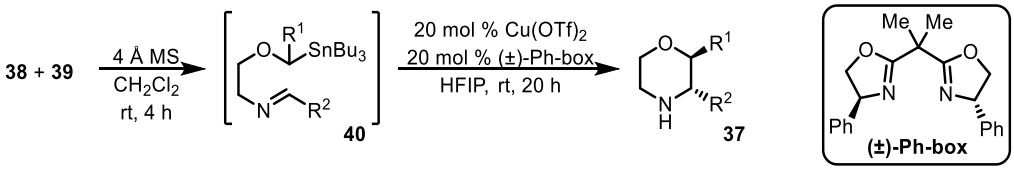
After initial formation of imine **40**, it is hypothesized that Cu^{II} oxidizes the stannane to a carbon-centered radical **IV**, with concomitant protonation of the imine (Scheme 22).[124] The resultant α-alkoxy radical attacks the iminium to form a N-centered radical cation **V**, which is reduced by the Cu^{I} generated in the first step, to form a morpholine **37**. The facile, intramolecular cyclization of this radical intermediate may explain the wide functional group compatibility and substrate scope of the reaction. Although this is a redox-neutral process, initially, a stoichiometric amount of Cu^{II} was required, since it appears that the Lewis basic products inhibit the reaction. Furthermore, aldehydes such as 2-pyridylcarboxaldehyde with proximal Lewis basic functionalities do not undergo cyclization.

Scheme 22. Putative Mechanism for SnAP Morpholine Synthesis



A breakthrough in SnAP chemistry was made when ligands were identified to allow for substoichiometric loadings of Cu^{II} (Scheme 23).[127] Although a number of ligand classes were screened, single-carbon-bridged bisoxazolines significantly outperformed all others, though extensive variation was observed within this class. Additionally, a decrease in the CH_2Cl_2/HFIP ratio of the solvent (or use of 100% HFIP) dramatically increased yield in the substoichiometric reaction, possibly by stabilizing the Lewis basic products by hydrogen-bonding.

Scheme 23. SnAP Reagent Synthesis of Morpholines

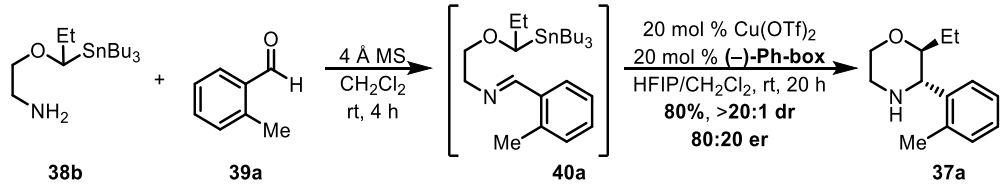


Under the substoichiometric protocol, morpholines **37** can be formed in excellent yield. The scope of aldehydes **39** included pendant phenols, esters, aryl pinacolboronate esters and protected heterocycles. Where R^1 = Me or Et, the diastereomeric ratio of all published examples has been >20:1 *anti*:*syn*. In any case involving substituted SnAP reagents, the more thermodynamically stable product is formed.

The substoichiometric protocol also paves the way for a synthetically useful, enantioselective process. Indeed, Bode was able to produce one example of a ligand, **(*S*,*S*)-Ph-box**, capable of forming enantioenriched morpholines from SnAP M **38a** (Scheme 24). Morpholine **37a** was produced in 80% yield, 80:20 er, and ≥20:1 dr. This result gives credence to the hypothesis that SnAP cyclization proceeds *via* an intermediate, achiral radical such as **IV**.

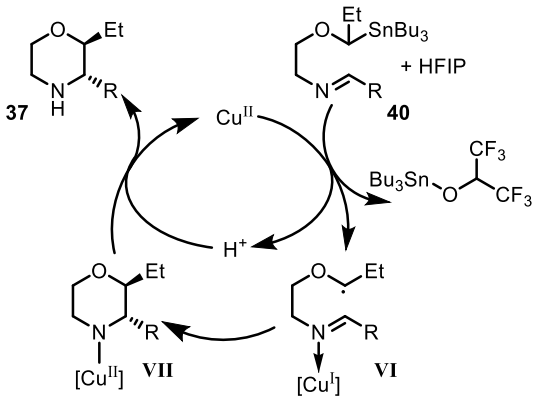
A stereoconvergent mechanism must be in operation, favoring one enantiomer of product from racemic precursor **40a**. Although this result is promising, the enantioselectivity so far is moderate. Additionally, since Bode's proposed mechanism (Scheme 22) does not involve the metal in the stereodetermining step, the true mechanism must differ from this.

Scheme 24. Enantioselective Cyclization of Ethyl SnAP M **38b**



A new, putative catalytic cycle is proposed (Scheme 25). After formation of the initial, achiral radical intermediate **VI**, the Cu bisoxazoline complex is coordinated to the Lewis basic N atom during cyclization to **VII**, allowing enantioselection. Rather than producing a radical cation bound datively to a reducing Cu^{I} species, it is likely that this process would form a Cu^{II} amide, which must be protonolysed to release morpholine **37** to allow catalytic turnover.

Scheme 25. New Proposed Catalytic Cycle



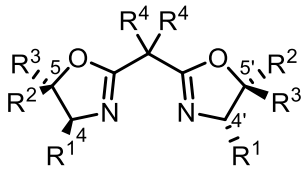
SnAP chemistry has also been used to make a wide variety of other *N*-heterocycles, including piperazines, thiomorpholines, spirocycles and fused bicycles, and 7–9-membered rings.[121–124,128] Ketimines formed from cyclic ketones or trifluoromethyl ketones may be used in place of aldimines as substrates.

2.2 Computational Background

Bode's promising result is a perfect candidate for the Denmark group's long-running interest in chemoinformatic optimization, with the aim to improve the suboptimal enantioselectivity. The group's chemoinformatic screening, developed by Jeremy Henle and Andrew Zahrt, involves selection of a maximally-diverse training set of ligands using a Kennard-Stone algorithm, from a very large *in silico* library of potential ligands. This strategy provides maximal diversity of the training set within chemical space, with some user-defined restrictions for ease of synthesis or from experimental determination of viable ligands.

2.2.1 The *in silico* Library

For the *in silico* library, only single-carbon-bridged bisoxazolines **41** with points of diversity at R^1, R^2, R^3 and R^4 were chosen (Figure 2). Based on literature results from the field of bisoxazoline catalysis and the proximity to the metal, the library had been made to include the greatest diversity at R^1, with 166 possible substituents, including alkyl, aryl, and benzyl groups, and their heteroatom- and functional group-substituted analogs (Figure 3).[129] R^2 and R^3 were chosen to be H, Me, *t*-Bu, Ph, *p*-MeO(C_6H_4) or *p*-F_3C(C_6H_4). For synthetic ease, an additional constraint was issued such that when neither $R^2 \neq R^3$, one of the two must be H, and no di-*t*-butyl substitution was permitted at C5. Lastly, R^4 must be H, Me, or a 3–6-membered carbocycle. After these constraints, the combinatorial library contained 15936 members, created from all permissible combinations of R^1, R^2, R^3, and R^4.



11

Figure 2. Bisoxazoline Points of Diversity and Standard Atom Numbering

At this point, electrostatic and steric interaction parameters are calculated for each of the potential ligands, followed by the calculation of descriptors, which allow the compounds to be mapped in multidimensional chemical space. A Kennard-Stone algorithm is applied to calculate the representative training set of ligands to be synthesized and tested, which reduces the original library of 15936 bisoxazolines to 39 representative ligands. Since the effects of each substitution

may be computationally deconvoluted, this is akin to testing a library of $\prod_i n_i$ potential catalysts (where *i* are the possible substituents and *n* the four points of diversity), without the extreme synthetic overhead. The bisoxazoline training set was made to contain 39 ligands (Figure 4). The aim of multiple projects in the Denmark group and between our collaborators was to synthesize the ligands of the training set, and test their merits in various enantioselective reactions.

2.2.2 Computational Modeling

From empirical enantioselectivity results, a quantitative structure-selectivity relationship (QSSR) is computationally determined. A QSSR compares structural parameters of a library of ligands to their selectivity, for example for binding a series of biological receptors. In this work, the QSSR will be between descriptors (calculated from electronic and steric parameters) of the *in silico* library of bisoxazolines, and their selectivity as ligands for the copper-catalysed enantioselective SnAP synthesis of *C*-substituted morpholines. Modeling will be performed using *n*-component partial least squares, and *k*-fold cross-validation, to test for overfitting.

Through this model, an optimal catalyst for the reaction will be predicted. Predictive catalyst modeling is a powerful field, thus far in its infancy, so this could be an exceptionally powerful tool for catalyst optimization.[130–135] The current state of the art is overwhelmingly retrospective explanation of a QSSR. Furthermore, since all calculations are based on the ligand alone, the library is applicable for predictive modeling of any reaction experimentally determined to be amenable to bisoxazoline catalysis. The group is taking advantage of this property to apply the library and initial training set to the optimization of other enantioselective reactions.

After an initial round of modeling, a small set of predicted catalysts are predicted for the reaction in question. These catalysts will in turn be synthesized and tested. If the data remain unsatisfactory, they too will be used to refine the model. An improved model is generated, and its predictive qualities tested in the same way. After some number of iterations, the model will be able to predict an optimal catalyst for this reaction, so long as the data spread is sufficient, and the optimal structure is within the domain of applicability of the model.

In the following sections, bisoxazolines **41** from the training set will be designated by their R^1 group for distinction.

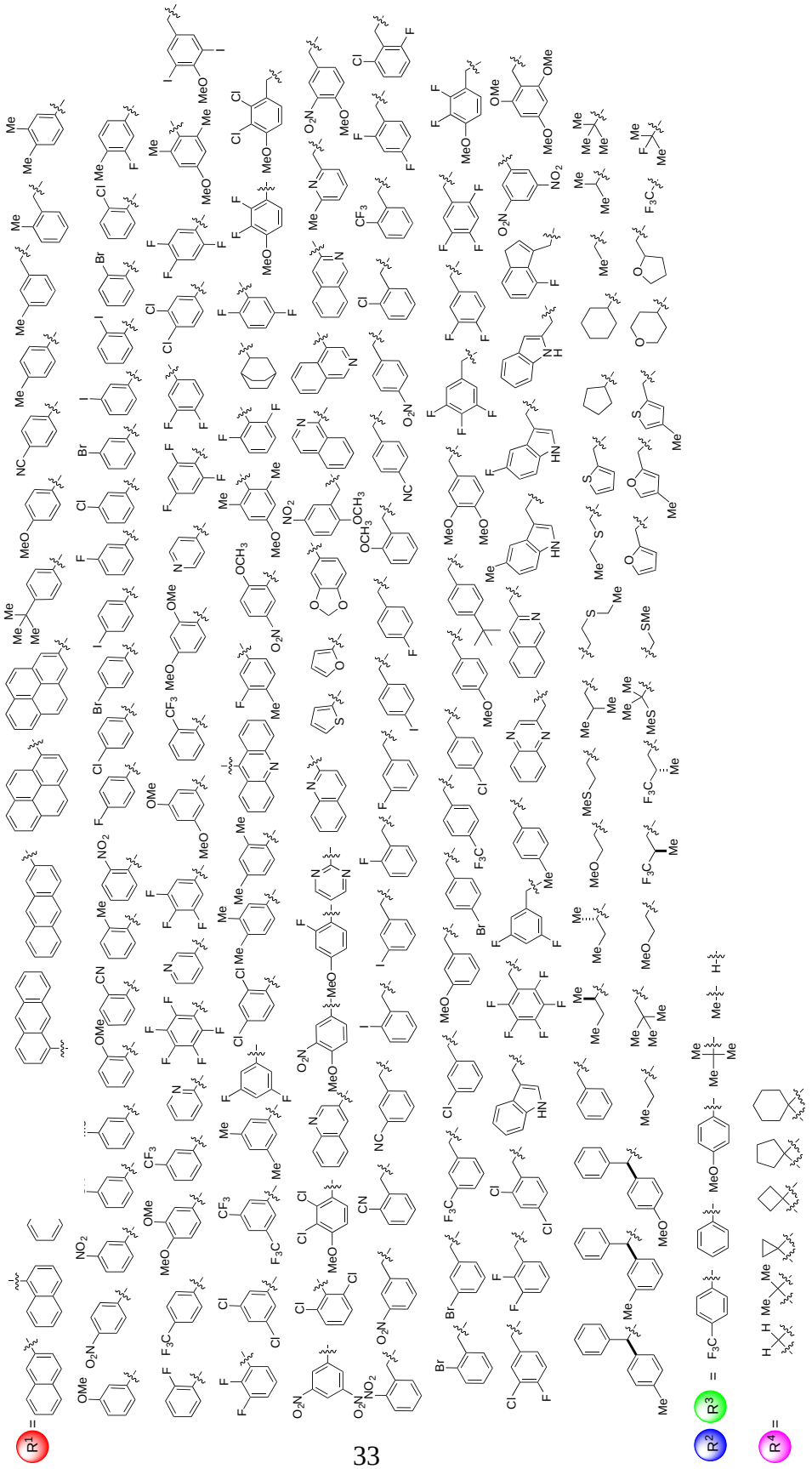


Figure 3. The Database of R^1 Substituents

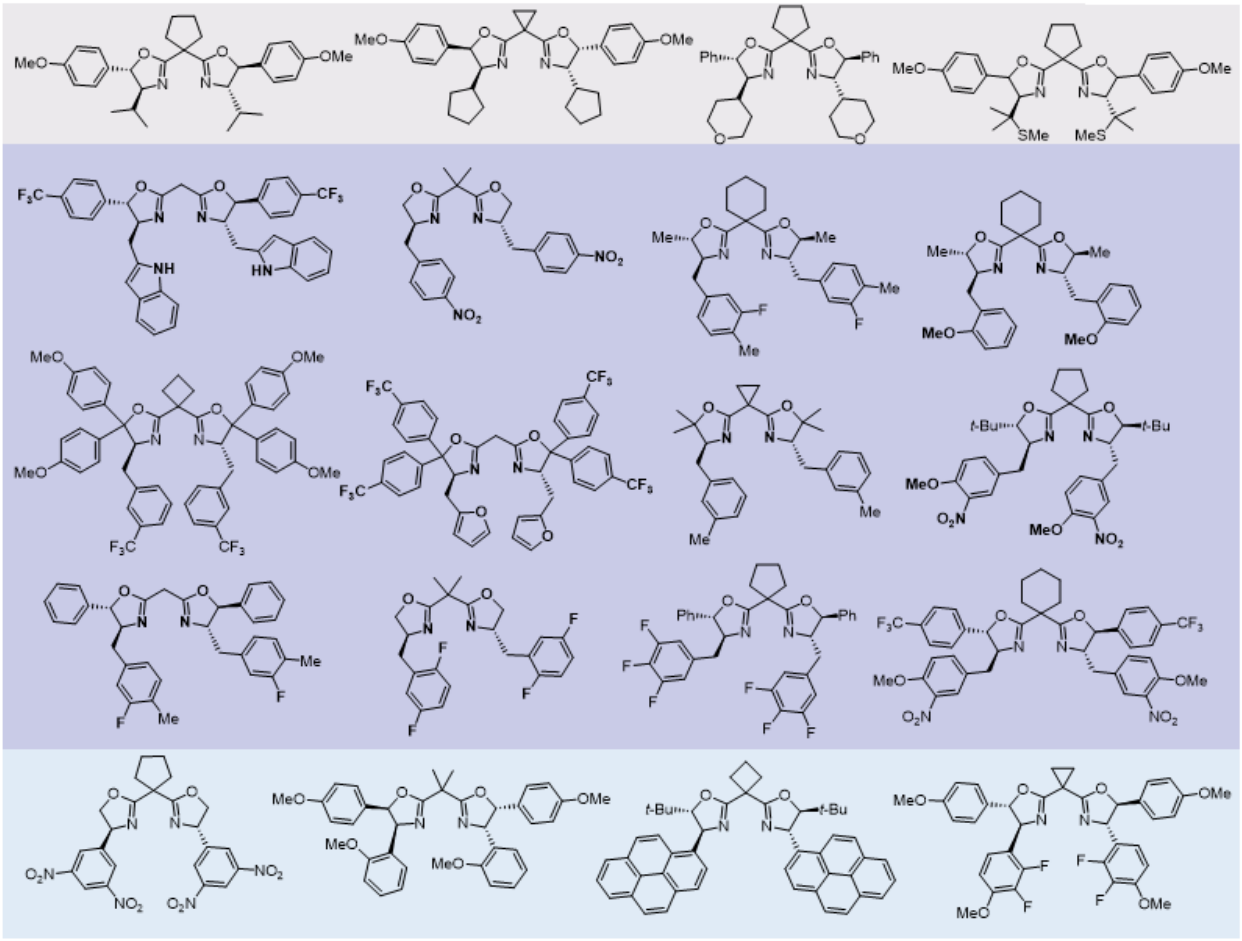


Figure 4. Final Training Set (Structures 1–20)

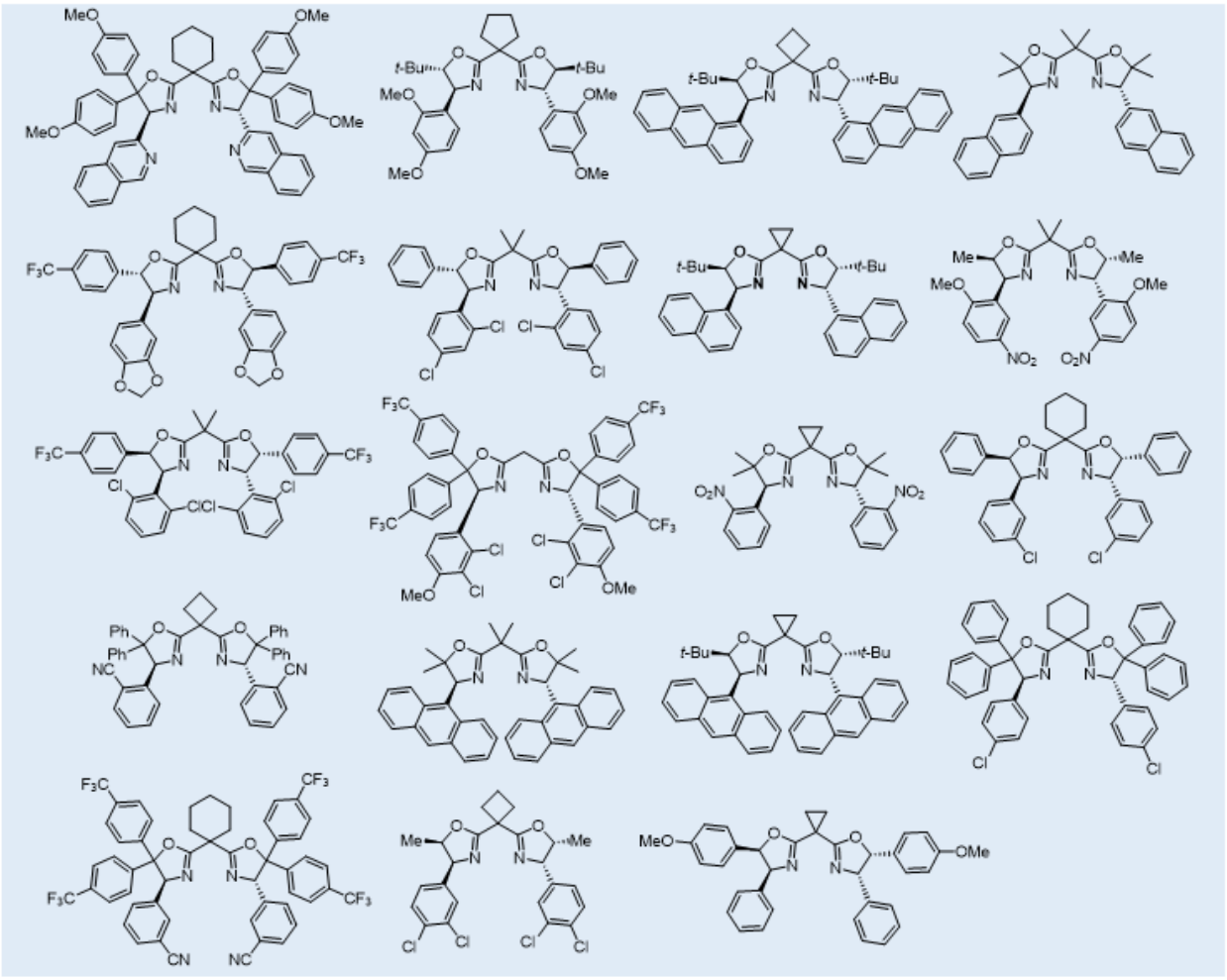


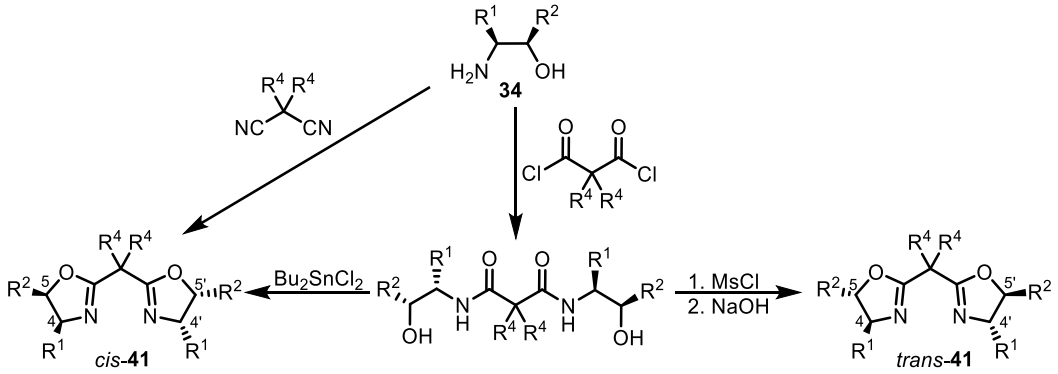
Figure 4 (cont.). Final Training Set (Structures 21–39)

3. BISOXAZOLINE SYNTHETIC PLANS

3.1 General Retrosynthetic Plans

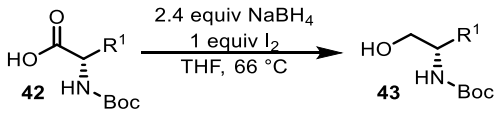
Only one training set bisoxazoline was already known in the literature.[136] However, multiple procedures exist for bisoxazoline cyclization from 1,2-amino alcohols **34** (Scheme 26).[129] These cyclizations may be made either retentive or invertive with respect to a stereocenter adjacent to the hydroxyl group, when present. Cyclization is often slow, many literature bisoxazolines only being formed after multiple days at reflux, although removal of the H_2O byproduct from the reaction mixture may speed up the reaction.

Scheme 26. Stereodivergent Cyclizations of Amino Alcohols **34**



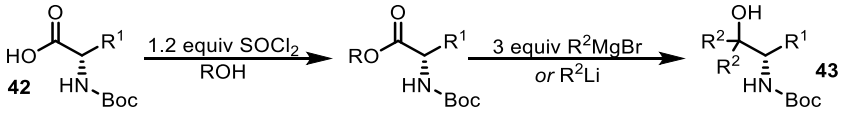
Synthesis of the 39 enantioenriched precursor amino alcohols **34** for the bisoxazoline training set is vastly more challenging. Where C5 is unsubstituted, the *N*-protected amino acid **42** may be synthesized and then reduced by a number of methods, commonly $LiAlH_4$, borane, or $NaBH_4$-iodine (Scheme 27).[137,138] A Boc protecting group gives higher yields during the reduction step.

Scheme 27. Reduction of Amino Acids **42**



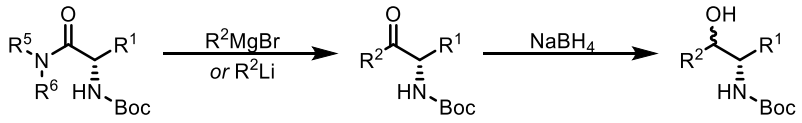
Where C5 is disubstituted (ie: $R^2 = R^3 \neq H$), the amino alcohol may be made from the amino acid **42** by esterification, followed by a double Grignard (or organolithium) addition (Scheme 28).[139] Again, use of a Boc protecting group tends to afford higher yields in the organometallic addition step.

Scheme 28. Tertiary Amino Alcohol Formation from Esters



The case where C5 is a stereocenter ($R^2 \neq R^3$, where according to our constraints one substituent must be H) is complicated by the potential for the formation of diastereomers. The precursor Boc-protected ketone **44** may be made selectively from the Weinreb amide **45** or morpholine amide **46**, without over-addition to form the tertiary alcohol (Scheme 29).[140–142] The stereochemical result of subsequent $NaBH_4$ reduction is inconsistent (and often unsubstantiated) in the literature, but typically gives high dr – a subsidiary goal of this project is to ascertain the true stereochemical nature of Boc-protected amino alcohols **43** formed *via* this method.[143–147]

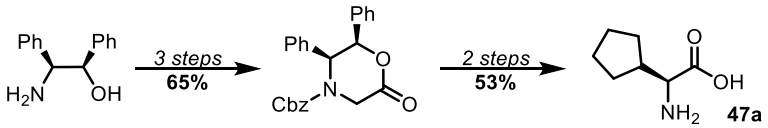
Scheme 29. Diastereoselective Reduction of Amino Ketones



3.2 Synthesis of Amino Alcohol Precursors

Only two of the desired amino alcohols could be produced directly from cheap, chiral pool amino acids. The magnitude of difficulty of synthesis of the other enantiopure α-amino acids is illustrated by desired 2-cyclopentylglycine **47a** being the sole subject of a *Tetrahedron Lett.* synthesis paper.[148] This work required five steps to form the unprotected amino acid as a single enantiomer and in 33% overall yield from reasonably-priced, commercially-available precursors, using an enantiopure, chiral amino alcohol template (Scheme 30).[149]

Scheme 30. Synthesis of (*S*)-2-Cyclopentylglycine **47a**



However, most of the required amino alcohols were made from their corresponding α-amino acids. These in turn were synthesized through a variety of precedented procedures (Chart 2). Alternatively, amino alcohols could be made from enantioenriched 1,2-diols, made *via* the Sharpless AD reaction, using cyclic sulfates as electrophilic intermediates.[150,151]

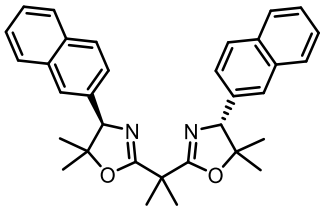
Chart 2. Methods used for Amino Acid Synthesis

Method	Example
Chiral pool amino acids	Isopropyl bisoxazoline
Racemic synthesis and resolution	5-Benzodioxolyl bisoxazoline
Chiral auxiliary methods	Cyclopentyl bisoxazoline
O'Donnell alkylation	3-Methylbenzyl bisoxazoline
Enantioselective Strecker reaction	4-Tetrahydropyranyl bisoxazoline
Corey-Link reaction	Initial attempt: 2-methoxyphenyl bisoxazoline (*vide infra*)

Where R^1 was benzylic, the relevant benzyl bromide could be used to install the group *via* an O'Donnell alkylation of a doubly-protected glycine.[152,153] Synthetic routes to these ligands were prepared by Andrew Zahrt, and as such will not be discussed here in further detail.

4. BISOXAZOLINE SYNTHESIS

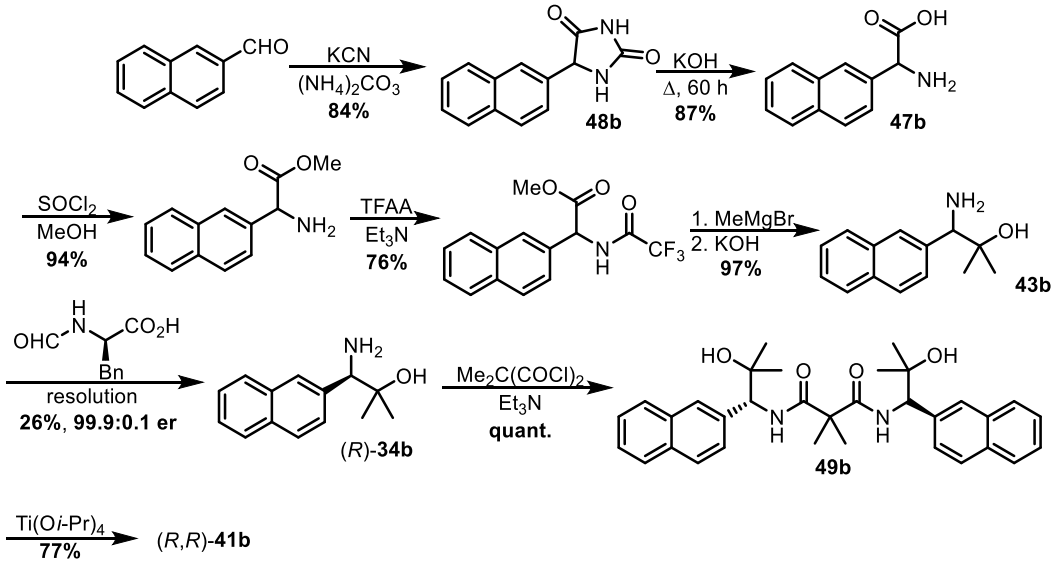
2-Naphthyl Bisoxazoline 41b



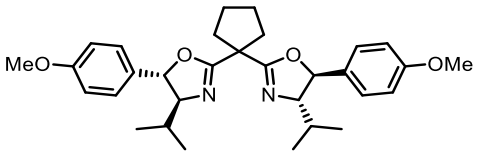
The first bisoxazoline to be made was the 2-naphthyl bisoxazoline, following a literature procedure.[136] Firstly, a Bucherer-Bergs reaction was used to synthesize hydantoin **48b** in high yield (Scheme 31). Hydrolysis with aqueous KOH at 115 °C in a sealed tube followed. The racemic amino acid **47b** was esterified in excellent yield, and the amine protected with a trifluoroacetyl group, which has been found to increase yields for the addition of Grignard reagents to amino esters. After the double addition of methylmagnesium bromide, the protecting group was removed quantitatively with KOH in aqueous methanol. Enantiomeric resolution was effected with (*S*)-*N*-formylphenylalanine, resulting in enantiopure amino alcohol **34b**, albeit in only 26% yield from the racemate. The bisamide **49b** was formed from dimethylmalonyl dichloride, and cyclization to **41b** was effected by reflux in xylene in the presence of 10 mol % Ti(O*i*-Pr)$_4$.

It was hoped that this synthesis would be didactic with respect to the synthetic routes chosen for other bisoxazolines, particularly the successful choice of protecting group and the ease of bisamide formation and Ti-mediated cyclization. However, the Bucherer-Bergs route was disadvantageous for generalization since an enantioselective variant is unknown, and this enantiomeric resolving agent is likely not applicable to a wide range of amino alcohols.

Scheme 31. Itagaki's Synthesis of 2-Naphthyl Bisoxazoline **41b**



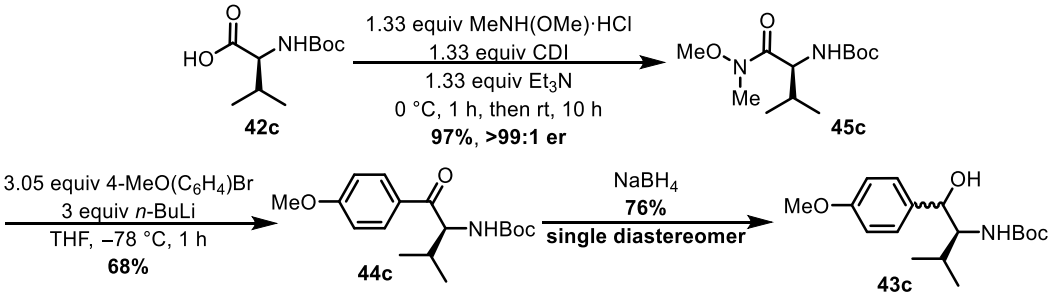
Isopropyl bisoxazoline 41c



Bisoxazoline **41c** is the only ligand of this training set whose R^1 group corresponds to the α-moiety of a chiral pool amino acid, in this case L-valine. Starting from commercially-available Boc-L-valine **42c**, Weinreb amide **45c** was formed in 97% yield without epimerization, by a literature procedure (Scheme 32).[154] Although reaction of similar Weinreb amides with Grignard reagents has often resulted in excellent yields, small changes in substrate structure have been shown to result in large variability in ketone yield, so 2.5 equiv 4-methoxyphenyllithium was produced and added to **45c** at −78 °C to give novel α-amino ketone **44c** in 68% yield, after an *in situ* quench with saturated aqueous NH_4Cl solution, again without epimerization.[143,155] This standard organolithium addition procedure was later confirmed within the group to cause very

little to no epimerization, even with substrates such as arylglycine derivatives, with much more labile stereocenters. $NaBH_4$ reduction of **44c** at −20 °C next proceeded to give 1,2-amino alcohol **43c** with complete diastereoselectivity.

Scheme 32. Synthesis of Amino Alcohol **43c**



Literature $NaBH_4$ reduction procedures for various *N*-alkoxycarbonyl α-amino ketones, while often reporting excellent diastereoselectivity, give mixed opinions on the relative configuration of the product that is formed, generally without evidence. To prove the relative configuration of the amino alcohol, diastereomeric oxazolidinones **50c** were formed separately (Scheme 33). Comparison of their spectral data to each other and to literature values confirmed that the $NaBH_4$ reduction had been *erythro*-selective, ie: it had produced amino alcohol (1*R*,2*S*)-**43c** (Table 4).[156] *Cis*-oxazolidinones generally show larger $^3J_{H4–H5}$ coupling constants and higher field C4 and C5 ^{13}C chemical shifts than their *trans*-analogs. The *erythro*-selective reduction was later confirmed to be general for other substrates, through oxazolidinone formation and NOE studies in our laboratories.

Scheme 33. Stereodivergent Formation of Oxazolidinones **50c**

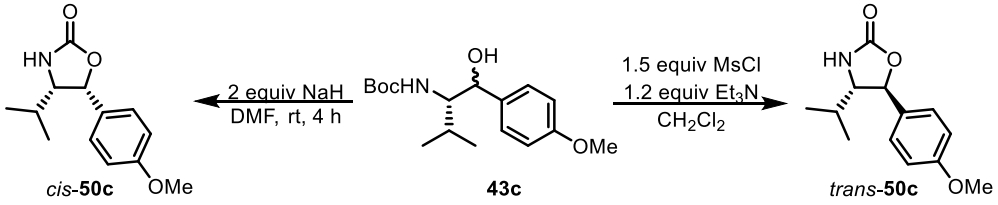
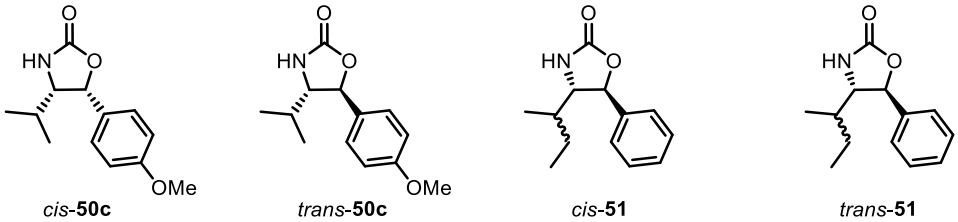


Table 4. NMR Data for Oxazolidinones **50c** and **51**

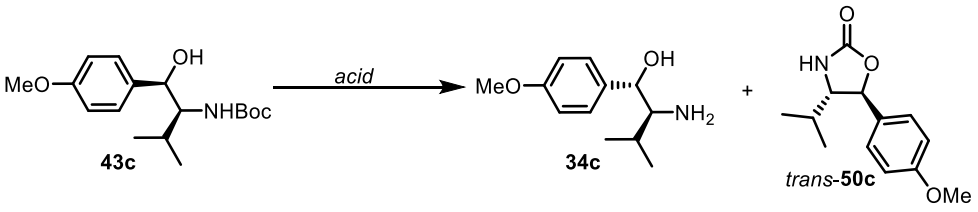


cis-**50c** *trans*-**50c** *cis*-**51** *trans*-**51**

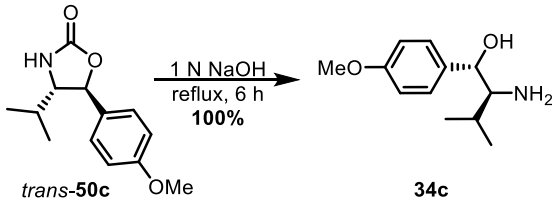
	cis-**50c**	*trans*-**50c**	*cis*-**51**	*trans*-**51**
$^3J_{H4–H5}$ / Hz	8.1	5.5	8.1	4.8
δ H4	3.85	3.53	3.93	3.64
δ H5	5.62	5.16	5.65	5.23
δ C4	63.1	66.0	61.4	64.8
δ C5	81.1	81.4	81.3	81.5

Acid-mediated deprotection attempts of **43c** with TFA in CH_2Cl_2/H_2O, HCl/Et_2O, HCl/dioxane, TMSCl, and TMSI gave partial invertive cyclization from the Boc group to oxazolidinone *trans*-**50c**, presumably due to the stabilization of a full or partial cationic charge adjacent to the electron-donating 4-methoxyphenyl group (Scheme 34). However, oxazolidinone *trans*-**50c** also provided a route to almost quantitative deprotection of the Boc group *via* NaOH-mediated oxazolidinone cleavage, yielding pure, unprotected amino alcohol **34c** after recrystallization (Scheme 35). Inversion of stereochemistry at this early point in the synthesis may be advantageous, compared to manipulation of the stereocenter in the last (bisoxazoline cyclization) step, as is required with a one-step Boc deprotection.

Scheme 34. Attempted Acidic Deprotection of **43c**

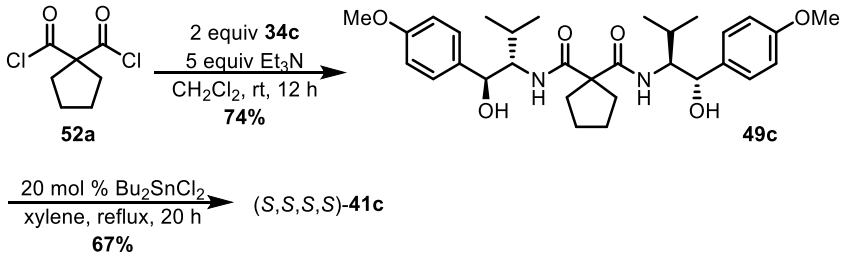


Scheme 35. Preparation of Unprotected Isopropyl Amino Alcohol **34c**

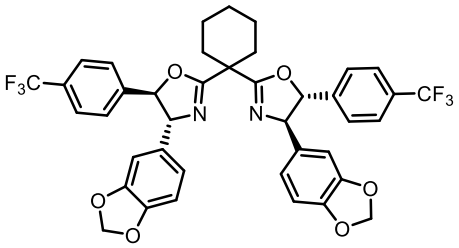


The formation of bisamide **49c** proceeded smoothly using diacid chloride **52a** (Scheme 36). A retentive cyclization using Bu_2SnCl_2 yielded isopropyl bisoxazoline **41c** in 67% yield after two recrystallizations, with no visible *meso*-diastereomer.

Scheme 36. Final Steps to Isopropyl Bisoxazoline **41c**



5-Benzodioxolyl Bisoxazoline 41d



The initial synthetic plan for 5-benzodioxolyl bisoxazoline **41d** involved producing the enantiopure amino acid *via* the modified Corey-Link reaction for arylglycine synthesis.[157]

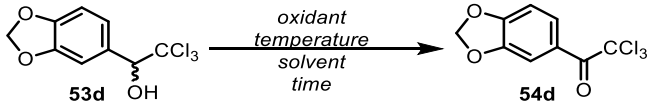
Although formation of the racemic trichloromethyl alcohol **53d** from piperonal was known and reproducible, it had been reported that subsequent Jones oxidation to form ketone **54d** was unsuccessful, presumably due to the lability of the benzodioxolane under strongly acidic conditions.[158] PDC and freshly-prepared bipy chlorochromate were initially tested in place of the Jones reagent, due to their compatibility with the benzodioxolyl group (Table 5, entries 1–2).[159] However, very low conversion was obtained based on NMR spectroscopy on the crude mixture. Although the bipy chlorochromate oxidation showed little undesired reactivity in 3 h, when instead heated and let run for 24 h, yield remained poor, yet side-products were formed (Table 5, entry 3).

A number of other oxidants were screened, a selection being shown in Table 5. Strongly-oxidizing species including RuO_4,[160] $KMnO_4$,[161] and nickel peroxide "NiO_2"[162–165] did not produce the desired product (Table 5, entries 4–6). The milder oxidants MnO_2 (both a commercial source and freshly-made)[166,167] and $BaMnO_4$[168] gave rise to poor yields and many side-products (Table 5,

entries 7–8). Catalytic TEMPO showed a useful yield (69%) of ketone, although roughly 30% of a mixture of side-products was also obtained (Table 5, entry 14).[169] However, PCC oxidation was highly successful, giving a 93% isolated yield of ketone **54d** with 3 equiv oxidant (Table 5, entry 15). This result was surprising in the light of its substantial superiority over the other, similar Cr^{VI} oxidants. The product was isolated simply by Kugelrohr distillation away from the residual chromium byproducts.

Following on from this success, a CBS reduction yielded the Corey-Link substrate, enantioenriched alcohol (*R*)-**53d** in 89% yield and 96.5:3.5 er (Scheme 37).[157,170]

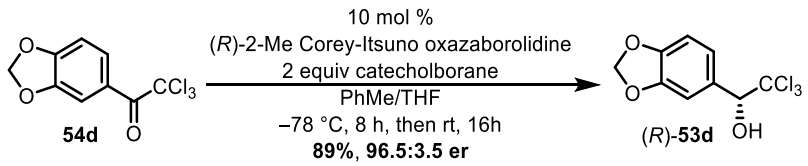
Table 5. Screening Conditions for Oxidation of Trichloromethyl Alcohol **53d**



Run	Oxidant	Temperature, °C	Solvent	Time, h	Conversion, %[a]	Yield, %[a]
1	1.1 equiv PDC	rt	CH_2Cl_2	15	45	20
2	3 equiv bipy $HCrO_3Cl$	rt	CH_2Cl_2	3	29	23
3	3 equiv bipy $HCrO_3Cl$	40	CH_2Cl_2	24	62	35
4	25 mol % RuO_2, 2 equiv $NaIO_4$	rt	CCl_4/H_2O	8	2	0
5	6 equiv $KMnO_4$	rt	PhMe	24	7	0
6	2 equiv NiO_2	50 then 111	PhMe	19 + 12	20	0
7	8 equiv MnO_2	81	Cyclohexane	24	83	50
8	5 equiv $BaMnO_4$	40	CH_2Cl_2	48	100	17
9	20 mol % TEMPO, 3 equiv $PhI(OAc)_2$	rt	CH_2Cl_2	21	100	69
10	3 equiv PCC	40	CH_2Cl_2	24	100	96 (93)[b]

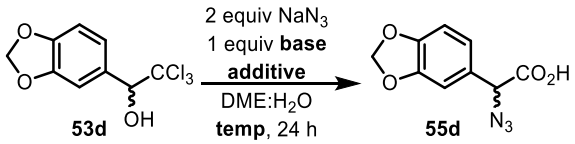
[a] By NMR analysis. [b] Isolated yield.

Scheme 37. CBS reduction of benzodioxolyl ketone **54d**



The azidation step was then attempted, using literature conditions for electron-rich aryl substrates.[157] A low conversion of 23% leading to a mixture of products was obtained after removal of the starting material by acid-base extraction (Table 6, entry 1).

Table 6. Screening Conditions for Azidation of Benzodioxolyl Alcohol **53d**



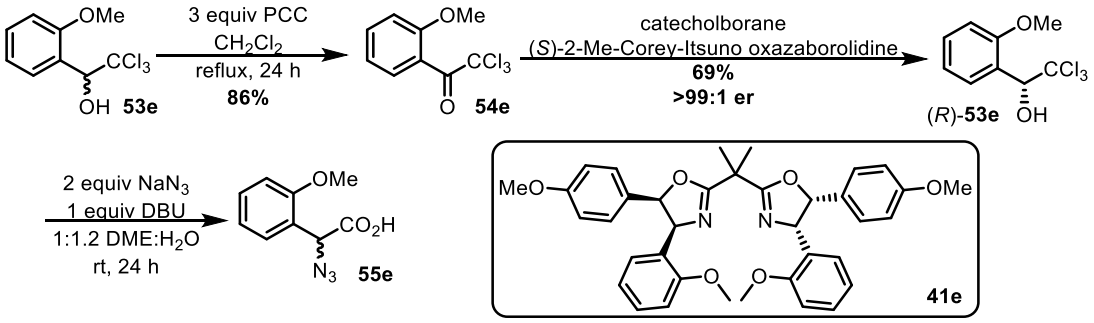
Run	Base	Additive	$DME:H_2O$ Ratio	Temperature, °C	Conversion, %[a]
1	DBU	-	2.75:1	rt	24
2	DBU	1 mol % 18-crown-6	2.75:1	rt	25
3	DBU	10 mol % BTEACl	2.75:1	rt	26
4	DBU	-	2.75:1	40	22
5	NaOH	-	2.75:1	rt	34
6	Cs_2CO_3	-	2.75:1	rt	9
7	DBN	-	2.75:1	rt	25
8	4 equiv NaOH	-	1:4.3	rt	51
9	NaOH	-	1:4.3	rt	31

[a] Mass balance reported of impure material after starting material removed *via* basic extraction

Addition of 1 mol % 18-crown-6 or 10 mol % of the PTC BTEACl did not significantly alter the conversion (Table 6, entries 2–3), despite literature precedent.[171] An increase in temperature to 40 °C also effected little change (Table 6, entry 4), other than the reaction mixture appearing more homogeneous. In no case was racemization of starting material observed.

Since 2-methoxyphenyl amino acid **42e** has been reported to be made *via* the aryl Corey-Link procedure and is relevant toward the synthesis of training set bisoxazoline **41e**, enantiopure trichloromethyl 2-methoxyphenyl carbinol (*R*)-**53e** was also synthesized in an attempt to reproduce the literature conditions (Scheme 38).[157] The PCC oxidation conditions used for benzodioxolyl trichloromethyl alcohol **53d** were again successful on this substrate, forming trichloromethyl ketone **54e** in 86% yield (compared to 60% yield for the literature Jones oxidation). CBS reduction was again highly effective.

Scheme 38. Enantioselective Synthesis of 2-Methoxyphenyl Alcohol **53e** toward Bisoxazoline **41e**



However, the azidation step, described as proceeding in 40% yield over two steps after azide reduction with only minimal racemization to 98.5:1.5 er, was not reproducible in these laboratories. Using freshly-distilled DBU as base, only a 13% mass yield of a complex mixture of substances was obtained once starting material was removed *via* basic extraction.

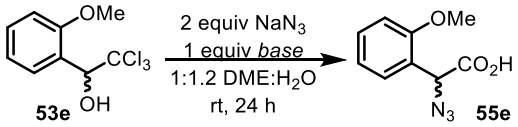
Base and Solvent Screen for Corey-Link Reactions

A small base and solvent screen was executed on racemic alcohol **53e**, in work performed with Jeremy Henle. Although weak organic bases gave no reactivity (Table 7, entry 2), the amidine base DBN offered a similar yield to the slightly less basic DBU, as did TBAOH (Table 7, entries 3–4). Since Aitken's work used unpurified DBU, one run was performed using DBU that appeared pure by NMR, from the bottle without further purification – this gave no conversion, and the starting material was recovered cleanly with no racemization (Table 7, entry 5). All other runs used DBN or DBU distilled recently from BaO, or pyridine or DIPEA distilled freshly from CaH_2. A change in solvent to allow full solubility of the substrate did not promote conversion (Table 7, entries 6–7).

Despite these attempts, the azide was not able to be isolated as a pure compound in the yield described in the original work. Although starting material could be recovered cleanly, the product mixture always contained multiple compounds. Submitting this crude reaction mixture to hydrogenative azide reduction with Pd/C, as in the literature, was unproductive.

Due to the irreproducibility of the literature protocol, a new synthetic route was chosen for the synthesis of 5-benzodioxolyl bisoxazoline **41d**, which was successfully performed between Jeremy Henle, Kevin Robb, Dr Yang Wang, and Robert Zhang in the Denmark group (synthetic route designed by Dr Yang Wang and the author of this document).

Table 7. Screening Conditions for Corey-Link Azidation

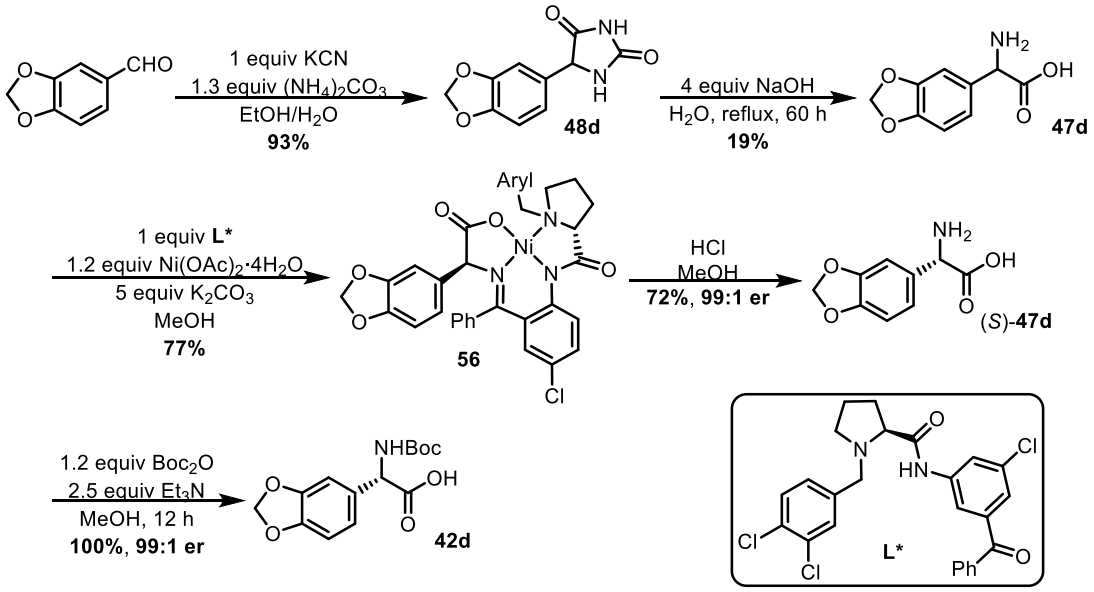


Run	Base	Solvent	Conversion, %[a]
1	DBU	1:1.2 DME/H_2O	13
2	pyridine *or* DIPEA	1:1.2 DME/H_2O	2
3	DBN	1:1.2 DME/H_2O	10
4	TBAOH	1:1.2 DME/H_2O	12
5	DBU[b,c]	1:1.2 DME/H_2O	0
6	DBU[d]	1:1 THF/H_2O	0
7	DBU[d]	MeOH	0

[a] Mass balance reported of impure material after starting material removed *via* basic extraction. [b] Substrate had 99:1 er and was recovered without racemization. [c] DBU was used from the bottle without further purification. [d] Work done by Jeremy Henle. 1 mol % 18-crown-6 was added.

Both a Strecker reaction and a Bucherer-Bergs reaction only gave very low yields of amino acid **47d**; however the low cost of the starting materials allowed enough to be produced to effect a DKR to form Ni complex **56** (Scheme 39). Hydrolysis of **56** produced (*S*)-**47d** in 99:1 er. The amine was then protected with a Boc group to form **42d** quantitatively without racemization.

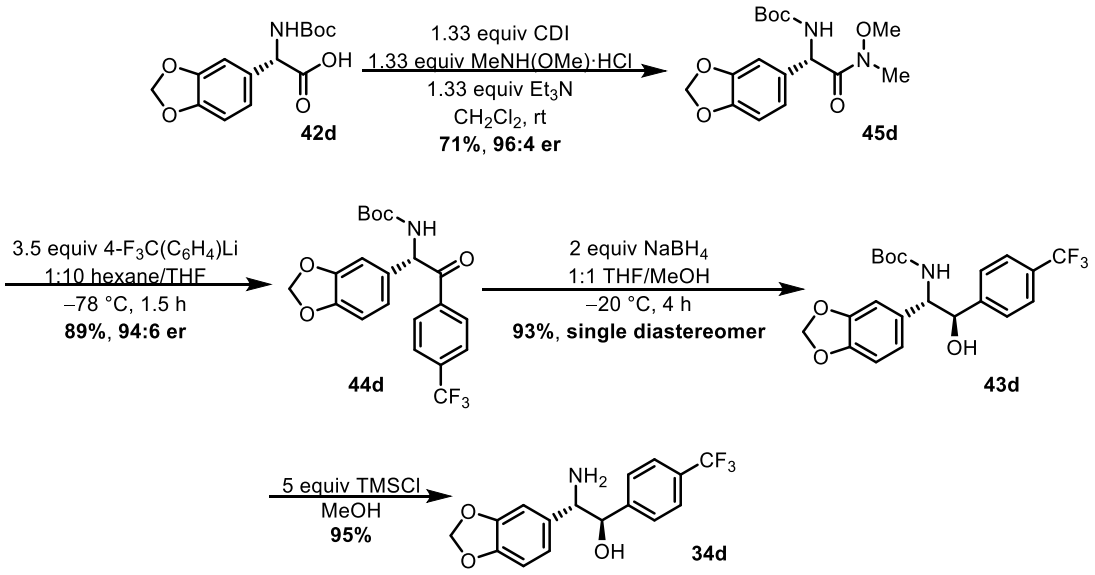
Scheme 39. Enantioselective Synthesis of Boc-protected Amino Acid **42d**



From this point, the route converged with the earlier proposed synthesis. As with isopropyl bisoxazoline **41c**, CDI proved an effective reagent for the formation of Weinreb amide **45d**, with

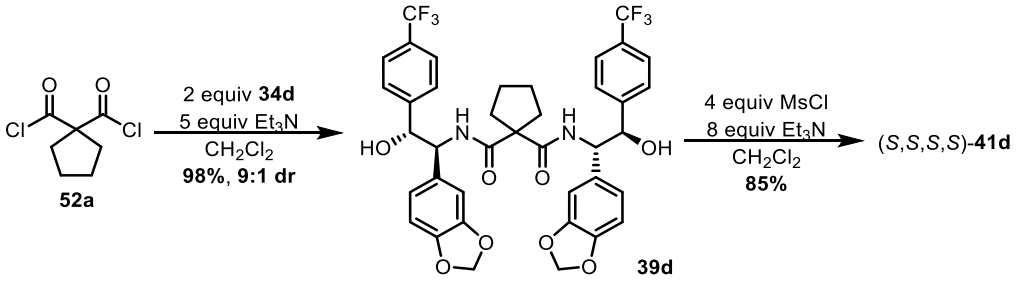
only minimal epimerization to 96:4 er (Scheme 40). The aforementioned organolithium addition conditions were modified slightly for solubility, yielding ketone **44d** in 89% yield and 94:6 er. $NaBH_4$ reduction again proceeded as for the isopropyl bisoxazoline precursor, giving *erythro-N*-Boc amino alcohol **43d** in 93% yield as a single diastereomer. The electron-deficient 4-trifluorophenyl group this time allowed TMSCl deprotection to proceed smoothly, unlike the previous synthesis involving a 4-methoxyphenyl group.

Scheme 40. Synthesis of Amino Alcohol **34d**

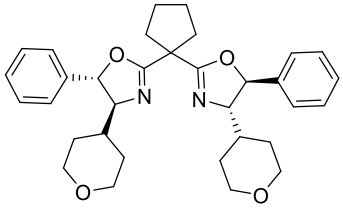


Following this, bisamide formation proceeded using similar conditions as for the isopropyl bisamide, benzodioxolyl bisamide **49d** being formed in roughly 9:1 dr, as would be statistically expected from the coupling of two amino alcohols of 94:6 er (Scheme 41). The mixture of diastereomers was invertively cyclized *via* the bismesylate to bisoxazoline **41d**, which could be separated from the *meso*-diastereomer *via* column chromatography. A statistical mixture of products would lead bisoxazoline **41d** to be formed with 99.6:0.4 er.

Scheme 41. Final Steps to Benzodioxolyl Bisoxazoline **41d**

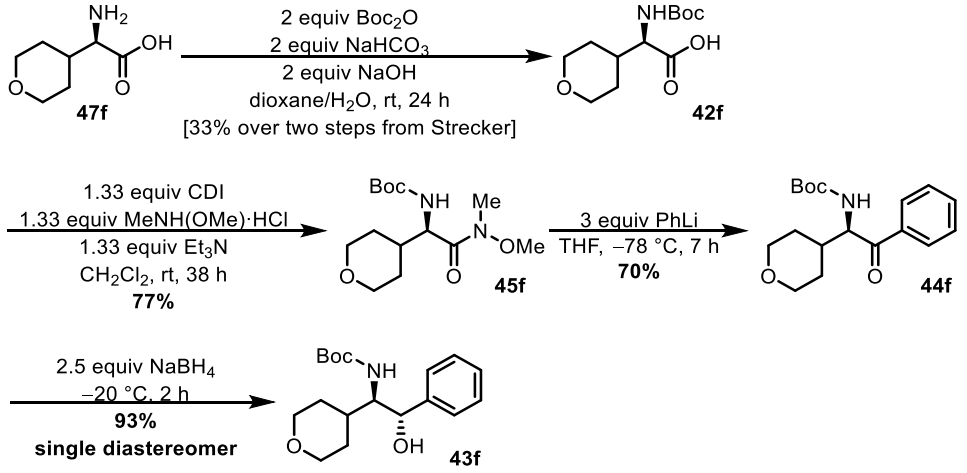


4-Tetrahydropyranyl Bisoxazoline 41f



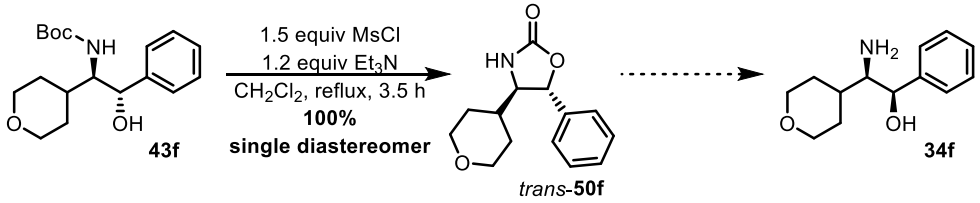
Tetrahydropyranyl bisoxazoline **41f** is the only member of the training set with a saturated heterocycle at R^1. The synthesis of the enantioenriched amino acid **47f** was performed by Jeremy Henle according to the method of Jacobsen.[172] Despite successes of this method with other amino acid syntheses in the group, **47f** was formed with only low er (not exactly quantified due to lack of chromatographic separation). The amine was then protected with a Boc group, and amidated to Weinreb amide **45f** (Scheme 42). This reaction was slow, giving 77% yield after 38 h. Attempts to use other coupling reagents only further decreased the yield or the rate of the reaction. Addition of 3 equiv PhLi gave amino ketone **44f**, the er being measured as only 79:21. Reduction with $NaBH_4$ proceeded in high yield to give a single diastereomer of **43f**.

Scheme 42. Synthesis of Tetrahydropyranyl Amino Alcohol **43f**



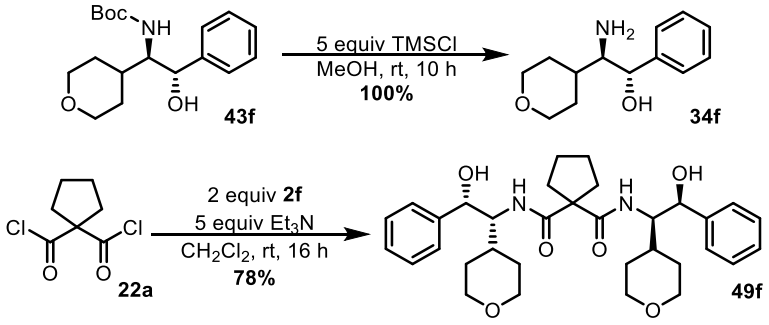
In analogy to isopropyl bisoxazoline **41c**, the oxazolidinone **50f** was next formed with the intention of effecting a two-step deprotection of the Boc group (Scheme 43). LiOH deprotection was attempted, but even under refluxing conditions, no conversion was observed. Since the substrate was insoluble in the reaction mixture, hydrolysis was next attempted with K_2CO_3 in MeOH. Although the substrate now dissolved, again no conversion was observed after 12 h at reflux – a similar result was obtained with $Ba(OH)_2$ in H_2O/1,4-dioxane. The stronger nucleophile LiOOH was generated *in situ* from LiOH and H_2O_2, but again in refluxing H_2O/THF, no conversion was observed. A last attempt was made using 6 N HCl. After 24 h at reflux, a complex mixture of substances oiled out of the reaction, and no starting material was recovered.

Scheme 43. Synthesis of Oxazolidinone *trans*-**50f**



Contrary to the synthesis of bisoxazoline **41f**, the oxazolidinone was not readily cleaved. Since there is no electron-donating group at C5, a TMSCl deprotection was performed, which caused quantitative deprotection of the Boc group. Amino alcohol **34f** was then reacted with **52a** to form bisamide **49f**.

Scheme 44. Synthesis of Bisamide **49f**



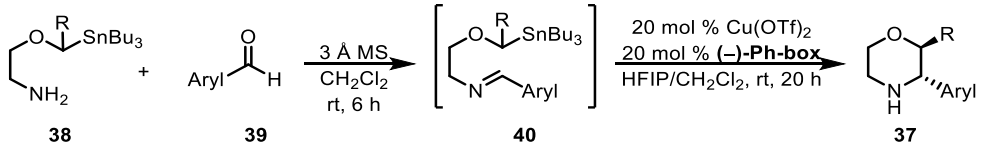
Invertive cyclization to the bisoxazoline **41f** was then attempted using MsCl and Et_3N. However, no conversion occurred under these conditions. When next, 10 mol % DMAP was added, a complex mixture of products was observed. Harsher conditions involving 1:1 MsCl/pyridine as the solvent also failed to yield any bismesylate or bisoxazoline. Further attempts to cyclize bisamide **49f** were put on hiatus since at this point in time the group had sufficient ligands for testing. This synthesis will be revisited in future. This synthesis also serves as an example that small changes in bisoxazoline structure (as for isopropyl bisoxazoline **41c**, this ligand has R^1 = secondary alkyl and R^3 = aryl) may necessitate restructuring of the synthetic plan.

5. Enantioselective SnAP Synthesis of Morpholines

Bode's single example of an enantioselective catalyst for the SnAP morpholine synthesis seemed an opportune potential medium to test these bisoxazoline ligands as part of the larger set generated in conjunction with other members of the Denmark group.

To recapitulate, Bode and coworkers developed a general, one-pot morpholine cyclization compatible with a wide range of pendant functionality. Although only one enantioselective catalyst is published, this transformation is the first of its kind.[127] Despite screening a number of substrates (Table 8) and bisoxazoline-type ligands (Chart 3), high enantioselectivity could not be obtained.[173] A number of ligands were therefore tested on this reaction by the author, with the aim of generating data sufficient to create a reliable, computational model.

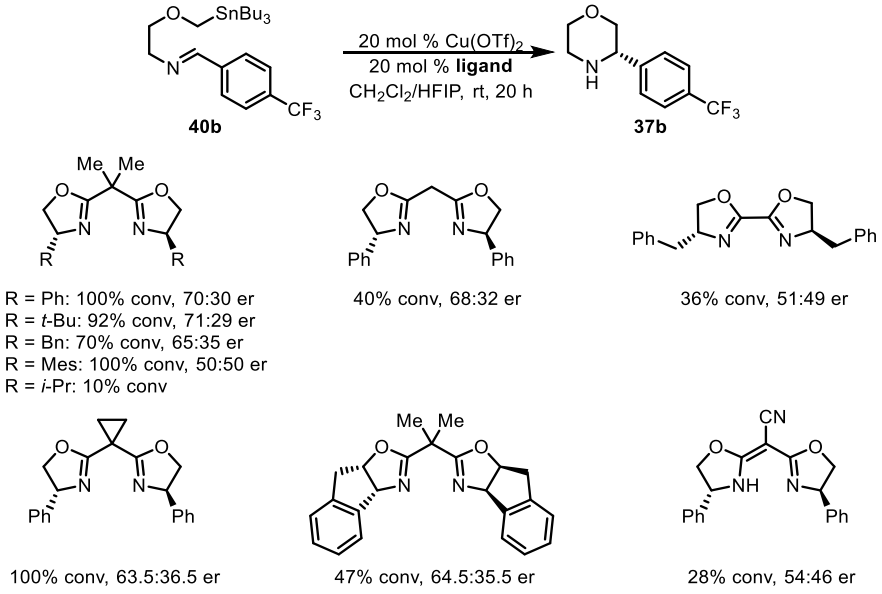
Table 8. Results of Bode's Enantioselective Morpholine Synthesis



Entry	R	Aryl	Yield	er	dr
1	Et	2-Toluyl	82%	80:20	≥20:1
2	Et	4-Triazolylphenyl	80%	72:28	≥20:1
3	Et	4-Quinolinyl	73%	70:30	≥20:1
4	H	2-Toluyl	70%	82:18	NA
5	H	4-Anisoyl	77%	77:23	NA
6	H	Phenyl	84%	71:29	NA
7	H	4-F_3C-phenyl	[a]	70:30	NA
8[b]	H	4-F_3C-phenyl	[a]	72:28	NA

NA = not applicable. Triazolyl = 1-(1*H*-1,2,4-triazolyl). [a] 100% conversion; yield not reported. [b] Cyclization was performed at 0 °C.

Chart 3. Ligand Screen for Bode's Enantioselective Morpholine Synthesis. conv = conversion

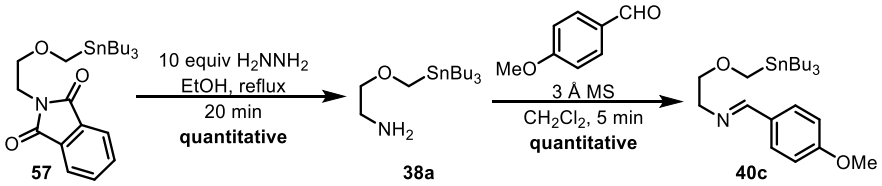


The imine substrate for screening purposes was generated from *p*-anisaldehyde **39b**, since it is readily-available, easily purified by distillation, and gave rise to some of the highest yields and enantioselectivities in Bode's reaction.

SnAP M **38a** was always generated immediately prior to reaction (Scheme 45). Although the free SnAP reagent is stable at rt or in a refrigerator for several weeks,

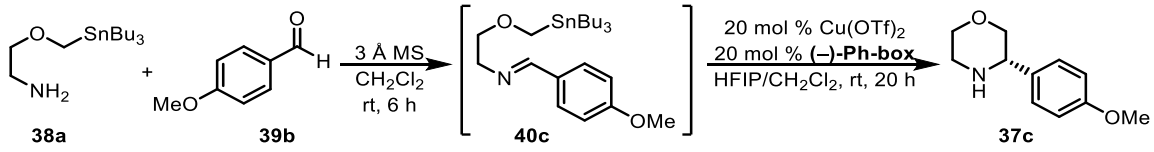
phthalimide-protected SnAP M **57** is stable indefinitely, so this practice removes an additional variable. The reaction takes only 20 minutes, and the product is purified simply by filtration and removal of solvent and residual hydrazine *in vacuo*. Imine **40** is then formed immediately on mixing SnAP M **38a** and the relevant aldehyde with powdered MS in CH_2Cl_2, and purified simply by filtration and removal of solvent *in vacuo*.

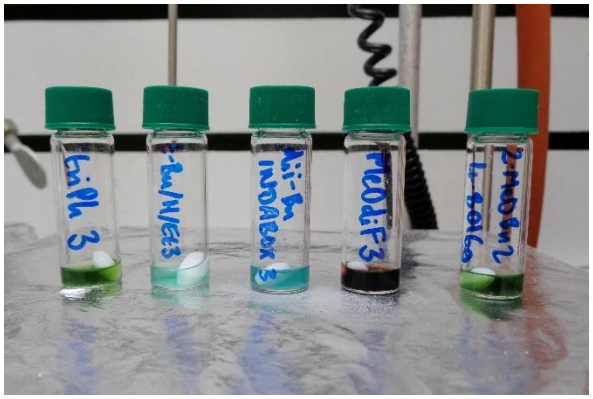
Scheme 45. Generation of Imine **40c** Immediately Prior to Cyclization



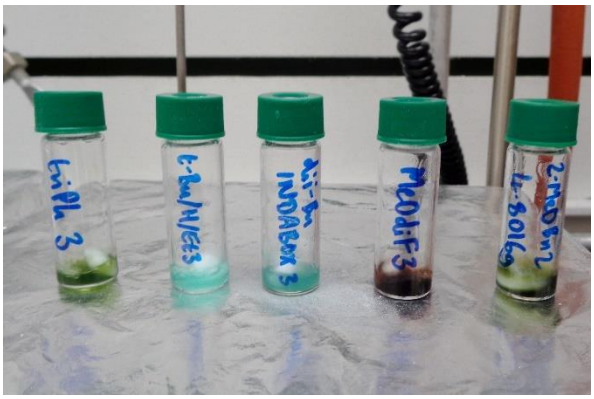
Formation of the active catalyst involves mixing equimolar amounts of bisoxazoline and $Cu(OTf)_2$ in 1:1 CH_2Cl_2/HFIP for 6 h at rt. A bold color change immediately occurs, tending to intensify over the course of the complexation (Figure 5). The imine is then injected as a solution in CH_2Cl_2, often inducing a second color change, and the reaction mixture stirred at rt for 20 h (Scheme 46).

Scheme 46. Screening conditions for Imine Cyclization to Morpholine **37c**

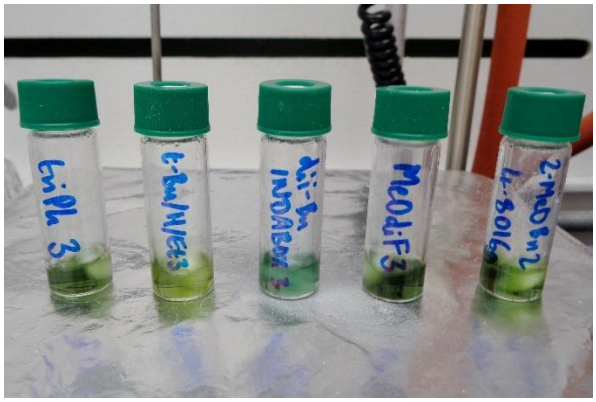




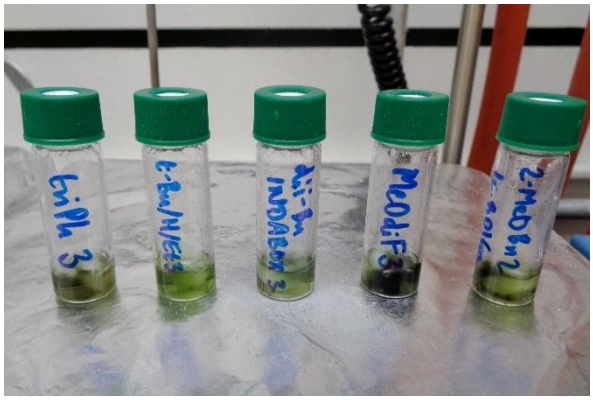
Complex formation immediately on $Cu(OTf)_2$ addition



Complex formation after 6 h



Reaction mixtures immediately on imine addition

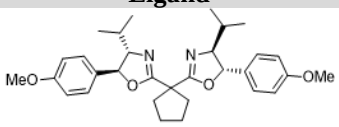
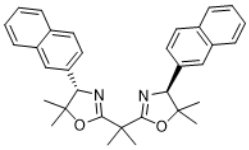
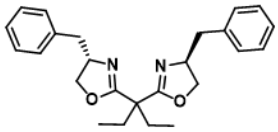
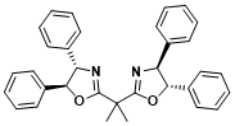
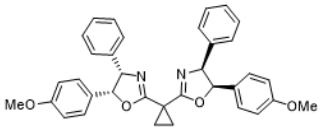
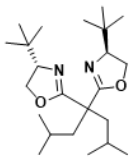
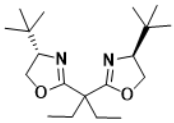
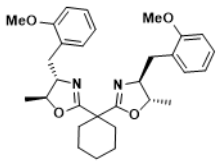
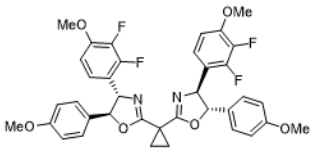


Reaction mixtures after 20 h

Figure 5. Appearance of SnAP Reaction Mixtures

The results of these reactions are shown in Table 9. Although Bode's group showed low levels of conversion with these ligands on the imine generated from 4-trifluoromethylbenzaldehyde (maximum: 40%), bisoxazolines with R^4 = H (a CH_2 bridge) showed no conversion with the *p*-anisaldehyde SnAP imine **40c** (entries 20–21, 23, and 25).

Table 9. Results of Enantioselective Morpholine Synthesis

Ligand	Entry	er
	**1a**	32:68
	1b	31:69
	**2a**	29:71
	2b	30:70
	**3a**	35:65
	3b	35:65
	**4a**	24:76
	4b	25:75
	**5a**	23:77
	5b	22:78
	**6a**	37:63
	6b	36:64
	**7a**	27:73
	7b[a]	32:68
	7c	26:74
	**8a**	37:63
	8b	36:64
	9a[a]	59:41
	**9b**	67:33
	9c	68:32

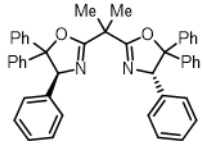
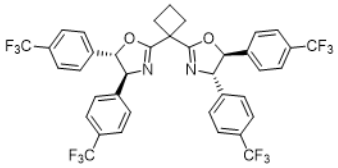
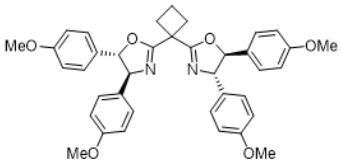
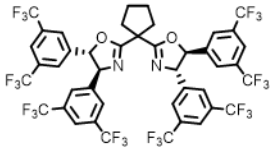
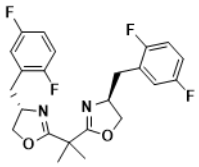
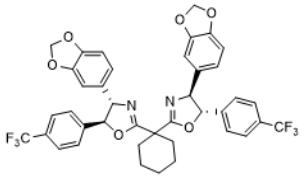
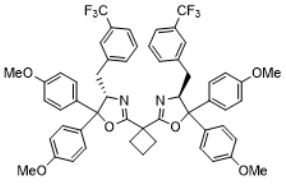
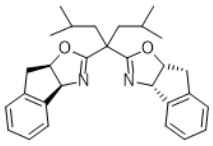
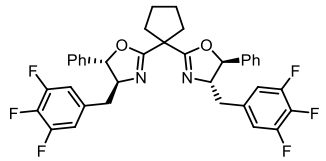
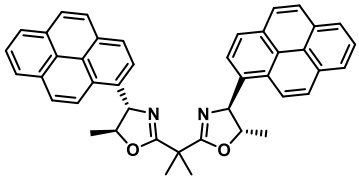
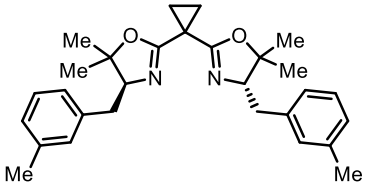
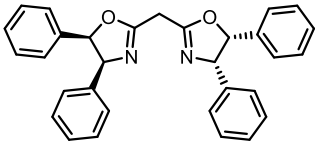
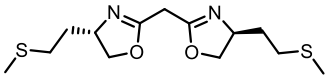
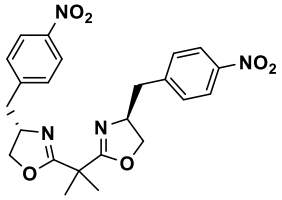
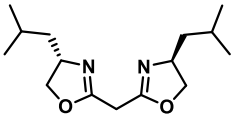
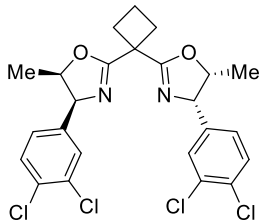
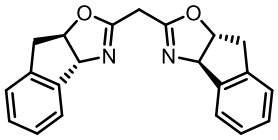
Ligand	Entry	er
	**10a**[a]	13:87
	10b	17:83
	10c	18:82
	**11a**	36:64
	11b	35:65
	**12a**	28:72
	12b	27:73
	**13a**	49:51
0.028 mmol scale	**13b**	50:50
	**14a**	43:57
	14b	44:56
	**15a**	37:63
0.036 mmol scale	**15b**	36:64
	**16a**	47:53
	16b	48:52
	**17a**	63:37
	17b	63:37

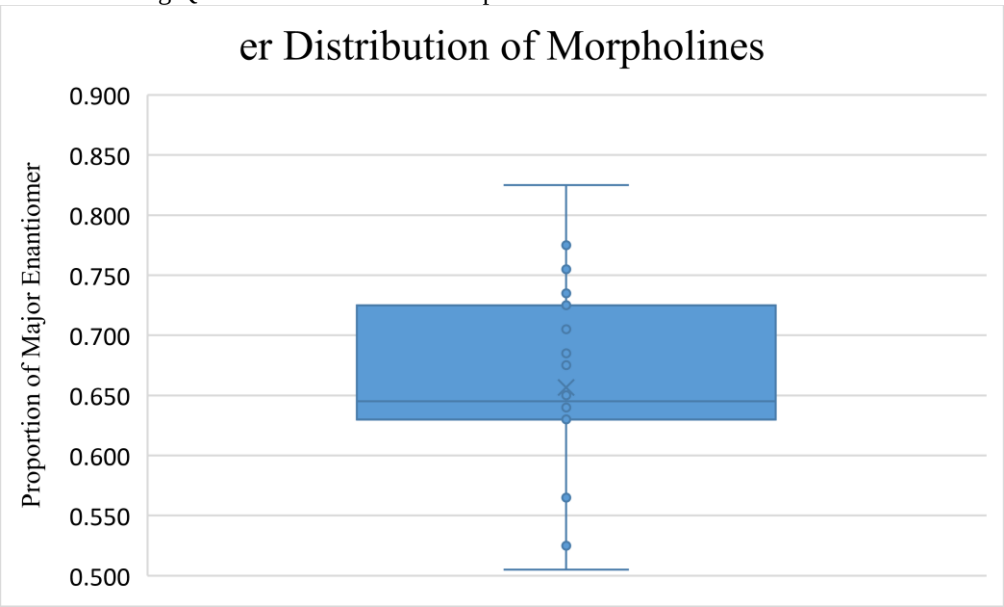
Table 9 (cont.). Results of Enantioselective Morpholine Synthesis

	**18a**	47:53		**23**	NR
	18b	47:53			
	**19a**	36:64		**24**	NR
	19b	36:64			
	**20**	NR		**25**	NR
	**21**	NR			
	**22**	NR		**26**	NR

NR = 0% yield of morpholine. [a] Anomalous result. All results not within ±2% ee were repeated until consistency was reached. The anomalous data were excluded from analysis

The data show a broad spread, indicating they may be suitable for computational model generation (Chart 4). Ligands which induced no reactivity will not be included in analysis toward the model. Values between 50:50 and 82:18 er are represented, with mean 65.3:34.7 and median 64:36 er. Chart 4 shows that although many data are clustered around the 63:37 er (26% ee) region, the rest of the data are more evenly spread.

Chart 4. Box Plot showing Quartile Distribution of Morpholine er. × = mean value



In general, it appears that aryl groups at R^1 give rise to higher selectivities than benzylic groups – all the selectivities above 70:30 other than in one case (entry 7) are generated from R^1 = aryl ligands. Average er from aryl bisoxazolines (69.4:30.6) is much higher than average er obtained from benzyl bisoxazolines (59.1:40.9). Alkyl bisoxazolines also show high average enantioselectivity (68.5:31.5), although this is only averaged over three results.

No obvious result of addition sterics at R^1 can be seen for alkyl bisoxazolines, since the two *t*-Bu bisoxazolines gave very different results (entries 6–7), and the isopropyl bisoxazoline resulted in enantioselectivity in the middle of these (entry 1).

Three of the four highest enantioselectivities were produced from bisoxazolines with R^1 = Ph (entries 4, 5, and 10). The best performing of these had diphenyl substitution. However, it is difficult to translate this into a trend, since, the best performing ligand (entry 10) and one of the worst (entry 16) both have diaryl substitution at C5. A single methyl or dimethyl substitution at C5 gave a low range of selectivity, between 29:71 and 37:63 er (entries 2, 8, and 19). No clear relationship between selectivity and simultaneous classes of group at C4 and C5 (eg: aryl-alkyl, alkyl-aryl, benzyl-aryl, etc.) is established, and it is notable that a broad range of selectivity is observed between the many *trans*-diaryl ligands.

Electron-withdrawing substituents at C5 appear to have a deleterious effect on enantioselectivity (entries 4 and 12 compared to entries 11 and 13). This may be true even with an electron-donating aryl group at R^1 (entry 15). However, another case with electron-donating aryl groups at both C4 and C5 showed somewhat diminished enantioselectivity (entry 9 compared to entry 12). Every case of an electron-withdrawing aryl group at C5 gave rise to below average selectivity. However, there appeared to be no advantage of electron-rich over electron-neutral substituents at this position.

Ligands with R^4 = Me (2,2'-propanediyl bridge) performed with a wide range of selectivity (entries 2, 4, 10, and 14). Direct comparison shows that R^4 = Et is favorable to R^4 = *i*-Bu for ligands similar to entries 6–7. Small bridging cycloalkanediyl rings seem to be more effective than normal rings, and five-membered rings seem to be particularly non-selective (entries 1, 13, and 18).

As well as the methylene-bridged ligands, the bisoxazoline with R^1 = 1-pyrenyl gave no reactivity (entry 23). This could be due to the large steric bulk at this position dissuading binding of the imine substrate. The lack of reactivity from the *p*-nitrobenzyl bisoxazoline (entry 25) may result from incompatibility of the nitro group with the reaction conditions, although aryl nitro groups pendant to the substrate have shown compatibility with the stoichiometric SnAP protocol.

6. Future Work

A computational model may now be generated, which will recommend a few bisoxazolines to be synthesized next, for testing in the morpholine synthesis. The data from these runs will be fed back into the model for improvement, and with this broad data spread it may be possible to generate a predictive model for catalytic, enantioselective SnAP synthesis of morpholines. This can then be extended to more substrates to check the generality of the model.

Not only can the model generate new candidate ligands to synthesize, but the areas of chemical space lacking representation may be evaluated, to further improve the model. For example, no bisoxazolines were tested with an *ortho*-substituted aryl group at R^1 (other than fluoro substitution). Any model generated from this data set will be unable to predict the effects of substitution here.

After a sufficient model has been generated, it will be important to evaluate the substrate scope. The optimal ligand will be tested for its generality for cyclization of SnAP imines from other aldehydes, including alkyl aldehydes and glyoxals previously tested by Bode. Other SnAP reagents may be tested, with particular interest in evaluating selectivity in reactions where diastereomers may be formed.

More ligands will need to be synthesized to evaluate the thesis of the computational work. Ideally, an entire training set will be synthesized. Since the more troublesome stages of bisoxazoline synthesis have been elucidated over the course of this project, a new training set will be generated that maintains excellent diversity while allowing for faster synthesis of some of the ligands. Ideally, the state of the art of bisoxazoline synthesis itself will be improved. A late-stage functionalization method for bisoxazolines is currently under development in the Denmark laboratory.

A study on the SnAP synthesis of piperazines using the same ligand set is currently underway in the Bode laboratory.

EXPERIMENTAL

General Experimental

Reaction Setup: Reactions were performed in oven-dried glassware. Room temperature (rt) was approximately 23 °C. Solvent evaporation was performed on a rotary evaporator at 30 °C unless otherwise specified.

Distillation: Bulb-to-bulb distillation was performed using a Kugelrohr, with boiling points (bp) corresponding to uncorrected air bath temperatures (ABT) under vacuum.

Chemicals: Copper(II) bromide, copper(II) triflate, lithium chloride, allylpalladium(II) chloride dimer, bis(benzonitrile)palladium(II) chloride, dipalladium(0) tris(benzylideneacetone), palladium(II) acetate, tetrakis(acetonitrile)palladium(II) tetrafluoroborate, tetrakis(triphenylphosphino)palladium(0), di(1-adamantyl) *n*-butyl phosphine, *rac*-BINAP, dppb, XPhos, Xantphos, sodium hydride, and dibutyltin dichloride were stored in a glovebox under Ar. **Note:** results of SnAP reactions depend strongly on Cu source. The cause for this is under investigation in the Bode group.

Cesium carbonate, lithium bromide, and sodium borohydride were stored in a dessicator over Drierite.

The following anhydrous reagents and solvents were freshly distilled from the dessicant in parentheses: DBN and DBU (BaO), *p*-cymene, Et_3N, *i*-Pr_2NH, TBME, and TMSCl (CaH_2), HFIP ($CaSO_4$), MeOH (Mg), bromobenzene and anisoyl bromide (molecular sieves), MeCN, 1,4-dioxane, and DME (Na), and cyclohexane (P_2O_5). Anhydrous CH_2Cl_2, DMF, Et_2O, hexane, THF, and toluene were dried by percolation through two columns packed with neutral alumina under positive Ar pressure. Solvent deoxygenation was performed where stated by passing Ar through the solvent for 20 min.

(*R*)-BINAP and (*R*)-Tol-BINAP were purified by basic aqueous extraction from toluene, trituration with degassed MeOH and subsequent recrystallization from 1:1 toluene:EtOH.[174] CDI was recrystallized from anhydrous benzene. $AsPh_3$ was recrystallized from EtOAc. dppf was dissolved in hot dioxane, cooled to rt, and triturated with pentane.

Commercially available organolithium and Grignard reagent solutions were titrated according to the methods of Gilman and Cartledge,[175] and Watson and Eastham[176] respectively within one month of use.

NMR Spectroscopy: Spectra were recorded on Varian 500 MHz spectrometers. ^{1}H and ^{13}C spectra were referenced to residual non-deuterated chloroform (7.26 ppm, ^{1}H; 77.02 ppm, ^{13}C), acetonitrile (1.94 ppm, ^{1}H; 1.32 and 118.26 ppm, ^{13}C), benzene (7.16 ppm, ^{1}H; 128.06 ppm, ^{13}C), or d_6- DMSO (2.49 ppm, ^{1}H; 39.52 ppm, ^{13}C). ^{11}B chemical shifts are reported relative to an external standard of boron trifluoride diethyl etherate (0.00 ppm). ^{19}F chemical shifts are reported relative to an external standard of trichlorofluoromethane (0.00 ppm). ^{31}P spectra were referenced to an external standard of 85% H_3PO_4 in H_2O (0 ppm). ^{13}C spectra were recorded with broadband decoupling of the ^{1}H nucleus, and ^{31}P spectra with broadband decoupling of the ^{13}C nucleus. Chemical shifts are reported in parts per million (ppm), multiplicities indicated by s (singlet), d (doublet), t (triplet), sext (sextet), sept (septet), oct (octet), br (broad), and m (multiplet). Coupling constants, *J*, are reported in Hz with integration provided and assignments indicated.

Infrared Spectroscopy: Infrared spectra (IR) were recorded using a Perkin-Elmer FTIR instrument. Peaks are reported in cm^{-1} with indicated relative absorption intensities: s (strong, 67–100%); m (medium, 34–66%); w (weak, 0–33%) and sh (sharp) and br (broad) assignments. Mass Spectrometry: Matrix-assisted laser desorption/ionization (MALDI) spectrometry was performed on an AB Voyager instrument. Electron Impact (EI) spectrometry was performed at 70 eV using methane as the carrier gas, with a time-of-flight (TOF) mass analyzer. Data are reported in the form of m/z (intensity relative to the base peak = 100). Electrospray Ionization (ESI) spectra were performed on a Micromass Q-Tof Ultima spectrometer.

Liquid Chromatography: Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} plates. Retention factor (R_f) values reported were measured using 10 × 2 cm silica TLC plates in a developing chamber containing the solvent system described. Visualization was accomplished with UV light and cerium(IV) ammonium molybdate solution (CAM), acidic 2,4-dinitrophenylhydrazine solution (DNP), potassium permanganate ($KMnO_4$), or a solution of silver nitrate and 2-phenoxyethanol with one drop of 30% aqueous hydrogen peroxide and UV irradiation for several minutes ($AgNO_3$-H_2O_2). Flash column chromatography was performed

using 40–63 μm particle size (230–400 mesh, 60 Å pore size) SiO_2. Analytical high-performance liquid chromatography (HPLC) was performed on an Agilent 1100 system using a UV detector (254 nm) and a Chiralpak AD-H, IB-3 or OJ-H column. Analytical supercritical fluid chromatography (SFC) was performed on an Agilent 1100 HPLC equipped with an Aurora Systems A-5 supercritical CO_2 adapter for SFC, using a UV detector (220 nm) and a Daicel Chiralcel OD column.

Gas Chromatography: Analytical gas chromatography (GC) was performed using a flame ionization detector. Retention times and integrated ratios were obtained from reporting integrators. Response factors for quantitative GC analysis were obtained with tetradecane as internal standard, using the following equation: response factor of compound = (area of compound × amount of standard) / (amount of compound × area of standard). Three samples of relative concentration 0.5, 1.0 and 2.0 with respect to internal standard were prepared and dissolved in EtOAc. An aliquot of each sample was injected into the GC in quadruplicate. The average of the twelve response factors was used for reaction analysis. Injections were made onto a Hewlett-Packard HP-1 25 m × 0.2 m × 33 μm capillary column. Injector temperature was 250 °C, detector temperature was 300 °C with a H_2 carrier gas flow of 16.7 mL min^{-1}. The column oven was programmed to hold the temperature at 140 °C for 2 min, then increase temperature at a rate of 50 °C min^{-1} over 2.4 min and hold at 260 °C for 5.6 min, a total run time of 10.0 min.

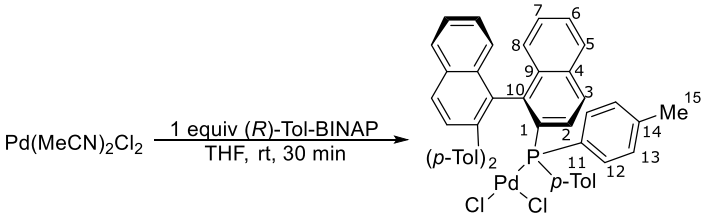
Literature Procedures

Allyl aryl ethers **17a**–**17d** were prepared according to a literature procedure,[24,177] were purified *via* Kugelrohr distillation or sublimation, and had spectroscopic data consistent with the literature.

$[Ir(cod)Cl]_2$[178] was made *via* a literature procedure, and stored in a desiccator. 1-Phenylhexane-1,3,5-trione,[179] 2-Bromobiphenyl,[180] and (2-biphenyl)dimethylsilane[181] were also made according to literature procedures. These compounds had spectral data conforming to the literature.

EXPERIMENTAL PROCEDURES: CHAPTER 1

Preparation and Isolation of Palladium Catalyst [(*R*)-Tol-BINAP 18]



(*R*)-Tol-BINAP 18

Complex **(*R*)-Tol-BINAP 18** was generated *in situ* for chlorohydroxylation reactions, and a sample was isolated for characterization purposes.

Bis(acetonitrile)dichloropalladium(II) (20 mg, 77 μmol) was charged to a 10-mL, two-necked, round-bottomed flask, in a glovebox. Anhydrous, degassed THF (0.5 mL) was added, followed by (*R*)-Tol-BINAP (51 mg, 77 μmol, 1.0 equiv), washing with further anhydrous, degassed THF (0.5 mL). The clear, orange-yellow solution was stirred at rt for 30 min. Anhydrous, degassed Et_2O (3 mL) was added, and a yellow precipitate was immediately produced. The solution was filtered, and the filtrand dried *in vacuo* to 62 mg (77 μmol, **97%** yield) of a bright yellow powder. Further drying under high vacuum (50 Pa) for over 24 h did not remove residual Et_2O.

Data for **(*R*)-Tol-BINAP 18**:

^{1}H NMR: (500 MHz, d_6-DMSO)

δ 7.73 (d, *J* = 8.9 Hz, 2 H), 7.70 (d, *J* = 8.2 Hz, 2 H), 7.61 (dd, *J* = 11.7, 8.2 Hz, 4 H), 7.50 (t, *J* = 7.5 Hz, 2 H), 7.39 (br s, 4 H), 7.33 (d, *J* = 7.4 Hz, 4 H), 7.14–7.24 (m, 4 H), 6.63 (d, *J* = 8.7 Hz, 2 H), 6.53 (br s, 4 H), 2.38 (s, 6 H, $H_{3,A}C(15)$), 1.98 (s, 6 H, $H_{3,B}C(15)$)

^{31}P NMR: (202 MHz, d_6-DMSO)

28.62

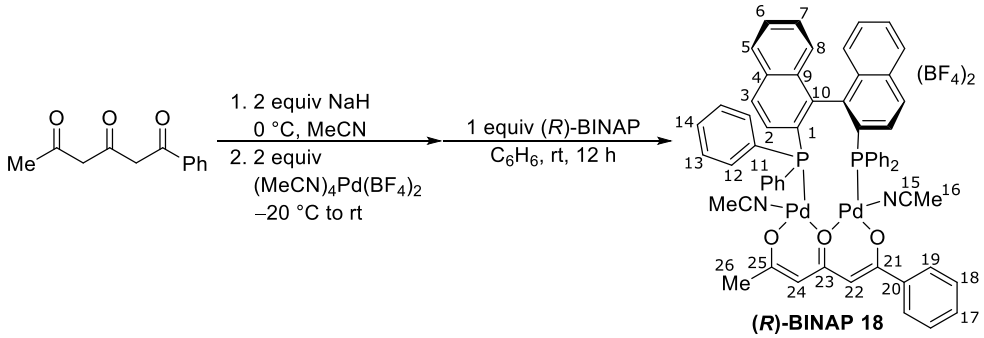
IR: (KBr; pressed under Ar)

3416 (s, v br), 3055 (s), 2976 (s), 2920 (s), 2866 (s), 1597 (s), 1557 (m), 1498 (s), 1444 (m), 1397 (m), 1308 (m), 1224 (w), 1192 (m), 1159 (w), 1101 (s), 1020 (w), 870 (w), 846 (w), 803 (s), 746 (s), 707 (m), 697 (m), 670 (m), 652 (m), 636 (m), 621 (m), 614 (m), 602 (m), 530 (m), 523 (m), 508 (s), 475 (m), 454 (m)

MS: (MALDI; solvent: THF)

819.96 ($[M-Cl]^+$)

Henry's Preparation of μ-(*R*)-BINAP μ-1-Phenylhexane-1,3,5-triketone Bis[(acetonitrile)palladium(II)] Tetrafluoroborate [(*R*)-BINAP 18]



The procedure was followed as closely as possible to that in Henry's report.[24]

To a stirred solution of tetrakis(acetonitrile)palladium(II) tetrafluoroborate (100 mg, 226 μmol, 2 equiv) in anhydrous acetonitrile (4.3 mL) under Ar in a 25-mL, round-bottomed flask was added, dropwise, a solution of 1-phenylhexane-1,3,5-trione (23 mg, 113 μmol) in anhydrous acetonitrile (2.0 mL). Anhydrous triethylamine (210 μL, 152 mg, 13.4 equiv) was then added dropwise, causing a color change from yellow to bold orange. The solution was stirred at rt for

30 min. A solution of (*R*)-BINAP (70 mg, 113 μmol, 1 equiv) in anhydrous benzene (1.3 mL) was then added dropwise to the reaction mixture, which was next stirred at rt for 12 h. The mixture was concentrated under high vacuum (50 Pa) to a pasty, brick red residue. Anhydrous Et_2O (10 mL) was added, and the suspension stirred at high frequency for 15 min. Solvent was removed under high vacuum to yield a brick red powder. This was washed in a glovebox with anhydrous Et_2O (5 × 30 mL) to give a yellow-brown powder, which was dried briefly *in vacuo* to 131 mg yellow-brown powder (100 μmol, **90%** yield). Residual Et_2O was not removed by further drying a sample *in vacuo* for over 24 h, and the ^{31}P NMR spectrum did not change after this process.

Data for **(*R*)-BINAP 15** (Henry's preparation):

^1H NMR: (500 MHz, d_6-DMSO)

δ 6.95-8.19 (m, 12.09 H), 6.83 (m, 0.41 H), 6.60 (m, 0.01 H), 6.40 (m, 0.12 H), 6.20 (m, 0.01 H), 5.87 (br s, 0.13 H), 5.43 (br s, 0.04 H), 3.33 (br m, 1.00 H), 3.07 (br q, *J* = 6.9 Hz, 11.86 H), 2.92 (br s, 0.14 H), 2.49 (s, 2.99 H), 2.23 (br m, 0.12 H), 2.06 (s, 0.47 H), 1.74 (s, 0.22 H), 1.67 (s, 0.03 H), 1.16 (t, *J* = 6.9 Hz, 20.70 H)

^{31}P NMR: (202 MHz, d_6-DMSO)

33.28, 33.09, 32.72, 32.51, 32.30 (major peak), 31.76, 31.54, 31.26, 31.06, 28.29, 25.36, 25.05, 22.32

IR: (KBr; pressed under Ar)

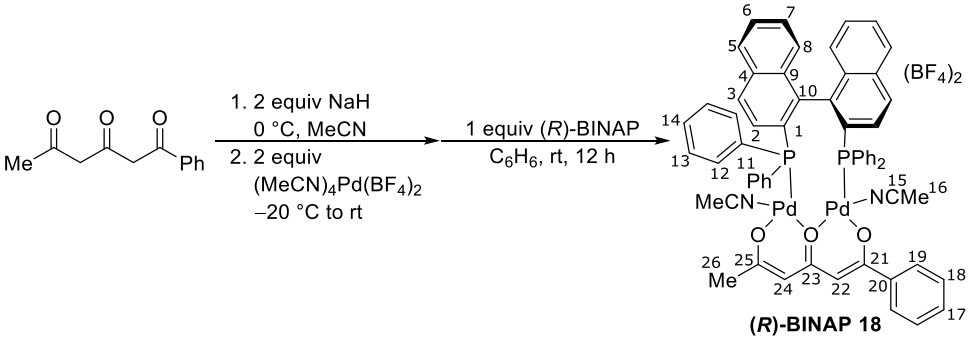
3169 (m), 3055 (m), 2986 (m), 2943 (m), 2680 (m), 2492 (m), 1673 (m), 1586 (m), 1531 (s), 1507 (s), 1478 (s), 1437 (s), 1399 (m), 1384 (m), 1311 (m), 1056 (s, v br), 872 (w), 847 (w), 815 (m), 746 (m), 697 (s), 668 (m), 619 (w), 609 (w), 582 (w), 552 (w), 523 (m), 501 (m), 475 (w)

New Preparation of Dinuclear Palladium Catalyst L·18

To a two-necked, 15-mL, pear-shaped flask charged with a suspension of sodium hydride (5.4 mg, 226 μmol, 2 equiv) in anhydrous acetonitrile (1.0 mL) at 0 °C was added 1-phenylhexane-1,3,5-trione (23 mg, 113 μmol) portionwise under Ar, and the mixture stirred at rt for 15 min. The solution turned clear, bright yellow, and H_2 evolution was observed. Tetrakis(acetonitrile)palladium(II) tetrafluoroborate (100 mg, 226 μmol, 2 equiv) was dissolved

in anhydrous acetonitrile (1.5 mL) under Ar in a separate 10-mL Schlenk flask, and cooled to −20 °C. The solution of deprotonated triketone was added slowly to the palladium-containing solution *via* cannula at −20 °C, washing with anhydrous acetonitrile (0.5 mL). The mixture was brought to rt, and stirred for 30 min. This was accompanied by a color change to orange. The mixture was cooled to −20 °C, then a solution of bisphosphine ligand (113 μmol, 1 equiv) in anhydrous benzene (0.9 mL, 0.2 M in ligand) was added dropwise over 3 min. The reaction mixture was stirred at rt for 12 h. It was then concentrated under high vacuum (120 Pa) to a brown powder. This was washed in a glovebox with anhydrous Et_2O (10 mL), then anhydrous toluene (3 × 10 mL), removing a yellow filtrate. The solids were dissolved in anhydrous acetone to yield a yellow-brown solution, which was quickly filtered to remove a white solid. The filtrate was concentrated under high vacuum (120 Pa), and washed with anhydrous Et_2O (4 × 10 mL), then anhydrous toluene (3 × 10 mL). The solid was collected. The dinuclear palladium catalysts decompose quickly, and decomposition appears to be accelerated under vacuum. The complexes must be kept under inert atmosphere, and should be used and characterized without delay.

New Preparation of μ-(*R*)-BINAP μ-1-Phenylhexane-1,3,5-triketone Bis[(acetonitrile)palladium(II)] Tetrafluoroborate [(*R*)-BINAP 18]



Dinuclear complex **(*R*)-BINAP 18** was synthesized from tetrakis(acetonitrile)palladium(II) tetrafluoroborate (226 μmol), producing 131 mg (101 μmol, **90%** yield) of a yellow-brown powder.

Data for **(*R*)-BINAP 18** (new preparation):

^{1}H NMR: (500 MHz, d_6-DMSO)

δ 8.04 (br d), 7.65–8.00 (br m), 7.60 (br s), 7.52 (br t), 7.38 (br m), 7.13–7.28 (br m), 7.04 (br), 6.72–6.95 (br m), 6.54 (br d, J = 6.2 Hz), 6.35 (br), 2.28 (s), 2.06 (s), 1.82 (s), 1.74 (s), 1.67 (s), 1.07 (t, H_3C(16))

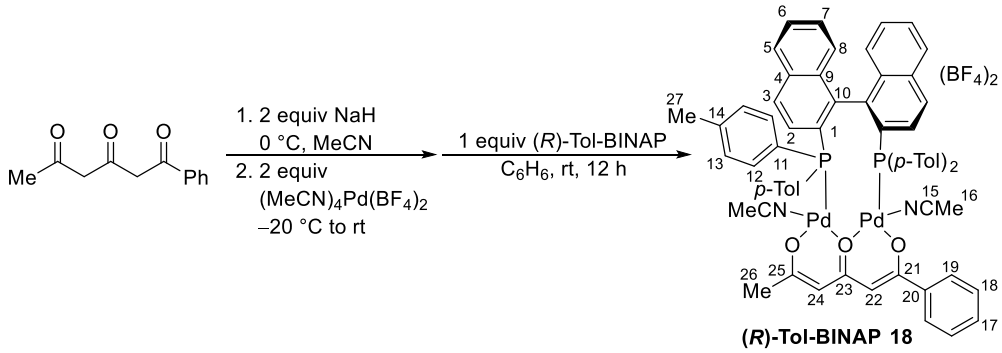
^{31}P NMR: (202 MHz, d_6-DMSO)

33.10

IR: (powder, under air)

3694 (w), 3434 (br w), 2924.16 (w), 1439 (w), 1376 (w), 1084 (w), 1023 (w), 1003 (w), 833 (w), 697 (w), 558 (w), 539 (w), 498 (w), 470 (w)

New Preparation of μ-(*R*)-Tol-BINAP μ-1-Phenylhexane-1,3,5-triketone Bis[(acetonitrile)palladium(II)] Tetrafluoroborate [(*R*)-Tol-BINAP 18]



Dinuclear complex **(*R*)-Tol-BINAP 18** was synthesized from tetrakis(acetonitrile)palladium(II) tetrafluoroborate (108 μmol) to yield 64 mg (47 μmol, **88%** yield) of a light brown powder.

Data for **(*R*)-Tol-BINAP 18**:

^{1}H NMR: (500 MHz, d_6-DMSO)

δ 8.04 (d, *J* = 7.5 Hz), 7.89 (d, *J* = 8.6 Hz), 7.73–7.87 (m), 7.35–7.70 (m), 7.12–7.32 (m), 7.09 (t, *J* = 7.9 Hz), 6.79 (d, *J* = 8.5 Hz), 6.49–6.75 (m), 6.40 (s), 6.31 (s), 5.73 (s), 2.07 (s), 2.06 (s), 1.74 (s, $H_{3,A}C(27)$), 1.64 (s, $H_{3,B}C(27)$)

^{31}P NMR: (202 MHz, d_6-DMSO)

32.39

IR: (powder, under air)

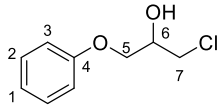
3427 (br w), 3058 (w), 1590 (w), 1557 (w), 1437 (w), 1313 (w), 1238 (w), 1055 (w), 1022 (w), 997 (w), 745 (w), 696 (w), 523 (w), 498 (w)

Preparation of Racemic Chlorohydrin Standards

Preparation of *rac*-16b and *rac*-16c

Racemic standards of chlorohydrins **16b** and **16c** were prepared according to a literature procedure and had spectroscopic data consistent with the literature.[182]

Preparation of *rac*-(2-Chloro-3-hydroxypropoxy)benzene 16a



Data for **16a**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.31 (m, 2 H, HC(2)), 7.00 (tt, *J* = 7.4, 1.0 Hz, 1 H, HC(1)), 6.93 (m, 2 H, HC(3)), 4.23 (sext, *J* = 5.5 Hz, 1 H, HC(6), 4.10 (m, 2 H, $H_2C(5)$), 3.77 (m, 2 H, $H_2C(7)$), 2.59 (d, *J* = 5.8 Hz, 1 H, OH)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 158.1 (C(4)), 129.6 (C(2)), 121.4 (C(1)), 114.5 (C(3)), 69.9 (C(5)), 68.4 (C(6)), 46.0 (C(7))

IR: (neat)

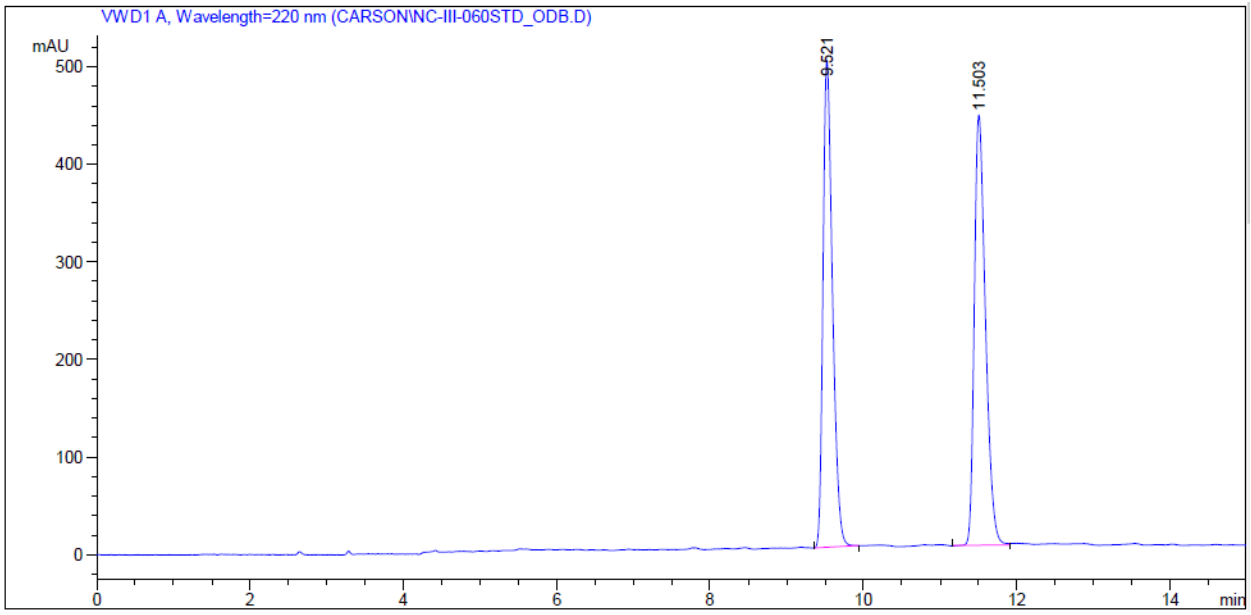
3407 (br, w), 2928 (w), 1739 (w), 1599 (m), 1588 (w), 1495 (m), 1457 (w), 1240 (m), 1173 (w), 1078 (m), 1042 (m), 751 (s), 690 (m), 509 (m)

MS: (EI)

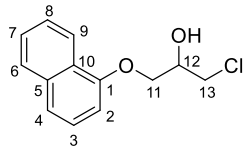
188.0 (22, M^+), 186.0 (59, M^+), 144.0 (9), 142.0 (30), 137.0 (18), 119.0 (18), 108.0 (11), 107.0 (63), 95.0 (61), 94 (100), 79.1 (20), 78.1 (13), 77.0 (69, Ph^+), 66.1 (14), 65.1 (18), 51.0 (23)

TLC: R_f 0.22 (70:30 hexane:Et_2O) [UV/CAM]

SFC: t_R 9.5 min (49.8%); t_R 11.5 min (50.2%) (OD, MeOH:CO_2 = 1:99 for 10 mins then 10:90 for 6 mins then 5:95 for 4 mins, 2.5 mL min^{-1}, 220 nm, 40 °C)



Preparation of *rac*-1-(2-Chloro-3-hydroxypropoxy)naphthalene 16c



Data for **16c**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.21 (d, *J* = 7.1 Hz, 1 H, HC(9)), 7.82 (d, *J* = 6.9 Hz, 1 H, HC(6)), 7.45–7.54 (m, 3 H), HC(4), HC(7), HC(8)), 7.39 (t, *J* = 7.9 Hz, 1 H, HC(3)), 6.85 (d, *J* = 7.5 Hz, 1 H, HC(2)), 4.39 (sext, *J* = 5.5 Hz, 1 H, HC(12)), 4.28 (m, 2 H, H_2C(11)), 3.89 (m, 2 H, H_2C(13)), 2.59 (d, *J* = 6.1 Hz, OH)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 153.7 (C(10)), 134.5 (C(5)), 127.6 (C(6)), 126.5 (C(7)), 125.7 (C(3)), 125.4 (C(8)), 125.3 (C(1)), 121.5 (C(9)), 121.0 (C(4)), 105.0 (C(2)), 69.9 (C(11)), 68.6 (C(12)), 46.3 (C(13))

IR: (powder)

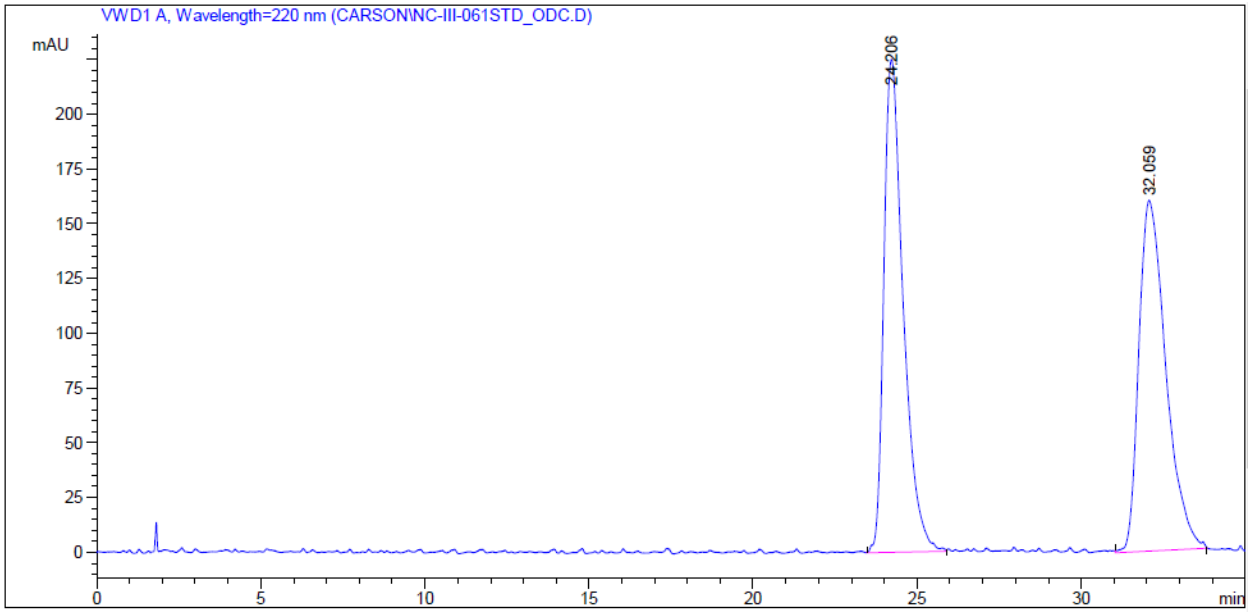
3312 (br, w), 3056 (w), 2926 (w), 2853 (w), 1738 (w), 1627 (w), 1577 (m), 1509 (w), 1456 (w), 1393 (m), 1322 (w), 1270 (m), 1208 (m), 1100 (m), 1021 (m), 904 (m), 793 (m), 770 (s), 707 (m), 574 (m), 514 (w)

MS: (EI)

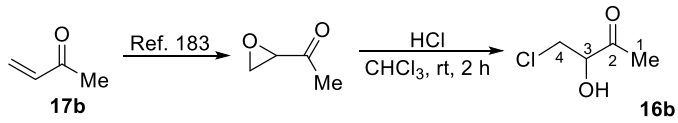
238.0 (8, M^+), 236.0 (25, M^+), 145.0 (13), 144.0 (100), 127.0 (10, $Naph^+$), 116 (15), 115 (25), 94.0 (10)

TLC: R_f 0.17 (70:30 hexane:Et_2O) [UV/CAM]

SFC: t_R 24.2 min (50.2%); t_R 32.1 min (49.8%) (OD, MeOH:CO_2 = 10:90, 2.5 mL min^{-1}, 220 nm, 40 °C)



Preparation of *rac*-4-Chloro-3-hydroxybutan-2-one 16b



1-(Oxiran-2-yl)ethanone was prepared on a 2 mmol scale, according to a literature procedure.[183] The crude, colorless oil produced in this reaction was then cooled to 0 °C in a 7-mL vial, and $CHCl_3$ (0.5 mL) and concentrated HCl (0.25 mL) were added to form a colorless/yellow biphase. The mixture was stirred at rt for 2 h. H_2O (3 mL) was added, and the organic components were extracted with $CHCl_3$ (3 × 5 mL). The organic extracts were dried over $CaCl_2$, filtered, and concentrated *in vacuo* to a crude, dark, brown oil. This complex mixture was separated *via* column chromatography using an eluent gradient from 95:5 to 80:20 hexane:ethyl acetate, to yield 71 mg (0.58 mmol, **29%** yield over two steps) of a volatile, colorless oil **16b**.

Data for **16b**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 4.29 (t, *J* = 5.6 Hz, 1 H, HC(3)), 3.92 (m, 2 H, $H_2C(4)$), 3.02 (br s, 1 H, OH), 2.33 (s, 3 H, $H_3C(1)$)

^{13}C NMR: (126 MHz, $CDCl_3$)

203.39 (C(2)), 63.42 (C(3)), 62.54 (C(4)), 27.40 (C(1))

IR: (neat)

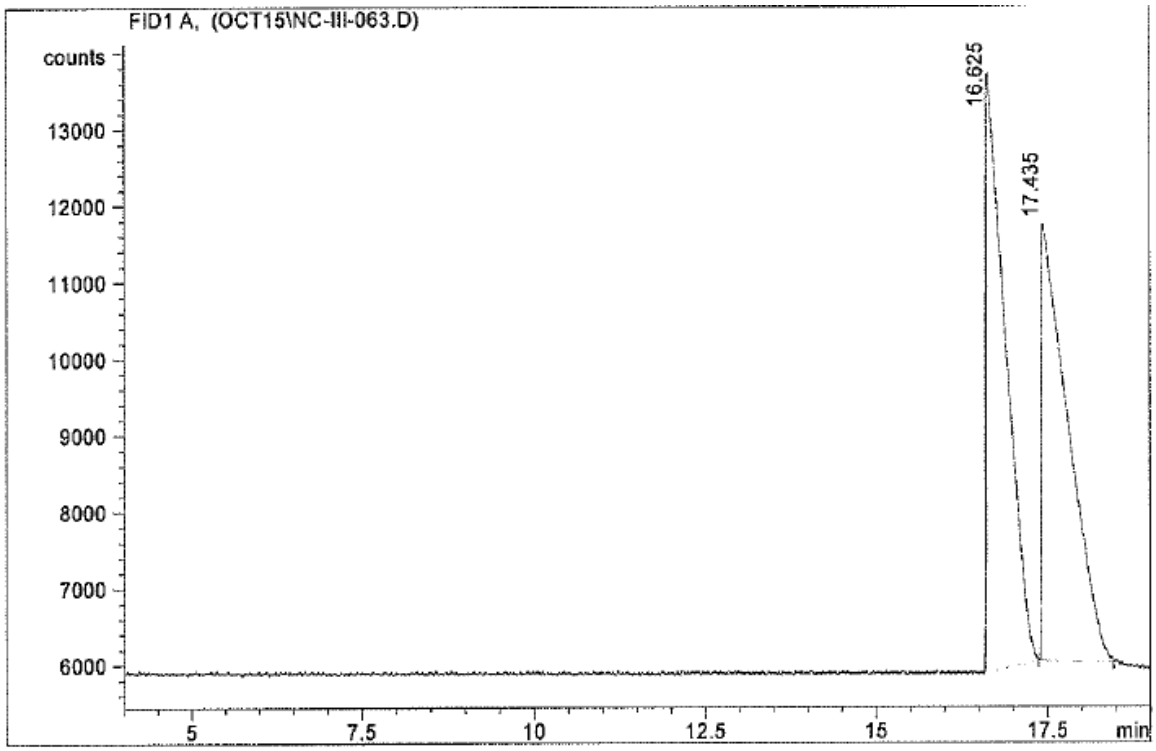
3419 (br, w), 2941 (w), 1715 (s), 1420 (m), 1358 (m), 1224 (m), 1162 (w), 1075 (m), 1041 (m), 929 (w), 796 (w), 733 (m), 680 (m), 629 (m), 593 (m), 559 (m), 474 (s)

MS: (EI)

128.0 (10), 126.0 (16), 109.1 (7.4, $[M\text{-}Me]^+$), 107.0 (23.0, $[M\text{-}Me]^+$), 94.0 (12), 92.0 (37.6), 91.1 (11.9), 87.1 (20.2, $[M\text{-}Cl]^+$), 86.1 (13.5), 81.1 (16.3, $[M\text{-}Ac]^+$), 79.0 (53.8, $[M\text{-}Ac]^+$), 77.0 (17.2), 76.0 (11.2), 71.1 (21.2), 69.1 (15.2), 64.1 (47.7), 62.1 (100), 57.2 (15.9), 55.1 (14.2)

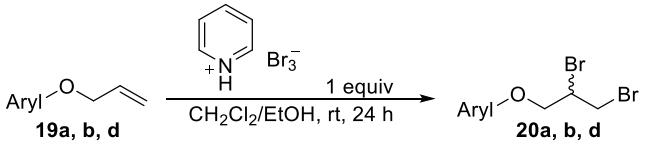
TLC: R_f 0.37 (70:30 hexane:EtOAc) [DNP]

GC: t_R 16.6 min (50.3%); t_R 17.4 min (49.7%) (CycloSil-B, 70 °C)



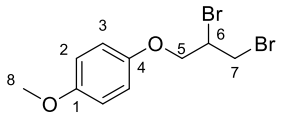
Preparation of Racemic Dibromide Standards

Preparation of *rac*-20a, *rac*-20b and *rac*-20d



A 20-mL scintillation vial was charged with the requisite allylic ether **19** (0.50 mmol) and CH_2Cl_2 (1.5 mL, 0.33 M in **19**). Pyridinium tribromide (88% active, 182 mg, 0.50 mmol, 1.0 equiv) was then added in one portion, followed by 95% ethanol (1.5 mL, 0.33 M in **19**). The vial was capped with a plastic-lined cap, and the orange-yellow solution stirred for 24 h, during which time the color is lost. Reaction progress was monitored by TLC. The reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$ solution (1.0 mL), and the mixture diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL). The layers were separated, and the organic phase was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give racemic dibromides **20**.

Preparation of *rac*-1-(2,3-Dibromopropoxy)-4-Methoxybenzene (20a)



Dibromide **20a** was synthesized from **19a** (0.3 mmol) to yield 94 mg (290 μmol, **97%** yield) of a white solid. Spectroscopic data were consistent with those of Henry.[27]

Data for **20a**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 6.82–6.91 (m, 4 H, HC(2,3)), 4.38–4.44 (ABX, 1 H, HC(6)), 4.28–4.36 (ABX, 2 H, H_2C(5)), 3.86–3.95 (ABX, 2 H, H_2C(7)), 3.78 (s, 3 H, H_3C(8))

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 154.5 (C(1)), 152.1 (C(4)), 116.2 (C(3)), 114.7 (C(2)), 70.1 (C(5)), 55.7 (C(8)), 48.0 (C(6)), 32.8 (C(7))

IR: (neat)

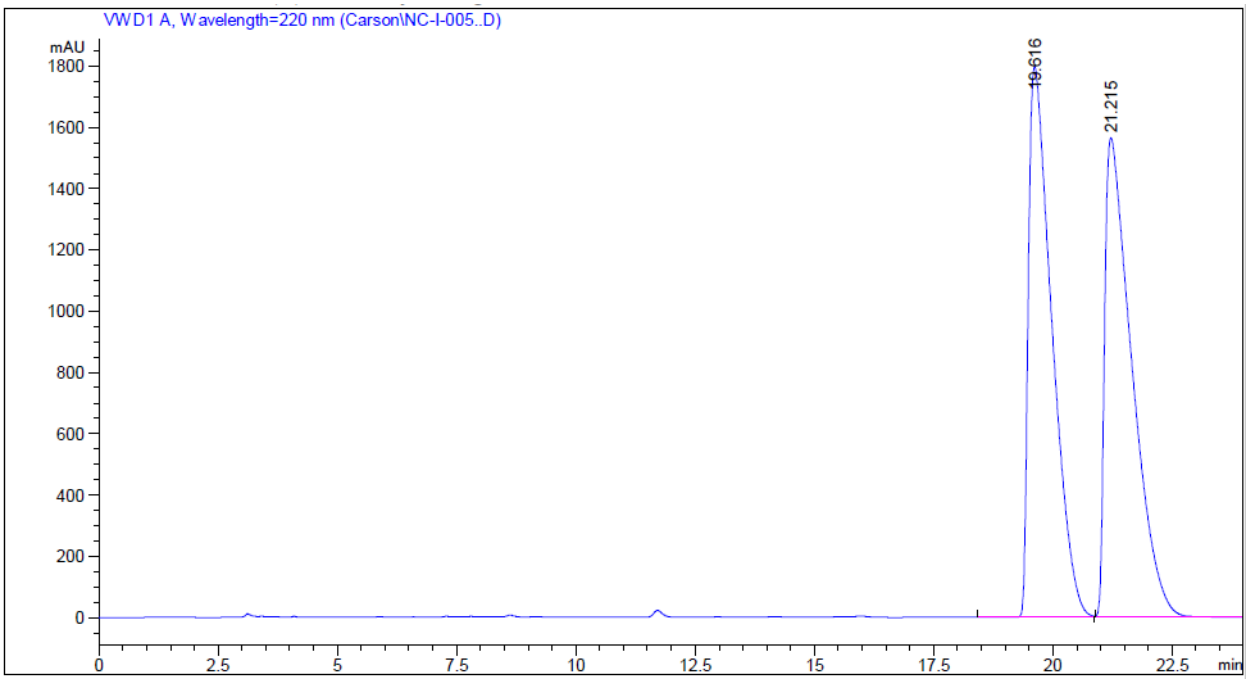
2999 (w), 2932 (2), 2968 (w), 1593 (w), 1505 (s), 1456 (m), 1290 (w), 1223 (s), 1108 (w), 1034 (m), 822 (s), 751 (m), 574 (m), 522 (w)

MS: (EI)

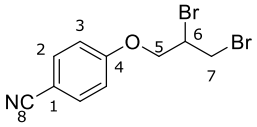
325.9 (11, M^+), 323.9 (20, M^+), 321.9 (11, M^+), 164.1 (9, $[M-Br_2]^+$), 124.1 (90), 123.1 (100, $[M-C_3H_5Br_2]^+$), 109.0 (15), 95.0 (19), 62.0 (11)

TLC: R_f 0.36 (90:10 hexane:EtOAc) [UV/CAM]

HPLC: t_R 19.6 min (49.8%); t_R 21.2 min (50.2%) (OJ-H, hexane/isopropanol = 95.5:4.5, 1.0 mL min^{-1}, 220 nm, 20 °C)



Preparation of 1-(2,6-Dibromopropoxy)-4-Cyanobenzene (20b)



Dibromide **20b** was synthesized from **19b** (0.3 mmol) to yield 92 mg (288 µmol, **96%** yield) of a white solid. Spectroscopic data were consistent with those of Henry.[27]

Data for **20b**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.61 (d, *J* = 9.0 Hz, 2 H, HC(2)), 7.00 (d, *J* = 9.0 Hz, 2 H, HC(3)), 4.39–4.48 (m, 3 H, H_2C(5), HC(6)), 3.87–3.93 (m, 2 H, H_2C(7))

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 161.1 (C(4)), 134.1 (C(2)), 118.8 (C(1)), 115.4 (C(3)), 105.1 (C(8)), 69.2 (C(5)), 46.6 (C(6)), 32.1 (C(7))

IR: (powder)

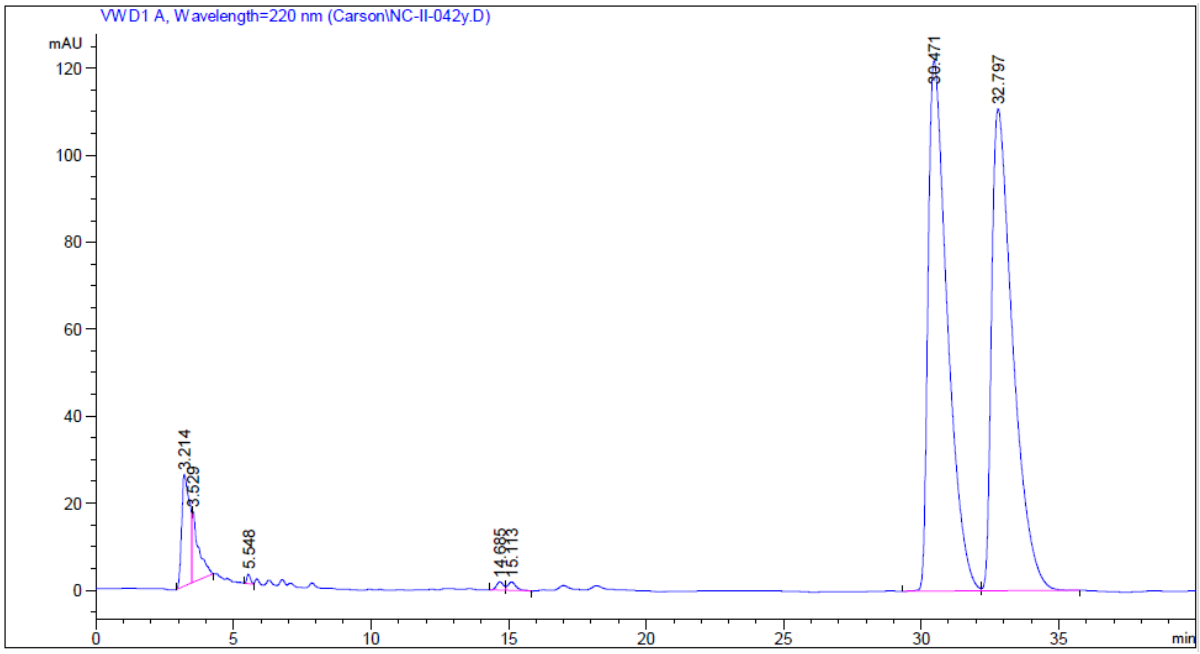
2924 (w), 2227 (m), 1904 (w), 1651 (w), 1605 (m), 1509 (m), 1453 (w), 1302 (w), 1270 (m), 1253 (m), 1173 (m), 1119 (w), 1043 (w), 990 (w), 834 (m), 575 (m), 546 (m)

MS: (EI)

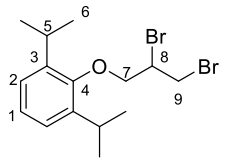
320.9 (11, M^+), 318.9 (22, M^+), 316.9 (11, M^+), 240.0 (2, $[M-HBr]^+$), 238.0 (2, $[M-HBr]^+$), 202.9 (39, $[M-OAryl^+]$, 200.9 (82, $[M-OAryl^+]$, 198.9 (42, $[M-OAryl^+]$, 120.9 (36, $[M-BrOAryl]^+$), 119.0 (100, $[M-BrOAryl]^+$), 102.0 (14, $[C_6H_4CN]^+$), 90.0 (8), 62.1 (45)

TLC: R_f 0.15 (90:10 hexane:EtOAc) [$AgNO_3$-H_2O_2]

HPLC: t_R 30.5 min (50.0%); t_R 32.8 min (50.0%) (IB-3, hexane/isopropanol = 92:8, 1.0 mL min^{-1}, 220 nm, 20 °C)



Preparation of *rac*-1-(2,3-Dibromopropoxy)-2,6-Diisopropylbenzene (20d)



Dibromide **20d** was synthesized from **19d** (0.2 mmol) to yield 73 mg (193 μmol, **97%** yield) of colorless needles. Spectroscopic data were consistent with those of Henry.[27]

Data for **19d**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.09–7.13 (m, 3 H, HC(1,2)), 4.45 (ABX, 1 H, HC(8)), 4.15 (ABX, 2 H, H_2C(7)), 3.96 (ABX, 2 H, H_2C(9)), 3.42 (sept, J = 6.8 Hz, 2 H, HC(5)), 1.24 (d, J = 6.8 Hz, 12 H, H_3C(6))

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 151.7 (C(4)), 141.9 (C(3)), 125.2 (C(2)), 124.1 (C(1)), 74.1 (C(7)), 48.6 (C(8)), 32.3 (C(9)), 26.3 (C(5)), 24.1 (C(6))

IR: (neat)

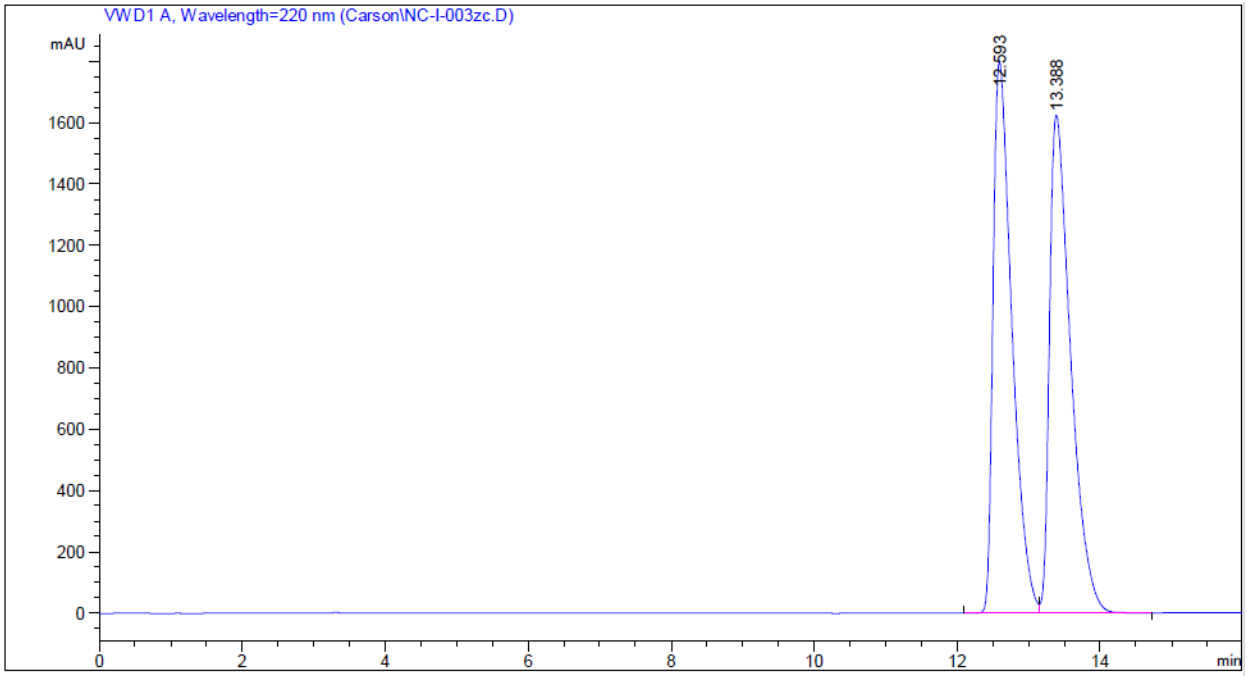
2962 (w), 2927 (w), 2868 (w), 1589 (w), 1457 (w), 1442 (w), 1328 (w), 1256 (w), 1180 (m), 1035 (w), 981 (w), 914 (w), 799 (w), 759 (m), 577 (m)

MS: (EI)

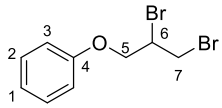
380.0 (11, M^+), 378.0 (22, M^+), 376.0 (11, M^+), 218.2 (5), 202.9 (6, $[M-Aryl]^+$), 200.9 (12, $[M-Aryl]^+$), 198.9 (6, $[M-Aryl]^+$), 178.1 (100, $[M-C_3H_4Br_2]^+$), 163.1 (92), 147.1 (10), 135.1 (47), 121.0 (12), 107.1 (13), 91.1 (17), 77.1 (7), 62.1 (6)

TLC: R_f 0.60 (90:10 hexane:EtOAc) [UV/CAM]

HPLC: t_R 12.5 min (49.7%); t_R 13.9 min (50.3%) (IB-3, hexane/isopropanol = 99.9:0.1, 1.0 mL min^{-1}, 220 nm, 20 °C)



Preparation of *rac*-(2,3-Dibromopropoxy)benzene (20c)



Dibromide **20c** was prepared according to a literature procedure, and had spectroscopic data consistent with the literature.[184]

Data for **20c**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.31 (dd, *J* = 8.5, 7.5 Hz, 2 H, HC(2)), 7.00 (t, *J* = 7.4 Hz, 1 H, HC(1)), 6.94 (d, *J* = 7.9 Hz, 2 H, HC(3)), 4.35–4.47 (m, 3 H, H_2C(6), HC(7)), 3.88–3.96 (m, 2 H, H_2C(8))

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 157.9 (C(4)), 129.6 (C(2)), 121.7 (C(1)), 114.8 (C(3)), 69.0 (C(5)), 47.7 (C(6)), 32.8 (C(7))

IR: (neat)

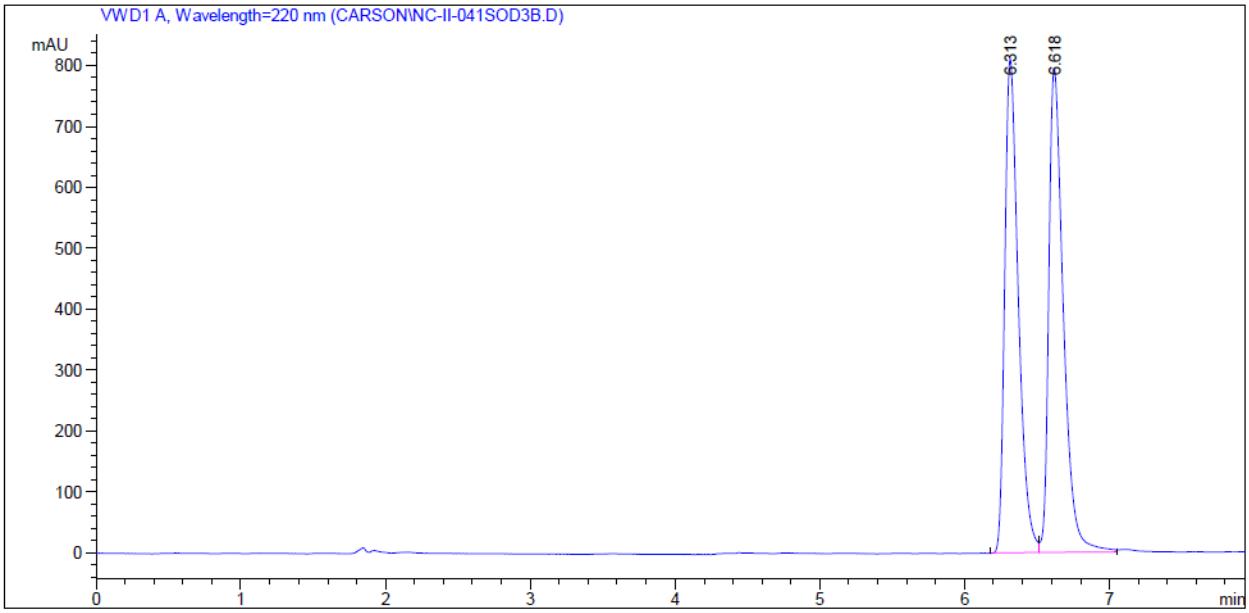
2927 (w), 2869 (w), 1598 (m), 1495 (m), 1240 (m), 1047 (w), 908 (w), 884 (w), 814 (w), 752 (s), 690 (m), 509 (w)

MS: (EI)

295.9 (10, M^+), 293.9 (21, M^+), 291.9 (11, M^+), 202.9 (6, $[M-OPh]^+$), 200.9 (13, $[M-OPh]^+$), 198.9 (7, $[M-OPh]^+$), 121.0 (14, $[M-BrOPh]^+$), 119.0 (14, $[M-BrOPh]^+$), 95.0 (11), 94.0 (100), 77.1 (16.9, Ph^+), 65.1 (13)

TLC: R_f 0.78 (90:10 hexane:Et_2O) [UV/CAM]

SFC: t_R 6.3 min (49.8%); t_R 6.6 min (50.2%) (OD, MeOH:CO_2 = 3:97, 2.5 mL min^{-1}, 220 nm, 40 °C)



Conditions and Spectra for Dibromination Reactions:

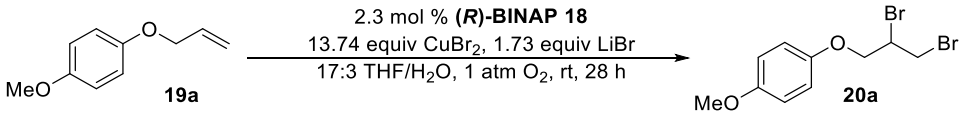
Reactions were run according to Henry's procedures.[27] The procedures were all reproduced as rigorously as the described procedures allow, other than changing the scale and reaction time – with the exception of Run 3, which was reproduced exactly. Reaction progress was monitored by TLC. Concentrations are calculated with respect to total solvent volume.

Table 10. Conditions for Dibromination Reactions

Run	Product	Scale, mmol	Pd complex, mol %	$CuBr_2$ equiv	$CuBr_2$ molarity, M	LiBr equiv	LiBr molarity, M	THF/H_2O ratio	Time, h
1	**20a**†	0.25	2.3	13.74	2.0 M	1.75	0.26 M	17:3	28
2	**20a**†	0.25	2.3	13.74	2.0 M	1.75	0.26 M	17:3	28
3	**20a**†	3.0	2.3	13.73	2.1 M	1.73	0.26 M	17:3	144
4	**20a**†	0.25	2.3	13.75	2.1 M	1.75	0.27 M	17:3	6
5	**20b**	0.25	2.4	15.83	2.0 M	1.01	0.13 M	1:9	24
6	**20c**	0.25	1.4	10.65	2.0 M	1.11	0.20 M	17:3	24
7	**20d**	0.25	2.5	15.83	2.2 M	1.24	0.17 M	87:13	24

† Nuclearity of palladium(II) catalyst is ambiguous in the original report for dibromination of **19a**.

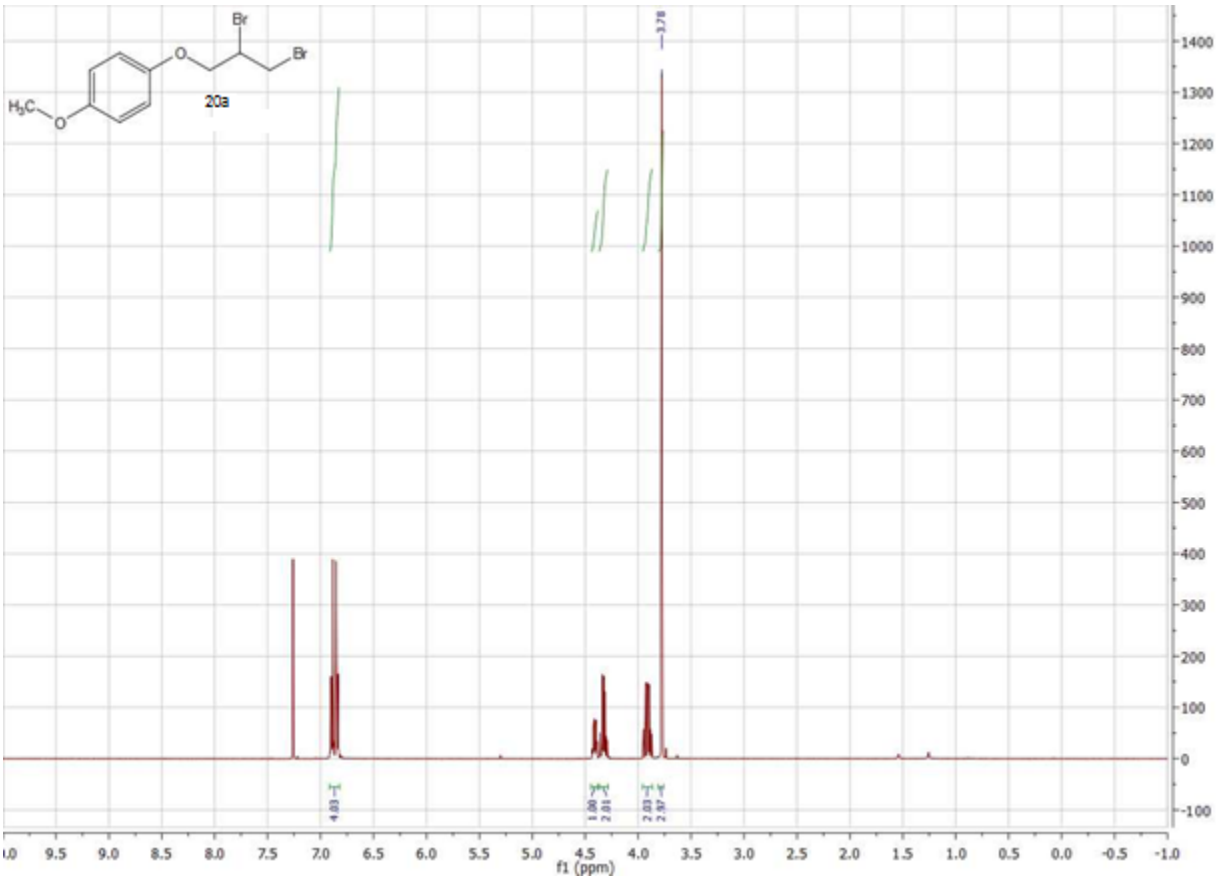
Run 1: Dibromination of 19a with Henry's catalyst preparation, 0.25 mmol, 28 h†

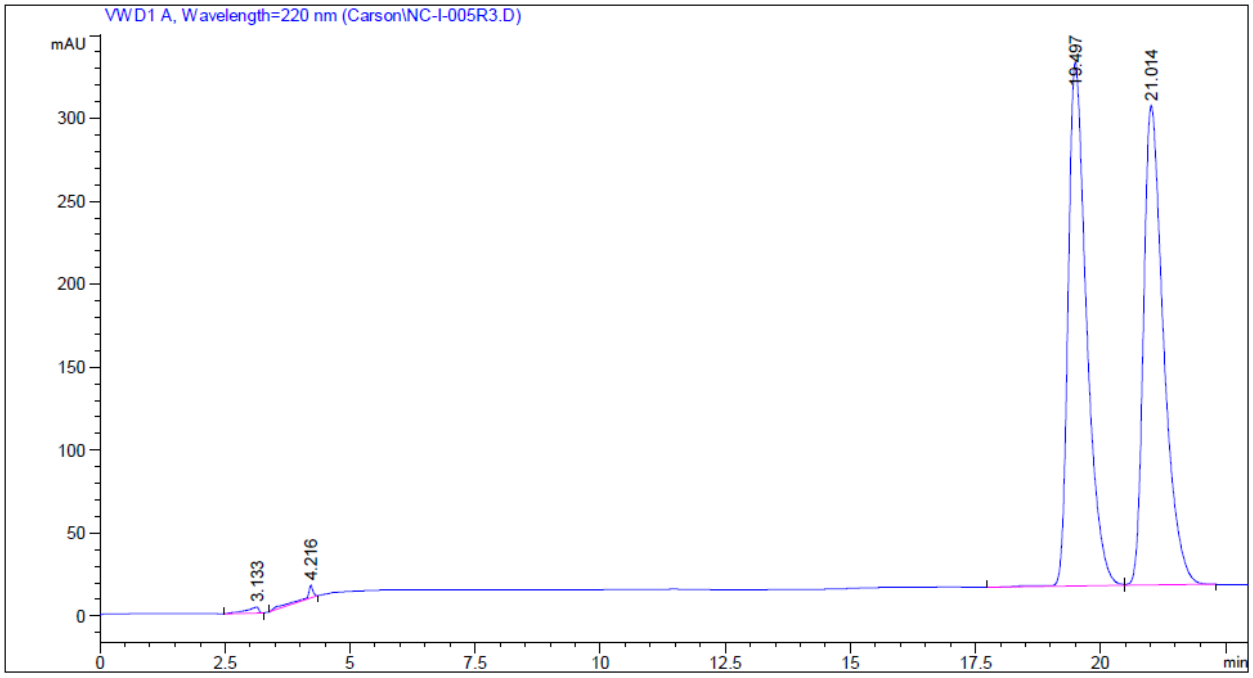


A 25-mL, round-bottomed flask containing a Teflon-coated, magnetic stir bar was charged with **(*R*)-BINAP 18**,† freshly prepared according to Henry's method (7.5 mg, 5.8 μmol, 2.3 mol %), and weighed out in a glovebox. The system was sealed under Ar, and removed from the glovebox, then an Ar line inserted, and 17:3 THF:H_2O (1.0 mL) injected to give a yellow solution. Then, copper(II) bromide (767 mg, 3.43 mmol, 13.74 equiv, 2.0 M) was added in one portion to form a deep green solution, followed by lithium bromide (38 mg, 0.43 mmol, 1.73 equiv, 0.26 M) in one portion, which gave slight yellowing of the solution. The atmosphere was replaced with 1 atm O_2 by sparging, and the reaction run under 1 atm O_2 from an oxygen manifold. **19a** (41 mg, 0.25 mmol) was then added to the mixture, washing with 17:3 THF:H_2O (0.7 mL). The mixture was left to stir at rt, monitoring periodically by TLC. Completion was reached at 28 h, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL), then dried over $MgSO_4$. Hexane (5 mL) was added, and the precipitated orange Pd complex removed by filtration, washing with hexane (3 × 5 mL). Solvent was removed *in vacuo*, then the mixture purified *via* column chromatography using 93:7 hexane:ethyl acetate as eluent, to yield dibromide **20a** as a white solid, 70 mg (0.22 mmol, **86%** yield). This was found to be racemic by CSP-HPLC. ^{1}H NMR spectroscopic data were identical to those of the racemic standard.

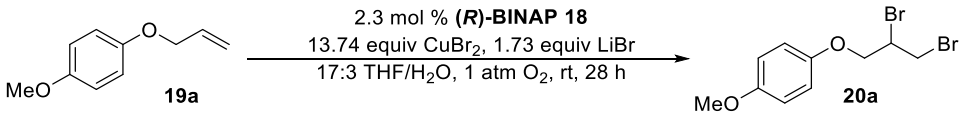
Data for **20a**:

HPLC: t_R 19.5 min (50.1%); t_R 21.0 min (49.9%) (OJ-H, hexane/isopropanol = 95.5:4.5, 1.0 mL min^{-1}, 220 nm, 20 °C)





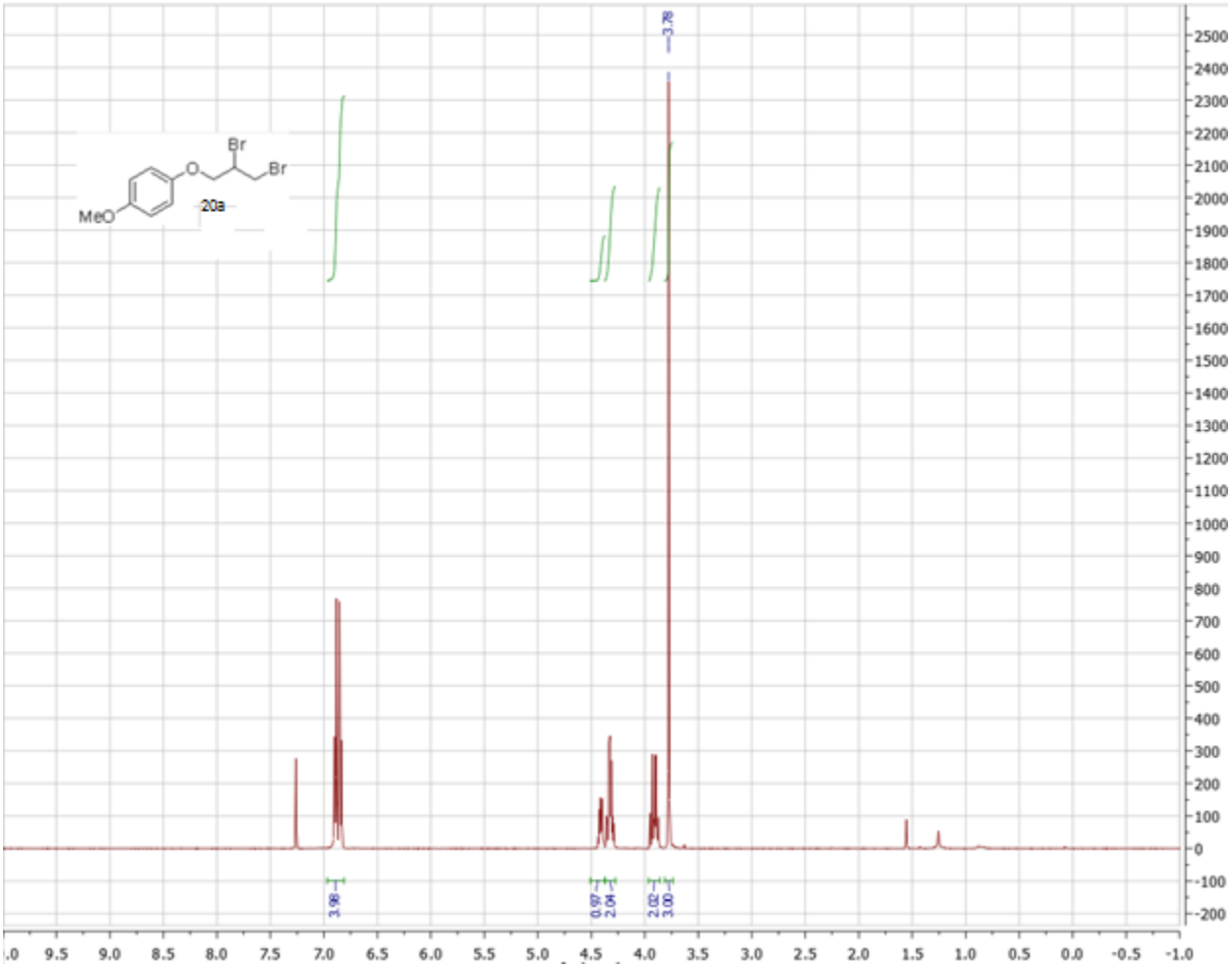
Run 2: Dibromination of 19a with New Catalyst Preparation, 0.25 mmol, 28 h[†]

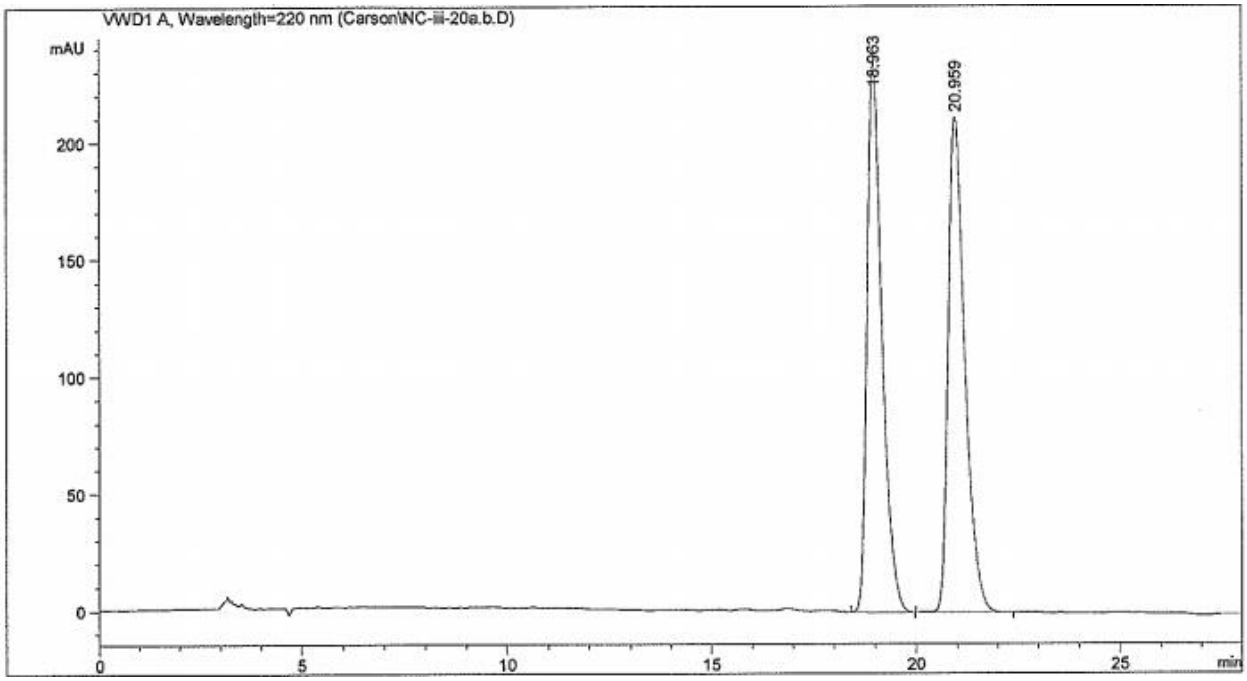


Run 1 was replicated, with the exception of using catalyst **(*R*)-BINAP 18** prepared by the new method described above. Dibromide **20a** was produced as a white solid, 69 mg (0.21 mmol, **85%** yield). This was found to be racemic by CSP-HPLC. ^{1}H NMR spectroscopic data were identical to those of the racemic standard.

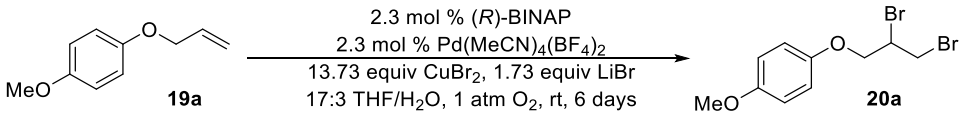
Data for **20a**:

HPLC: t_R 19.0 min (50.0%); t_R 21.0 min (50.0%) (OJ-H, hexane/isopropanol = 95.5:4.5, 1.0 mL min^{-1}, 220 nm, 20 °C)


Br
Br
O
MeO
20a
3.78
3.98
0.97
2.04
2.02
3.00


VWD1 A, Wavelength=220 nm (Carson\NC-iii-20a.b.D)
mAU
18.963
20.959
min

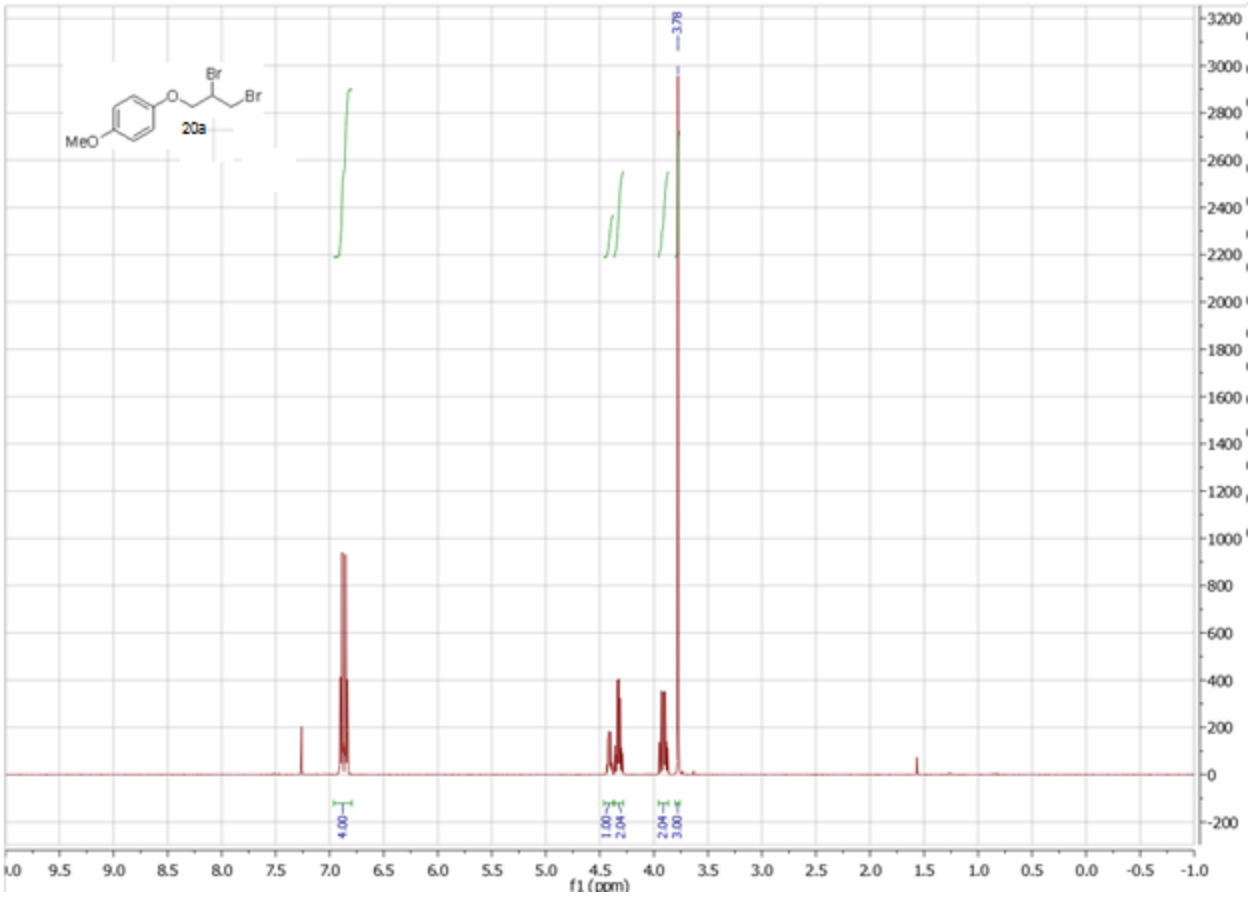
Run 3: Dibromination of 19a, 3.00 mmol, 6 days[†]

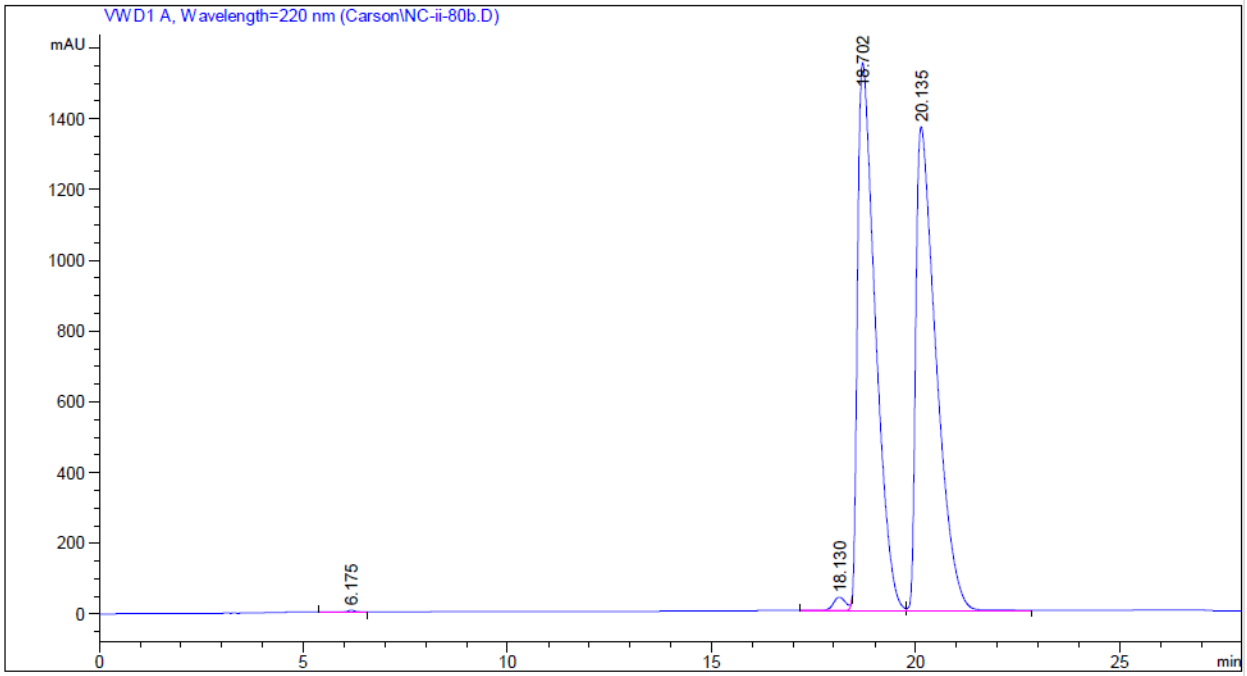


An oven-dried, 50-mL, round-bottomed flask containing a Teflon-coated, magnetic stir bar was charged with tetrakis(acetonitrile)palladium(II) tetrafluoroborate (31 mg, 69 μmol, 2.3 mol %) and (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl ((*R*)-BINAP) (43 mg, 69 μmol, 2.3 mol %) in a glovebox. The system was sealed under Ar, and removed from the glovebox, then an Ar line inserted, and 17:3 THF:H_2O (15 mL) injected. The solution was stirred at rt for 10 min, and turned from light to dark orange color. Then, copper(II) bromide (9.20 g, 41.2 mmol, 13.73 equiv, 2.1 M) was added in one portion to form a deep green solution, followed by lithium bromide (450 mg, 5.2 mmol, 1.73 equiv, 0.26 M) in one portion, which gave slight yellowing of the solution. The atmosphere was replaced with 1 atm O_2 by sparging, and the reaction run under 1 atm O_2 from an oxygen manifold. **19a** (493 mg, 3.00 mmol) was then added to the mixture, washing with 17:3 THF:H_2O (5 mL). The mixture was left to stir at rt. After 6 days, the mixture was extracted with CH_2Cl_2 (3 × 50 mL), then dried over $MgSO_4$. Hexane (15 mL) was added, and the precipitated orange Pd complex removed by filtration, washing with hexane (3 × 10 mL). Solvent was removed *in vacuo*, then the mixture purified *via* column chromatography using 95:5 hexane:ethyl acetate as eluent, to yield dibromide **20a**, 754 mg (2.33 mmol, **78%** yield) of a white solid. This was found to be racemic by CSP-HPLC. ^{1}H NMR spectroscopic data were identical to those of the racemic standard.

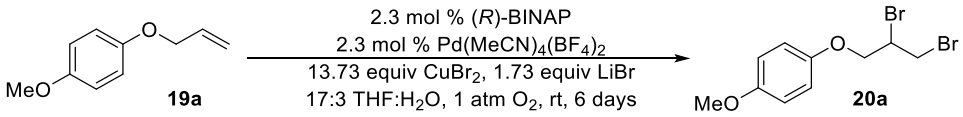
Data for **20a**:

HPLC: t_R 18.7 min (49.9%); t_R 20.1 min (50.1%) (OJ-H, hexane/isopropanol = 95.5:4.5, 1.0 mL min^{-1}, 220 nm, 20 °C)


Br
Br
O
MeO
20a
3.78
4.00
1.00
2.04
2.04
3.00
f1 (ppm)


VWD1 A, Wavelength=220 nm (Carson\NC-ii-80b.D)
mAU
6.175
18.130
18.702
20.135
min

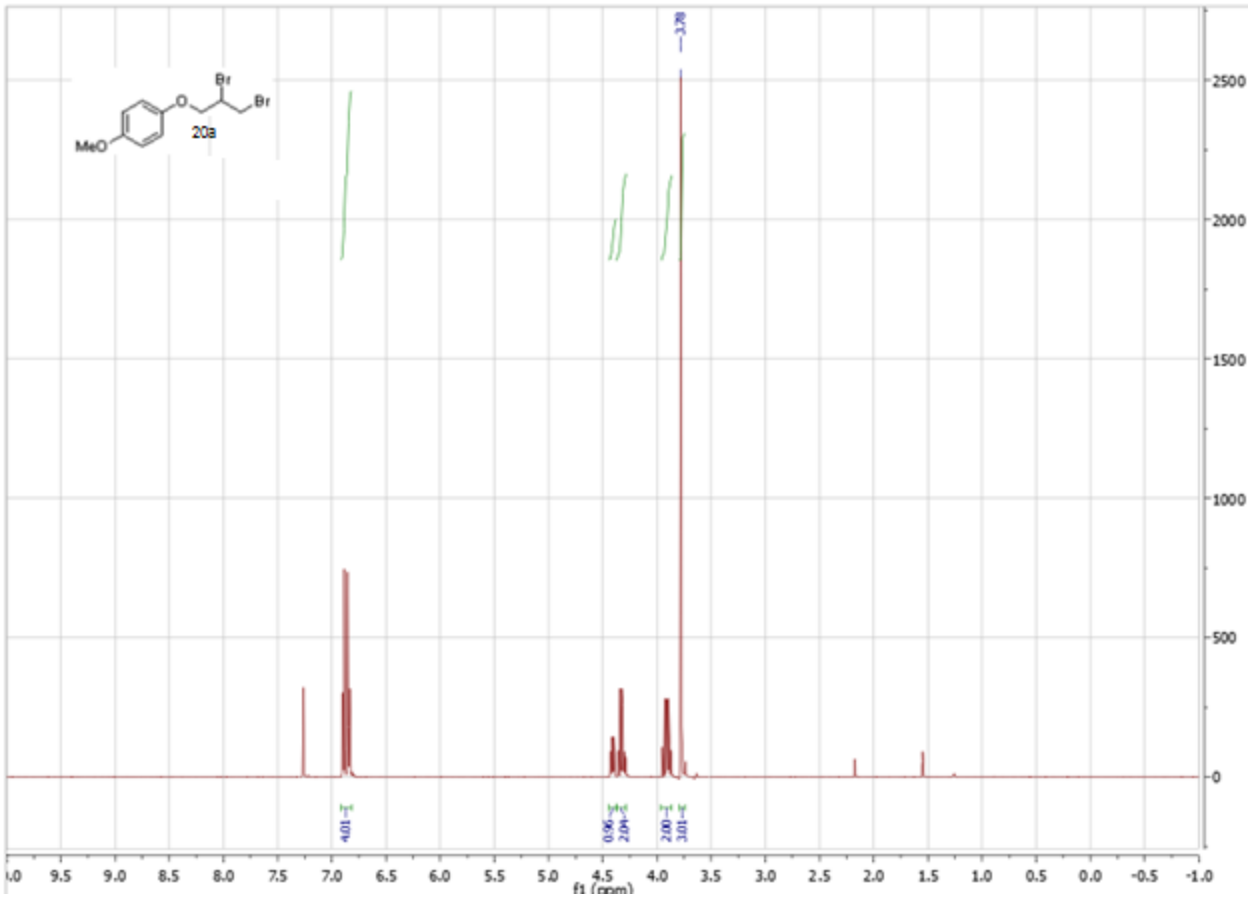
Run 4: Dibromination of 19a, 0.25 mmol, 6 h[†]

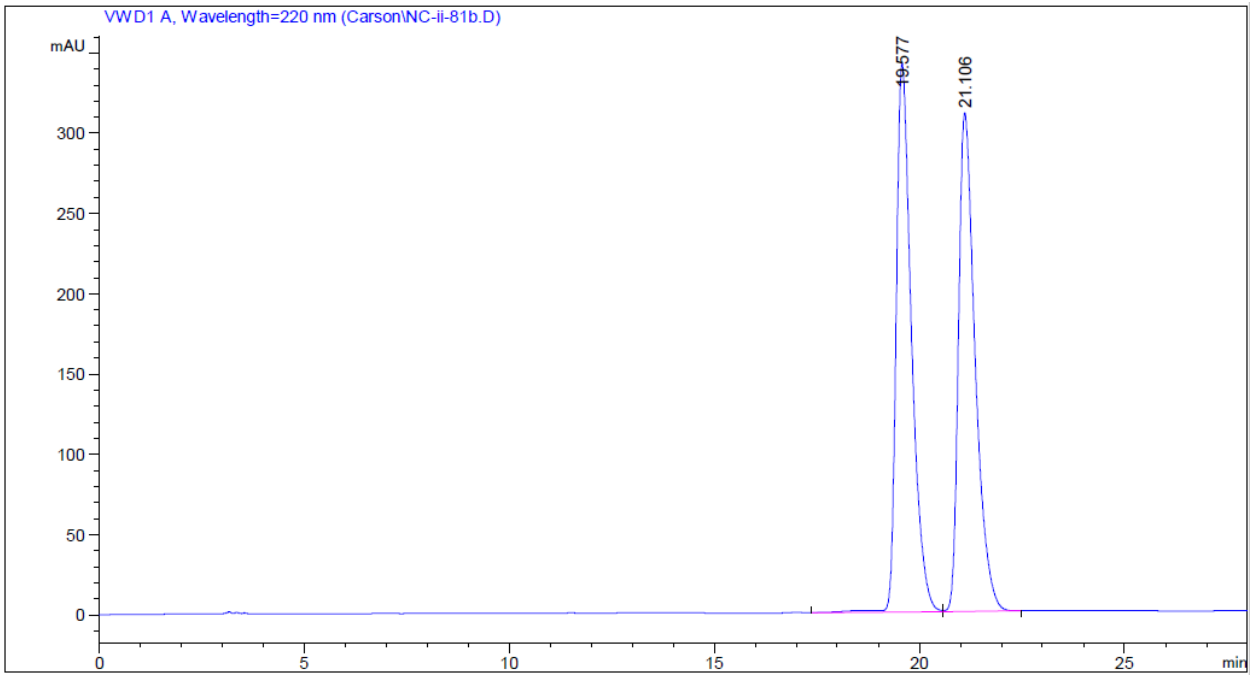


An oven-dried, 15-mL, round-bottomed flask containing a Teflon-coated, magnetic stir bar was charged with tetrakis(acetonitrile)palladium(II) tetrafluoroborate (2.6 mg, 5.7 μmol, 2.3 mol %) and (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl ((*R*)-BINAP) (3.6 mg, 5.7 μmol, 2.3 mol %) in a glovebox. The system was sealed under Ar, and removed from the glovebox, then an Ar line inserted, and 17:3 THF:H_2O (1.0 mL) injected. The solution was stirred at rt for 10 min, and turned from light to dark orange color. Then, copper(II) bromide (758 mg, 3.43 mmol, 13.75 equiv, 2.1 M) was added in one portion to form a deep green solution, followed by lithium bromide (38 mg, 0.43 mmol, 1.75 equiv, 0.27 M) in one portion, which gave slight yellowing of the solution. The atmosphere was replaced with 1 atm O_2 by sparging, and the reaction run under 1 atm O_2 from an oxygen manifold. **19a** (41 mg, 0.25 mmol) was then added to the mixture, washing with 17:3 THF:H_2O (0.6 mL). The mixture was left to stir at rt, and stopped after 6 h. The mixture was extracted with CH_2Cl_2 (3 × 15 mL), then dried over $MgSO_4$. Hexane (5 mL) was added, and the precipitated orange Pd complex removed by filtration, washing with hexane (3 × 5 mL). Solvent was removed *in vacuo*, then the mixture purified *via* column chromatography using 93:7 hexane:ethyl acetate as eluent, to yield dibromide **20a**, 54 mg (0.17 mmol, **67%** yield) as a white solid. This was found to be racemic by CSP-HPLC. ^{1}H NMR spectroscopic data were identical to those of the racemic standard.

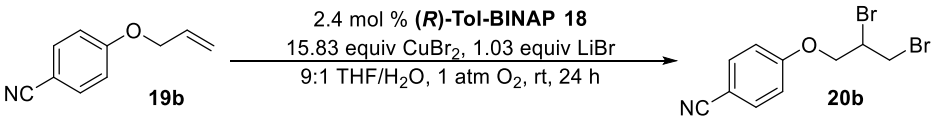
Data for **20a**:

HPLC: t_R 19.6 min (50.3%); t_R 21.1 min (49.7%) (OJ-H, hexane/isopropanol = 95.5:4.5, 1.0 mL min^{-1}, 220 nm, 20 °C)


Br
Br
O
MeO
20a
3.78
4.01
0.96
2.04
2.00
3.01
2500
2000
1500
1000
500
0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


VWD1 A, Wavelength=220 nm (Carson\NC-ii-81b.D)
mAU
300
250
200
150
100
50
0
19.577
21.106
0
5
10
15
20
25
min

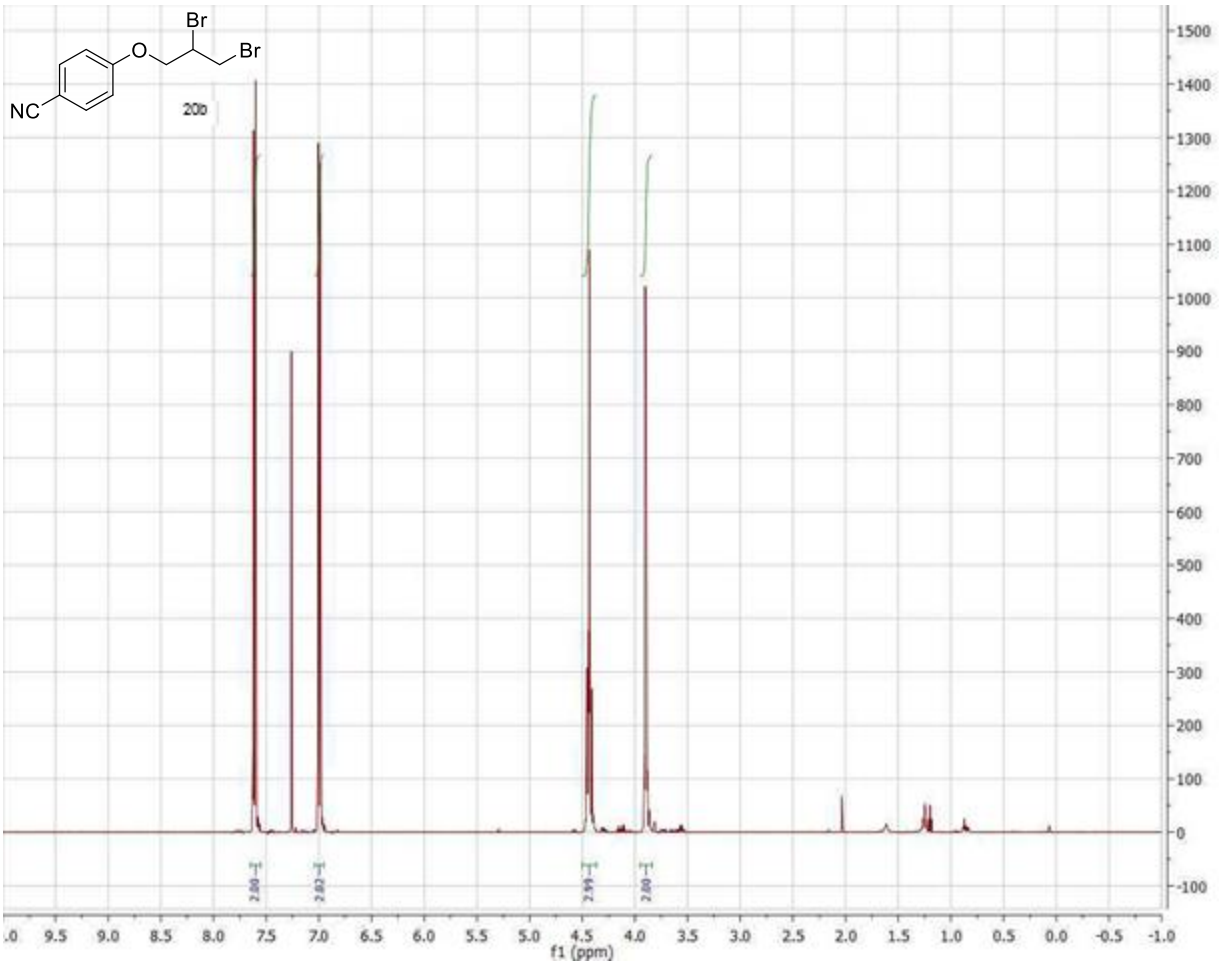
Run 5: Dibromination of 19b, 0.25 mmol, 24 h

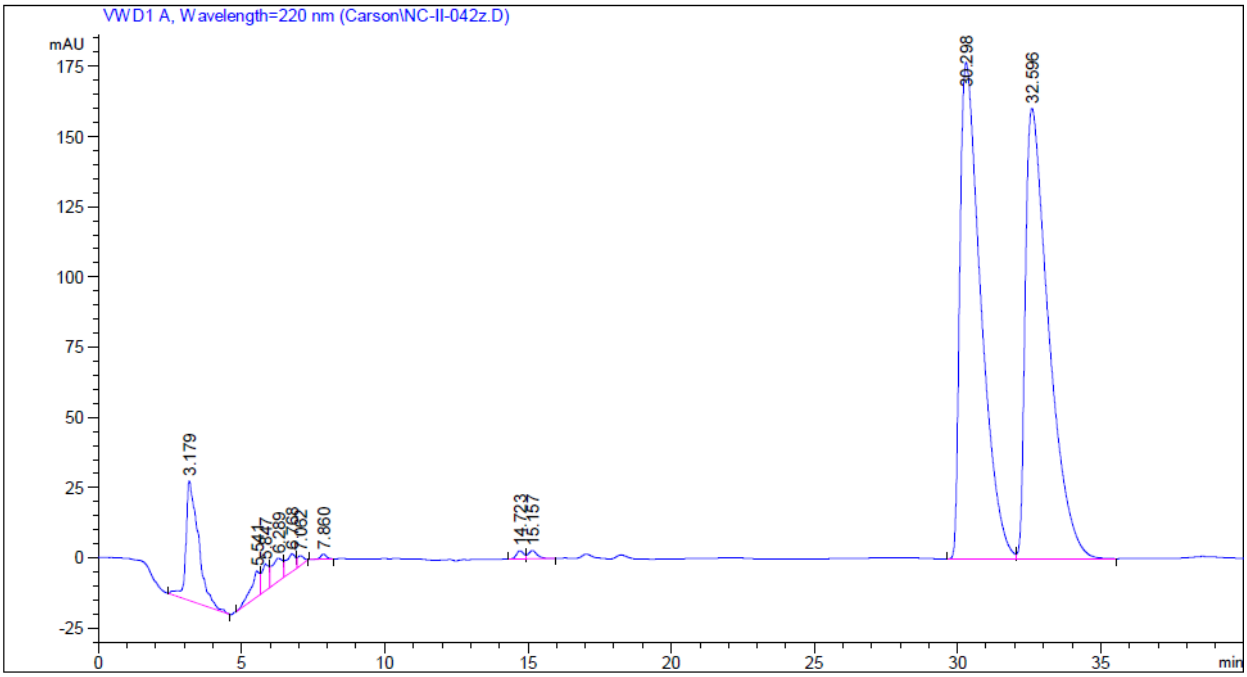


A 25-mL, round-bottomed flask containing a Teflon-coated, magnetic stir bar was charged with freshly-prepared **(*R*)-Tol-BINAP 18** (8.1 mg, 6.0 μmol, 2.4 mol %), weighed out in a glovebox. The system was sealed under Ar, and removed from the glovebox, then an Ar line inserted, and 9:1 THF:H_2O (1.0 mL) injected. Then, copper(II) bromide (884 mg, 3.96 mmol, 15.83 equiv, 2.0 M) was added in one portion to form a deep green solution, followed by lithium bromide (22 mg, 0.26 mmol, 1.03 equiv, 0.13 M) in one portion, which gave slight yellowing of the solution. The atmosphere was replaced with 1 atm O_2 by sparging, and the reaction run under 1 atm O_2 from an oxygen manifold. **19b** (40 mg, 0.25 mmol) was then added to the mixture, washing with 9:1 THF:H_2O (1.0 mL). The mixture was left to stir at rt, monitoring periodically by TLC. Completion was reached at 24 h, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL), then dried over $MgSO_4$. Hexane (5 mL) was added, and the precipitated yellow Pd complex removed by filtration, washing with hexane (3 × 5 mL). Solvent was removed *in vacuo*, then the mixture purified *via* column chromatography using 9:1 hexane:ethyl acetate as eluent, to yield dibromide **20b** as a white solid, 68 mg (0.21 mmol, **85%** yield). This was found to be racemic by CSP-HPLC. ^{1}H NMR spectroscopic data were identical to those of the racemic standard.

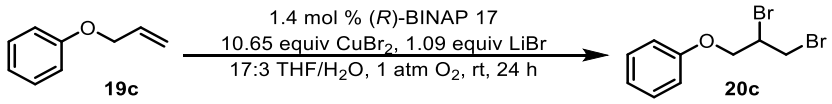
Data for **20b**:

HPLC: t_R 30.3 min (49.8%); t_R 32.6 min (50.2%) (IB-3, hexane/isopropanol = 92:8, 1.0 mL min^{-1}, 220 nm, 20 °C)


Br
O
Br
NC
20b
f1 (ppm)


VWD1 A, Wavelength=220 nm (Carson\NC-II-042z.D)
mAU
min
3.179
5.541
5.947
6.289
6.768
7.062
7.860
14.723
15.157
30.298
32.596

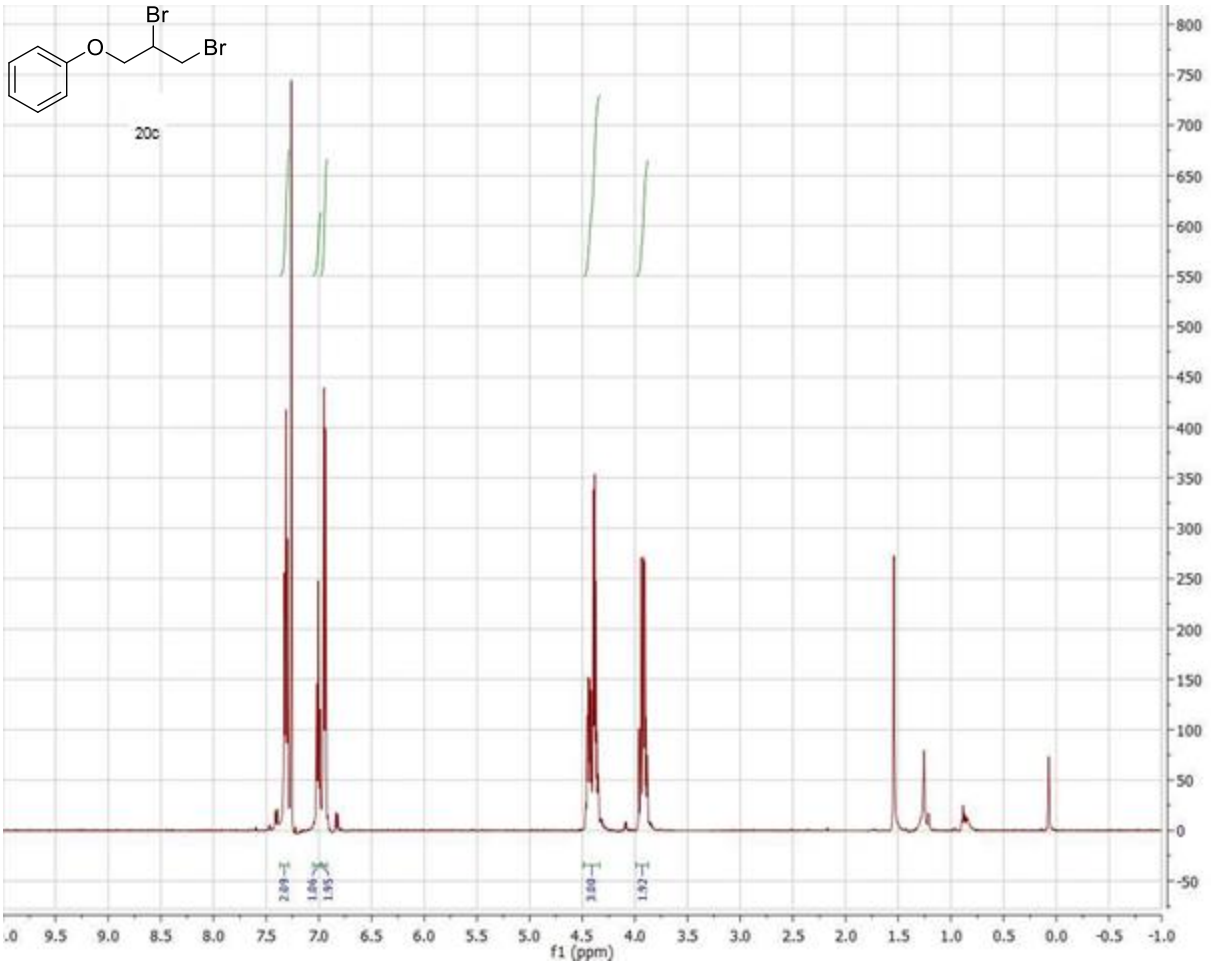
Run 6: Dibromination of 19c, 0.25 mmol, 24 h

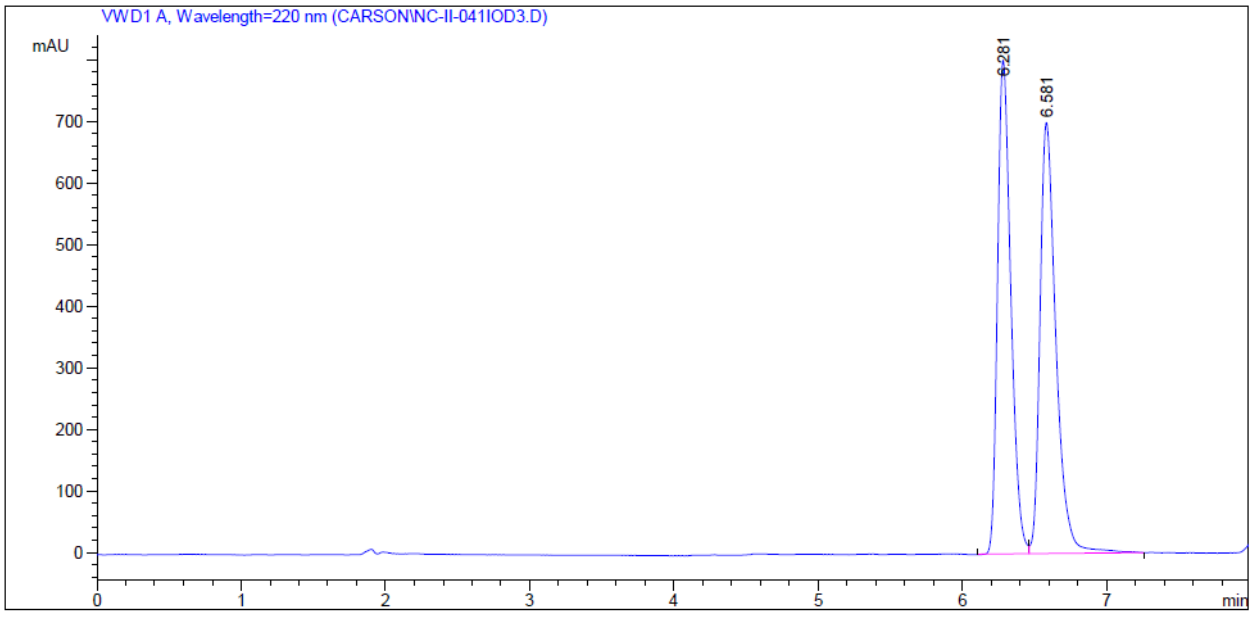


A 25-mL, round-bottomed flask containing a Teflon-coated, magnetic stir bar was charged with **(*R*)-BINAP 18**, freshly prepared according to the new procedure described above (4.4 mg, 3.4 μmol, 1.4 mol %), and weighed out in a glovebox. The system was sealed under Ar, and removed from the glovebox, then an Ar line inserted, and 17:3 THF:H_2O (1.0 mL) injected. Then, copper(II) bromide (595 mg, 2.66 mmol, 10.65 equiv, 2.0 M) was added in one portion to form a deep green solution, followed by lithium bromide (24 mg, 0.27 mmol, 1.09 equiv, 0.20 M) in one portion, which gave slight yellowing of the solution. The atmosphere was replaced with 1 atm O_2 by sparging, and the reaction run under 1 atm O_2 from an oxygen manifold. **19c** (34 mg, 0.25 mmol) was then added to the mixture, washing with 17:3 THF:H_2O (0.35 mL). The mixture was left to stir at rt, monitoring periodically by TLC. Completion was reached at 24 h, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL), then dried over $MgSO_4$. Hexane (5 mL) was added, and the precipitated orange Pd complex removed by filtration, washing with hexane (3 × 5 mL). Solvent was removed *in vacuo*, then the mixture purified *via* column chromatography using hexane as eluent, to yield dibromide **20c** as a pale yellow oil, 51 mg (0.17 mmol, **69%** yield). This was found to be racemic by CSP-SFC. ^{1}H NMR spectroscopic data were identical to those of the racemic standard.

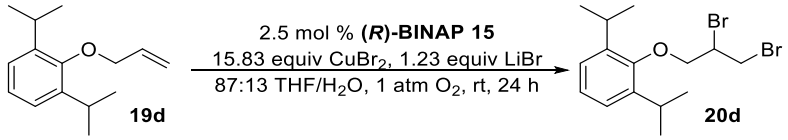
Data for **20c**:

SFC: t_R 6.3 min (49.9%); t_R 6.6 min (50.1%) (OD, MeOH:CO_2 = 3:97, 2.5 mL min^{-1}, 220 nm, 40 °C)


Br
O
Br
20c
f1 (ppm)


VWD1 A, Wavelength=220 nm (CARSON\NC-II-041IOD3.D)
mAU
6.281
6.581
min

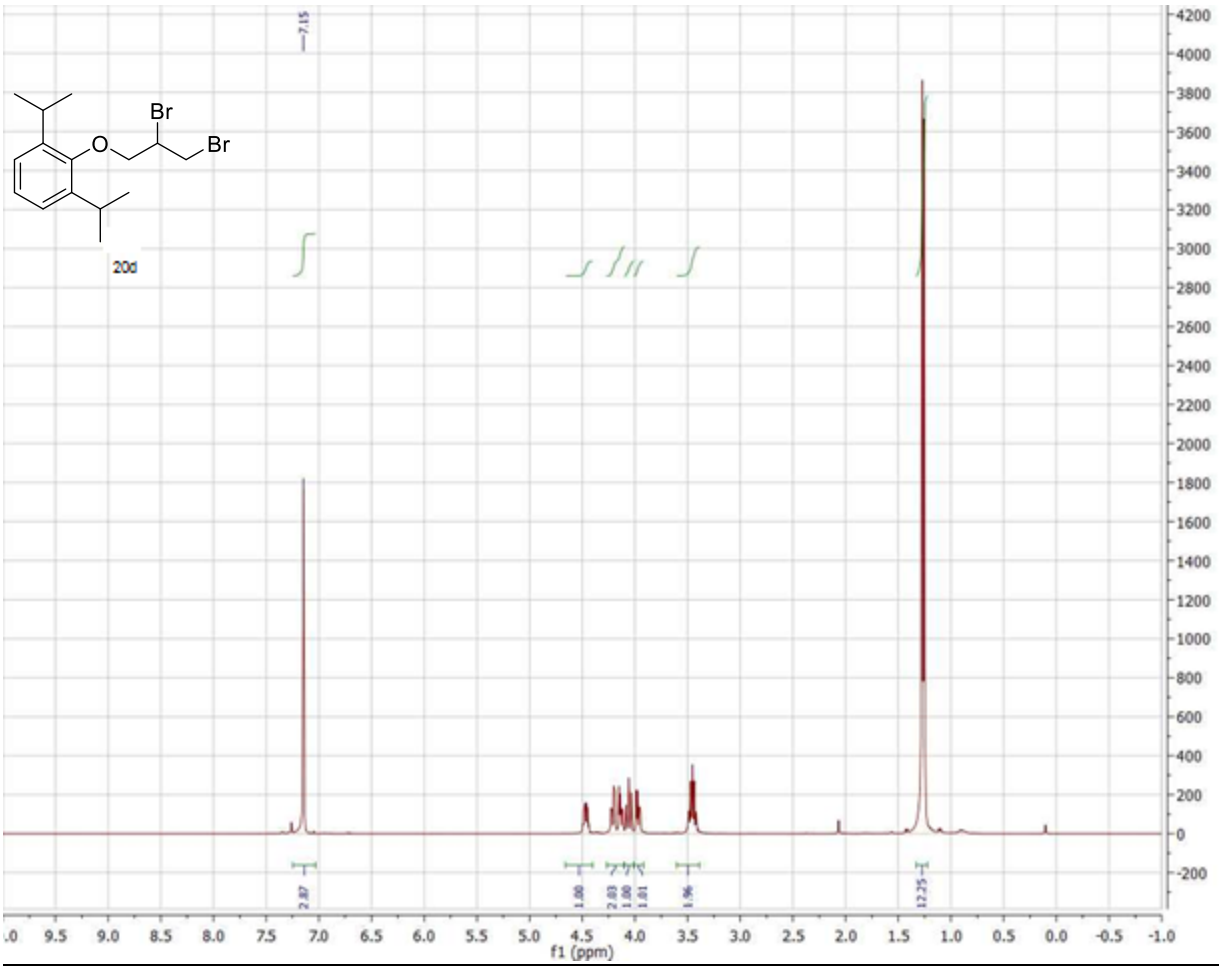
Run 7: Dibromination of 19d, 0.25 mmol, 24 h

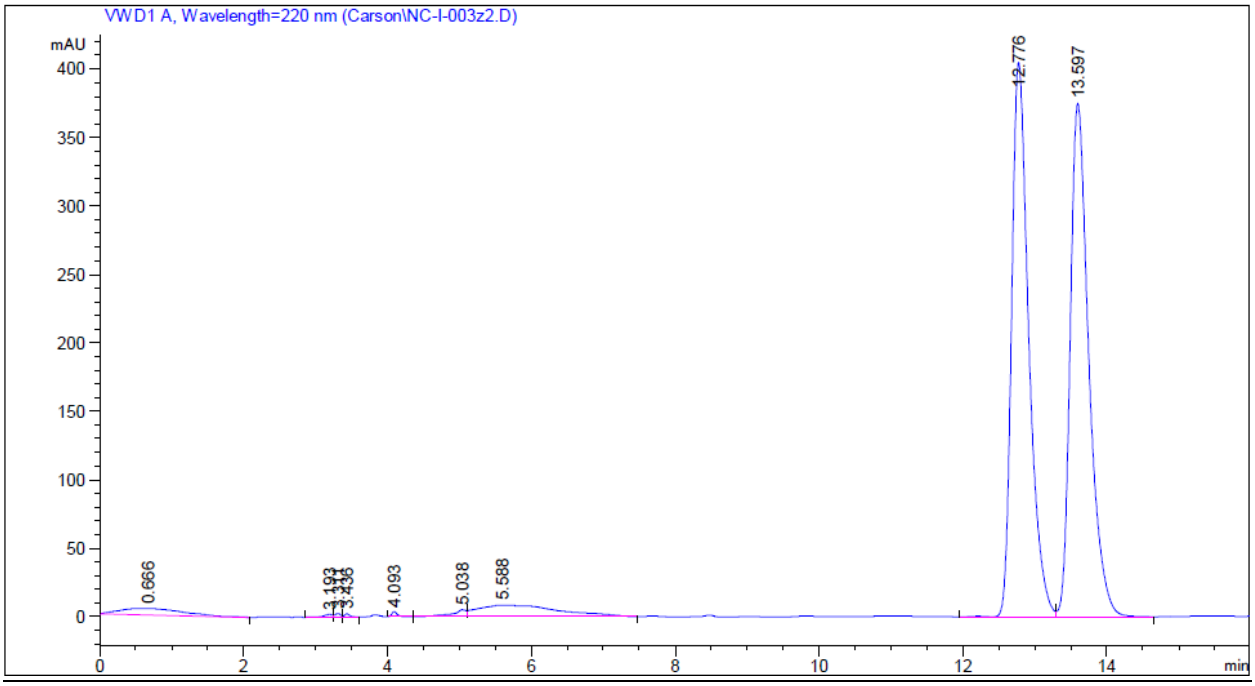


A 25-mL, round-bottomed flask containing a Teflon-coated, magnetic stir bar was charged with freshly-prepared **(*R*)-BINAP 15** (6.2 mg, 6.3 μmol, 2.5 mol %), weighed out in a glovebox. The system was sealed under Ar, and removed from the glovebox, then an Ar line inserted, and 87:13 THF:H_2O (1.0 mL) injected to give a bright yellow solution. Then, copper(II) bromide (884 mg, 3.96 mmol, 15.83 equiv, 2.2 M) was added in one portion to form a deep green solution, followed by lithium bromide (27 mg, 0.31 mmol, 1.23 equiv, 0.17 M) in one portion, which gave slight yellowing of the solution. The atmosphere was replaced with 1 atm O_2 by sparging, and the reaction run under 1 atm O_2 from an oxygen manifold. **19d** (55 mg, 0.25 mmol) was then added to the mixture, washing with 87:13 THF:H_2O (0.8 mL). The mixture was left to stir at rt, monitoring periodically by TLC. Completion was reached at 24 h, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL), then dried over $MgSO_4$. Hexane (5 mL) was added, and the precipitated yellow Pd complex removed by filtration, washing with hexane (3 × 5 mL). Solvent was removed *in vacuo*, then the mixture purified *via* column chromatography using 99:1 hexane:ethyl acetate as eluent, to yield dibromide **20d** as colorless needles, 85 mg (0.22 mmol, **90%** yield). This was found to be racemic by CSP-HPLC. ^{1}H NMR spectroscopic data were identical to those of the racemic standard.

Data for **20d**:

HPLC: t_R 12.8 min (49.9 %); t_R 13.6 min (50.1%) (IB-3, hexane/isopropanol = 99.9:0.1, 1.0 mL min^{-1}, 220 nm, 20 °C)


Br
O
Br
20d
f1 (ppm)


VWD1 A, Wavelength=220 nm (Carson\NC-I-003z2.D)
mAU
0.666
4.093
5.038
5.588
12.776
13.597
min

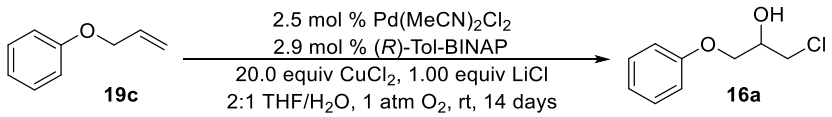
Conditions and Spectra for Chlorohydroxylation Reactions:

Reactions were run according to Henry's procedures.[25] The procedures were all reproduced as rigorously as the described procedures allow, other than changing the scale. Reaction progress was monitored by ^{1}H NMR of aliquots. Concentrations are calculated with respect to total solvent volume.

Table 11. Conditions for Chlorohydroxylation Reactions

Run	Product	Scale, mmol	Pd complex, mol %	$CuCl_2$ equiv	$CuCl_2$ molarity, M	LiCl equiv	LiCl molarity, M	THF/H_2O	Time, days
8	**16a**	0.5	2.5	20.00	4.0	1.00	0.20	2:1	14
9	**16a**	0.5	1.2	14.59	1.8	2.43	0.30	92:8	5
10	**16b**	1.0	1.0	8.00	8.0	0.40	0.40	2:1	10
11	**16c**	0.5	1.5	13.38	2.9	0.92	0.20	90:10	10

Run 8: Chlorohydroxylation of 19c with (*R*)-Tol-BINAP 15, 0.50 mmol, 14 days

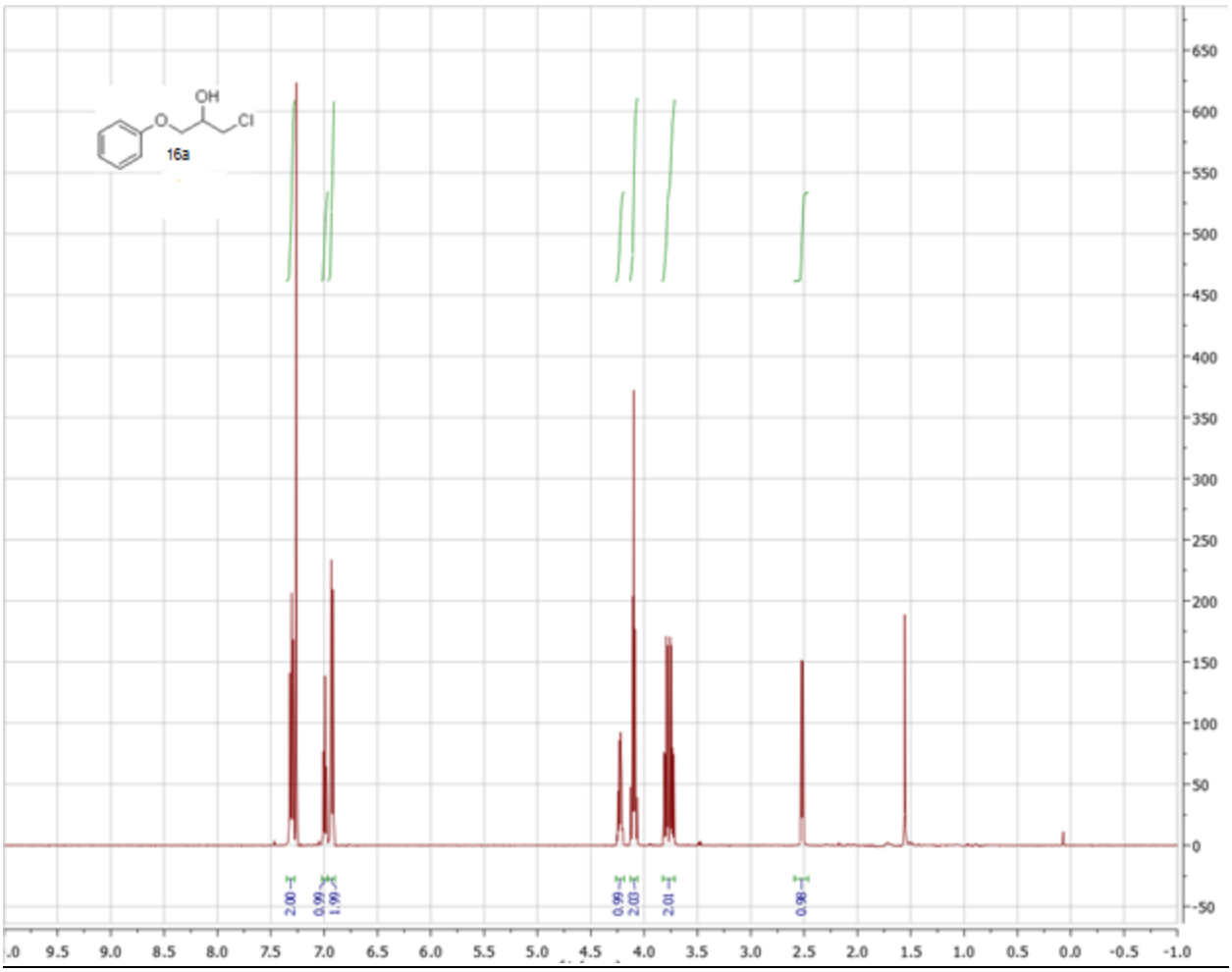


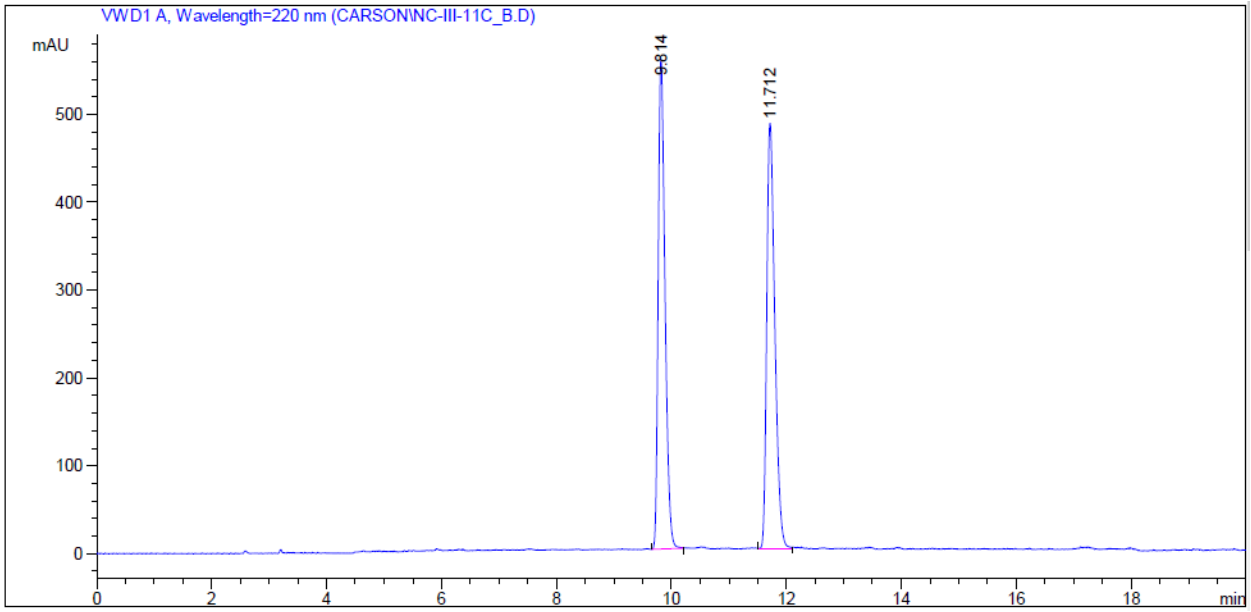
In a glovebox, a 10-mL, two-necked flask containing a Teflon-coated, magnetic stir bar was charged with bis(acetonitrile)dichloropalladium(II) (3.2 mg, 12 μmol, 2.5 mol %). The flask was sealed under Ar and removed from the glovebox. An Ar line was inserted, and anhydrous THF (1.0 mL) was injected. (*R*)-Tol-BINAP (9.5 mg, 14 μmol, 2.9 mol %) was added to form a yellow solution, which was stirred at rt for 30 min. Then, a separate 10-mL, round-bottomed flask containing a Teflon-coated, magnetic stir bar was charged with anhydrous copper(II) chloride (1.344 g, 10.0 mmol, 20.0 equiv) and lithium chloride (21 mg, 0.5 mmol, 1.00 equiv), and 45:55 THF/H_2O (0.5 mL) was added to form a green solution. The catalyst solution was cannulated into the second flask, washing with 45:55 THF/H_2O (0.5 mL). The atmosphere was replaced with 1 atm O_2 by sparging, and the reaction run under 1 atm O_2 from an oxygen manifold. **19c** (67 mg, 0.5 mmol) was then added to the mixture, washing with 45:55 THF/H_2O (0.5 mL). The eventual solvent mixture was 2:1 THF/H_2O. The mixture was left to stir at rt, monitoring periodically by NMR spectroscopy of aliquots. Despite low conversion, the reaction was stopped after 14 days. H_2O (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL), then dried over $CaCl_2$. Solvent was removed *in vacuo*, then the mixture purified *via* column chromatography using

a gradient from 93:7 to 85:15 hexane:ethyl acetate as eluent, to yield chlorohydrin **16a** as a pale yellow oil, 14 mg (0.075 mmol, **15%** yield). This was found to be racemic by CSP-SFC. ^{1}H NMR spectroscopic data were identical to those of the racemic standard.

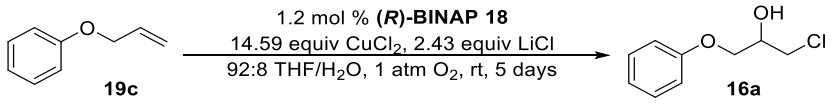
Data for **16a**:

SFC: t_R 9.8 min (49.5%); t_R 11.7 min (50.5%) (OD, MeOH:CO_2 = 1:99 for 10 mins then 10:90 for 6 mins then 5:95 for 4 mins, 2.5 mL min^{-1}, 220 nm, 40 °C)


OH
O
Cl
16a
2.00
0.99
1.99
0.99
2.03
2.01
0.98


VWD1 A, Wavelength=220 nm (CARSON\NC-III-11C_B.D)
mAU
9.814
11.712
min

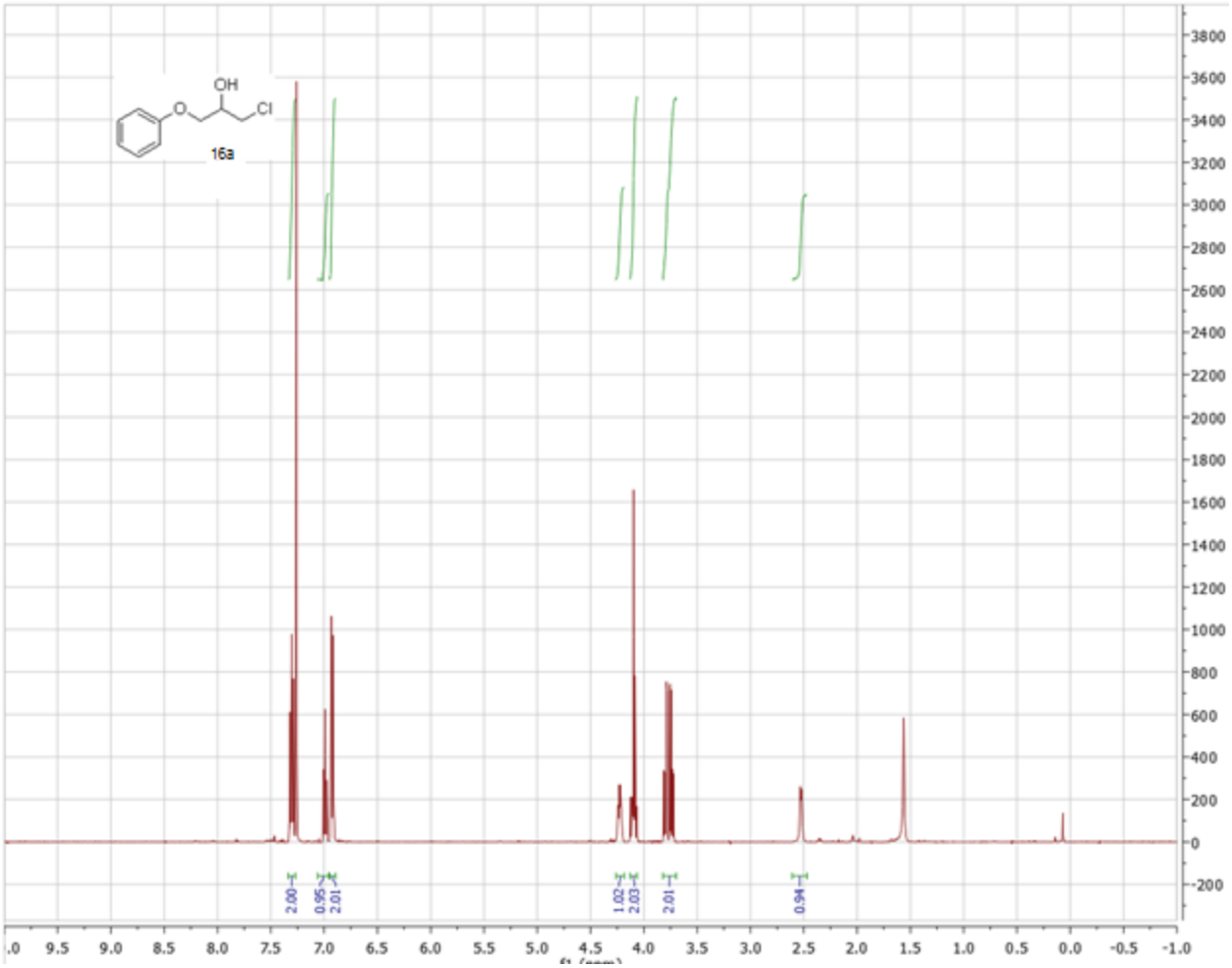
Run 9: Chlorohydroxylation of 19c with (*R*)-BINAP 18, 0.50 mmol, 5 days

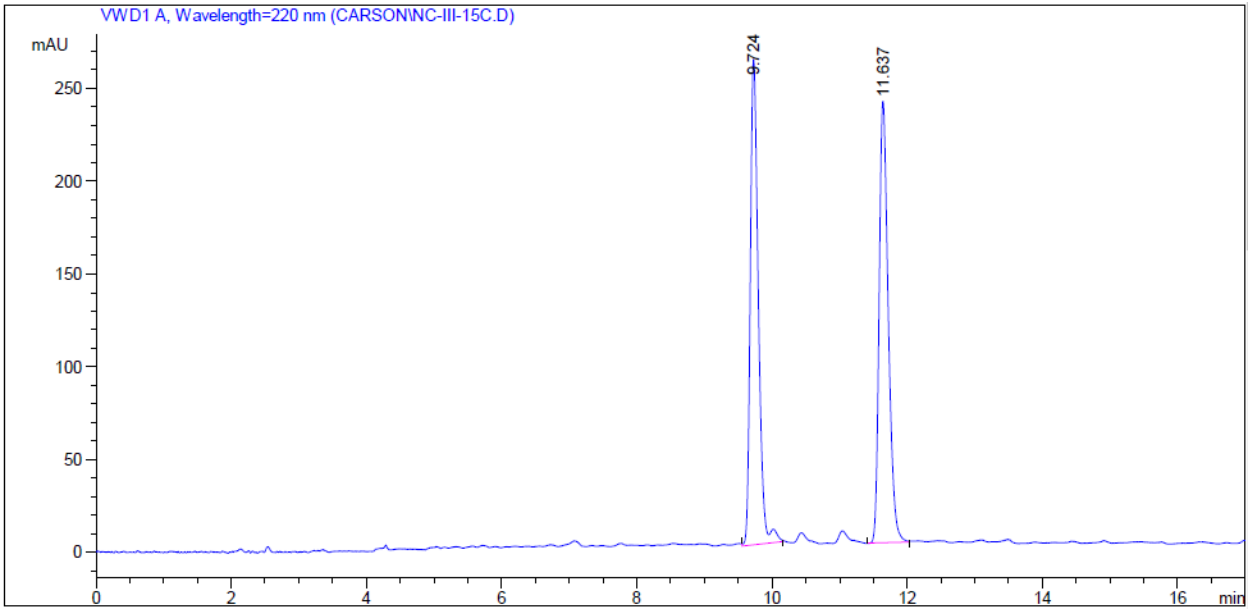


In a glovebox, a 10-mL, two-necked flask containing a Teflon-coated, magnetic stir bar was charged with **(R)-BINAP 18**, freshly prepared according to Henry's method (7.9 mg, 6.1 μmol, 1.2 mol %). The flask was sealed under Ar and removed from the glovebox. An Ar line was inserted, and anhydrous THF (1.0 mL) was injected. Anhydrous copper(II) chloride (981 mg, 7.30 mmol, 14.59 equiv) and lithium chloride (52 mg, 1.21 mmol, 2.43 equiv) were then added, followed by 89:11 THF:H_2O (2.05 mL), to form a green solution. The atmosphere was replaced with 1 atm O_2 by sparging, and the reaction run under 1 atm O_2 from an oxygen manifold. **19c** (67 mg, 0.5 mmol) was then added to the mixture, washing with 92:8 THF:H_2O (1.0 mL). The eventual solvent mixture was 92:8 THF:H_2O. The mixture was left to stir at rt, monitoring periodically by NMR spectroscopy of aliquots, and stopped after 5 days. H_2O (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL), then dried over $CaCl_2$. Solvent was removed *in vacuo*, then the mixture purified *via* column chromatography using a gradient from 93:7 to 85:15 hexane:ethyl acetate as eluent, to yield chlorohydrin **16a** as a pale yellow oil, 37 mg (0.20 mmol, **40%** yield). This was found to be racemic by CSP-SFC. ^{1}H NMR spectroscopic data were identical to those of the racemic standard.

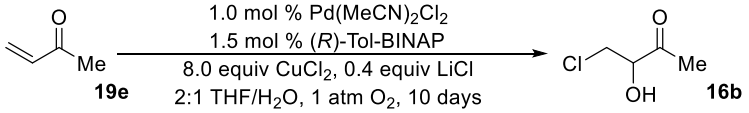
Data for **16a**:

SFC: t_R 9.7 min (49.5%); t_R 11.6 min (50.5%) (OD, MeOH:CO_2 = 1:99 for 10 mins then 10:90 for 6 mins then 5:95 for 4 mins, 2.5 mL min^{-1}, 220 nm, 40 °C)


OH
O
Cl
16a
2.00
0.95
2.01
1.02
2.03
2.01
0.94


VWD1 A, Wavelength=220 nm (CARSON\NC-III-15C.D)
mAU
9.724
11.637
min

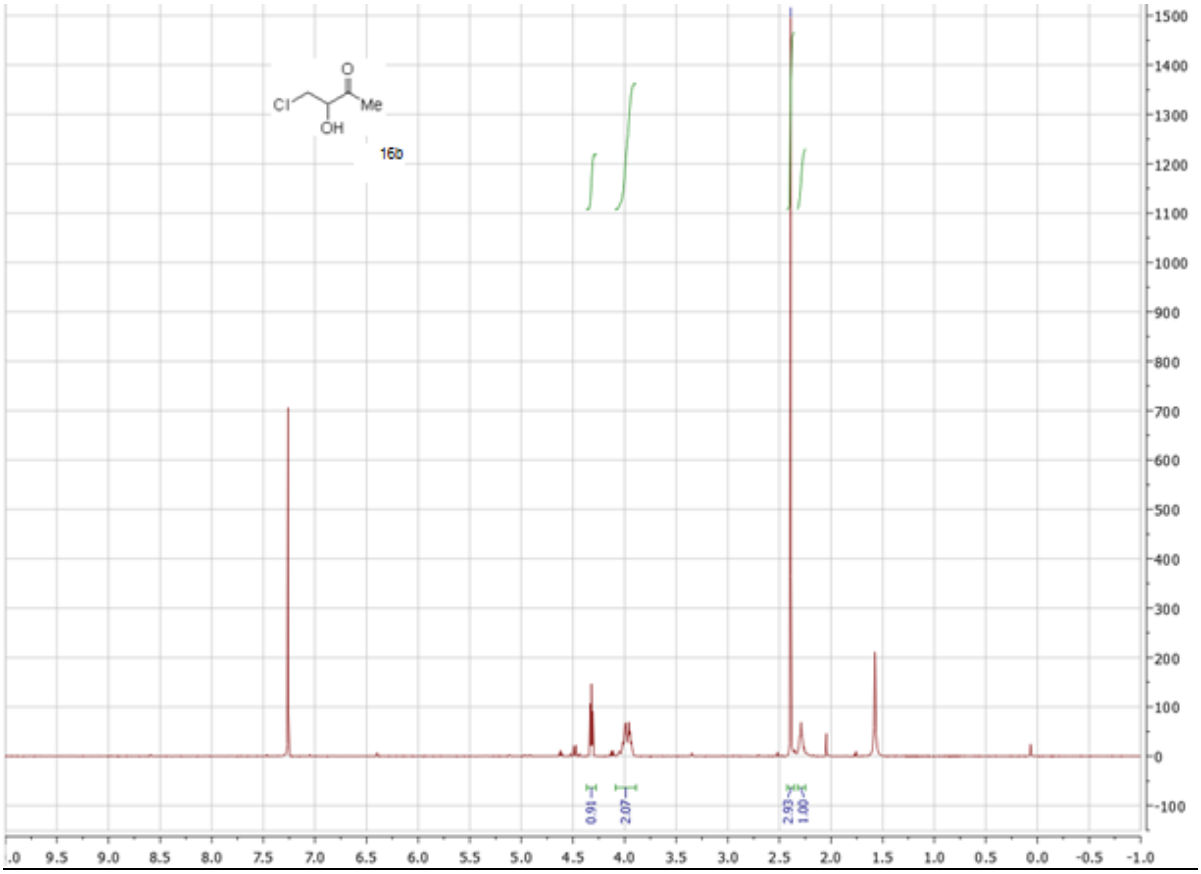
Run 10: Chlorohydroxylation of 19e with (*R*)-Tol-BINAP 14, 1.00 mmol, 10 days

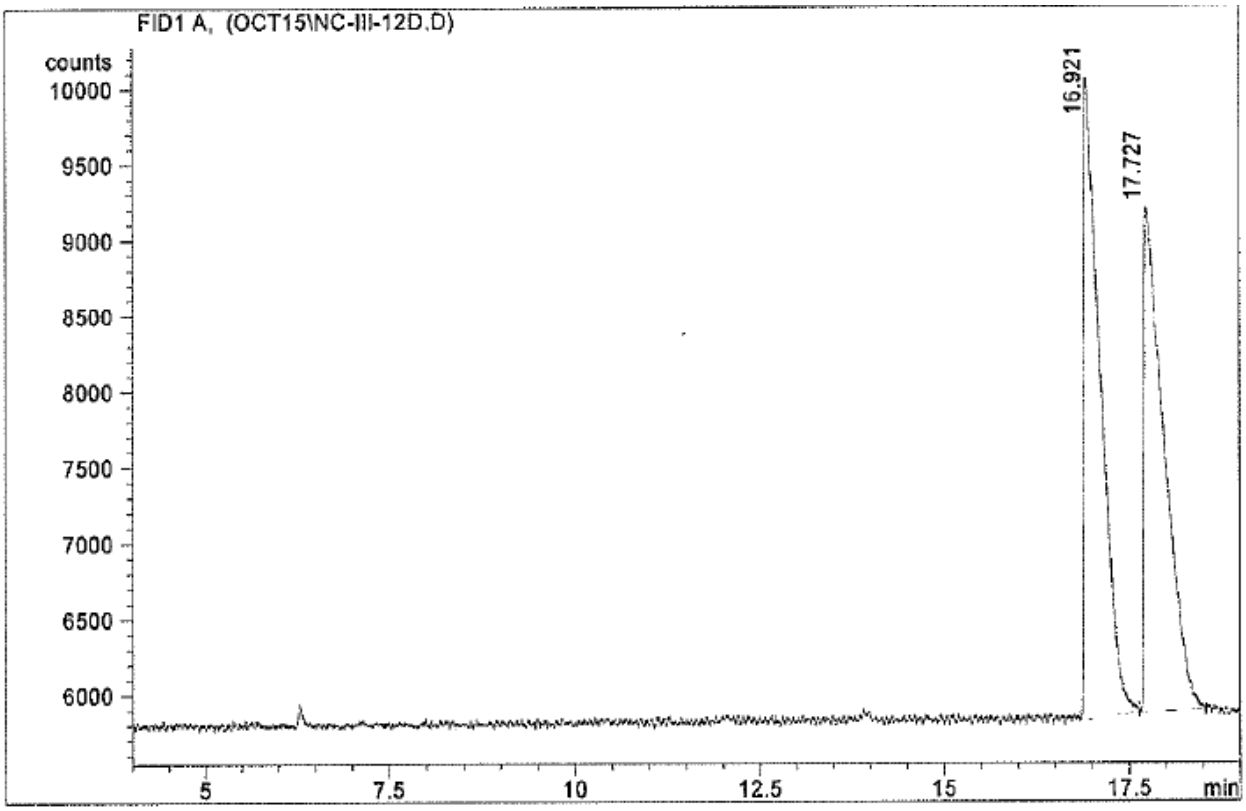


In a glovebox, a 10-mL, two-necked flask containing a Teflon-coated, magnetic stir bar was charged with bis(acetonitrile)dichloropalladium(II) (2.6 mg, 10 μmol, 1.0 mol %). The flask was sealed under Ar and removed from the glovebox. An Ar line was inserted, and anhydrous THF (1.0 mL) was injected. (*R*)-Tol-BINAP (9.9 mg, 15 μmol, 1.5 mol %) was added to form a yellow solution, which was stirred at rt for 30 min. Then, a separate 10-mL, round-bottomed flask containing a Teflon-coated, magnetic stir bar was charged with anhydrous copper(II) chloride (1.076 g, 8.0 mmol, 8.0 equiv) and lithium chloride (17 mg, 0.4 mmol, 0.4 equiv), then 1:2 THF\$H_2O$ (0.3 mL) was added to form a green solution. The catalyst solution was cannulated into the second flask, washing with 1:2 THF\$H_2O$ (0.3 mL). The atmosphere was replaced with 1 atm O_2 by sparging, and the reaction run under 1 atm O_2 from an oxygen manifold. Methyl vinyl ketone **19e** (70 mg, 1.0 mmol) was then injected into the mixture, washing with 1:2 THF\$H_2O$ (0.4 mL). The eventual solvent mixture was 2:1 THF\$H_2O$. The mixture was left to stir at rt, monitoring periodically by NMR spectroscopy of aliquots, and stopped after 10 days. H_2O (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL), then dried over $CaCl_2$. Solvent was removed *in vacuo*, then the mixture purified *via* column chromatography using a gradient from 95:5 to 80:20 hexane:ethyl acetate as eluent, to yield chlorohydrin **16b** as a colorless oil, 40 mg (0.33 mmol, **33%** yield). This was found to be racemic by CSP-GC. ^{1}H NMR spectroscopic data were identical to those of the racemic standard.

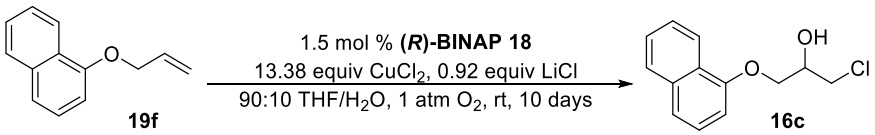
Data for **16b**:

GC: t_R 16.9 min (50.3%); t_R 17.7 min (49.7%) (CycloSil-B, 70 °C)


O
Cl
Me
OH
16b
0.91
2.07
2.93
1.00


FID1 A, (OCT15\NC-III-12D.D)
counts
16.921
17.727
min

Run 11: Chlorohydroxylation of 19f with (*R*)-BINAP 18, 0.50 mmol, 14 days

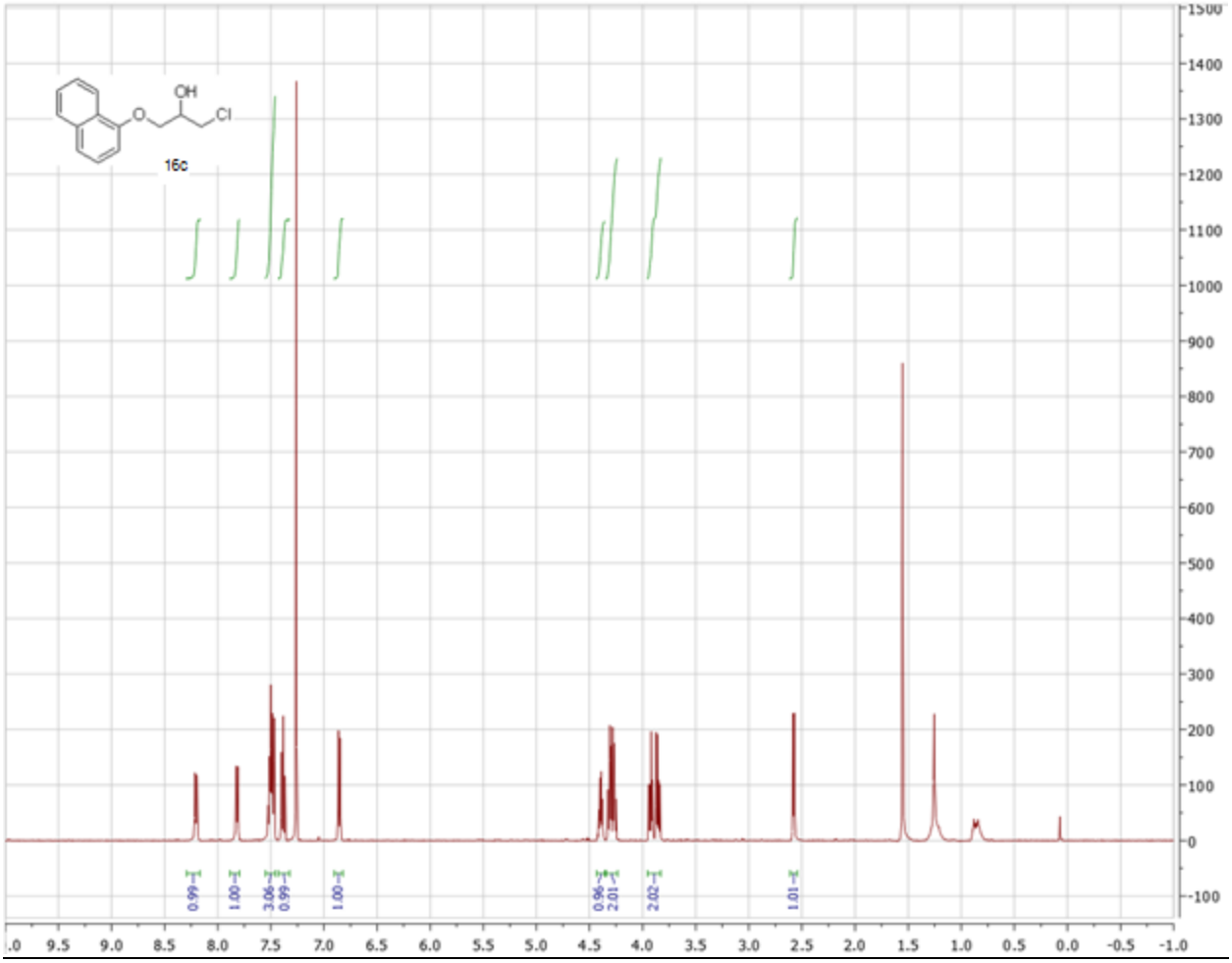


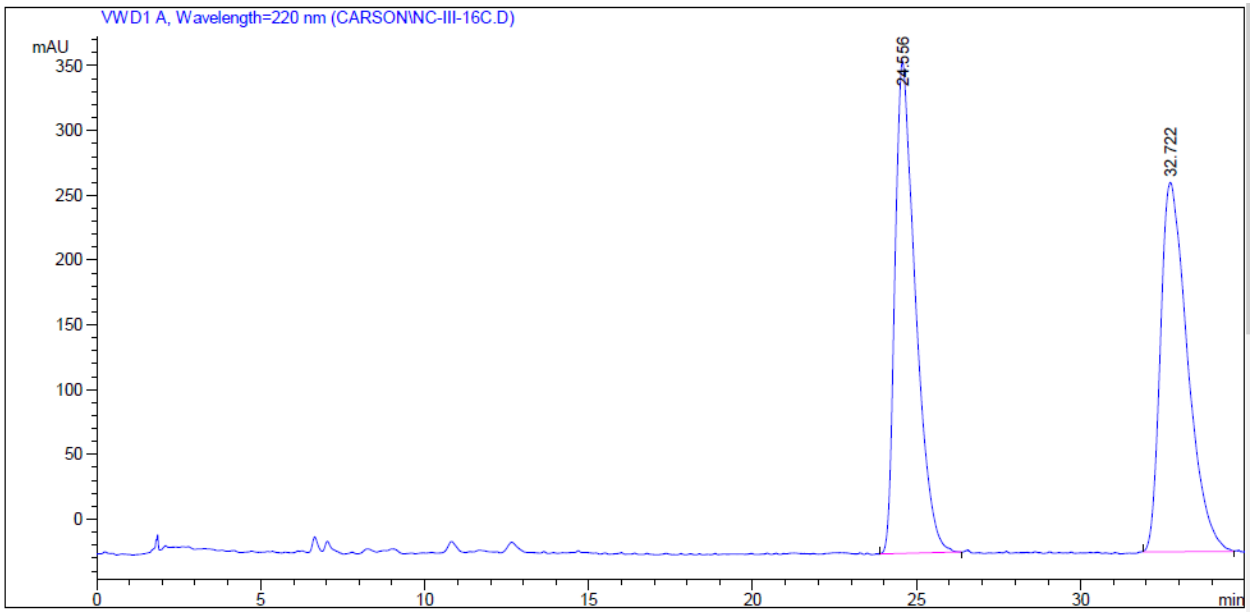
NOTE: The major product was mischaracterized in Henry and coworkers' original report.[25] The product there characterized was present in small amounts (roughly 9%) in the crude reaction mixture and is proposed to be the constitutionally isomeric chlorohydroxylation product.

In a glovebox, a 10-mL, two-necked flask containing a Teflon-coated, magnetic stir bFar was charged with **(*R*)-BINAP 18**, freshly prepared according to Henry's method (9.9 mg, 7.7 μmol, 1.5 mol %). The flask was sealed under Ar and removed from the glovebox. An Ar line was inserted, and anhydrous THF (1.0 mL) was injected. Anhydrous copper(II) chloride (900 mg, 6.69 mmol, 13.38 equiv) and lithium chloride (20 mg, 0.46 mmol, 0.92 equiv) were then added, followed by 82:18 THF:H_2O (0.7 mL), to form a green solution. The atmosphere was replaced with 1 atm O_2 by sparging, and the reaction run under 1 atm O_2 from an oxygen manifold. **19f** (92 mg, 0.5 mmol) was then added to the mixture, washing with 82:18 THF:H_2O (0.6 mL). The eventual solvent mixture was 90:10 THF:H_2O. The mixture was left to stir at rt, monitoring periodically by NMR spectroscopy of aliquots. Despite incomplete conversion, the reaction was stopped after 10 days. H_2O (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL), then dried over $CaCl_2$. Solvent was removed *in vacuo*, then the mixture purified *via* column chromatography using a gradient from 90:10 to 30:70 hexane:Et_2O as eluent, to yield firstly recovered 54 mg of pink solid **19f** (0.29 mmol, 59% yield of recovered starting material), and secondly chlorohydrin **16c** as a pale yellow oil, 34 mg (0.14 mmol, **29%** yield). This was found to be racemic by CSP-SFC. ^{1}H NMR spectroscopic data were identical to those of the racemic standard.

Data for **16c**:

SFC: t_R 24.6 min (50.1%); t_R 32.7 min (49.9%) (OD, MeOH:CO_2 = 10:90, 2.5 mL min^{-1}, 220 nm, 40 °C)

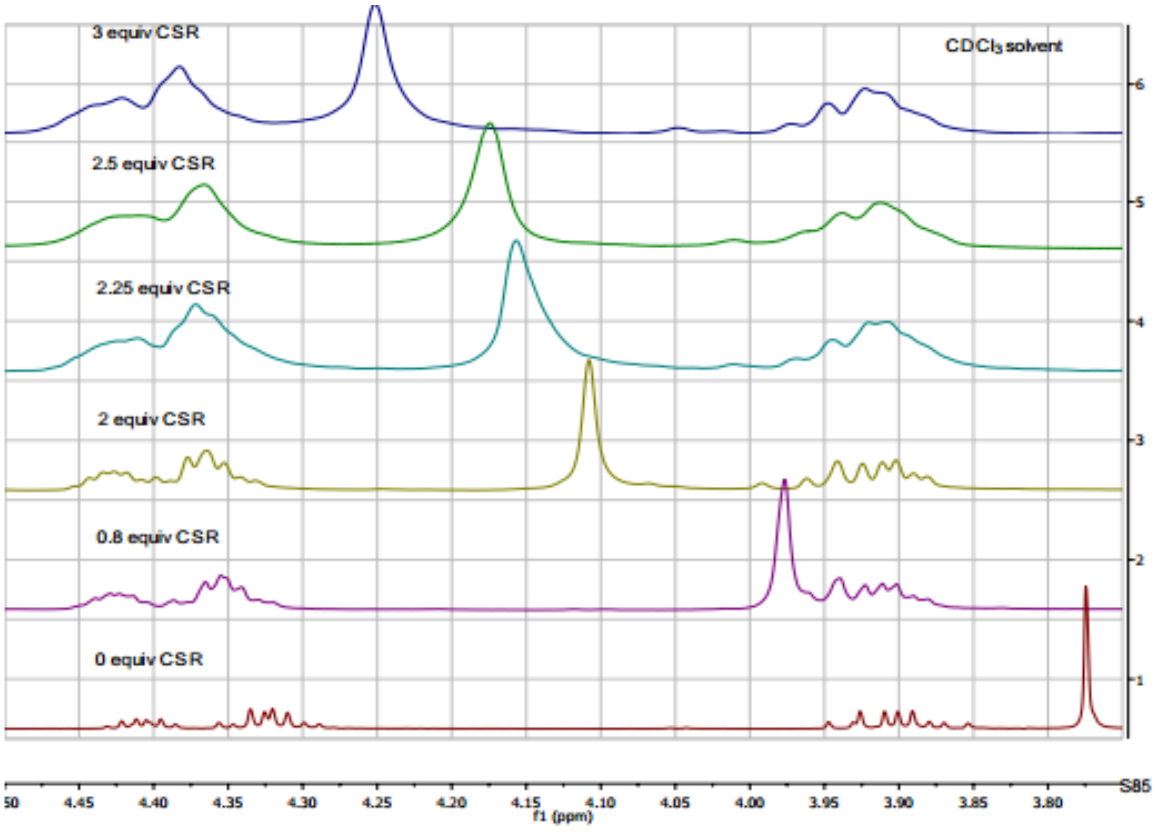

OH
Cl
O
16c
0.99
1.00
3.06
0.99
1.00
0.96
2.01
2.02
1.01

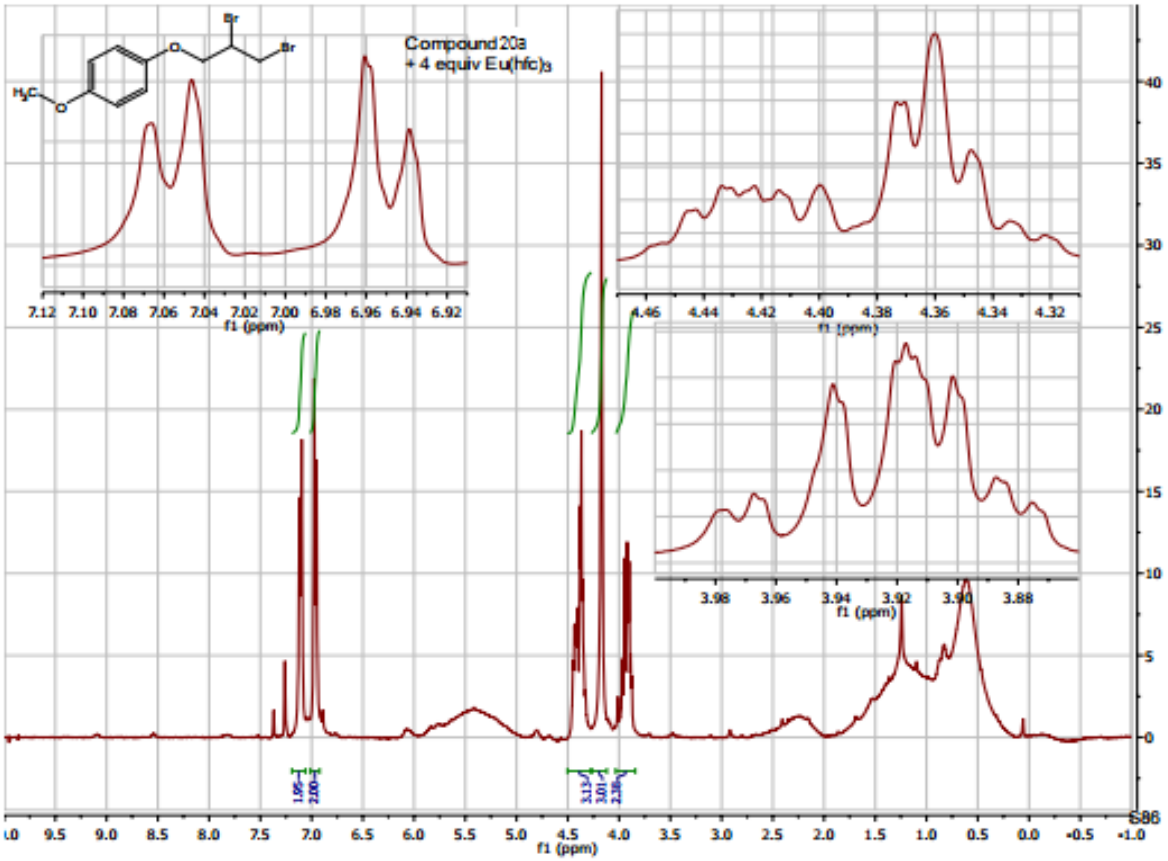

VWD1 A, Wavelength=220 nm (CARSON\NC-III-16C.D)
mAU
24.556
32.722
min

Chiral Shift NMR Experiment

$CDCl_3$ was purified by passing through a dry neutral Al_2O_3 column (70 × 7 mm diameter). $Eu(hfc)_3$ (448 mg, 375 µmol) was dissolved in 2.0 mL of this purified $CDCl_3$, and the bright yellow solution filtered through a Celite column (25 × 6 mm diameter) with a slight positive Ar flow. Dibromide **20a** (40.5 mg, 125 µmol) was dissolved in purified $CDCl_3$ (0.5 mL) in an NMR tube. The $Eu(hfc)_3$ solution was added portionwise to the solution of **20a**, and ^1H NMR spectra (400 MHz) were recorded after each subsequent addition. The spectrum corresponding to 4 equiv $Eu(hfc)_3$ was taken in $CDCl_3$ (0.8 mL), containing **20a** (23.8 mg, 70 µmol) and $Eu(hfc)_3$ (334 mg, 280 µmol). The processing parameters for this spectrum were:

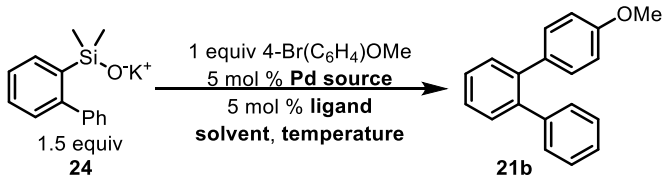
Spectrometer frequency	400 MHz
Delay time	10 s
Number of scans	16




Compound 20a
+ 4 equiv Eu(hfc)3
Br
Br
O
O
H3C
7.12 7.10 7.08 7.06 7.04 7.02 7.00 6.98 6.96 6.94 6.92
f1 (ppm)
4.46 4.44 4.42 4.40 4.38 4.36 4.34 4.32
f1 (ppm)
3.98 3.96 3.94 3.92 3.90 3.88
f1 (ppm)
1.95
2.00
3.13
3.01
2.38
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)
40 35 30 25 20 15 10 5 0
6.86

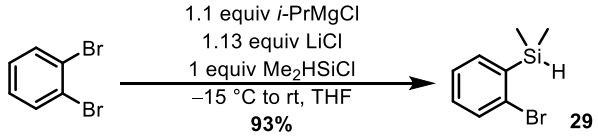
EXPERIMENTAL PROCEDURES: CHAPTER 2

General Procedure 1: Hiyama-Denmark Reaction for the Synthesis of 4-Methoxy-1,1':2',1''-Terphenyl 21b



Ligand (100 μmol, 5 mol %), **Pd source** (100 μmol, 5 mol %) and **24** (40 mg, 150 μmol, 1.5 equiv) were added sequentially to a flame-dried, 5-mL vial in a glovebox, and the vial sealed under Ar and removed from the glovebox. *n*-Tetradecane (26 μL, 20 mg, 0.1 mmol) was then added as an internal GC standard, followed by 4-bromoanisole (12.5 μL, 18.7 mg, 0.1 mmol), and anhydrous toluene (1 mL). The vial was placed in a sand bath (preheated to **temperature**), and stirred under an Ar blanket. At the required times, 50 μL aliquots were removed and quenched by addition to 1 mL brine, and the organic phase was extracted with EtOAc (1.5 mL) in a vial, and the organics removed *via* pipette and filtered through a silica plug.

Preparation of (2-Bromophenyl)dimethylsilane 29



LiCl (2.395 g, 56.5 mmol, 1.13 equiv) was added to a three-necked, 250-mL, round-bottomed flask, equipped with a gas adapter, a septum, and a stopper, in a glovebox. The apparatus was removed from the glovebox and flame-dried *in vacuo* (85 Pa), then back-filled with argon and cooled to rt. *i*-PrMgCl (1.86 M in THF, 30 mL, 55 mmol, 1.1 equiv) was added, and the heterogeneous brown mixture stirred at rt for 15 min. The reaction was cooled to −15 °C, then 1,2-dibromobenzene (6.03 mL, 11.8 g, 50 mmol) was added dropwise over 7 min. The reaction was then stirred at −15 °C for 2 h. A solution of chloro(dimethyl)silane (5.55 mL, 4.73 g, 50.0 mmol, 1.0 equiv) in THF (anhydrous, 60 mL, 0.83 M in Me_2HSiCl) in a two-necked, round-bottomed flask under Ar was then transferred into the reaction dropwise over 22 min, *via* cannula. The cloudy brown suspension was stirred for 15 min at −15 °C, then warmed to rt and stirred for a further 1 h. At this point, the reaction was quenched with H_2O (120 mL), and the organic

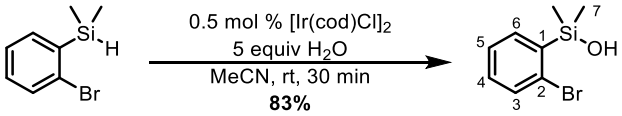
components extracted with CH_2Cl_2 (3 × 100 mL), and washed with H_2O (100 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The crude yellow oil was purified by column chromatography, using hexane as eluent, to give 9.971 g (**93%**) of the title product as a colorless oil. Spectral data matched the literature.[185]

Additional data for **29**:

bp: 58 °C (ABT), 67 Pa

TLC: hexane (UV/I_2): R_f = 0.57

Preparation of (2-Bromophenyl)dimethylsilanol 30



To a solution of silane **29** (2.28 g, 10.6 mmol, 1.0 equiv) in MeCN (anhydrous, 10 mL) in a flame-dried, 25-mL recovery flask was added $[Ir(cod)Cl]_2$ (36 mg, 0.053 mmol, 0.5 mol %). H_2O (955 µL, 53 mmol, 5 equiv) was added dropwise, and reaction loosely capped. Vigorous H_2 evolution was observed. The clear, yellow mixture was stirred for 30 min at rt, accompanied by a slight color change to yellow-orange. The mixture was poured into brine (10 mL), and extracted with Et_2O (3 × 10 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The crude, cloudy yellow oil was purified via Kugelrohr distillation (100 °C, 13 Pa) to 1.78 g (**83%**) of the title compound as a colorless oil. Spectral data matched the literature.[186]

NB: silanol **30** is unstable in the presence of acid (including SiO_2) or base, to the disiloxane, which may be hydrolysed to **30** in **77%** yield by the method of Fleming.[187] Data for the disiloxane is included below for comparison.

Additional data for silanol **30**:

^{1}H NMR: (400 MHz, $CDCl_3$)

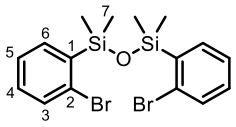
δ 7.54 (m, 2 H, HC(3), HC(6)), 7.32 (td, *J* = 7.3 Hz, 1.2 Hz, 1 H, HC(5)), 7.24 (td, *J* = 7.5 Hz, 1.9 Hz, 1 H, HC(4)), 2.24 (br s, 1 H, OH), 0.52 (s, 6H, H_3C(7))

^{13}C NMR: (126 MHz, $CDCl_3$)

140.26 (C(1)), 135.91 (C(6)), 132.53 (C(4)), 131.35 (C(3)), 129.13 (C(2)), 126.65 (C(5)), 0.39 (C(7))

bp: 100 °C (ABT), 13 Pa

TLC: basic Al_2O_3, 9:1 hexane/EtOAc (UV/I_2): R_f = 0.32



Data for disiloxane of **30**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.61 (dd, 1 H, *J* = 7.3, 1.9 Hz, HC(4)), 7.53 (dd, 1 H, *J* = 7.9, 1.0 Hz, HC(3)), 7.29 (td, 1 H, *J* = 7.3, 1.1 Hz, HC(5)), 7.24 (td, 1 H, *J* = 7.7, 1.9 Hz, HC(6)), 0.53 (s, 6 H, H_3C(7))

^{13}C NMR: (126 MHz, $CDCl_3$)

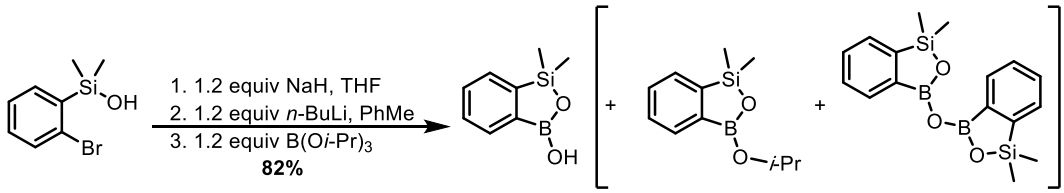
δ 140.65 (C(1)), 136.29 (C(6)), 132.65 (C(4)), 131.12 (C(3)), 129.05 (C(2)), 126.43 (C(5)), 1.56 (C(7))

MS: (EI-LRMS)

426.9 $(M–Me)^+$

TLC: basic Al_2O_3, 9:1 hexane/EtOAc (UV/I_2): R_f = 0.82

Preparation of 1,3-Dihydro-3-hydroxy-1,1-dimethyl-1,2,3-benzosiloxaborole 31



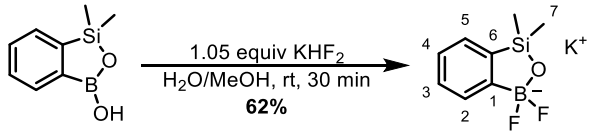
NB: Fast warming to rt over about 9 min is **necessary** to avoid decomposition. On smaller scale (0.5 mmol of **30**), this occurred without the aid of a warm water bath.

A Schlenk flask under Ar was charged with NaH (160 mg, 6.65 mmol, 1.2 equiv), followed by THF (anhydrous, 2 mL). The white suspension was cooled to 0 °C, then a solution of **30** (1.28 g, 5.54 mmol) in THF (anhydrous, 2 mL) was added, dropwise. Vigorous H_2 evolution was observed. The mixture was allowed to warm to rt, and stirred for 30 min. Then, the mixture was diluted with PhMe (anhydrous, 6 mL), and cooled to −78 °C. *n*-BuLi (2.47 M in hexane, 2.69 mL, 6.65 mmol, 1.2 equiv) was added dropwise, and now clear, yellow solution stirred for 1 h at −78 °C. B(O*i*-Pr)$_3$ (1.53 mL, 6.65 mmol, 1.2 equiv) was added dropwise, and the reaction warmed quickly in a 40 °C bath to rt over 9 min, turning cloudy white. The suspension was cooled to 0 °C in an ice bath, and opened to air. The mixture was acidified to pH 1 with HCl (1 N, 2.5 mL, checked with pH paper), forming a bright, clear, yellow organic layer and a faint pink aqueous layer. This biphase was stirred vigorously at rt for 30 min. The organic components were extracted with Et_2O (3 × 15 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to 883 mg crude, off-white solid (**82%** on the basis of **31**). The crude mixture of **31**, its isopropyl boronate ester, and the boronic anhydride was used without further purification. Spectral data for **31** matched the literature.[185]

Additional data for **31**:

TLC: 9:1 hexane/EtOAc (UV/CAM): R_f = 0.64

Preparation of Potassium 3,3-Difluoro-1,3-dihydro-1,1-dimethyl-1,2,3-benzosiloxaborolate 24



CAUTION! THIS REACTION GENERATES HIGHLY TOXIC HYDROGEN FLUORIDE (HF). USE PLASTIC VESSELS.

The crude mixture containing siloxaborolol **31** (1.02 g, 5.72 mmol based on **31**) was dissolved in MeOH (10 mL) in a round-bottomed, 100-mL, Teflon flask. A solution of KHF_2 (470 mg, 6.01 mmol, 1.05 equiv) in H_2O (3 mL) was added to the mixture, dropwise. The reaction was stirred at rt for 30 min, and then solvent removed *in vacuo*. The residue was extracted with rt acetone (2 × 5 mL), then hot acetone (2 × 5 mL). The organic extracts were filtered through a pad of $CaCO_3$ (10 × 40 mm diameter), and concentrated *in vacuo* at 50 °C, azeotropic H_2O with PhMe, to a white solid. This mixture was purified *via* Soxhlet extraction with anhydrous TBME for 4 days. If any of the ring-opened trifluoroboryl silyl fluoride impurity remains, washing the material repeatedly with boiling, anhydrous Et_2O under an Ar funnel will afford the pure product. The title compound was thus isolated as 846 mg white solid (**62%**).

NB: running the reaction for too long will result in increased side-product formation. Spectral data for the trifluoroboryl silyl fluoride side-product matched the literature.[185]

Data for **24**:

^{1}H NMR: (500 MHz, d_6-DMSO)

δ 7.25 (d, J = 7.0 Hz, 1 H, HC(2)), 7.22 (d, J = 7.2 Hz, 1 H, HC(5)), 7.07 (td, J = 7.2 Hz, 1.3 Hz, 1 H, HC(3)), 6.98 (td, J = 7.2 Hz, 1.2 Hz, 1 H, HC(4)), 0.10 (s, 1 H, H_3C(7))

^{13}C NMR: (126 MHz, d_6-DMSO)

δ 128.8 (C(2)), 128.1 (C(5)), 127.1 (C(4)), 124.6 (C(3)), 1.61 (H_3C(7))

(126 MHz, CD_3CN)

δ 130.4 (C(2)), 129.4 (C(5)), 128.9 (C(4)), 126.6 (C(3)), 1.21 (H_3C(7), under solvent signal)

^{19}F NMR: (376 MHz, d_6-DMSO)

δ −138.4 (m)

(376 MHz, CD_3CN)

δ −138.2, −138.3, −138.5, −138.6

^{11}B NMR: (128 MHz, CD_3CN)

δ 6.35 (t, J = 54.8 Hz)

IR (thin film): 3249 (br w), 2980 (w), 2954 (w), 1652 (br w), 1252 (w), 1199 (w), 1175 (w), 1006 (m), 951 (m), 915 (m), 901 (m), 826(m), 787 (m), 755 (s), 711 (m), 649 (m), 469 (m)

MS: (ESI-LRMS)

221.4 $(M-K-H+Na)^-$

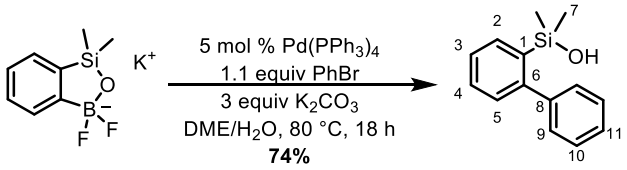
TLC: 22:3 hexane/EtOAc (UV/CAM): R_f = 0.27

Analysis: $C_8H_{10}BF_2KOSi$ (238.16)

Calc.: C, 40.35 %; H, 4.23 %; K, 16.42 %; F, 15.95 %

Found: C, 40.22 %; H, 4.19 %; K, 16.12 %; F, 14.1 %

Optimized Preparation of (2-Biphenyl)dimethylsilanol 23a



To a flame-dried, 50-mL, round-bottomed flask fitted with a condenser, in a glovebox was added **24** (297 mg, 1.25 mmol) and $(PPh_3)_4Pd$ (72 mg, 63 μmol, 5 mol %). The apparatus was sealed under Ar, then removed from the glovebox. Bromobenzene (145 μL, 215 mg, 1.37 mmol, 1.10 equiv) was then added, followed by DME (degassed, 11 mL). A solution of potassium carbonate (517 mg, 3.74 mmol, 3 equiv) in H_2O (degassed, 1.3 mL, 2.85 M in K_2CO_3) was then added *via* syringe. The reaction was stirred at 80 °C under Ar for 18 h. The mixture was cooled to rt, then brine was added and the organic phase was extracted with EtOAc (3 × 20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to 236 mg of a crude yellow-brown oil. This material was purified *via* column chromatography using 9:1 hexane/EtOAc as eluent to yield the title compound as a pale, yellow oil as the fourth fraction (210 mg, 920 μmol, **74%**).

For the purposes of accelerated screening, **23a** can also be synthesized from literature compound (2-biphenyl)dimethylsilane similarly to the $[Ir(cod)Cl]_2$-catalysed oxidation of silane **29** above.

Data for **23a**:

TLC: 17:3 hexane/EtOAc (UV/I_2): R_f = 0.48

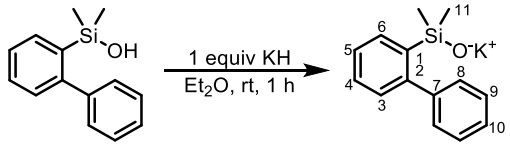
^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.69 (d, 1 H, *J* = 7.4 Hz, HC(5)), 7.32–7.46 (m, 7 H, HC(3), HC(4), HC(9), HC(10), HC(11)), 7.22–7.29 (m, 1 H, HC(2)), 1.38 (s, 1 H, OH), 0.12 (s, 6 H, H_3C(7))

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 148.41 (C(6)), 144.14 (C(8)), 137.77 (C(1)), 134.16 (C(2)), 129.43 (C(4)), 129.18 (C(10)), 129.18 (C(3)), 129.15 (C(9)), 128.07 (C(11)), 127.42 (C(5)), 1.54 (C(7))

Preparation of Potassium (2-Biphenyl)dimethylsilanolate 22a



A suspension of KH (275 mg, 6.85 mmol, 1 equiv) in Et_2O (anhydrous, 10 mL) in a flame-dried, 50-mL Schlenk flask under Ar was cooled to 0 °C. A solution of silanol **23a** (1.564 g, 6.85 mmol) in Et_2O (anhydrous, 5 mL) under Ar was then added to the reaction mixture, dropwise. Vigorous H_2 evolution was observed. The mixture was stirred at rt for 1 h, then passed through a cannula filter to any residual KH. The filtrate was concentrated on high vacuum to give 1.67 g (**91%**) of the title compound as a foamy, white solid. This was stored in a Schlenk flask under Ar in a glovebox.

Data for **22a**:

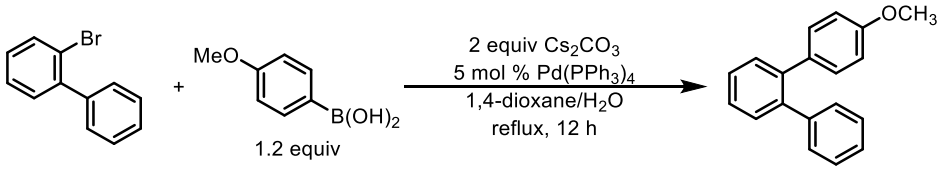
^{1}H NMR: (500 MHz, C_6D_6)

δ 7.82 (dd, *J* = 7.4 Hz, 1.3 Hz, 1 H, HC(4)), 7.39 (d, *J* = 7.0 Hz, 2 H, HC(3), HC(6)), 7.35 (td, *J* = 7.2 Hz, 1.6 Hz, 1 H, C(5)), 7.24 (m, 2H, HC(8)), 7.10 (t, *J* = 7.7 Hz, 2 H, HC(9)), 7.00 (t, *J* = 7.4 Hz, 1 H, HC(10)), 0.14 (s, 6 H, H_3C(7))

^{13}C NMR: (101 MHz, C_6D_6)

δ 148.2 (C(2)), 146.9 (C(7)), 146.4 (C(6)), 135.1 (C(1)), 130.6 (C(4)), 130.0 (C9)), 129.9 (C(5)), 128.0 (C(8)), 126.7 (C(10)), 126.6 (C(3)), 6.6 (C(7))

Preparation of 4-Methoxy-1,1':2',1"-Terphenyl 21b

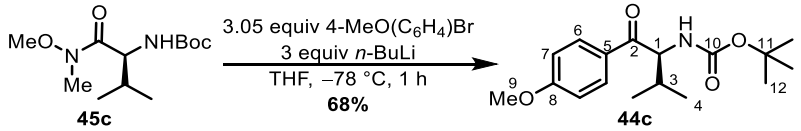


Teraryl **21b** was synthesized independently as a GC standard.

4-Anisoylboronic acid (55 mg, 360 μmol, 1.2 equiv) and Cs_2CO_3 (195 mg, 600 μmol, 2 equiv) were added to a 10-mL condenser flask equipped with a septum. $(PPh_3)_4Pd$ (17 mg, 15 μmol, 5 mol %) was added in a glovebox, then the flask sealed under an Ar atmosphere and removed from the glovebox. 2-Bromobiphenyl (52 μL, 70 mg, 300 μmol) was added, followed by 4:1 1,4-dioxane/H_2O (1.6 mL, 0.18 M in 2-bromobiphenyl). The orange-yellow biphasic mixture was stirred at reflux under positive Ar pressure for 12 h without color change. The mixture was cooled to rt, then H_2O (3 mL) added and the organic phase was extracted with EtOAc (3 × 10 mL), washed with H_2O (20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to 83 mg of a crude brown oil. This material was purified *via* column chromatography with 99:1 hexane/Et_2O as eluent to yield the title compound as white crystals (63 mg, 217 μmol, **72%**). Spectral data matched literature values.[188]

EXPERIMENTAL PROCEDURES: CHAPTER 3

Preparation of (*S*)-2-(*N*-Boc-amino)-1-(4-methoxyphenyl)-3-methylbutan-1-one 44c



To a solution of 4-bromoanisole (4.5 mL, 6.57 g, 3.51 mmol, 3.05 equiv) in THF (anhydrous, 135 mL, 0.26 M) at −78 °C in a 250-mL, two-necked, round-bottomed flask was added *n*-BuLi (1.6 M in hexanes, 21.6 mL, 34.6 mmol, 3 equiv) over 11 min. The solution became cloudy white over the course of the addition. The mixture was stirred at −78 °C for 40 min. A solution of **45c** (3.000 g, 11.5 mmol) in THF (anhydrous, 11.5 mL, 1.0 M) was then added at −78 °C over 11 min. The now clear, pale yellow reaction mixture was stirred at −78 °C for a further 1 h. Saturated aqueous NH_4Cl solution (46 mL) was then added slowly to quench, maintaining the temperature below −40 °C. The mixture was then warmed slowly to rt. The layers were separated, and the organic components extracted with further Et_2O (3 × 80 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and concentrated *in vacuo* to 5.386 g crude, yellow oil. On standing for several hours, large, white crystals form. These were crushed and washed with hexane (3 × 15 mL), and then recrystallized from hot hexane to yield a total of 2.399 g (7.80 mmol, **68%** yield) white crystals, from two crops.

Data for **44c**:

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 7.96 (d, *J* = 8.9 Hz, 2 H, HC(6)), 6.95 (d, *J* = 8.9 Hz, 2 H, HC(7)), 5.44 (d, *J* = 9.0 Hz, 1 H, NH), 5.17 (dd, *J* = 9.1, 4.2 Hz, 1 H, HC(1)), 3.88 (s, 3 H, H_3C(9)), 1.95-2.21 (m, 1 H, HC(3)), 1.44 (s, 9 H, H_3C(12)), 1.02 (d, *J* = 6.8 Hz, 3 H, $H_{3,A}C$(4)), 0.75 (d, *J* = 6.8 Hz, 3 H, $H_{3,B}C$(4))

^{13}C NMR: (101 MHz, $CDCl_3$)

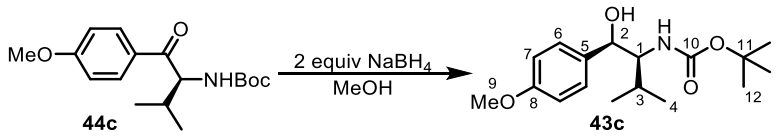
δ 197.99 (C(2)), 163.91 (C(10), 156.01 (C(8)), 130.96 (C(5)), 128.20 (C(6)), 113.98 (C(7)), 79.50 (C(1)), 59.13 (C(11)), 55.56 (C(9)), 31.99 (C(3)), 28.36 (C(12)), 20.07 (C_A(4)), 16.52 (C_B(4))

IR (powder): 3319 (w), 2973 (w), 1695 (s), 1677 (s), 1601 (m), 1575 (m), 1514 (w), 1423 (w), 1442 (m), 1384 (m), 1252 (m), 1232 (w), 1168 (s), 1084 (w), 1013 (w), 830 (w), 794 (w), 608 (w), 540 (w)

MS: (ESI-LRMS)

330.2 $(M+Na)^+$, 308.4 $(M+H)^+$, 252.3 $(M-t\text{-Bu}+2H)^+$, 208.3 $(M-Boc+2H)^+$

Preparation of (1*R*,2*S*)-2-(*N*-Boc-amino)-1-(4-methoxyphenyl)-3-methyl-1-butanol 43c



To a solution of **44c** (1.455 g, 4.73 mmol) in MeOH (anhydrous, 59 mL, 0.08 M) at −20 °C was added $NaBH_4$ (358 mg, 9.47 mmol, 2 equiv), portionwise. The white suspension was stirred at −20 °C for 90 min. H_2O (12 mL) was added at −20 °C, and the mixture allowed to warm to rt. MeOH was removed *in vacuo*, then EtOAc (20 mL) was added, and the layers separated. The organic layer was washed with H_2O (15 mL), then brine (15 mL), dried (Na_2SO_4), and concentrated *in vacuo* to white crystals. These were washed with hexane (3 × 20 mL), and dried *in vacuo* to 1.108 g (3.58 mmol, **76%** yield) of white crystals of the title compound as a single diastereomer.

Data for **43c** (appearing as a mixture of rotamers at 20 °C):

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.27 (d, *J* = 8.7 Hz, 2 H, HC(6)), 6.88 (d, *J* = 8.7 Hz, 2 H, HC(7)), 4.81 (t, *J* = 4.5 Hz, 0.9 H, $H_aC(2)$), 4.54 (m, 0.1 H, $H_bC(2)$), 4.32 (d, *J* = 9.8 Hz, 0.9 H, NH_a), 4.03 (m, 0.1 H, NH_b), 3.80 (s, 3.6 H, $H_3C(9)$), 3.75 (dt, *J* = 10.9, 5.9 Hz, 1 H, $H_aC(1)$), 3.65 (m, 0.1 H, $H_bC(1)$), 2.94 (d, *J* = 4.2 Hz, 0.9 H, OH_a), 2.82 (d, *J* = 3.9 Hz, 0.1 H, OH_b), 1.69 (oct, *J* = 6.6 Hz, 0.9 H, $H_aC(3)$), 1.39 (s, 9.0 H, $H_3C(12)$, $H_bC(3)$), 1.04 (d, *J* = 6.7 Hz, 3 H, $H_{3,A,a}C(4)$), 0.98 (d, *J* = 6.7 Hz, 0.6 H, $H_{3,A,b}C(4)$), 0.88 (d, *J* = 6.7 Hz, 3.6 H, $H_{3,B}C(4)$)

^{13}C NMR: (125 MHz, $CDCl_3$)

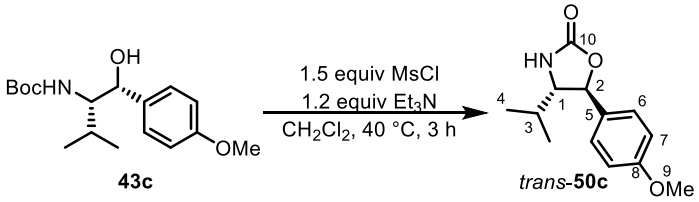
δ 159.12 (C(10)), 156.95 (C(8)), 133.09 (C(5)), 127.99 (C(6)), 113.58 (C(7)), 79.53 (C(2)), 74.92 (C(11)), 61.10 (C(1)), 55.29 (C(9)), 28.34 (C(3)), 28.24 (C(12)), 20.90 ($C_A(4)$), 17.99 ($C_B(4)$)

IR (powder): 3380 (w), 2978 (w), 2962 (w), 1836 (w), 1684 (m), 1614 (w), 1514 (s), 1351 (w), 1305 (w), 1244 (m), 1169 (m), 1032 (m), 981 (m), 812 (w), 636 (w), 582 (w), 554 (w)

MS: (ESI-LRMS)

332.5 $(M+Na)^+$

Preparation of *trans*-(4*S*,5*S*)-4-isopropyl-5-(4-methoxyphenyl)oxazolidin-2-one *trans*-50c



To a solution of (1*R*,2*S*)-**43c** (106 mg, 340 µmol) in CH_2Cl_2 (anhydrous, 1.1 mL, 0.3 M) at 0 °C was added Et_3N (57 µL, 42 mg, 410 µmol, 1.2 equiv), then MsCl (40 µL, 59 mg, 520 µmol, 1.5 equiv), dropwise, over 5 min. The mixture was stirred at 0 °C for 5 min, then heated to reflux for 3 h. Saturated, aqueous $NaHCO_3$ solution (1 mL) was added, and the layers separated. The organic layer was washed with further $NaHCO_3$ solution (2 mL), brine (2 × 2 mL), then dried (Na_2SO_4), and concentrated to a cloudy yellow oil. This was filtered through a pipette plug of Celite, washing with EtOAc, to yield a yellow oil which very slowly crystallizes under high vacuum to ivory crystals of the title compound (72 mg, **89%** yield, **96:4 dr**).

Data for *trans*-**50c**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.29 (d, *J* = 8.8 Hz, 2 H, HC(6)), 6.91 (d, *J* = 8.7 Hz, 2 H, HC(7)), 6.60 (br s, 1 H, NH), 5.16 (d, *J* = 5.5 Hz, 1 H, HC(2)), 3.81 (s, 3 H, H_3C(9)), 3.55 (t, *J* = 5.7 Hz, 1 H, HC(1)), 1.85 (oct, *J* = 6.7 Hz, 1 H, HC(3)), 1.00 (dd, *J* = 6.7, 1.2 Hz, 3 H, $H_{3,A}C$(4)), 0.93 (dd, *J* = 6.7, 1.2 Hz, 3 H, H_BC(4))

^{13}C NMR: (101 MHz, $CDCl_3$)

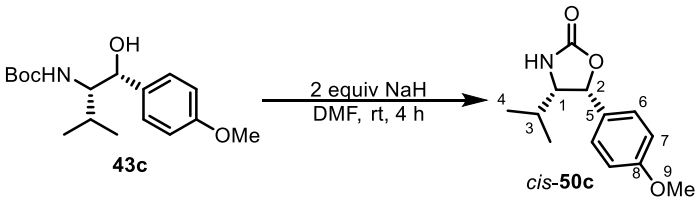
δ 159.83 (C(8), C(10)), 131.26 (C(5)), 127.58 (C(6)), 114.11 (C(7)), 81.43 (C(2)), 66.04 (C(1)), 55.23 (C(9)), 32.43 (C(3)), 18.18 (C_A(4)), 17.64 (C_B(4))

IR (crystals): 3326 (br w), 2960 (w), 2917 (w), 1751 (m), 1731 (s), 1614 (w), 1517 (w), 1370 (w), 1256 (m), 1227 (w), 1175 (m), 1081 (w), 1032 (m), 988 (s), 836 (m), 818 (m), 770 (w), 723 (w), 631 (m), 584 (w), 563 (w), 529 (w)

MS: (ESI-LRMS)

471.4 $(2M+H)^+$, 258.4 $(M+Na)^+$, 236.3 $(M+H)^+$, 192.3 $(M-CO_2+H)^+$

Preparation of *cis*-(4*S*,5*R*)-4-isopropyl-5-(4-methoxyphenyl)oxazolidin-2-one *cis*-50c



To a suspension of NaH (16 mg, 0.65 mmol, 2 equiv) in DMF (anhydrous, 0.3 mL, 0.11 M) was added a solution of (1*R*,2*S*)-**43c** (100 mg, 0.32 mmol) in DMF (anhydrous, 2.0 mL, 0.16 M). The white suspension was stirred at rt for 4 h, becoming a clear, pale yellow solution. Saturated, aqueous NH_4Cl solution was added slowly to quench, promoting effervescence. The organic components were extracted with Et_2O (3 × 4 mL), washed with 20% aqueous LiCl solution (2 × 3 mL), dried (Na_2SO_4) and concentrated *in vacuo* to a very pale yellow oil. This was filtered through a pipette plug of SiO_2, washing with CH_2Cl_2, which after solvent evaporation, yielded the title compound as white crystals (76 mg, **quantitative** yield, **98:2 dr**).

Data for *cis*-**50c**:

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 7.28 (d, *J* = 8.7 Hz, 2 H, HC(6)), 6.90 (d, *J* = 8.7 Hz, 2 H, HC(7)), 6.31 (s, 1 H, NH), 5.60 (d, *J* = 8.0 Hz, 1 H, HC(2)), 3.82 (s, 3 H, H_3C(9)), 3.79 (d, *J* = 7.9 Hz, 1 H, HC(1)), 1.51 (oct, *J* = 6.6 Hz, 1 H, HC(3)), 0.85 (d, *J* = 6.6 Hz, 3 H, $H_{3,A}C$(4)), 0.66 (d, *J* = 6.6 Hz, 3 H, $H_{3,B}C$(4))

^{13}C NMR: (101 MHz, $CDCl_3$)

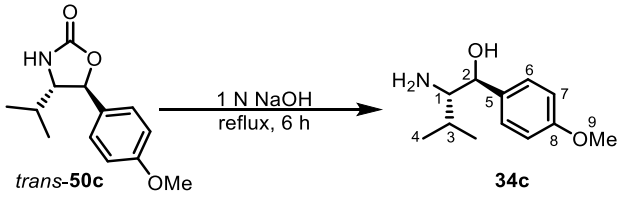
δ 162.46 (C(10)), 160.55 (C(8)), 128.1 (C(5)), 127.17 (C(6)), 113.55 (C(7)), 81.15 (C(2)), 63.17 (C(1)), 55.11 (C(9)), 31.27 (C(3)), 19.26 (C_A(4)), 18.40 (C_B(4))

IR (thin film): 3256 (br w), 2961 (w), 2926 (w), 1745 (s), 1612 (w), 1515 (m), 1365 (w), 1301 (w), 1250 (m), 1176 (m), 1033 (m), 1017 (w), 1001 (m), 837 (w)

MS: (ESI-LRMS)

471.4 $(2M+H)^+$, 236.3 $(M+H)^+$, 192.3 $(M-CO_2+H)^+$

Preparation of (1*R*,2*S*)-2-amino-1-(4-methoxyphenyl)-3-methyl-1-butanol 34c



A 10-mL, round-bottomed flask was charged with *trans*-**50c** (48 mg, 205 µmol), then 1 N NaOH solution (1.9 mL, 0.2 M in oxazolidinone). The oxazolidinone did not dissolve. The mixture was heated to reflux for 6 h. After cooling to rt, the organic components were extracted with EtOAc (4 × 4 mL), dried (Na_2SO_4), and concentrated *in vacuo* to a pale, yellow oil, which crystallized overnight to white crystals. Recrystallization from hexane gave the title compound as white crystals (43 mg, 200 µmol, **quantitative** yield).

Data for (1*R*,2*S*)-**34c**:

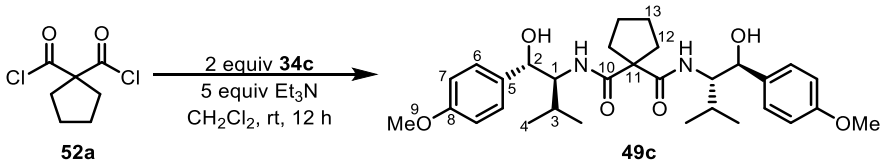
^{1}H NMR: (500 MHz, $CDCl_3$)
δ 7.27 (d, *J* = 8.9 Hz, 2 H, HC(6)), 6.87 (d, *J* = 8.7 Hz, 2 H, HC(7)), 4.56 (d, *J* = 6.3 Hz, 1 H, HC(2)), 3.80 (s, 3 H, H_3C(9)), 2.72 (t, *J* = 6.1 Hz, 1 H, HC(1)), 1.69 (oct, *J* = 6.5 Hz, 1 H, HC(3)), 1.01 (d, *J* = 6.8 Hz, 3 H, $H_{3,A}C$(4)), 0.89 (d, *J* = 6.8 Hz, 3 H, $H_{3,B}C$(4))

^{13}C NMR: δ 159.10 (C(8)), 133.98 (C(5)), 128.12 (C(6)), 113.69 (C(7)), 74.50 (C(2)), 61.82 (C(1)), 55.26 (C(9)), 29.1 (C(3)), 20.64 (C_A(4)), 17.11 (C_B(4))

MS: (ESI-LRMS)
192.4 $(M-H_2O)^+$

IR (thin film): 3361 (br, w), 2956 (w), 2928 (w), 1611 (w), 1511 (m), 1464 (w), 1367 (w), 1303 (w), 1245 (m), 1173 (w), 1034 (m), 833 (m), 574 (w)

Preparation of *N*,*N*'-bis((*S*,*S*)-1-hydroxy-1-(4-methoxyphenyl)-3-methylbutan-2-yl)cyclopentane-1,1-dicarboxamide 49c



To a solution of **34c** (215 mg, 1.03 mmol, 2 equiv) in CH_2Cl_2 (anhydrous, 1.4 mL, 0.75 M) was added Et_3N (360 µL, 259 mg, 2.6 mmol, 5 equiv) in one portion. A solution of **52a** (100 mg, 0.51 mmol) in CH_2Cl_2 (anhydrous, 2.6 mL, 0.2 M) was then added dropwise at 0 °C over 5 min. The mixture was brought to rt and stirred for 12 h. H_2O (3 mL) was added to quench. CH_2Cl_2 (3 mL) was added, and the layers separated. The organic components were extracted with further CH_2Cl_2 (2 × 6 mL), dried (Na_2SO_4), and concentrated *in vacuo* to a white solid. This was recrystallized from hexane/CH_2Cl_2 to white crystals of the title compound (204 mg, 380 µmol, **74%**).

Data for **49c**:

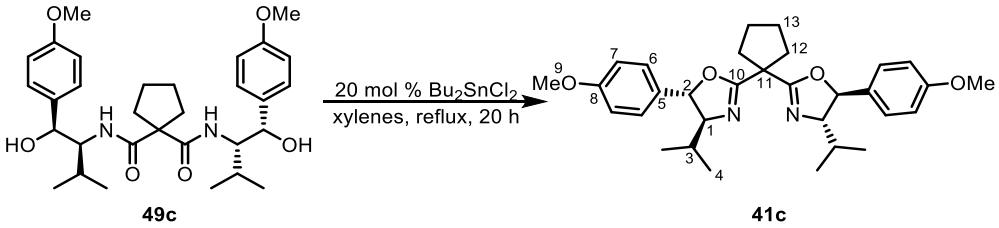
^{1}H NMR: (500 MHz, $CDCl_3$)
δ 7.25 (d, *J* = 8.5 Hz, 4 H, HC(6)), 6.87 (d, *J* = 8.7 Hz, 4 H, HC(7)), 6.22 (d, *J* = 9.5 Hz, 2 H, NH), 4.43 (dd, *J* = 6.5, 4.3 Hz, 2 H, HC(2)), 4.02 (ddd, *J* = 9.5, 7.0, 5.0 Hz, 2 H, HC(1)), 3.79 (s, 6 H, H_3C(9)), 3.31 (d, *J* = 4.9 Hz, 2 H, H_AC(12)), 2.39 (m, 2 H, H_BC(12)), 1.93 (m, 2 H, H_AC(13)), 1.61 (m, 6 H, HC(3), H_BC(13), OH), 0.88 (d, *J* = 6.8 Hz, 6 H, $H_{3,A}C$(4)), 0.80 (d, *J* = 6.9 Hz, 3 H, $H_{3,B}C$(4)).

^{13}C NMR: (125 MHz, $CDCl_3$)
δ 174.15 (C(10)), 159.19 (C(8)), 133.96 (C(5)), 127.56 (C(6)), 113.94 (C(7)), 74.50 (C(2)), 62.41 (C(1)), 59.95 (C(11)), 55.26 (C(9)), 34.78 (C(12)), 29.71 (C(3)), 28.69 (C(13)), 24.79 (C(13)), 20.49 (C_A(4)), 16.94 (C_B(4))

IR (thin film): 3455 (br w), 3405 (br w), 2957 (w), 2922 (br w), 2872 (w), 2851 (w), 1740 (w), 1655 (m), 1628 (w), 1613 (w), 1510 (s), 1462 (w), 1302 (w), 1241 (s), 1172 (w), 1041 (m), 822 (m), 584 (w), 538 (w)

MS: (ESI-LRMS)
541.5 $(M+H)^+$, 523.5 $(M-H_2O)^+$, 505.5 $(M-2H_2O)^+$

Preparation of (*S*,*S*,*S*,*S*)-2,2'-(cyclopentane-1,1-diyl)bis(4-isopropyl-5-(4-methoxyphenyl)-4,5-dihydrooxazole) 41c



49c **41c**

A 10-mL, round-bottomed flask was charged with **49c** (95 mg, 180 μmol) and xylenes (2.7 mL, 0.07 M), then Bu_2SnCl_2 (11 mg, 35 μmol, 20 mol %) was added. The mixture was brought to reflux and stirred for 20 h. The solvent was then removed *in vacuo* to yield a crude mixture of white crystals and yellow oil. This was separated *via* column chromatography using 1:9 Et_2O/PhMe as eluent, to give the title compound as white crystals (60 mg, 120 μmol, **67%**).

Data for (*S*,*S*,*S*,*S*)-**41c**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.13 (d, *J* = 8.7 Hz, 4 H, HC(6)), 6.68 (d, *J* = 8.7 Hz, 4 H, HC(7)), 5.04 (d, *J* = 6.6 Hz, 2 H, HC(1)), 3.85 (dd, *J* = 6.7, 5.3 Hz, 2 H, HC(2)), 3.75 (s, 6 H, H_3C(9)), 2.47–2.61 (m, 2 H, H_AC(12)), 2.14–2.24 (m, 2 H, H_BC(12)), 1.83 (m, 6 H, HC(3), H_2C(13)), 0.94 (d, *J* = 6.8 Hz, 6 H, $H_{3,A}C$(4)), 0.91 (d, *J* = 6.8 Hz, 6 H, $H_{3,B}C$(4))

^{13}C NMR: (126 MHz, $CDCl_3$)

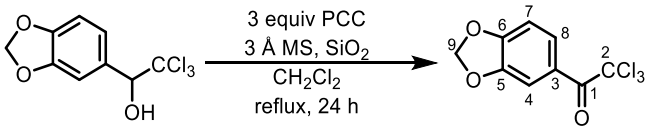
δ 167.44 (C(10)), 159.29 (C(8)), 133.81 (C(5)), 127.82 (C(6)), 113.81 (C(7)), 83.82 (C(2)), 80.32 (C(1)), 55.12 (C(9)), 49.39 (C(11), 36.05 (C(12)), 32.61 (C(3)), 25.11 (C(13)), 18.37 (C_A(4)), 17.96 (C_B(4))

IR (thin film): 2954 (w), 2875 (w), 2937 (w), 1655 (m), 1614 (w), 1516 (m), 1460 (w), 1306 (w), 1247 (s), 1178 (m), 1155 (w), 1032 (w), 926 (w), 821 (s), 781 (w), 546 (m)

MS: (ESI-LRMS)

505.6 $(M+H)^+$

Preparation of 1-(5-benzodioxolyl)-2,2,2-trichloroethanone 54d



To a solution of **53d** (100 mg, 370 μmol) in CH_2Cl_2 (anhydrous, 3.8 mL, 0.1 M) in a 10-mL recovery flask fitted with a reflux condenser was added PCC (240 mg, 1.11 mmol, 3 equiv), followed by 3 Å MS (100 mg), and silica gel (240 mg). The red solution was heated to reflux, at which point it turned brown. The reaction mixture was stirred under reflux for 24 h. After cooling to rt, Et_2O (4 mL) was added, and the mixture was filtered through Celite to remove the brown precipitate, washing with CH_2Cl_2 (3 × 10 mL). The filtrate was washed with 0.6 N HCl (2 × 10 mL), then saturated $NaHCO_3$ solution (2 × 10 mL), dried (Na_2SO_4), and concentrated *in vacuo* to 95 mg crude brown oil. This was purified by Kugelrohr distillation at 800 mTorr to yield 92 mg (345 μmol, **93%** yield) of a colorless oil.

Data for **54d**:

bp: 92 °C (ABT), 800 mTorr

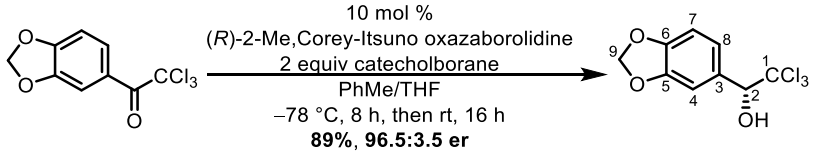
^{1}H NMR: (500 MHz, $CDCl_3$)
δ 7.95 (d, *J* = 8.1 Hz, HC(8)), 7.69 (s, 1 H, HC(4)), 6.89 (d, *J* = 8.2 Hz, 1 H, HC(7)), 6.90 (s, 2 H, H_2C(6))

^{13}C NMR: (126 MHz, $CDCl_3$)
δ 179.50 (C(1)), 152.81 (C(6)), 147.72 (C(5)), 128.75 (C(3)), 122.67(C(8)), 111.18 (C(4)), 107.96 (C(7)), 102.26 (C(9)), 95.62 (C(2)).

IR (neat): 2907 (w), 1697 (m), 1613 (m), 1503 (m), 1486 (m), 1442 (m), 1350 (m), 1248 (s), 1104 (m), 1036 (s), 932 (m), 872 (m), 842 (m), 828 (s), 761 (s), 727 (m), 673 (s), 636 (m), 566 (w)

MS: (ESI-LRMS)
288.9 $[M+Na]^+$

Preparation of (*R*)-1-(5-benzodioxolyl)-2,2,2,-trichloroethanol (*R*)-53d

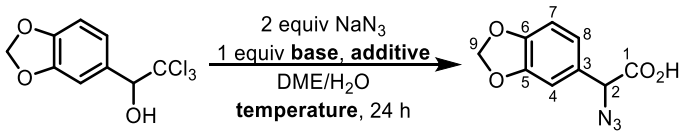


To a solution of **54d** (5.002 g, 18.7 mmol) in PhMe (anhydrous and degassed, 187 mL, 0.1 M) in a three-necked, 500-mL, round-bottomed flask equipped with an Ar line and two septa under Ar was added (*R*)-2-methyl-4,4-diphenyltetrahydro-1*H*,3*H*-pyrrolo[3,4-*c*][1,3,2]oxazaborole ((*R*)-2-Me-Corey-Itsuno oxazaborolidine) (1 M in PhMe, 1.87 mL, 1.87 mmol, 10 mol %). The colorless to pale yellow mixture was cooled to −78 °C. A solution of catecholborane (4.00 mL, 4.485 g, 37.4 mmol, 2 equiv) in THF (anhydrous and degassed, 37.5 mL, 1 M) was added dropwise over 13 min. The pale yellow solution was stirred at −78 °C for 8 h, then brought to rt and stirred for a further 16 h. H_2O (100 mL) was added, giving effervescence, and leading the yellow color to mostly disappear after about 30 s. The layers were separated, and the organic components extracted with further EtOAc (2 × 100 mL), and the organic layers washed with 1 M NaOH (3 × 50 mL), then 1 M HCl (3 × 50 mL), and dried ($MgSO_4$) and concentrated *in vacuo* to 5.206 g crude, green oil. This was separated *via* column chromatography using 4:1 hexane:ethyl acetate as eluent, to provide 4.501 g (16.7 mmol, **89%** yield) of a pale yellow oil as the second fraction, found to have 96.5:3.5 er. This had identical spectral data to the racemic compound known in the literature.[158] Absolute configuration of the stereocenter was assigned by analogy.

Additional data for **(*R*)-53d**:

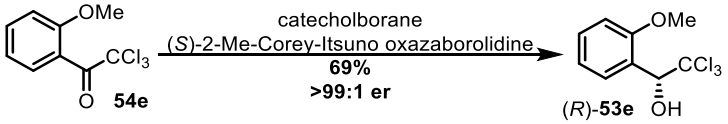
HPLC: t_R 16.4 min (96.5%); t_R 20.3 min (3.5%) (OJ-H, hexane/isopropanol = 90:10, 1.0 mL min^{-1}, 220 nm, 20 °C)

Screening Conditions for the Attempted Preparation of 1-azido-1-(5-benzodioxolyl)acetic acid 55d



Conditions were modified from the method of Aitken.[157] A solution of base (1 equiv), additive, and NaN_3 (2 equiv) in H_2O (0.8 mL, 0.9 M in NaN_3) was added to a vigorously-stirred solution of **38r** (100 mg, 0.4 mmol) in DME (2.2 mL, 0.17 M) in a 7-mL vial at 10 °C, dropwise. The mixture was stirred at 10 °C for 5 min, then warmed to the reaction temperature, and stirred for 24 h. Et_2O (1 mL) was added, and the layers separated. The organic layer was washed with 1.25 N NaOH solution (1 mL), and the aqueous phase cooled to 0 °C. This first organic layer was dried ($MgSO_4$), and concentrated *in vacuo* to yield recovered starting material. 1 M KH_2PO_4 solution, or solid KH_2PO_4, was then added to the aqueous phase until pH 4 was attained. The cloudy solution was extracted with EtOAc (3 × 1 mL), giving a clear biphase. The organic layers were dried ($MgSO_4$), and concentrated *in vacuo* to yield the crude product mixture.

Preparation of 1-(2-methoxyphenyl)-2,2,2-trichloroethanol (*R*)-53e

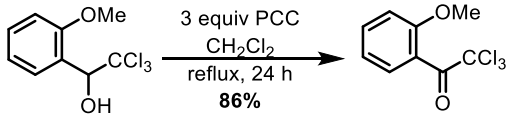


(*R*)-53e was produced *via* a modified literature procedure, using (*R*)-2-methyl Corey-Itsuno oxazolidinone rather than the 2-butyl variant. Spectral data matched the literature.[157]

Additional Data for **(*R*)-53e**:

HPLC: t_R 10.9 min (99.3%); t_R 13.0 min (0.7%) (OJ-H, hexane/isopropanol = 85:15, 1.0 mL min^{-1}, 220 nm, 20 °C)

Improved preparation of 1-(2-methoxyphenyl)-2,2,2-trichloroethanone 54e by PCC oxidation

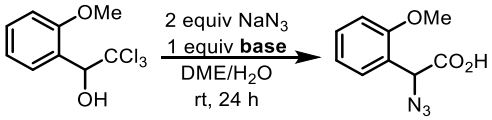


To a solution of **53e** (17.794 g, 70.4 mmol) in CH_2Cl_2 (anhydrous, 700 mL, 0.1 M) in a 2-L, round-bottomed flask fitted with a reflux condenser was added PCC (45.515 g, 211 mmol, 3 equiv), followed by 3 Å MS (2 g), and silica gel (46 g). The red solution was heated to reflux, at which point it turned brown. The reaction mixture was stirred under reflux for 24 h. After cooling to rt, *i*-PrOH (18 mL) was added to quench, followed by Et_2O (300 mL), and the mixture was filtered through Celite to remove the brown precipitate, washing with CH_2Cl_2 (2 × 100 mL). The filtrate was concentrated *in vacuo* to half its original volume to facilitate workup. The concentrated filtrate was washed with 0.6 N HCl (2 × 200 mL), then saturated $NaHCO_3$ solution (2 × 200 mL), and brine (200 mL). Lastly, it was dried (Na_2SO_4), and concentrated *in vacuo* to 17.418 g crude, green oil. Chromium byproducts were removed by Kugelrohr distillation at 300 mTorr, to yield 16.639 g yellow oil. This was purified *via* column chromatography in two portions using 9:1 hexane:ethyl acetate as eluent, to yield 15.407 g (345 μmol, **93%** yield) of a colorless oil. Spectral data matched the literature.[157]

Additional Data for **54e**:

bp: 115 °C (ABT), 300 mTorr

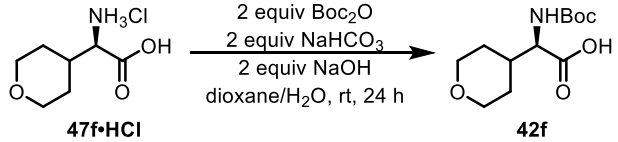
Screening Conditions for the Attempted Preparation of 1-azido-1-(2-methoxyphenyl)acetic acid 55e



Conditions were modified from the method of Aitken.[157] A solution of base (1 equiv) and NaN_3 (2 equiv) in H_2O (1.3 mL, 0.33 M in base) was added to a vigorously-stirred solution of **53e** (100 mg, 0.4 mmol) in DME (1.0 mL, 0.40 M) at 10 °C. The mixture was stirred at 10 °C for 5 min, then warmed to rt and stirred for 24 h. Et_2O (1 mL) was added, and the layers separated. The organic layer was washed with 1.25 N NaOH solution (1 mL), and the aqueous phase cooled

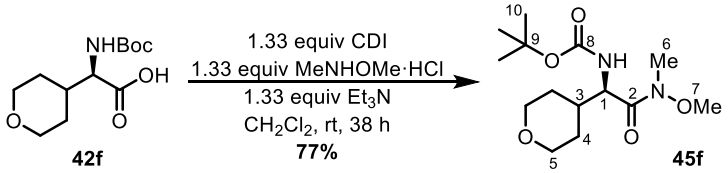
to 0 °C. This first organic layer was dried ($MgSO_4$), and concentrated *in vacuo* to yield recovered starting material. 1 M KH_2PO_4 solution, or solid KH_2PO_4, was then added to the aqueous phase until pH 4 was attained. The cloudy solution was extracted with EtOAc (3 × 1 mL), giving a clear biphase. The organic layers were dried ($MgSO_4$), and concentrated *in vacuo* to yield a crude mixture.

Preparation of (*R*)-*N*-Boc-2-(4-tetrahydropyranyl)glycine 42f



The crude mixture containing **47f·HCl** (800 mg) from the Strecker hydrolysis according to Jacobsen was dissolved in 2:1 H_2O/1,4-dioxane (18 mL). 1 N NaOH (12 mL) was added, checking the pH regularly so as not to let the mixture become >pH 8. The brown solution turns yellow. The reaction mixture is cooled to 0 °C, then Boc_2O and $NaHCO_3$ were added, and the solution turns cloudy yellow. The mixture was brought to rt and stirred for 24 h, becoming light yellow. The reaction mixture was diluted with H_2O (10 mL), and transferred to a separatory funnel, where it was extracted with EtOAc (4 × 15 mL). The aqueous layer was acidified to pH 4 with 1 M $KHSO_4$, at which point a substance oils out. This was extracted with CH_2Cl_2 (4 × 15 mL), dried (Na_2SO_4) and concentrated *in vacuo* to a white solid foam. This was dissolved in EtOAc and filtered. The white crystals of the filtrand were collected by dissolution in MeOH, as the title compound (385 mg). This crude compound was brought onto the next reaction without further purification. Spectral data matched published values.[189]

Preparation of (*R*)-*N*-methoxy-*N*-methyl-2-(methylamino)-2-(4-tetrahydropyranyl)acetamide 45f



A solution of crude **42f** (200 mg, 0.77 mmol) in CH_2Cl_2 (8 mL, 0.1 M) was cooled to 0 °C, then CDI (166 mg, 1.03 mmol, 1.33 equiv) was added. The mixture was stirred at 0 °C for 30 min. Then, Et_3N (145 µL, 104 mg, 1.03 mmol, 1.33 equiv) was added, followed by

N,*O*-dimethylhydroxylamine hydrochloride (100 mg, 1.03 mmol, 1.33 equiv). The clear, pale yellow solution was allowed to warm slowly to rt in the ice bath, and stirred for 38 h. 1 N HCl (10 mL) was added, and the layers separated. The organic layer was washed with 1 N HCl (10 mL), saturated aqueous $NaHCO_3$ solution (2 × 10 mL), then brine, and dried ($MgSO_4$) and concentrated *in vacuo* to the title compound as a yellow solid (180 mg, **77%**).

Data for **45f**:

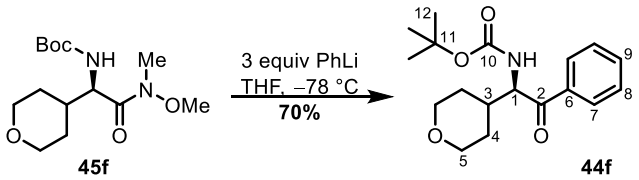
^{1}H NMR: ^{1}H NMR (500 MHz, $CDCl_3$)
δ 5.16 (d, *J* = 9.7 Hz, 1 H, HC(1)), 4.65 (br m, 1 H, NH), 3.97 (ddd, *J* = 15.8, 11.8, 4.9 Hz, 2 H, $H_{2,A}C(5)$), 3.78 (s, 3 H, $H_3C(7)$), 3.34 (dddd, *J* = 13.8, 11.8, 3.9, 2.0 Hz, 2 H, $H_{2,B}(C(5))$, 3.22 (s, 3 H, $H_3C(6)$), 2.07–1.73 (m, 1 H, HC(3)), 1.50–1.62 (m, 2 H, $H_{2,A}C(4)$), 1.39–1.50 (m, 11 H, $H_{2,B}C(4)$, $H_3C(10)$)

^{13}C NMR: ^{13}C NMR (126 MHz, $CDCl_3$)
δ 155.66 (C(2)), 79.66 (C(9)), 67.76 ($C_A(5)$), 67.61 ($C_B(5)$), 61.70 (C(7)), 53.81 (C(1)), 38.61 (C(3)), 31.82 (C(6)), 29.34 (C(4)), 28.35 ($C_A(10)$), 28.19 ($C_B(10)$)

IR (thin film): 2940 (w, br), 2845 (w), 1709 (s), 1655 (s), 1520 (w), 1390 (w), 1366 (w), 1247 (w), 1168 (s), 1093 (w), 1018 (w), 986 (w), 856 (w)

MS: (ESI-LRMS)
303.4 $[M+H]^+$

Preparation of (*R*)-2-(Boc-amino)-1-phenyl-2-(4-tetrahydropyranyl)ethan-1-one 44f



To a solution of **45f** (256 mg, 0.85 mmol) in THF (anhydrous and degassed, 8 mL, 0.11 M) at −78 °C was added PhLi (1.74 M in Bu_2O, 1.5 mL, 2.5 mmol, 3 equiv) over 14 min. The light brown reaction mixture was stirred at −78 °C for a further 7 h. Saturated aqueous NH_4Cl solution (46 mL) was then added slowly to quench, maintaining the temperature below −40 °C. The mixture was then warmed slowly to rt. The layers were separated, and the organic components extracted with further Et_2O (3 × 80 mL). The combined organic layers were washed with brine

(50 mL), dried ($MgSO_4$), and concentrated *in vacuo* to a crude, yellow oil. This was separated *via* column chromatography using 1:4 EtOAc/hexanes as eluent, to yield the title compound as a white solid (190 mg, **70%**).

Data for **44f**:

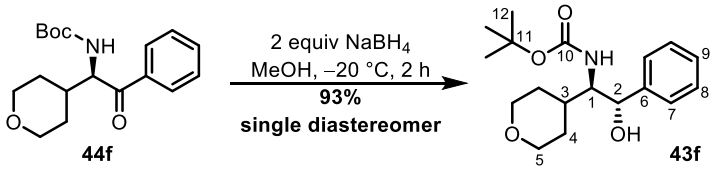
^{1}H NMR: (500 MHz, $CDCl_3$)
δ 8.00 (d, *J* = 7.5 Hz, 2 H, HC(7)), 7.61 (t, *J* = 7.5 Hz, 1 H, HC(9)), 7.51 (t, *J* = 7.8 Hz, 2 H, HC(8)), 5.47 (d, *J* = 8.9 Hz, 1 H, NH), 5.27 (dd, *J* = 8.9, 4.6 Hz, 1 H, HC(1)), 3.78–4.01 (m, 2 H, $H_{2,A}C(5)$, $H_{2,B}C(5)$), 3.31 (td, *J* = 11.3, 3.7 Hz, 1 H, $H_{2,C}C(5)$), 3.23 (td, *J* = 11.9, 2.3 Hz, 1 H, $H_{2,D}C(5)$), 2.04 (m, 3 H, HC(3), $H_{2,A}C(4)$), 1.52–1.67 (m, 2 H, $H_{2,B}C(4)$), 1.45 (s, 9 H, $H_3C(12)$)

IR (thin film): 2925 (w), 2852 (w), 1710 (m), 1682 (s), 1697 (w), 1500 (w), 1448 (w), 1366 (w), 1240 (w), 1164 (m), 1090 (w), 1002 (w), 918 (w), 876 (w), 690 (w), 570 (w), 517 (w)

MS: (ESI-LRMS)
342.4 $(M+Na)^+$, 203.4 $(M-NHBoc)^+$

Optical Rotation: $[\alpha]_D^{22}$ −3.42 (c = 0.567, MeOH)

Preparation of (1*S*,2*R*)-2-(Boc-amino)-1-phenyl-2-(4-tetrahydropyranyl)ethan-1-ol 43f



To a solution of **44f** (190 mg, 0.6 mmol) in MeOH (anhydrous, 7.5 mL, 0.08 M) at −20 °C was added $NaBH_4$ (45 mg, 1.2 mmol, 2 equiv), portionwise over 7 min. The white suspension was stirred at −20 °C for 2 h. H_2O (2.5 mL) was added at −20 °C, and the mixture allowed to warm to rt. MeOH was removed *in vacuo*, then EtOAc (5 mL) was added, and the layers separated. The organic layer was washed with H_2O (5 mL), then brine (5 mL), dried (Na_2SO_4), and concentrated *in vacuo* to the title compound as a white solid (178 mg, **93%**).

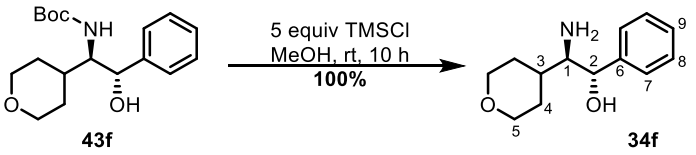
Data for **43f**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.28–7.40 (m, 5 H, HC(7), HC(8), HC(9)), 4.87 (t, *J* = 4.6 Hz, 1 H, HC(2)), 4.46 (d, *J* = 9.9 Hz, 1 H, HC(1)), 3.87–4.06 (m, 3 H, $H_AC(5)$, $H_BC(5)$, $H_CC(5)$), 3.85 (m, 1 H, $H_DC(5)$), 3.32 (m, 3 H, HC(3), $H_{2,A}C(4)$), 3.12 (br s, 1 H, OH), 1.53–1.69 (m, 2 H, $H_{2,B}C(4)$), 1.39 (s, 9 H, $H_3C(12)$)

IR (thin film): 3356 (br w), 2936 (w), 2848 (w), 1694 (s), 1496 (w), 1454 (w), 1391 (w), 1366 (m), 1243 (w), 1169 (s), 1022 (m), 998 (w), 853 (w), 766 (w), 701 (m), 528 (w)

Preparation of (1*S*,2*R*)-2-amino-1-phenyl-2-(4-tetrahydropyranyl)ethan-1-ol 34f



To a solution of **34f** (34 mg, 0.1 mmol) in MeOH (anhydrous, 1 mL, 0.1 M) was added TMSCl (68 μL, 57 mg, 0.53 mmol, 5 equiv) in one portion. The mixture was stirred at rt for 10 h. The reaction mixture was then extracted with EtOAc (3 × 5 mL). The aqueous layer was basified with 28% NH_4OH to pH 12, and the mixture extracted with EtOAc (3 × 5 mL), dried (Na_2SO_4) and concentrated *in vacuo* to the title compound as a white solid (23 mg, **100%**).

Data for (1*R*,2*S*)-**34f**:

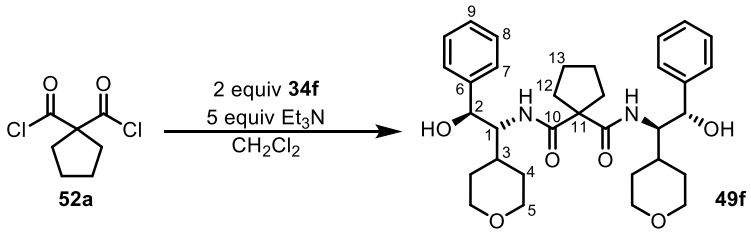
^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.26–7.40 (m, 5 H, HC(7), HC(8), HC(9)), 4.62 (d, *J* = 5.9 Hz, 1 H, HC(2)), 3.86–4.03 (m, 2 H, $H_{2,A}C(5)$), 3.31 (dtd, *J* = 18.4, 11.4, 2.1 Hz, 2 H, $H_{2,B}C(5)$), 2.79 (t, *J* = 5.3 Hz, 1 H, HC(1)), 1.51–1.69 (m, 4 H, $H_2C(4)$), 1.43 (tdd, *J* = 12.3, 9.0, 6.0 Hz, 1 H, HC(3))

HRMS: (ESI)

Calcd. for $C_{13}H_{20}NO_2^+$ $(M+H)^+$: 222.1494, found: 222.1495

Preparation of *N*,*N*'-bis((1*S*,2*R*)-2-hydroxy-2-phenyl-1-(4-tetrahydropyranyl)ethyl)cyclopentane-1,1-dicarboxamide 49f



To a solution of **34f** (21 mg, 0.1 mmol, 2 equiv) in CH_2Cl_2 (anhydrous, 0.4 mL) was added Et_3N (33 μL, 24 mg, 0.24 mmol, 5 equiv) in one portion. A solution of **52a** (9.3 mg, 0.05 mmol) in CH_2Cl_2 (anhydrous, 0.24 mL, 0.2 M) was then added dropwise at 0 °C over 1 min. The white suspension was brought to rt and stirred for 16 h. H_2O (3 mL) was added to quench. CH_2Cl_2 (3 mL) was added, and the layers separated. The organic components were extracted with further CH_2Cl_2 (2 × 6 mL), dried (Na_2SO_4), and concentrated *in vacuo* to the title compound as a white solid (21 mg, **78%**), as a mixture of diastereomers.

Data for **49f**:

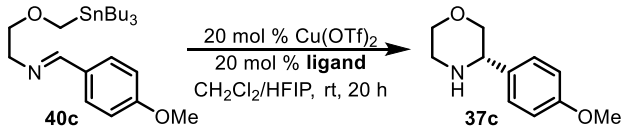
^{1}H NMR: (500 MHz, $CDCl_3$)
δ 7.27–7.41 (m, 10 H, HC(7), HC(8), HC(9)), 6.16 (d, *J* = 9.5 Hz, 2 H, NH), 4.85 (d, *J* = 5.6 Hz, 2 H, HC(2)), 4.19 (m, 2 H, HC(1)), 3.77–3.89 (m, 4 H, $H_{2,A}$C(5)), 3.22–3.34 (m, 4 H, $H_{2,B}$C(5)), 3.10 (d, *J* = 4.0 Hz, 2 H, OH), 2.09 (br t, *J* = 7.3 Hz, 2 H, HC(3)), 1.84–1.93 (br m, 2 H, $H_{2,A}$C(12)), 1.28–1.72 (m, 16 H, H_2C(4), $H_{2,B}$C(12), H_2C(13))

IR (thin film): 3347 (br w), 2961 (w), 2926 (w), 2852 (w), 1673 (m), 1472 (w), 1368 (w), 1269 (w), 1173 (m), 1098 (m), 1029 (m), 798 (m)

MS: (ESI-LRMS)
565.3 $(M+H)^+$

Conditions and Spectra for Morpholine Synthesis

General Screening Procedure for Enantioselective SnAP Synthesis of 3-(4-Methoxyphenyl)morpholine 37c



Reactions were run according to the procedure of Bode, outlined below.[173]

The bisoxazoline ligand (see Table 12 for masses used, 0.01 mmol, 20 mol %) and anhydrous $Cu(OTf)_2$ (3.6 mg, 0.01 mmol, 20 mol %) were dissolved in HFIP/CH_2Cl_2 (1:1, anhydrous, 0.4 mL) and stirred at rt for 6 h under Ar in a 1-dram vial. An immediate color change occurred, the color often intensifying over the course of stirring. A solution of freshly-prepared imine **40c** (24 mg, 0.05 mmol) in CH_2Cl_2 (anhydrous, 0.6 mL) was injected in one portion and the resulting mixture was stirred at rt for 20 h. The reaction mixture was diluted with a stock solution of 1,3,5-trimethoxybenzene (internal standard, 0.025 mmol, 0.5 M) in CH_2Cl_2 (anhydrous, 0.5 mL), treated with a solution of 12% aq NH_4OH and brine (1:1, 1 mL), and stirred vigorously for 15 min at rt. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 2 mL). The combined organic layers were washed with H_2O (2 mL) and brine (2 mL), dried (Na_2SO_4), and concentrated *in vacuo*. A sample for HPLC analysis was obtained by dissolving roughly half of this crude mixture in hexane (0.5 mL) in a 2-dram vial, washing with 3 N HCl (1 mL) and separating the layers. The aqueous layer was basified to pH 12 with 3 N NaOH (~1 mL), and extracted with hexane (2 × 0.5 mL) to yield the purified title compound. Spectral and chromatographic data matched the literature.[127]

Additional Data for **37c**:

HPLC: t_R 10.0 min (49.8%); t_R 10.9 min (50.2%) (AD-H, hexane/isopropanol = 96:4 + 0.1% DEA, 1.0 mL min^{-1}, 220 nm, 24 °C)

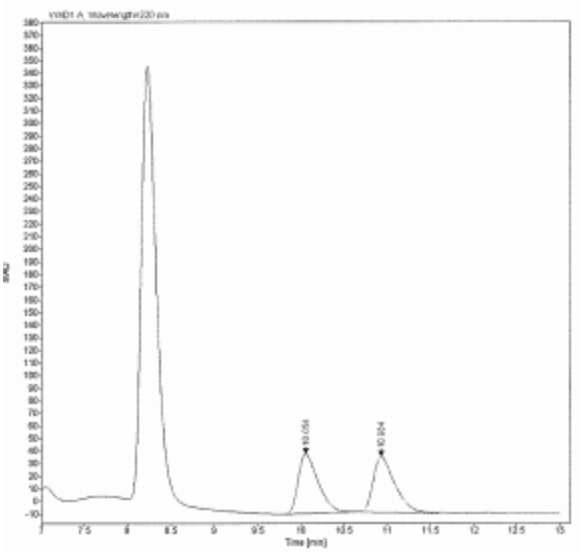


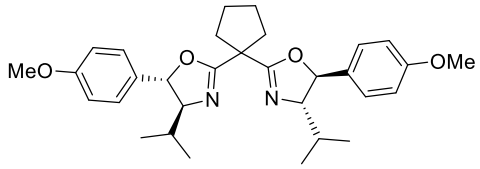
Figure 6. HPLC Chromatogram of Racemic **37c**

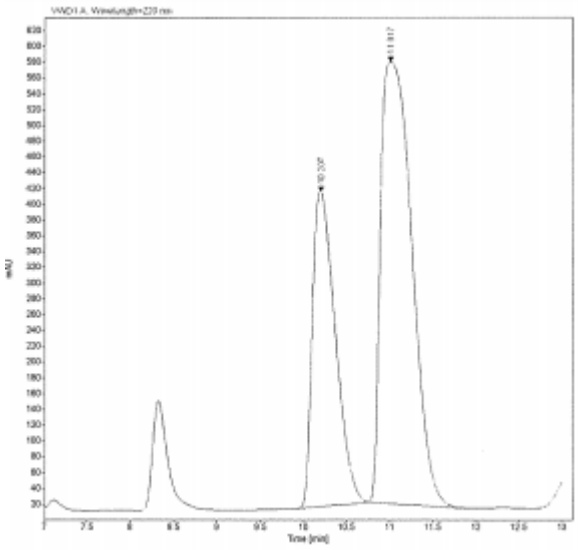
Table 12. Bisoxazoline Screening Reactions and CSP-HPLC Chromatograms

Run 1

Ligand MW: 504.67

5.0 mg ligand



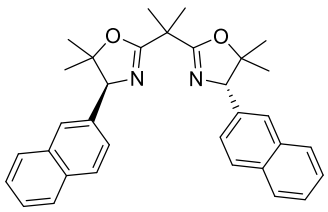


Enantiomeric Ratio of 37c

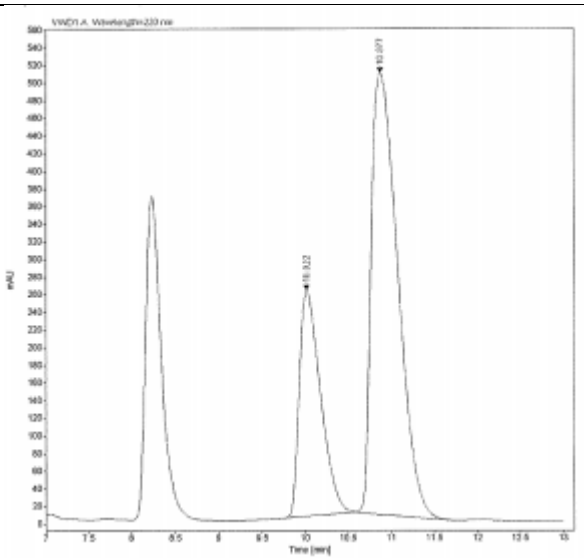
a 32:68

b 31:69

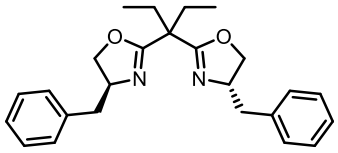
Run 2
Ligand MW: 490.65
4.9 mg ligand



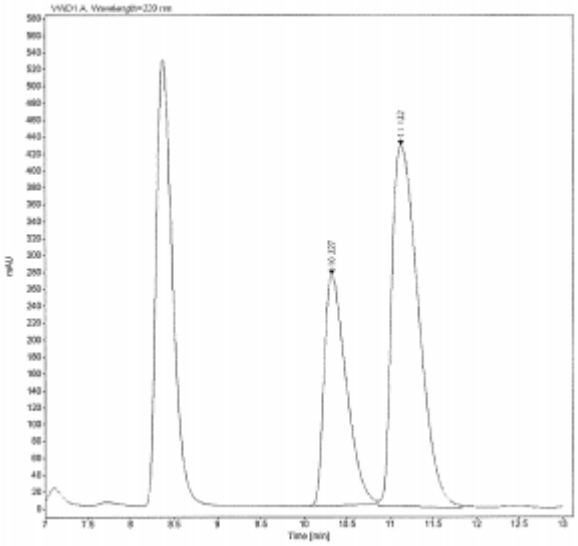
Enantiomeric Ratio of 37c
a 29:71
b 30:70



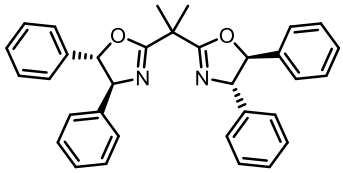
Run 3
Ligand MW: 390.53
3.9 mg ligand



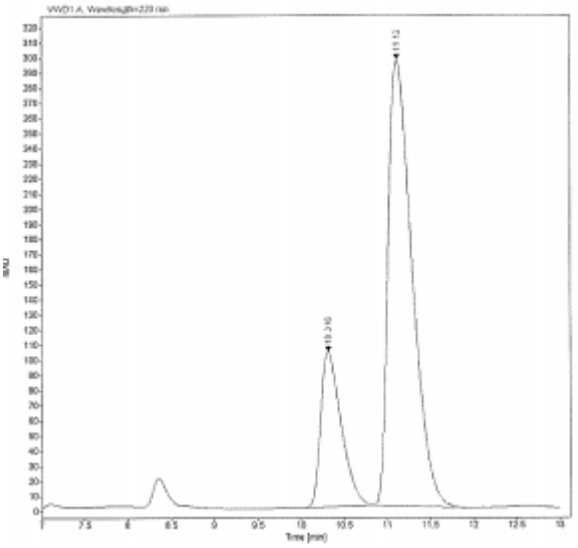
Enantiomeric Ratio of 37c
a 35:65
b 35:65



Run 4
Ligand MW: 486.62
4.9 mg ligand



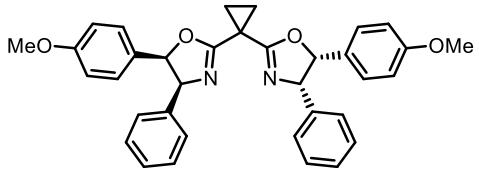
Enantiomeric Ratio of 37c
a 24:76
b 25:75

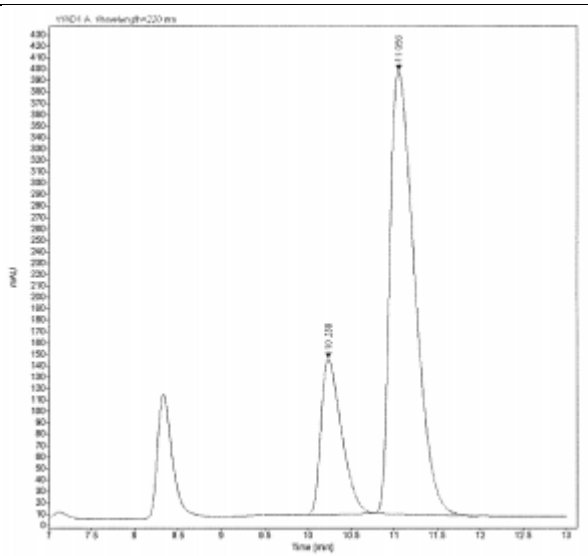


Run 5

Ligand MW: 544.65

5.4 mg ligand





Enantiomeric Ratio of 37c

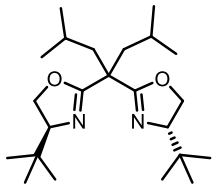
a 23:77

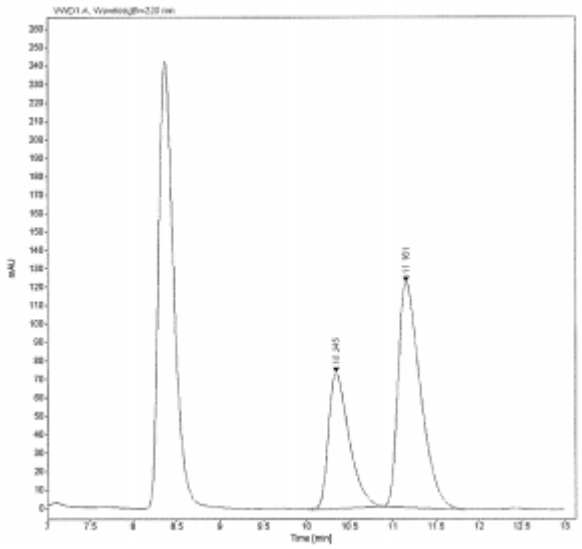
b 22:78

Run 6

Ligand MW: 378.60

3.8 mg ligand





Enantiomeric Ratio of 37c

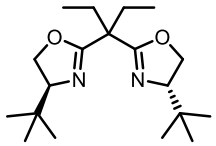
a 37:63

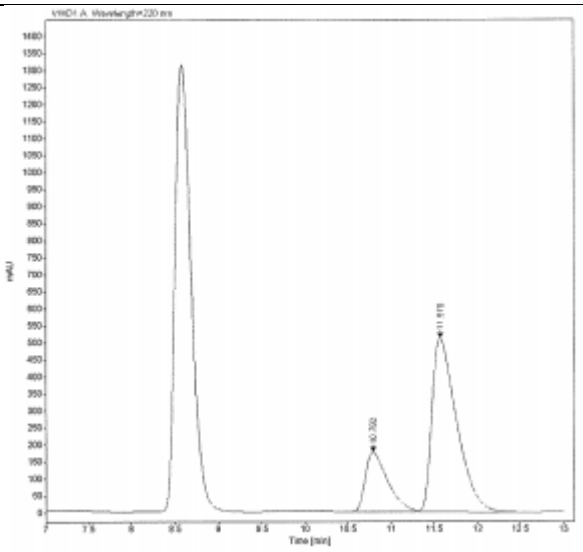
b 36:64

Run 7

Ligand MW: 322.49

3.2 mg ligand





Enantiomeric Ratio of 37c

a 27:73

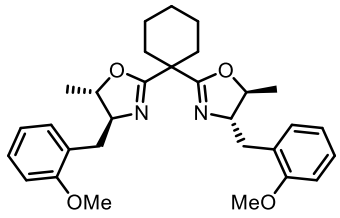
b 32:68

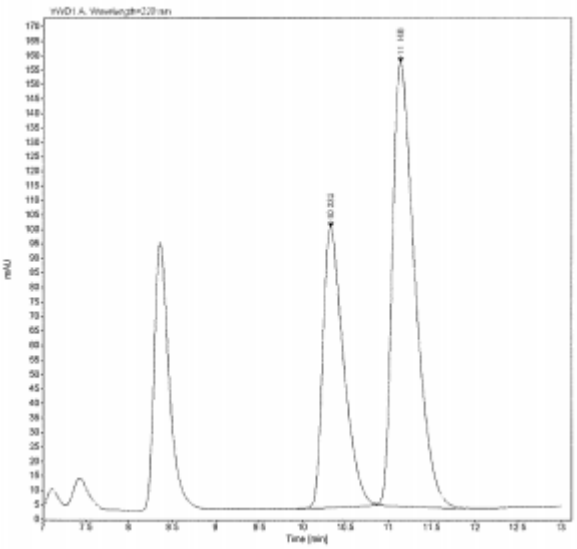
c 26:74

Run 8

Ligand MW: 490.64

4.9 mg ligand





Enantiomeric Ratio of 37c

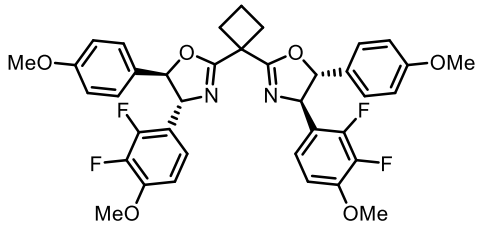
a 37:63

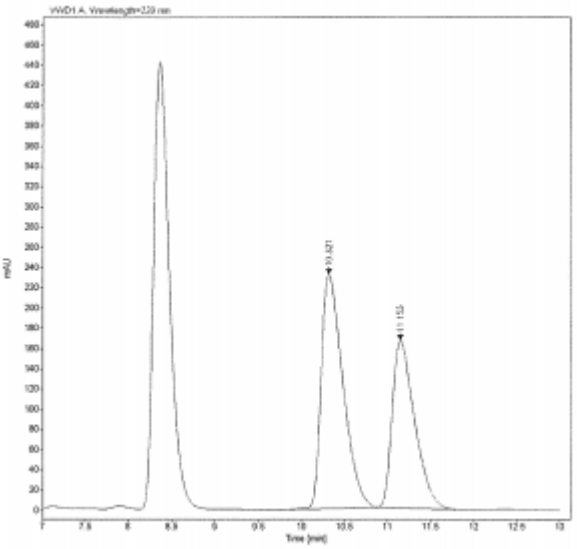
b 36:64

Run 9

Ligand MW: 690.69

6.9 mg ligand





Enantiomeric Ratio of 37c

a 59:41

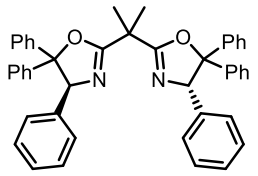
b 67:33

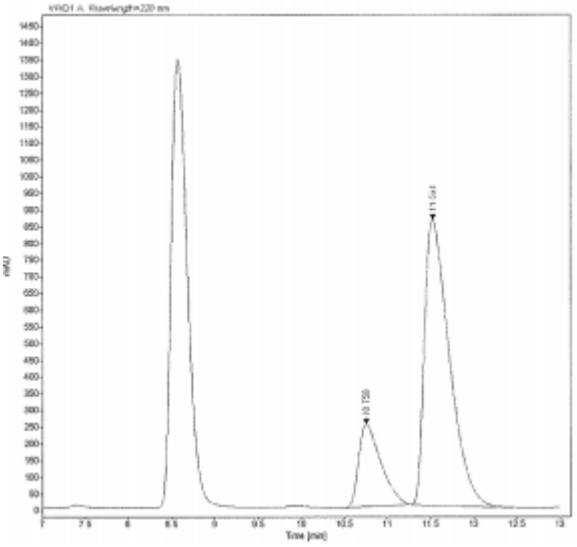
c 68:32

Run 10

Ligand MW: 638.81

6.4 mg ligand





Enantiomeric Ratio of 37c

a 13:87

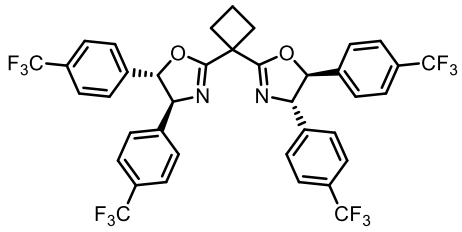
b 17:83

c 18:82

Run 11

Ligand MW: 770.62

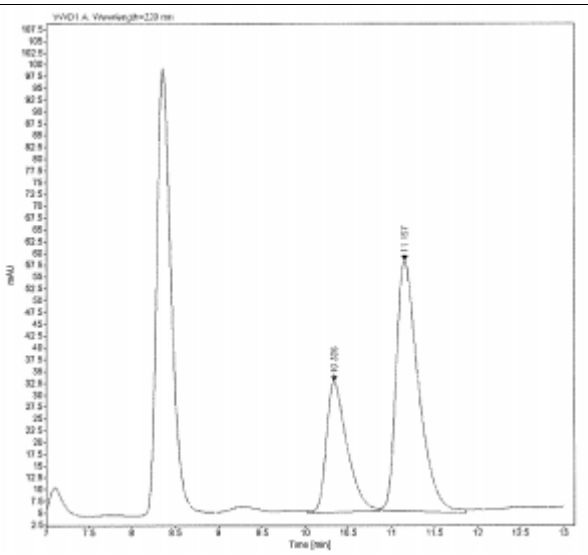
7.7 mg ligand



Enantiomeric Ratio of 37c

a 36:64

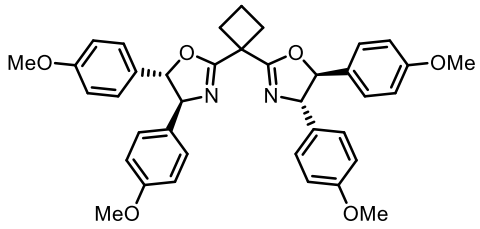
b 35:65



Run 12

Ligand MW: 618.73

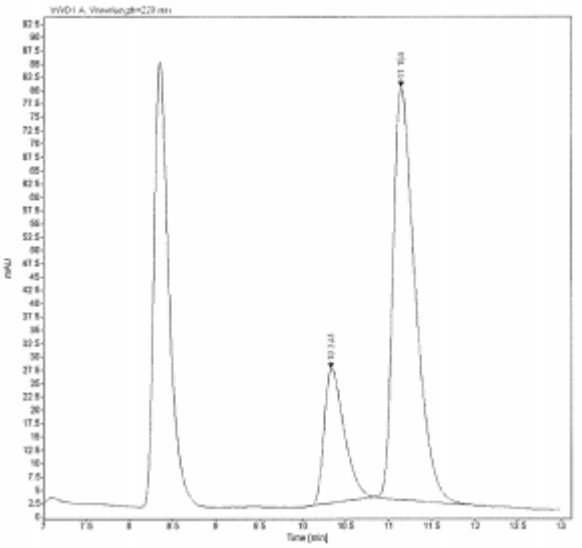
6.2 mg ligand



Enantiomeric Ratio of 37c

a 28:72

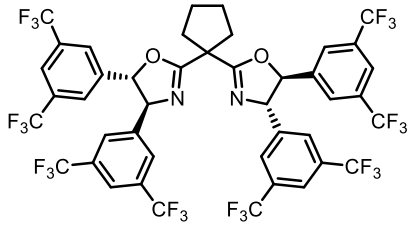
b 27:73



Run 13

Ligand MW: 1056.64

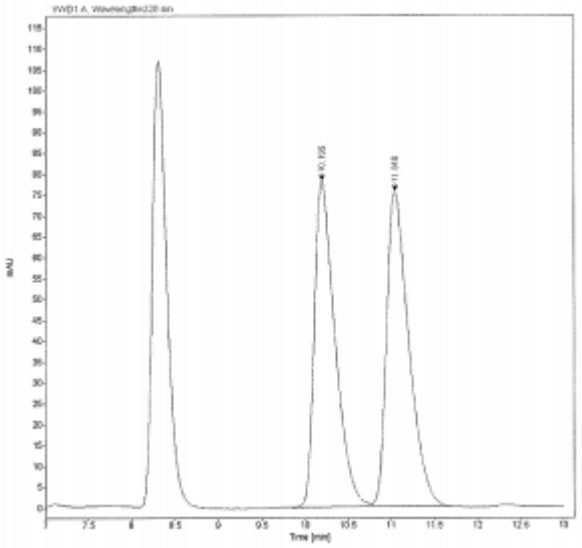
10.6 mg ligand



Enantiomeric Ratio of 37c

a 49:51

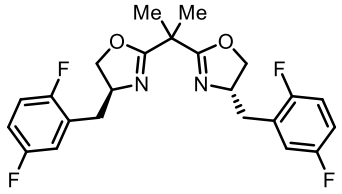
b 50:50



Run 14

Ligand MW: 434.43

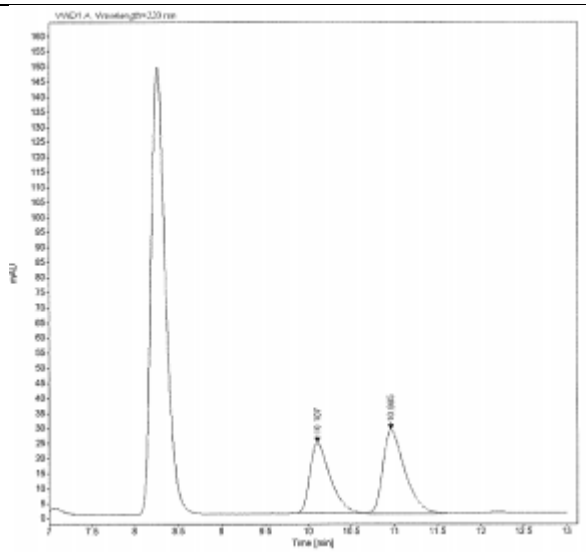
4.3 mg ligand



Enantiomeric Ratio of 37c

a 43:57

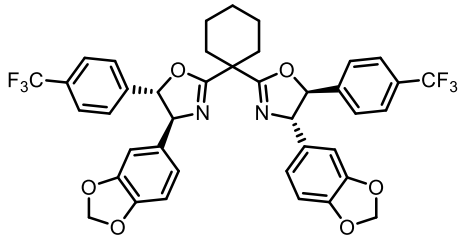
b 44:56



Run 15

Ligand MW: 750.69

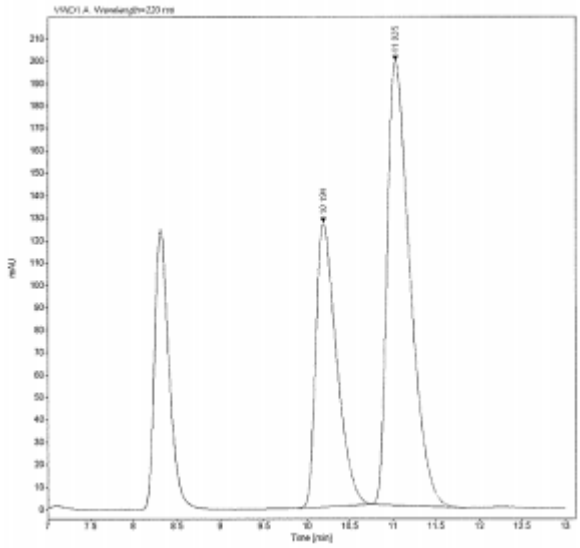
7.5 mg ligand



Enantiomeric Ratio of 37c

a 37:63

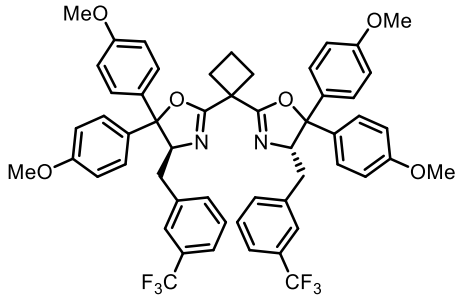
b 36:64

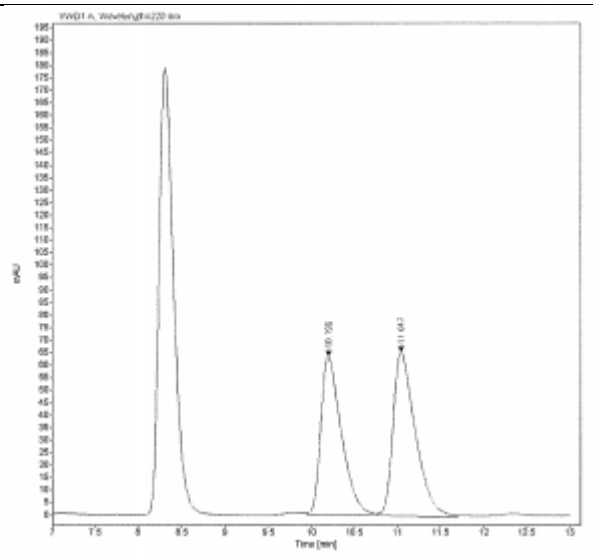


Run 16

Ligand MW: 934.98

9.3 mg ligand





Enantiomeric Ratio of 37c

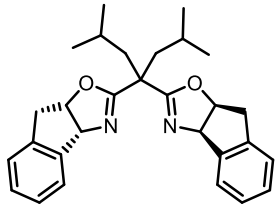
a 47:53

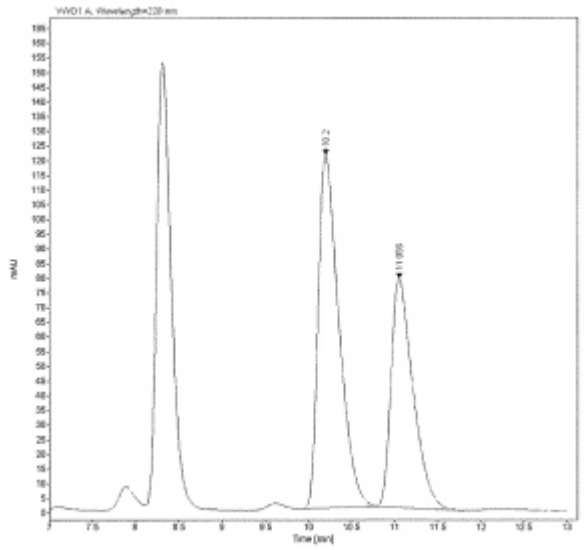
b 48:52

Run 17

Ligand MW: 442.60

4.4 mg ligand





Enantiomeric Ratio of 37c

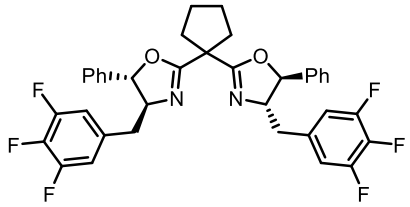
a 63:37

b 63:37

Run 18

Ligand MW: 648.65

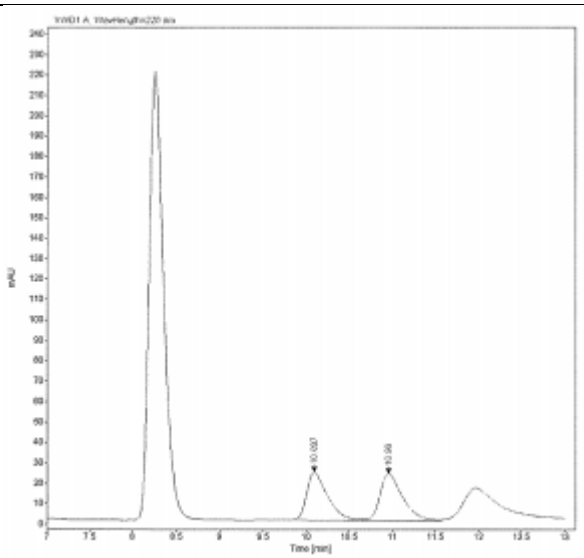
6.5 mg ligand



Enantiomeric Ratio of 37c

a 47:53

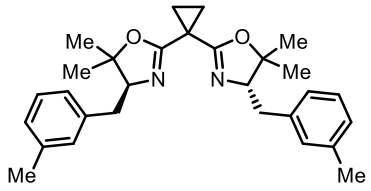
b 47:53



Run 19

Ligand MW: 444.62

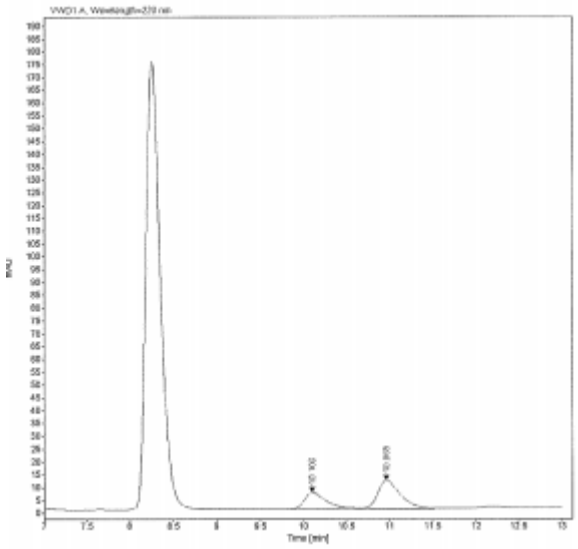
4.4 mg ligand



Enantiomeric Ratio of 37c

a 36:64

b 36:64

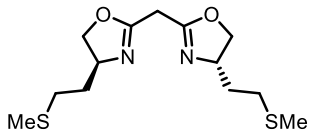


Run 20

No conversion to **37c**

Ligand MW: 302.45

3.0 mg ligand

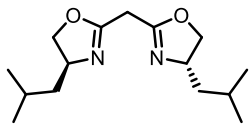


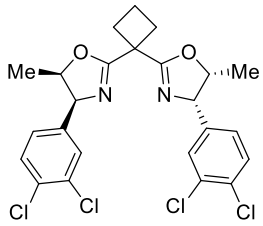
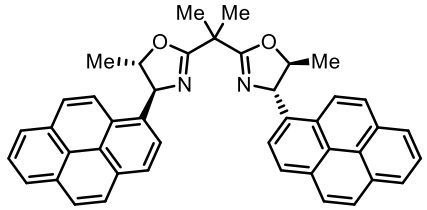
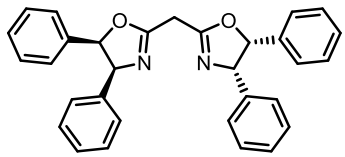
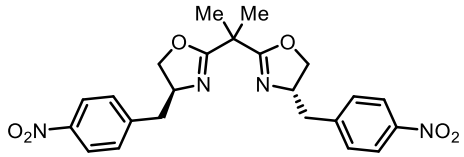
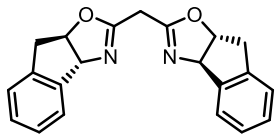
Run 21

No conversion to **37c**

Ligand MW: 266.39

2.7 mg ligand



Run 22 Ligand MW: 512.25 5.1 mg ligand 	No conversion to **37c**
Run 23 Ligand MW: 610.76 6.1 mg ligand 	No conversion to **37c**
Run 24 Ligand MW: 458.56 4.6 mg ligand 	No conversion to **37c**
Run 25 Ligand MW: 452.47 4.5 mg ligand 	No conversion to **37c**
Run 26 Ligand MW: 330.39 3.3 mg ligand 	No conversion to **37c**

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