ENANTIOSELECTIVE, LEWIS BASE-CATALYZED TRANSFORMATIONS: I. POLYENE SULFENOCYCLIZATION (PREPARATIVE AND MECHANISTIC ASPECTS) II. SULFENOFUNCTIONALIZATION OF ALKENYL BORONATES ENABLED BY 1,2-BORONATE MIGRATION

BY

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DISSERTATION

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Abstract

This thesis covers two independent projects which are united under the umbrella of Lewis base catalysis. Following an overview of the key principles behind Lewis base catalysis and how it is used to enhance the electrophilicity of Lewis acids (Chapter 1), the bulk of this thesis will focus on the development of a catalytic, enantioselective sulfenocyclization of polyenes (Chapter 2). Sulfenyl group transfer from a highly reactive, cationic, Lewis acid-base adduct to an unactivated alkene generates a cyclic thiiranium ion, which serves as the initiating event for a highly stereoselective polyene cyclization that is terminated by arenes or phenols. This reaction was enabled by the identification of hexafluoroisopropyl alcohol (HFIP) as a superior solvent which dramatically improves site selectivity of thiiranium ion generation. A broad substrate scope is demonstrated, and the tricyclic products are isolated in good yield and enantioselectivity. Furthermore, a number of functional group interconversions (FGIs) of the resulting thioether moiety are demonstrated. This method is employed for the concise, enantioselective syntheses of the natural products (+)-ferruginol and (+)-hinokiol. Additionally, investigations into the sulfenocyclization of trienes to form even more complex products are disclosed. Preliminary mechanistic experiments to elucidate the rate-determining step of the catalytic cycle and the order in each reaction component were also performed.

Chapter 3 of this thesis will cover the development of a Lewis base-catalyzed, enantioselective carbosulfenylation of alkenylboronate complexes which is enabled by a 1,2-boronate migration. The generation of “iranium” ions from alkenylboronates triggers a diastereospecific, ring-opening migration of an alkyl or aryl group to form 1,2-difunctionalized organoboron compounds. This strategy was employed together with Lewis base-catalyzed, enantioselective sulfenyl group transfer to ultimately afford chiral, non-racemic alkylboronic esters in generally high yield, high enantioselectivity, and perfect diastereospecificity. The products of the transformation are useful synthetic intermediates, and a number of useful FGIs are demonstrated.

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Finally, I would like to thank my wonderful wife, Mrs. Bowie Yi. Meeting you was the best thing to happen to me here. Thank you for making the past year and a half so much more enjoyable than the previous four. I love you, and I'm so excited for our life together.

Onward to Hastings!

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Chapter 1. A Brief Overview of Lewis Base Catalysis[1]

Nearly one hundred years ago, American physical chemist Gilbert N. Lewis proposed novel definitions of acidity and basicity which subsumed, and improved upon, the existing Arrhenius and Brønsted-Lowry definitions. In his 1923 work *Valence and the Structure of Atoms and Molecules*, Lewis stated that "the basic substance furnishes a pair of electrons for a chemical bond" and "the acid substance accepts such a pair."[2] This simple tenet is one of the fundamental, unifying principles of organic chemistry. Like any neutralization process, the combination of a Lewis acid and a Lewis base tends to exert a stabilizing effect. For example, the Lewis acid boron trifluoride is a toxic, highly reactive gas at standard temperature and pressure, but it forms a stable adduct with the Lewis base diethyl ether. The resulting $BF_3 \cdot Et_2O$ complex is a liquid at standard temperature and pressure which is safely and easily handled.

A 'stable' Lewis acid-base adduct does not, however, imply that it is non-reactive. Indeed, Lewis acids can be used to activate and enhance the reactivity of Lewis bases, and vice versa. The ability of Lewis acidic metal salts (cerium trichloride, aluminum trichloride, etc.) to enhance the reactivity of Lewis basic carbonyl compounds is well-known.[3] The transfer of electron density from the Lewis basic donor to the Lewis acidic acceptor results in an electronic deficiency at the carbonyl carbon, rendering this center more electrophilic, i.e. more reactive. This is the principle behind such workhorse reactions as the Friedel-Crafts acylation and the Luche reduction. In the past several decades, the use of Lewis acids as catalytic rather than stoichiometric reagents has become more common, for example, in the activation of dienophiles to enhance the rate of Diels-Alder cycloadditions. Rationalizing the role of Lewis acids in catalytic and stoichiometric processes is straightforward and intuitive. The net transfer of electron density in an acid-base adduct is *away* from the donor and *toward* the acceptor. Therefore, Lewis acids invariably enhance the *electrophilicity* of the Lewis basic reagent to which they are bound.

At first glance, it would seem that the opposite must simply be true for Lewis base activation of Lewis acids. In other words, Lewis bases must serve to enhance the nucleophilicity of Lewis acidic compounds, which is indeed true in many cases. The Morita-Baylis-Hillman reaction[4] (Figure 1) and the related Rauhut-Currier reaction[5] are two classic examples of this type of Lewis base catalysis. Conjugate addition of a tertiary amine or phosphine Lewis basic catalyst to an α,β-unsaturated carbonyl compound generates an enolate which displays enhanced

nucleophilicity. Subsequent inter- or intra-molecular attack on an electrophile, followed by proton transfer and elimination to reform a conjugated alkene, completes the reaction and regenerates the Lewis basic catalyst.

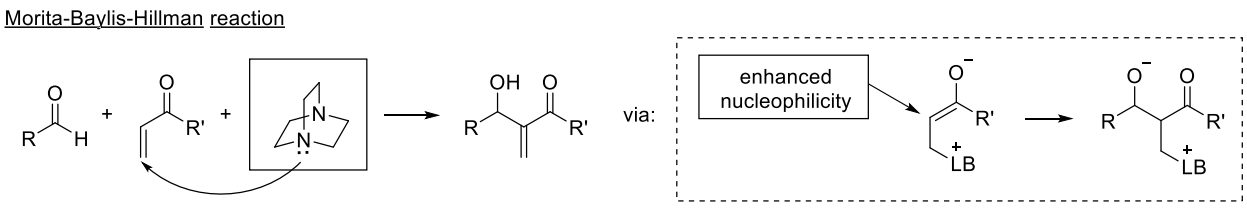


Figure 1. Enhancing nucleophilicity with (n→π*) Lewis base catalysis.

Using Lewis basic catalysts to enhance the nucleophilicity of other reaction components is intuitive and enjoys widespread use, so it is understandable that the terms "Lewis base catalysis" and "nucleophilic catalysis" are often used interchangeably. Unfortunately, the latter term is misleading because it does not capture the full spectrum of reactivity changes induced by Lewis basic catalysts, because Lewis base catalysis can enhance the nucleophilicity *or* electrophilicity (or both!) of a Lewis acid in the reaction mixture.[6] Adding catalytic amounts of 4-(dimethylamino)pyridine (DMAP) to acylation reactions is one of the most common Lewis base-catalyzed reactions.[7] Addition of DMAP to an acid chloride generates a tetrahedral intermediate with enhanced *O*-nucleophilicity, but this immediately collapses to eject chloride anion and form a cationic intermediate with enhanced C-electrophilicity. The Lewis base-catalyzed lactonization reaction of ketenes with aldehydes is another excellent example of a catalyst imparting both enhanced nucleophilicity and electrophilicity to the substrate.[8]

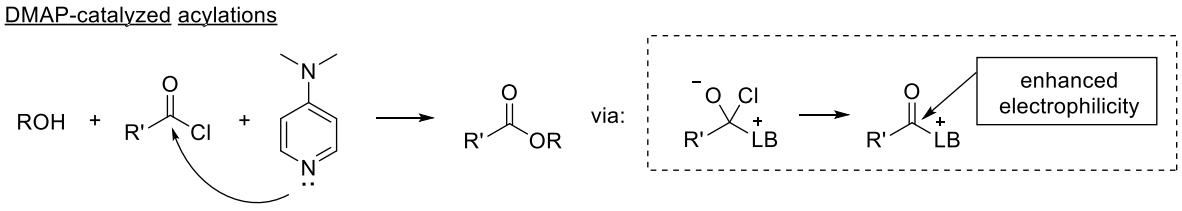


Figure 2. Enhancing electrophilicity with (n→π*) Lewis base catalysis.

The reactions just discussed are all examples of (n→π*) Lewis base catalysis, that is, they involve donation from a lone pair of the Lewis base into a π-antibonding orbital of the Lewis acid. This is not the only manner in which Lewis bases may activate Lewis acids. Another common mode which is less well-recognized is the (n→σ*) process.[9-10] Consider the interaction between a generic, Lewis basic electron pair donor and the Lewis acid silicon tetrachloride (Figure 3). The resulting adduct is commonly drawn as a zwitterion, with a positive formal charge on the Lewis basic atom and a negative formal charge on the silicon atom, to symbolize the transfer of electron density from the donor to the acceptor.

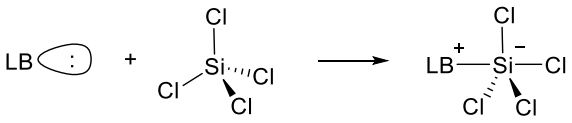


Figure 3. A (n→σ*) Lewis acid-base adduct, with formal charges shown.

The formalized charge separations drawn in Figure 3, however, are not borne out by reality. Both computational and crystallographic studies on a variety of acid-base adducts have identified significant changes in bond lengths which occur throughout the complex. This bond lengthening and shortening is a physical manifestation of a re-distribution of electron density within the donor-acceptor complex, following the initial (n→σ*) donation. For example, in the crystal structure of the adduct between tetrachloroethylene carbonate and antimony pentachloride,[11] the carbonyl C=O bond and the Sb–Cl σ-bonds are all lengthened considerably (Figure 4). This is indicative of polarization of electron density towards the oxygen and chlorine atom, and by necessity, *away* from the antimony atom.

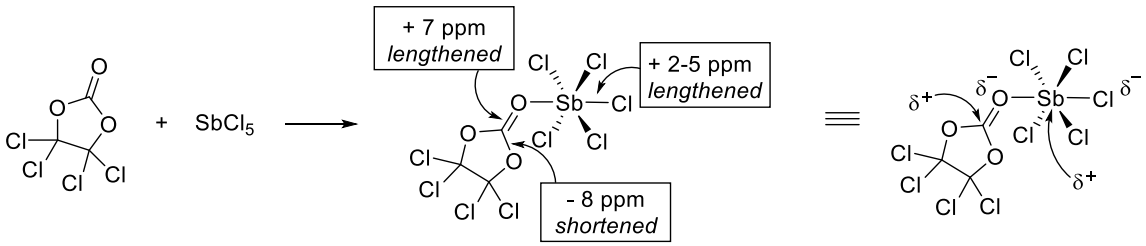


Figure 4. The effect of adduct formation on bond length and polarization.

The results of this and other studies led Gutmann and co-workers to enunciate a series of empirical rules for electronic re-distribution in the formation of an acid-base adduct.[11-12] The most important conclusion was best stated by Jensen in a corollary to Gutmann's rules: "*although a donor-acceptor interaction will result in a net transfer of electron density from the donor species to the acceptor species, it will, in the case of polyatomic species, actually lead to a net increase or "pileup" of electron density at the donor atom of the donor species and to a net decrease or "spillover" of electron density at the acceptor atom of the acceptor species. This results from the accompanying changes in the intramolecular charge distribution induced by the primary donor-acceptor interaction. These disperse the net change in electron density among all the atoms and in so doing, overcompensate for the initial changes induced at the donor and acceptor atoms. This result is important as it contradicts the usual assumption of the organic chemist that the net changes in formal charges remain localized on the donor and acceptor atoms.*"[9] The conclusions reached by Gutmann are non-intuitive, indeed, counter-intuitive, but they are crucial for understanding how Lewis bases can enhance the electrophilicity of Lewis acids through (n→σ*) interactions.

Perhaps the clearest way to rationalize this phenomenon is through a molecular orbital analysis of the three center, four electron (3c, 4e) bond (Figure 5).[13-15] Consider again the (n→σ*) interaction between a generic Lewis base and silicon tetrachloride. Lewis acid-base adduct formation leads to a pentacoordinate silicon atom and the formation of a linear (3c, 4e) sigma bond, consisting of the Lewis basic atom, the silicon atom (central atom of Lewis acid), and a chlorine atom (peripheral atom of Lewis acid). The lone pair of the Lewis basic donor contributes two electrons to the three-center bond, as does the Si–Cl sigma bond, for a total of four electrons. These four electrons fill a bonding molecular orbital and a non-bonding molecular orbital which contains a node at the central atom of the three-center bond. The result is an increase of electron density on the peripheral chlorine atom, but a decrease of electron density on the central silicon atom, i.e. increased electrophilicity. The (3c, 4e) bonding argument is also used to explain the unique reactivity of hypervalent iodine reagents, and a similar electronic re-distribution also occurs in the transition state of an S_N2 reaction.[16]

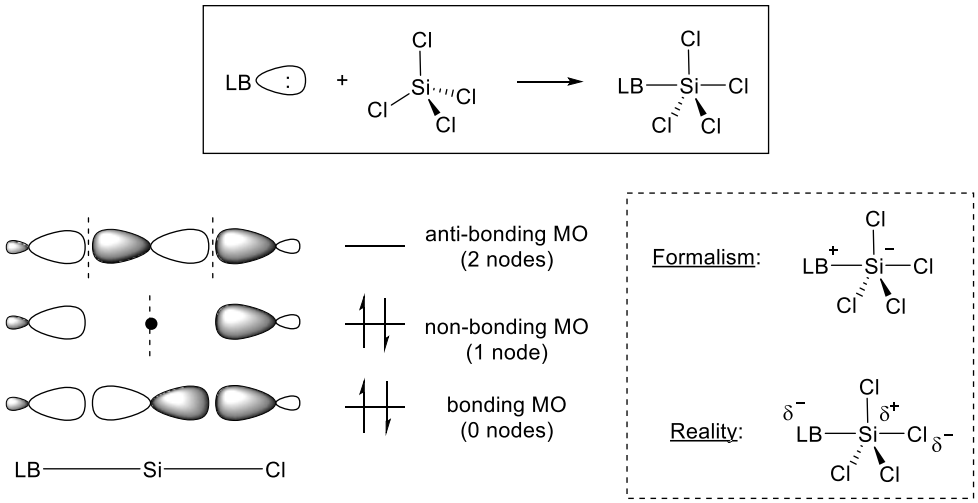


Figure 5. Molecular orbital diagram for the (3c, 4e) bond.

The partial charges shown in Figure 5 are a better representation of the actual electronic distribution as predicted by molecular orbital theory and by Gutmann's rules. In the net transfer of electron density from donor to acceptor, a "pile-up" of electron density on the Lewis basic atom occurs as a result of bond polarization, while a "spillover" effect results in increased electron density on the peripheral atom. When this trend is taken to its logical conclusion, i.e. complete ionization of a chloride anion, a *cationic, donor-acceptor complex* is formed (Figure 6). This highly electrophilic species undergoes rapid nucleophilic displacement to forge a new silicon sigma bond and release the neutral Lewis basic reagent.

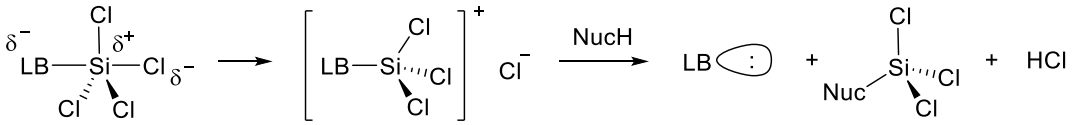


Figure 6. Formation and reactivity of the cationic, donor-acceptor complex.

As depicted in Figure 6, the Lewis base is regenerated after nucleophilic attack on the cationic, donor-acceptor complex. In many cases, only a catalytic amount of Lewis base is required to activate a Lewis acidic substrate or reagent in a reaction of interest.[17] The Denmark laboratory has pioneered the use of chiral Lewis bases as catalysts for the (n→σ*) activation of Lewis acids.

One of the earliest demonstrations of this paradigm was in the catalytic, enantioselective Mukaiyama aldol reaction of silyl ketene acetals with aldehydes.[18] The combination of dimeric, BINAM-derived, bis(phosphoramide) (*R*,*R*)-**1** with silicon tetrachloride generates a chiral, cationic, donor-acceptor complex (Figure 7). The central silicon atom is sufficiently electron-deficient that a weakly donating aldehyde substrate readily coordinates, which in turn enhances the electrophilicity of the carbonyl carbon. Subsequent nucleophilic attack of a silyl enol ether occurs with high enantioselectivity, influenced by the chiral environment created by the dimeric, Lewis basic catalyst. After the addition is complete, the Lewis base readily dissociates from the hexacoordinate silicon atom and re-enters the catalytic cycle.

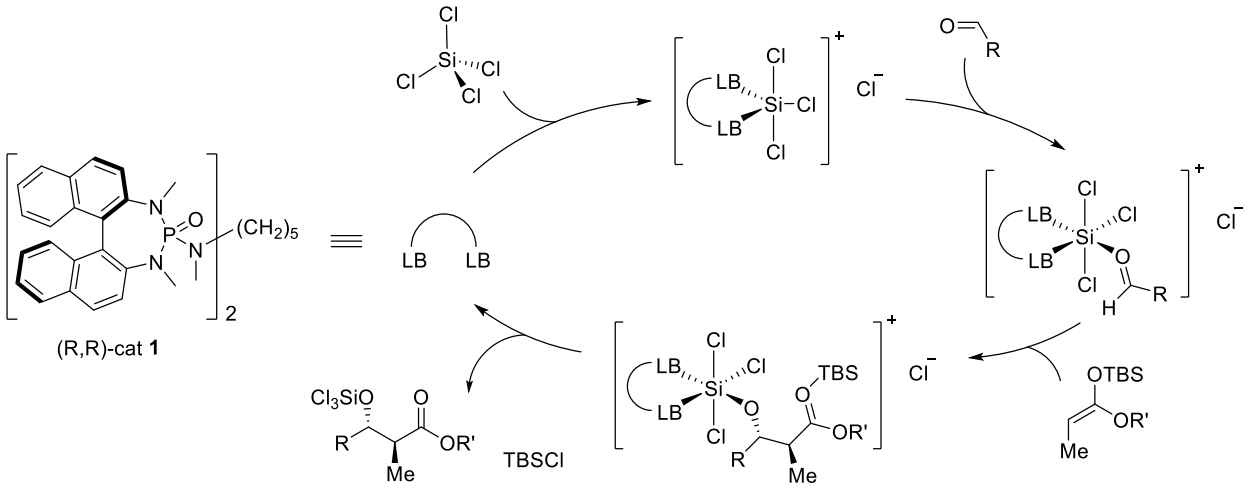


Figure 7. Mechanism of Lewis base-catalyzed, Lewis acid activation in an enantioselective, Mukaiyama aldol reaction.

In subsequent years, the Denmark laboratory has presented many elaborations on this theme, utilizing chiral Lewis basic catalysts to activate Group 14, 16, and 17 Lewis acids in a wide variety of asymmetric transformations. The activation of sulfur-containing Lewis acids (Group 16) has proven to be a particularly fruitful endeavor.[19] Although sulfur(II) compounds are not generally categorized as Lewis acids, they will react analogously to Group 14 Lewis acids (*vide infra*) in the presence of a Lewis basic catalyst, provided that a sufficiently electron-withdrawing group is present (Figure 8). Sulfides derived from phthalimide, benzotriazole, and saccharin, to name a few, display this reactivity. Except in the case of highly withdrawing groups, the addition

of a Brønsted acid to the reaction mixture is necessary to assist with the ionization of X^- to generate the cationic, donor-acceptor complex.

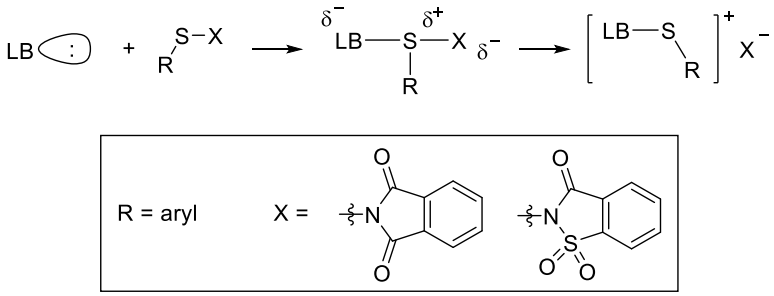
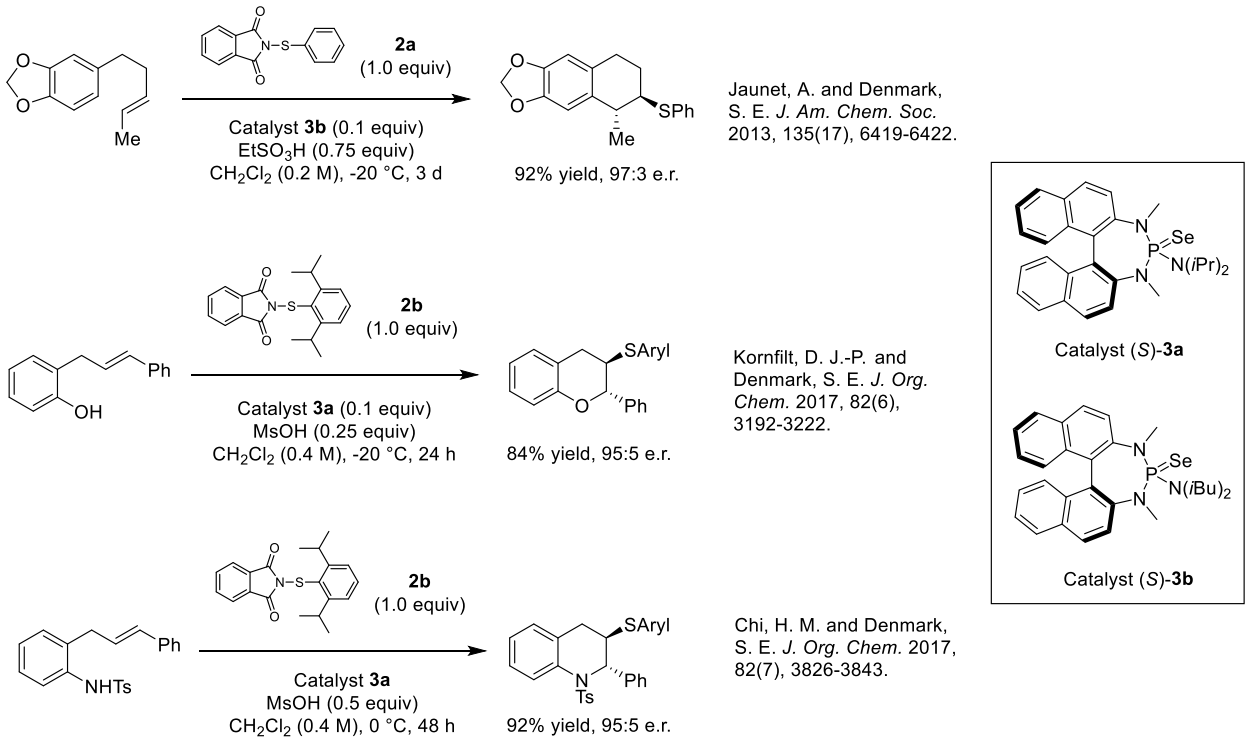


Figure 8. Lewis base (n→σ*) activation of sulfur Lewis acids.

The resulting cationic, donor-acceptor complex is highly electrophilic at the central atom (sulfur) and readily reacts with even relatively poor nucleophiles, such as unactivated alkenes. The Denmark laboratory has applied this method to the enantioselective, *anti*-sulfenofunctionalization of alkenes (Scheme 1). Intramolecular carbosulfenylations[20-21] (Scheme 1a), oxysulfenylations[22-23] (Scheme 1b), and sulfenoaminations[24-25] (Scheme 1c) proceed in good yield with a high degree of stereochemical control.

Scheme 1.



The mechanism of sulfenofunctionalization has been thoroughly investigated,[26-27] and the reactions depicted in Scheme 1 are all proposed to follow the same, general catalytic cycle (Figure 9). With the assistance of a Brønsted acid additive (traditionally, methanesulfonic acid or a closely related species), the interaction between selenophosphoramide catalyst **3a** and sulfenylating agent **2b** forms the cationic, donor-acceptor complex **4** with concomitant ejection of phthalimide. The conversion of **3a** to **4** can be monitored by ^{31}P NMR, and the existence of **4** as a discrete intermediate has been confirmed by X-ray crystallographic evidence. Species **4** is proposed to be the resting state of the catalyst. Nucleophilic attack of an alkene **5** on the electrophilic sulfur atom within **4** generates thiiranium ion **6** in what is proposed to be the rate- and enantio-determining step. This step also regenerates the neutral Lewis base catalyst **3a**, which likely remains coordinated to cationic **6**. Thiiranium **6** is configurationally stable, and undergoes diastereospecific, ring-opening, nucleophilic attack to generate 1,2-*anti*-difunctionalized products **7**. The reaction is first-order in alkene **5** and catalyst **3a**, and is zeroth order in sulfenylating agent **2b**. This kinetic profile is consistent with sulfenyl group transfer from **4** to **5** as the rate-determining

step. Catalyst **3a** affords high enantioselectivities in products **7** derived from *trans*-1,2-disubstituted alkenes **5**, especially when the bulky di-*ortho*-substituted sulfenylating agent **2b** is used. Trisubstituted and terminal alkenes display diminished enantioselectivity, and *cis*-alkenes display dramatically reduced enantioselectivity and rate in sulfenofunctionalization reactions catalyzed by **3a**.

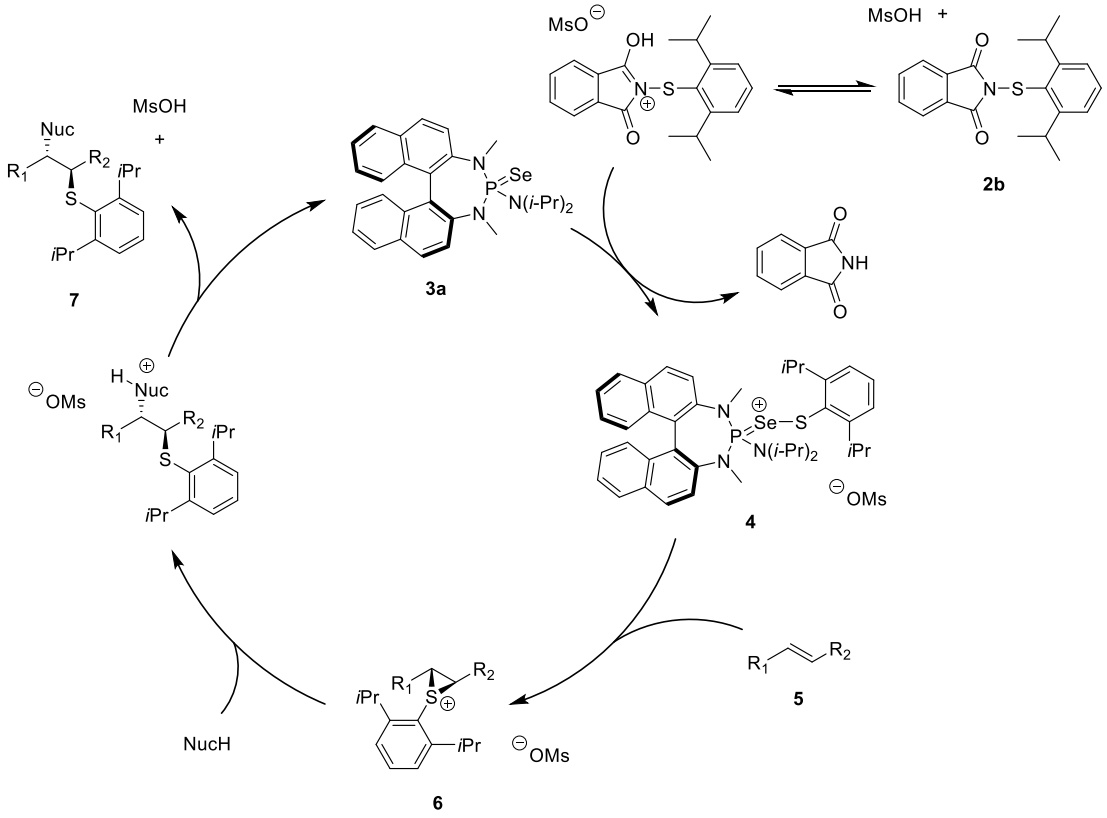


Figure 9. Mechanism of enantioselective, Lewis base-catalyzed, sulfenofunctionalization.

In summary, Lewis base catalysis can be used to enhance either the nucleophilicity or the electrophilicity of a Lewis acidic reactant or reagent. The most common modes of interaction for Lewis base catalyzed processes are the (n→π*) and (n→σ*) interactions. How the (n→σ*) interaction can enhance the electrophilicity of the central atom of a Lewis acid is understood by molecular orbital analysis of the three-center, four-electron (3c, 4e) bond. The Denmark laboratory has developed a number of catalytic, enantioselective methods based on the activation of Group

14, 16, and 17 Lewis acids through (n→σ*) interactions. The activation of Group 16 Lewis acids has been employed for 1,2-sulfenofunctionalization of alkenes with a high degree of stereochemical control.

Chapter 2. Enantioselective, Lewis Base-Catalyzed, Polyene Sulfenocyclization

2.1. Background, Prior State-of-the-Art, Research Objectives

The isolation of complex organic molecules from living organisms is a source of continuing inspiration for synthetic chemists. Steroids (Figure 10) are one such class of molecules which carry biological, chemical, and historical significance. Equilenin **8** (of the estrogen class) and testosterone **9** (of the androstane class) are important human sex hormones. Ethinylestradiol **10**, a synthetic estrogen, is commonly used in oral contraceptive formulations and is one of the most widely prescribed drugs in human history.[28] Cholesterol **11** is an essential component of the lipid cell membrane in animals. These molecules are modified di- or tri-terpenoids which share a similar pattern of fused 6- and 5-membered rings, and contain varying degrees of unsaturation, oxidation, and methylation. Additionally, these molecules share a common biosynthetic precursor, lanosterol **12**, a tetracyclic tri-terpenoid.

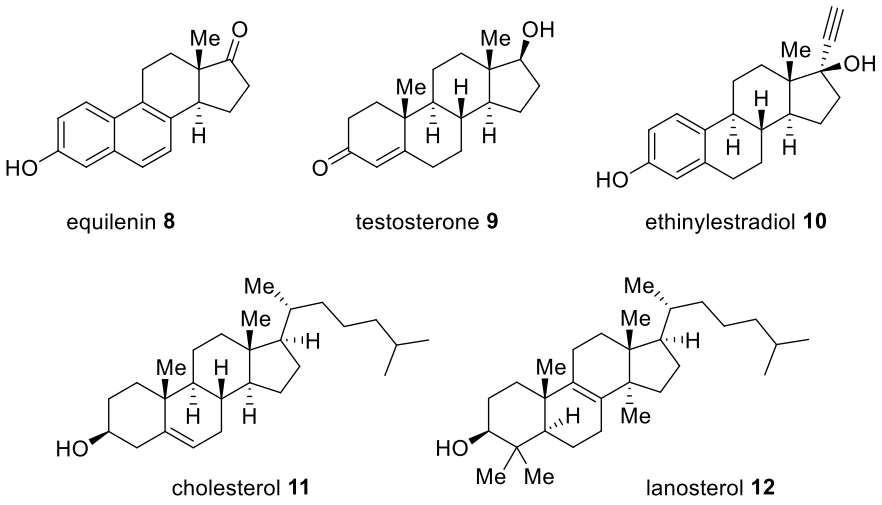


Figure 10. Representative steroid structures.

The origin of the steroid structure was a topic of intense study in the mid-twentieth century. Although Bachmann's laboratory synthesis of equilenin **8** in 1940 was a landmark achievement in organic chemistry,[29] the biosynthesis of steroids had already been proposed to follow a significantly more elegant route. In 1934, Robinson first proposed a conceptual biosynthesis of cholesterol **11** from squalene **13** (Figure 11a), a linear tri-terpene, which proceeded by a series of

trans-annular ring-closing events.[30] A series of metabolic labeling experiments identified squalene **13** as a precursor to cholesterol.[31-32] Once the structure of lanosterol **12** was elucidated,[33] this compound was suggested as a likely intermediate in the conversion of squalene to cholesterol. So compelling were the biosynthetic connections between squalene, lanosterol, and the entire steroid class that in 1953, Ruzicka and his school at the ETH Zürich enunciated the biogenetic isoprenoid rule, which stated that cyclic terpenoids were ultimately derived from 5-carbon isoprenyl building blocks, and not merely represented by them.[34] In light of new evidence obtained from ^{13}C labeling experiments, Bloch and Woodward modified the Robinson hypothesis (Figure 11b), proposing an alternative reactive conformer of squalene **13** which gives rise to lanosterol **12**,[35] a proposal which was ultimately proven to be correct. It would be several decades before the enzymes responsible for these incredible reactions were isolated and characterized.[36]

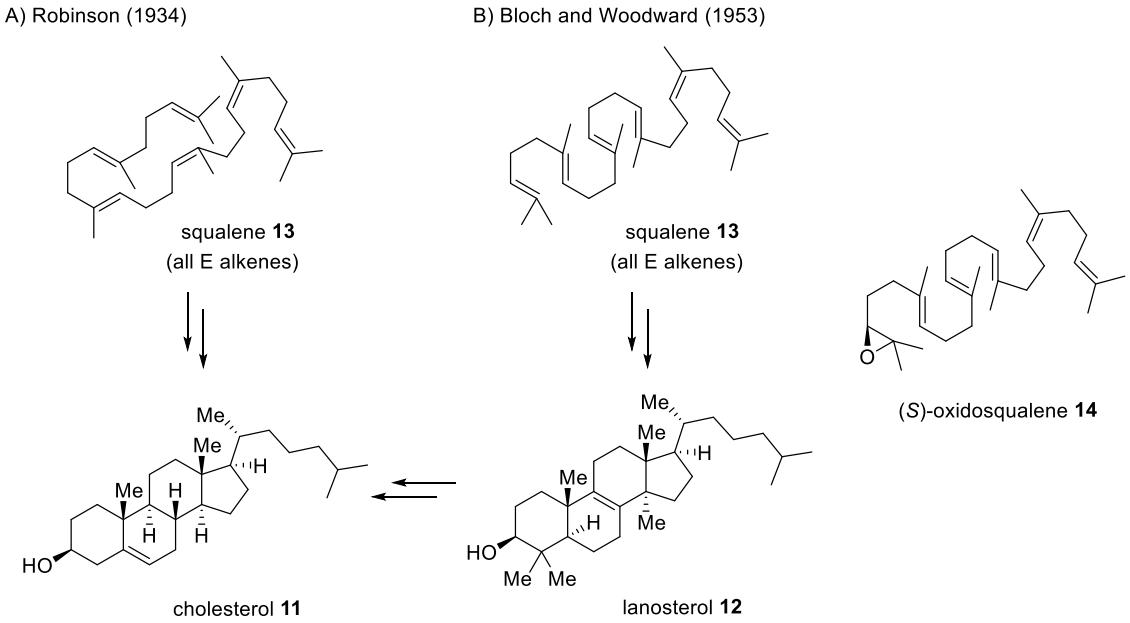


Figure 11. Early proposals for the conformation of squalene prior to polycyclization.

As to the mechanism of the aforementioned *polyene cyclization* reaction, Stork[37] and Eschenmoser[38-39] independently proposed a series of 1,5-diene cationic cyclization events. Stork suggested the addition of "HO^+" across squalene as the initiating event for the cationic cascade process, a hypothesis validated by the identification of (*S*)-oxidosqualene **14** as a discrete

intermediate in this pathway a decade later.[40-41] Conceptually, acid-mediated opening of **14** generates a tertiary carbocation, and subsequent attack by an alkene forges a new carbon-carbon bond and generates a new tertiary carbocation (Figure 12a). The process continues until a terminating event (nucleophilic capture or an elimination event), which, in the case of lanosterol synthesis, is accompanied by several proton and methyl shifts to arrive at the observed structure. Although this stepwise mechanism is sufficient to explain the connectivity in the product framework, it cannot adequately explain the degree of stereo-control observed in the products. Stepwise attack on discreet cationic intermediates could occur from either face. The polycyclization of (*S*)-oxidosqualene **14** to the protolanosterol cation **15** generates seven new stereogenic centers for a total of 128 possible stereoisomers of **15**! In fact, enzymatic polyene cyclizations proceed with high selectivity for a single isomer, and even non-enzymatic reactions on similar substrates (*vide infra*) can display modest to good selectivity. This led the groups of Stork and Eschenmoser to conclude that the cyclization of **14** to **15** proceeds through a concerted mechanism. A chair-boat-chair transition state is required to produce the observed configuration of **15** (Figure 12b). A series of suprafacial proton and methyl shifts followed by elimination converts protolanosterol cation **15** to lanosterol **12**. The chair-chair-chair transition state (Figure 12c) leads to the stereoisomeric dammarenyl cation **16** which is also observed in nature. Different cyclase enzymes lead to different products, depending on their ability to stabilize the two transition states. In fact, negatively-charged residues in cyclase enzymes help stabilize the cationic intermediate, and the location and direction of these "point charges" are what influence the stereoselectivity of cyclization. The point charge theory was first proposed by W. S. Johnson[42-43] and later supported by numerous site-directed mutagenesis studies.

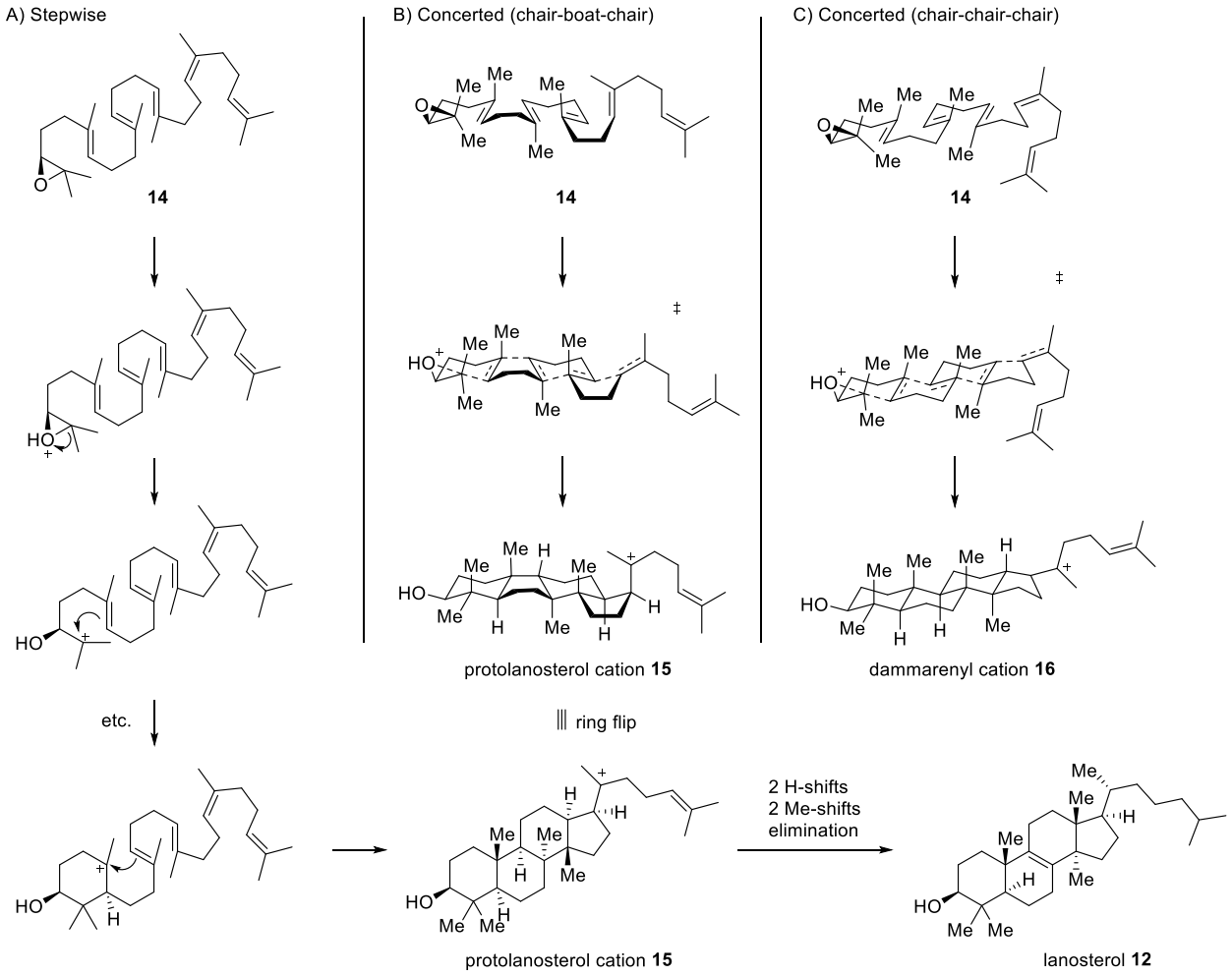


Figure 12. Stereochemistry of polyene cyclization: the Stork-Eschenmoser hypothesis.

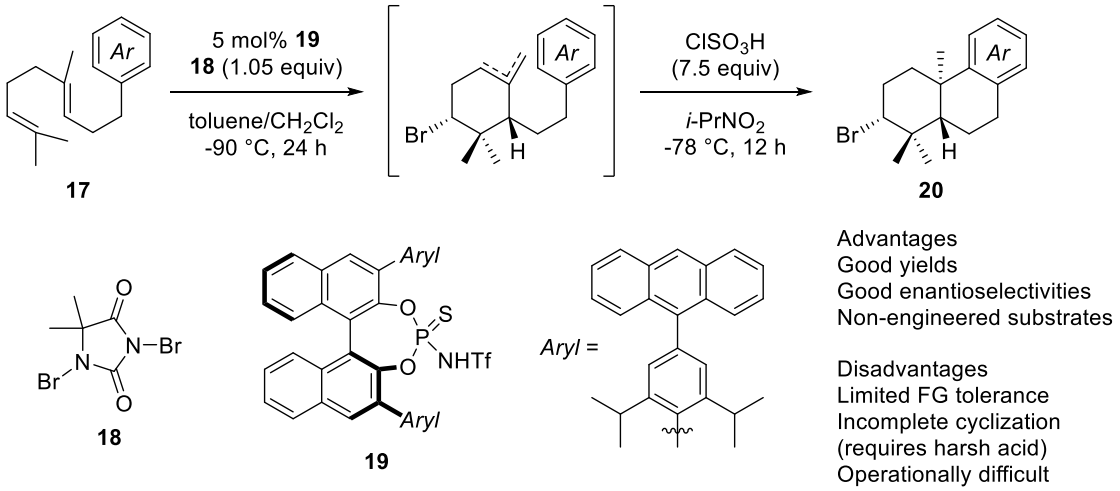
It follows from the Stork-Eschenmoser hypothesis that in the absence of enzymes, the "all-chair" transition state for acid-mediated polyene cyclization would be inherently lowest in energy, and the major product would contain all *trans*-decalin ring fusions. This hypothesis was the basis for the pioneering works of W. S. Johnson[44-45] and E. E. van Tamelen,[46] who first demonstrated polyene cyclizations under solely chemical conditions. These non-enzymatic polyene cyclizations still proceed with high diastereoselectivity and modest to good yields, affording products predicted by the Stork-Eschenmoser hypothesis. Almost immediately after its discovery, non-enzymatic polyene cyclization became a workhorse strategy for the total synthesis of natural products.[47] Starting from a linear starting material containing, in most cases, a single stereogenic center,

multiple rings and additional stereogenic centers can be constructed in a single chemical step with high diastereoselectivity and in a highly predictable fashion. Often, the pre-installed stereogenic center arises from an enantioselective epoxidation, dihydroxylation, or other such reliable methods. This is true for the enzymatic case as well, in which squalene **13** is first epoxidized to (*S*)-oxidosqualene **14** prior to a highly diastereoselective cyclization catalyzed by oxidosqualene cyclase.[40-41]

By contrast, enantioselective polyene cyclizations of substrates lacking any pre-existing stereogenic centers are more desirable from the standpoint of synthetic efficiency, but these methods are less well-developed. A seminal report by Yamamoto and co-workers in 1999 employed a Lewis acid-activated, chiral Brønsted acid (LBA) system for enantioselective, proton-initiation polycyclization of dienes and trienes.[48] Mostly good yields and diastereomeric ratios were obtained, although the observed enantioselectivities were modest and the reaction required a stoichiometric amount of the chiral promoter. Following this initial report, several additional methods for enantioselective, proton-initiated polycyclization employing stoichiometric amounts of chiral acids were disclosed by the groups of Yamamoto, Ishihara, and Loh. Catalytic, enantioselective variants soon followed from Yamamoto and others, but these early examples required very high catalyst loadings. These pioneering works have been thoroughly reviewed elsewhere[49] and are not the primary focus of this section. Within the last decade, truly catalytic, enantioselective methods for polyene cyclization have finally been realized, and these are critically analyzed in the following paragraphs.

In 2017, Yamamoto and co-workers disclosed a catalytic, enantioselective bromocyclization of homogeranylarenes **17** (Scheme 2).[50] Activation of electrophilic bromine reagent **18** with Lewis basic catalyst **19** generates a chiral "Br^+" species which reacts with the substrate alkene. The subsequent bromonium-opening cascade reaction affords products **20** in generally good yields and good enantioselectivities (~90:10 e.r.). Very low temperature (–90 °C) is required, presumably to bias the site selectivity of bromonium ion formation. The bromination is complete within 24 h but affords a mixture of fully cyclized and partially cyclized products. The addition of chlorosulfonic acid (after a solvent swap to 2-nitropropane) forces the reaction to completion within 12 h, again at cryogenic temperatures. This protocol is somewhat cumbersome, but the real drawback is the requirement for harsh acid to force the final ring closure, which severely limits the functional group tolerance of the reaction.

Scheme 2.



A major advantage of Yamamoto's method is the ability to use "non-engineered" substrates (Figure 13). In this document, "non-engineered" refers to polyene substrates containing a geranyl (or farnesyl) chain composed of repeating five-carbon isoprenyl subunits. Non-engineered substrates do not contain special functional groups at the site of initiation, though they may contain diverse terminating groups, such as functionalized arenes. The benefits of using non-engineered substrates are two-fold. First, they are easy to prepare because they are derived from abundant, naturally-occurring geraniol and farnesol. For example, compounds **17** are prepared in one step by the reaction of inexpensive geranyl acetate with benzylic Grignard reagents (see Section 2.2). Secondly, the polycyclization products of **17** are more useful as intermediates *en route* to natural products, because they already contain the correct A-ring substitution pattern. The bioactive natural products shown in Figure 13 all bear geminal dimethyl groups at the C(1) position. Additionally, many of these compounds are also functionalized at the C(2) position. Methods which initiate a cationic cascade by reacting the *gem*-dimethylated olefin of **17** with "X^+" (where $X \neq H$) ultimately lead to products bearing a functional group handle at the C(2) position, so such methods are therefore quite valuable. Of course, developing methods capable of using non-engineered substrates is quite challenging, because of the requirement for differentiation of two (or more) alkenes with nearly identical steric and electronic properties. Using engineered substrates avoids this problem, and also expands the scope of initiation modes beyond generation

of carbenium ions. As a result, most modern methods of catalytic, enantioselective polyene cyclization utilize engineered substrates (*vide infra*). The substrates require extra synthetic overhead to access, and they lead to products lacking proper A-ring functionality, so further derivatization to desirable natural products requires many chemical steps, or is not possible.

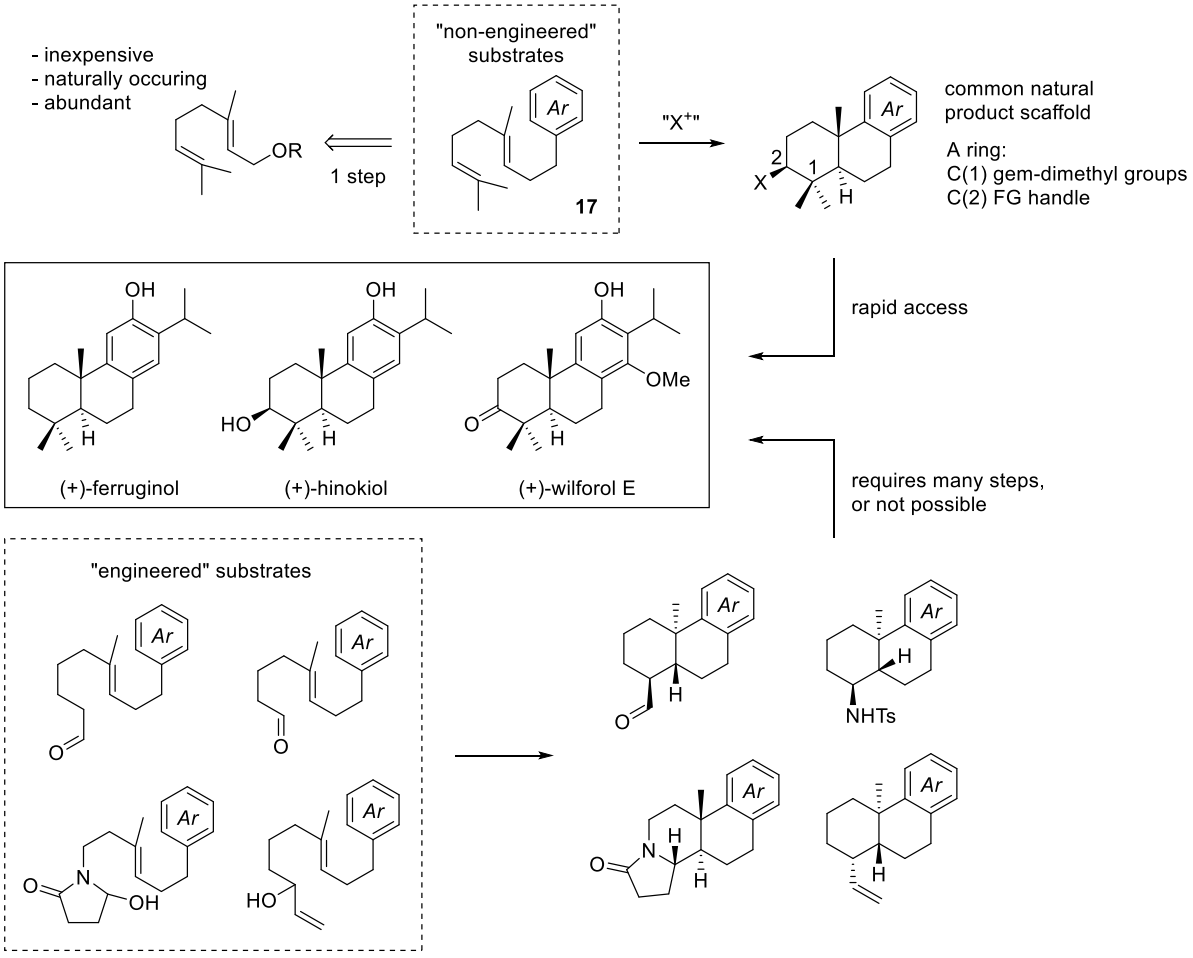
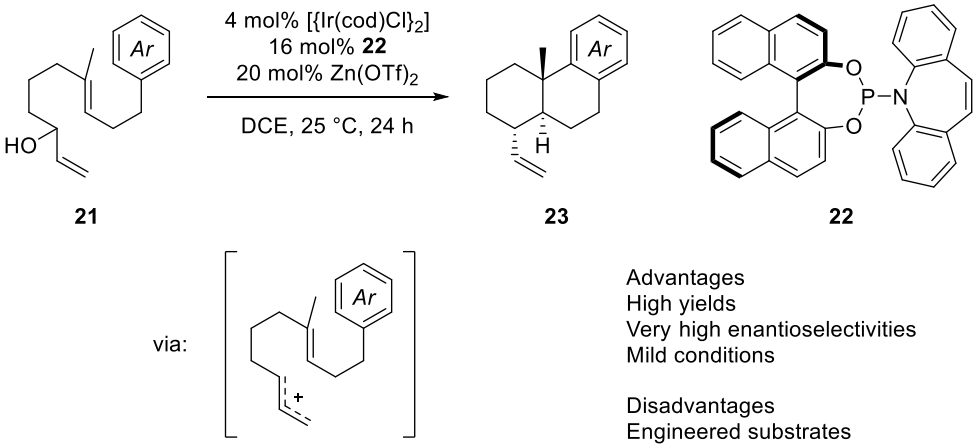


Figure 13. Engineered vs. non-engineered substrates for polyene cyclization.

Carreira and co-workers have reported a catalytic, enantioselective polycyclization of allylic alcohols **21** initiated by a cationic, π-allyl-iridium complex (Scheme 3).[51] Employing a chiral phosphoramidite ligand **22** leads to products **23** with exquisite enantioselectivities (>99:1 in all cases). The reaction proceeds under mild conditions, and longer chain polyenes were also competent substrates (although delayed introduction of strong acid was required to reach full

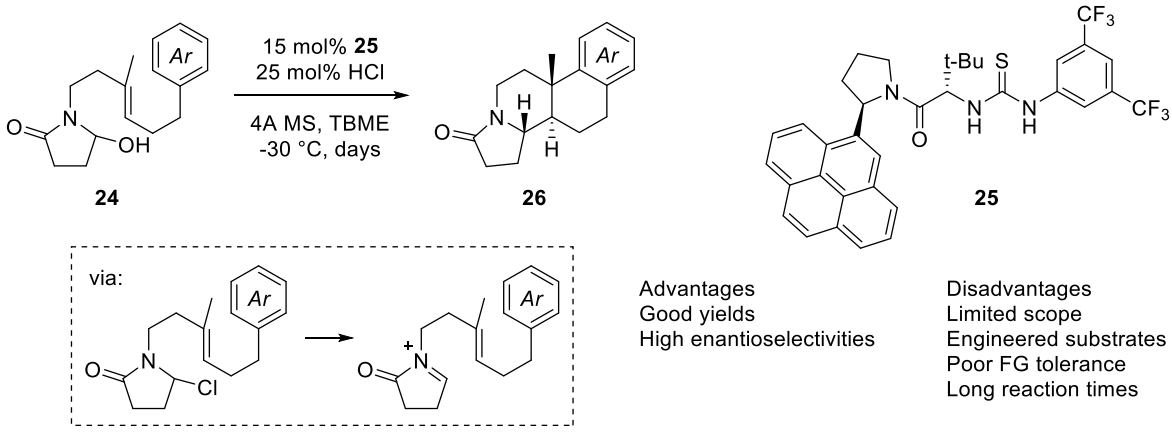
conversion to fully cyclized product). This method does introduce a stereodefined vinyl group at the C(1) position of the A-ring as a locus for further functionalization, although several chemical steps would be required to access any of the natural products shown in Figure 13.

Scheme 3.



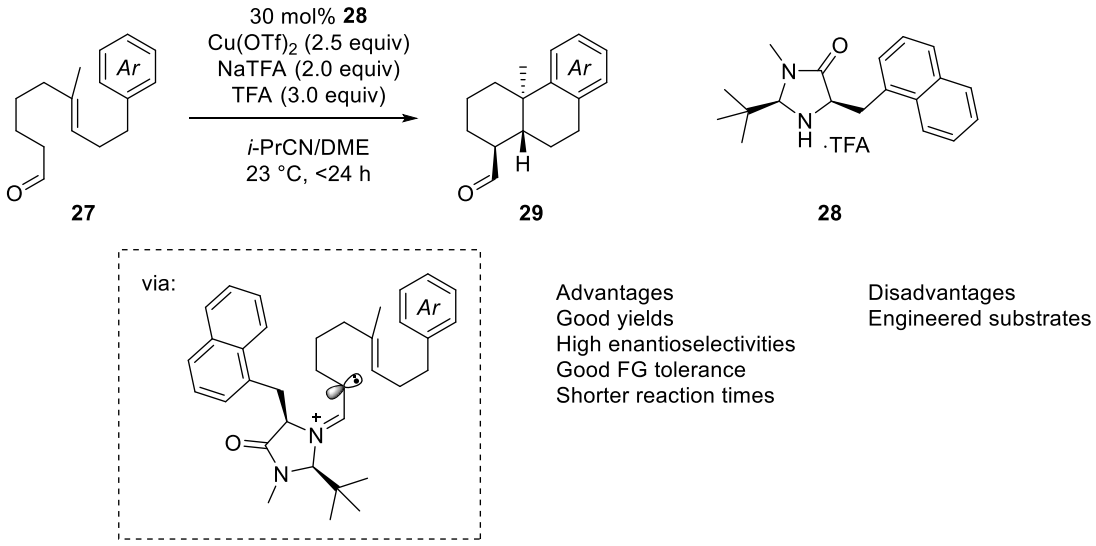
Jacobsen and co-workers have reported an organocatalyzed, enantioselective polycyclization of hydroxylactam-derived substrates **24** (Scheme 4).[52] Ionization of a transient chlorolactam intermediate, through the action of hydrogen-bonding thiourea catalyst **25**, generates an *N*-acyliminium ion, which serves as the initiating species for cascade cyclization. High enantioselectivities result from cation-π interactions between the ionized polyene and the extended aromatic surfaces of the catalyst. The reaction proceeds in good yields and enantioselectivities to form products **26**. Drawbacks include long reaction times (minimum of 3 days), limited functional group tolerance (due to requirement for HCl additive), and the necessity to use engineered substrates **24** (leading to products **26** which do not map onto common natural product cores).

Scheme 4.



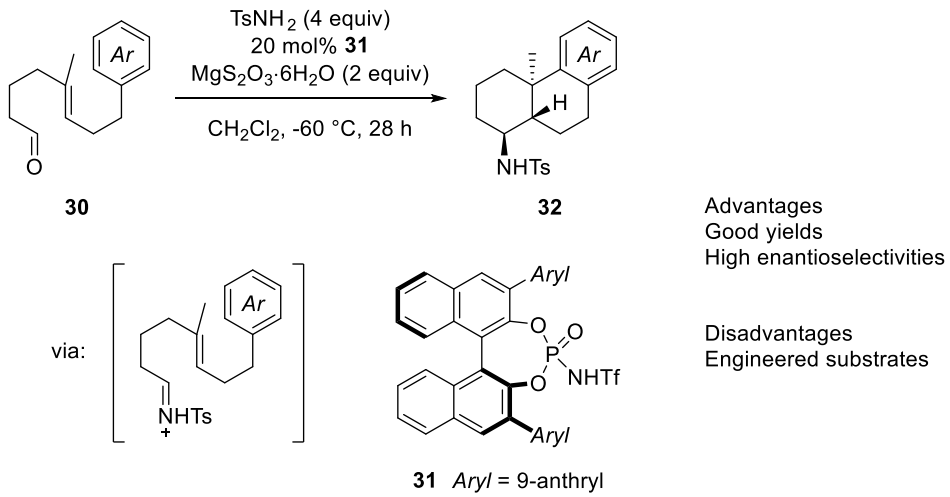
Contemporaneously, MacMillan and co-workers also reported an organocatalyzed, enantioselective polycyclization of aldehydes **27** (Scheme 5).[53] The reaction proceeds through one-electron oxidation of a chiral, *in situ* generated iminium ion to form a radical cation intermediate. Subsequent radical cascade polycyclization and one-electron oxidation afforded products **29**. This singly-occupied molecular orbital (SOMO) activation strategy proved highly effective. Good yields and high enantioselectivities were observed, using milder conditions than those required for the Jacobsen method. Additionally, MacMillan extended the reaction scope beyond bicyclizations to include tri-, tetra-, penta-, and even hexacyclizations. These striking examples required nitrile-substituted polyenes to stabilize the radical intermediate, so the products are of limited utility in the context of natural product synthesis. In all cases, products **29** would require significant manipulation of the A-ring in order to access any of the compounds shown in Figure 13.

Scheme 5.



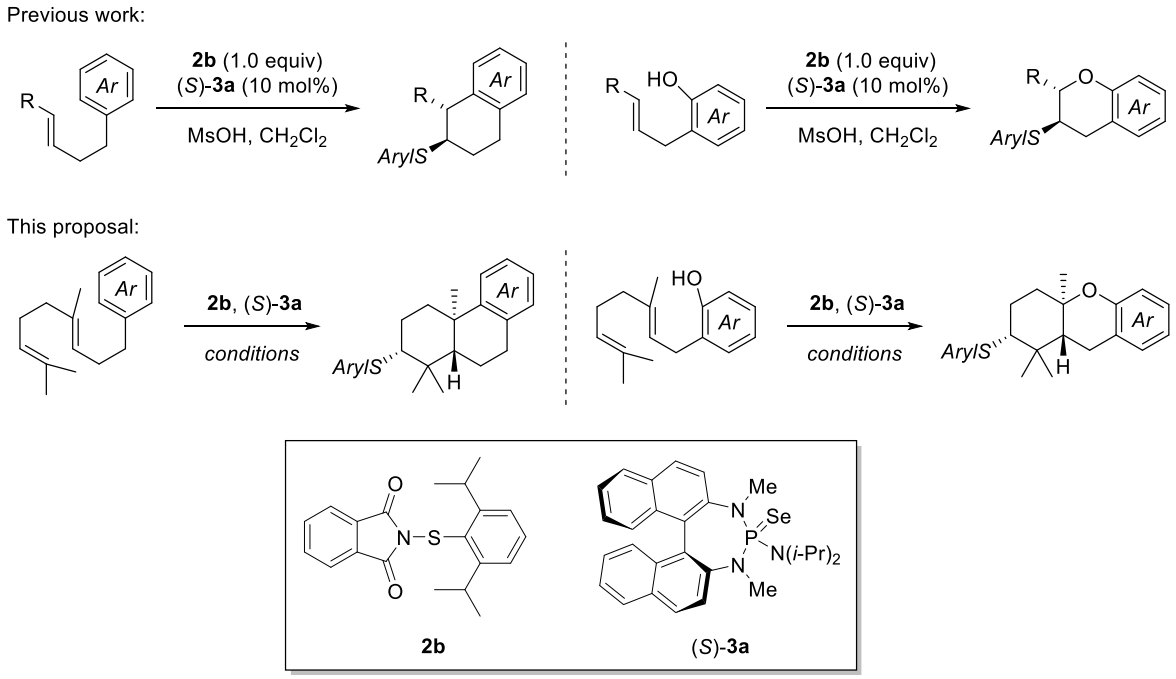
Zhao and co-workers have recently reported a catalytic, enantioselective polycyclization of aldehydes **30** which is initiated by acid-catalyzed *in situ* iminium ion formation (Scheme 6).[54] Employing the chiral Brønsted acid catalyst **31** leads to the isolation of polycyclic amines **32** in high enantioselectivity and good yield. This method also uses engineered substrates, although the authors did demonstrate the total synthesis of (–)-ferruginol in eight steps post-cyclization. Included in this lengthy (albeit robust) sequence is the stereo-ablative conversion of a secondary amine to an all-carbon quaternary center. This is illustrative of the potential challenges faced when using cyclization products of engineered substrates as intermediates for natural product syntheses.

Scheme 6.



As outlined in the examples above, several modern methods exist for non-enzymatic, catalytic, enantioselective polyene cyclization, each with its advantages and disadvantages. Given the ubiquitous application of polyene cyclization to the total synthesis of complex molecules, the organic chemistry community would benefit from a new, complementary method, particularly one which could utilize non-engineered substrates. The Denmark laboratory has developed an efficient system for sulfenofunctionalization of olefins with a high degree of stereochemical control (see Chapter 1). Activation of a sulfenyl transfer reagent with a chiral, Lewis basic catalyst generates a chiral sulfenium ion source which converts simple olefins to enantiomerically enriched thiiranium ions. It was hypothesized that this process could serve as an initiation event for a catalytic, enantioselective, polyene sulfenocyclization, which would be a logical extension of the oxy- and carbo-sulfenylation processes previously demonstrated (Scheme 7). Polyene sulfenocyclization was previously accomplished in racemic form by Livinghouse[55] and also by Shaw,[56] who employed Lewis acids to activate sulfenyl transfer reagents. Additionally, Snyder and co-workers have reported the use of pre-formed, alkyldisulfonium ion salts to initiate polyene cyclizations.[57-58] Given this precedent, the development of an enantioselective polyene cyclization employing the Denmark catalyst system for electrophilic sulfur delivery seemed to be a reasonable prospect.

Scheme 7.



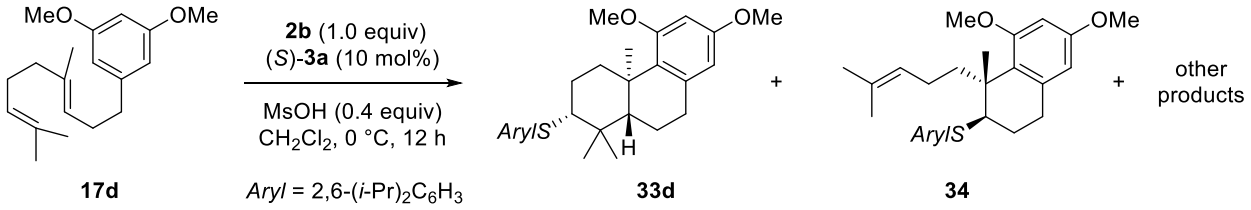
The research objectives for this project are summarized as follows: (1) demonstration of a catalytic, enantioselective sulfenocyclization of polyenes characterized by (a) good yields, (b) good enantioselectivities, (c) broad functional group tolerance, (d) operational simplicity and mild conditions, and (e) applicability toward non-engineered substrates; (2) demonstration of robust procedures for conversion of the newly-installed sulfenyl group to useful carbon and oxygen functionality; (3) extension of the method to longer-chain trienes and tetraenes; and (4) interrogation of the reaction mechanism and rate-determining step through kinetic studies.

2.2. Development and Scope

For the proposed method to be compatible with non-engineered substrates, the catalyst system must be able to differentiate between alkenes with very similar steric and electronic properties. This aspect was anticipated to be one of the more challenging parts of the project, and indeed, preliminary attempts at sulfenocyclization of **17d** under standard conditions (1.0 equiv **2b**, 10 mol% (*S*)-**3a**, 0.4 equiv of mesic acid, 0.1 M in CH_2Cl_2) afforded complex product mixtures, owing in large part to poor site selectivity for thiiranium generation (Scheme 8).[59-60] A small

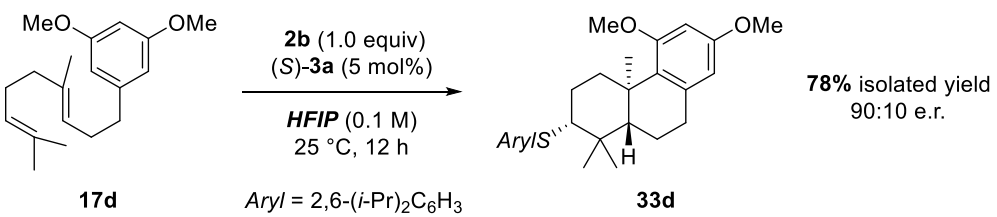
quantity of desired product **33d** and undesired isomer **34** could be isolated from the product mixtures in a roughly 2:1 ratio. Encouragingly, enantiomeric ratios of 90:10 or slightly better were consistently observed for isolated **33d**.

Scheme 8.



The relative lack of chemoselectivity was not unexpected, as the two alkenes are sterically and electronically similar. Mostly similar results were observed under a variety of reaction conditions, until an extensive solvent survey identified 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HFIP) as a highly effective medium for this transformation.[59] Remarkably, sulfenocyclization of **17d** in HFIP improved the site selectivity from 2:1 to approximately 10:1 and cleanly afforded desired **33d** as the major product in good yield (Scheme 9). Just prior to the publication of this work, Gulder and co-workers also described the beneficial effect of HFIP on site selectivity in the racemic bromocyclization of dienes **17**.[61] Previously, Qu and co-workers disclosed a cyclization of epoxy-polyenes in HFIP containing a high concentration of dissolved salt.[62] Although in this case the site of initiation is already defined, it is still notable that good yields are observed for cyclization of longer-chain epoxy-polyenes in this highly polar reaction medium, even in the absence of any organizing interactions between the substrate and reagents (see Section 2.1).

Scheme 9.



The beneficial effect of HFIP on site selectivity in these polyene cyclizations may be attributed to solvophobic interactions. Neat HFIP forms extensive hydrogen-bonded networks in the liquid phase. In this polar medium, it is hypothesized that lipophilic polyene substrates **17** adopt a folded conformation which minimize disruptions to the solvent hydrogen-bonding network.[63] In this "foldamer" the distal alkene is more accessible to the catalyst system than the internal alkene. Therefore, the alkenes are differentiated in a manner which does not rely on inherent steric or electronic properties. Additionally, the strongly polar HFIP provides stabilization for the reactive cationic intermediate, which helps mitigate undesired side reactions.[61] For the sulfenocyclization chemistry, an additional benefit of HFIP is its acidity (pK_a = 9),[64] which obviates the need for mesic acid to generate a donor-acceptor complex and enables broader functional group tolerance.

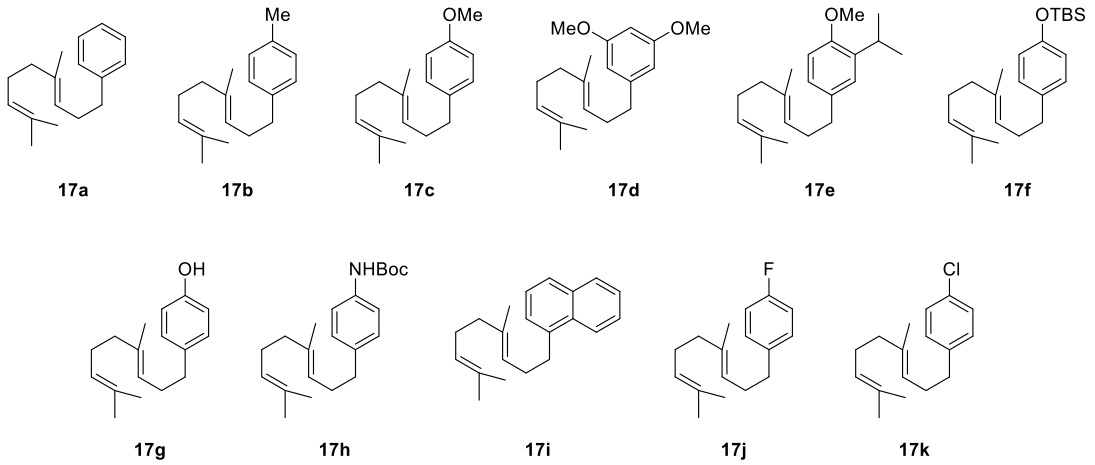
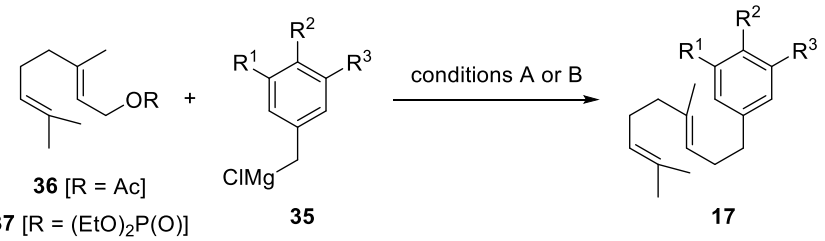


Figure 14. Substrates examined in catalytic, enantioselective polyene sulfenocyclization.

The next stage in the study involved a thorough investigation of substrate scope. Homogeranylarenes **17** bearing diverse electron-donating and electron-withdrawing groups were selected for initial study (Figure 14). In keeping with one of the original project goals, substrates **17** are non-engineered. As such, they are rapidly accessed from abundant, inexpensive geraniol derivatives. Coupling an appropriate benzylic Grignard reagent **35** with geranyl acetate **36** or geranyl diethyl phosphate **37** afforded most substrates **17** in high yield (Table 1). Substrates **17a** through **17e**, as well as **17j** and **17k**, were prepared using this method.

Table 1. Preparation of substrates **17**.



36 [R = Ac]
37 [R = $(EtO)_2P(O)$]

35

17

entry	reagent	R_1	R_2	R_3	conditions	product	yield of **10**
1	**35a**	H	H	H	A	**17a**	98%
2	**35b**	H	Me	H	A	**17b**	80%
3	**35c**	H	MeO	H	A	**17c**	95%
4	**35d**	MeO	H	MeO	A	**17d**	74%
5	**35e**	H	MeO	i-Pr	A	**17e**	87%
6	**35j**	H	F	H	B	**17j**	75%
7	**35k**	H	Cl	H	B	**17k**	20%*

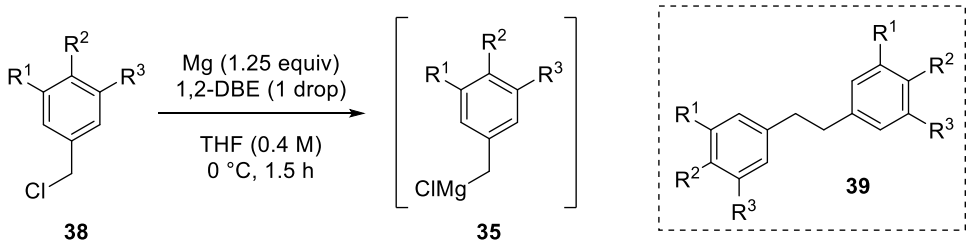
* Low yield due to sacrificial chromatographic separation from **39k.**
Actual yield estimated from 1H NMR of crude mixture = 73%.

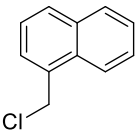
Conditions A:
36 (1.0 equiv), **35** (1.1 equiv), Li_2CuCl_4 (0.1 equiv), THF (0.2 M), -10 °C to 25 °C, 4 h

Conditions B:
37 (1.0 equiv), **35** (2.0 equiv), THF (0.25 M), -40 °C to 25 °C, 4 h

Of the Grignard reagents required to synthesize the compounds in Table 1, only the parent benzylmagnesium chloride **35a** is commercially available. The others were freshly prepared prior to use. The reliable preparation of benzylic Grignard reagents is non-trivial, as these species are prone to homocoupling to form bis(aryl)ethanes **39**.[65] In the optimized preparations of **35** (Table 2), only benzyl chlorides **38** (not bromides) were used, and the entire addition was performed below 5 °C (for electron-rich benzyl chlorides **38b** through **38e**) or below 30 °C (for electron-deficient benzyl chlorides **38j** and **38k**). Even with these optimized procedures, multiple challenges were encountered. Silyl ether-containing benzyl chloride **38f** failed to initiate Grignard formation under a variety of conditions. An increased amount of bis(aryl)ethane by-product **39k** was observed in the generation of reagent **35k**. All attempts to generate 1-(naphthyl)methylmagnesium chloride **35i** under these conditions resulted exclusively in dimerization to **39i**. Additionally, **35g** and **35h** were not expected to be stable Grignard reagents owing to functional group incompatibilities. Therefore, alternative routes were taken to access polyenes **17f** through **17i**.

Table 2. Reliable preparation of benzylic Grignard reagents **35**.



benzyl chloride	R_1	R_2	R_3	conditions	Grignard reagent	yield of **30***
38b	H	Me	H	A	**35b**	90%
38c	H	MeO	H	A	**35c**	73%
38e	H	MeO	*i*-Pr	A	**35e**	83%
38f	H	TBSO	H	A	**35f**	0%**
				B		0%**
38j	H	F	H	C	**35j**	82%
38k	H	Cl	H	C	**35k**	35%
38i				C		0%***
				D	**35i**	0%***

Conditions A:
Mg (1.25 equiv), 1,2-DBE (1 drop), THF (0.4 M), 0 °C, 1.5 h

Conditions B:
Mg (1.25 equiv), 1,2-DBE (1 drop), THF (0.5 M), sonication, 25 °C to 50 °C, 30 min

Conditions C:
Mg (6 equiv), THF (0.8 M), 25-30 °C, 1.5 h

Conditions D:
Mg (2 equiv), THF (0.4 M), 25 °C to 0 °C, 1.5 h

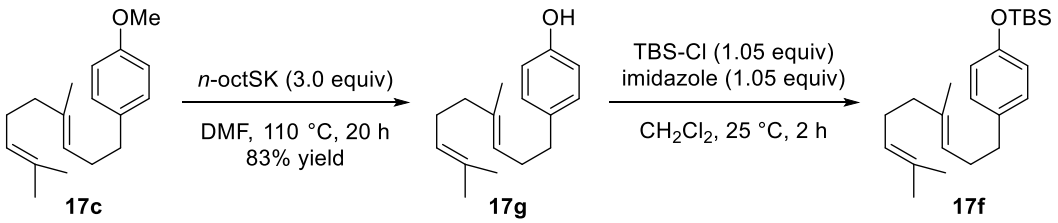
* Determined by titration against 1.0 M *sec*-butanol in xylenes with 1,10-phenanthroline as indicator.

** No initiation observed.

*** Only **39i** observed.

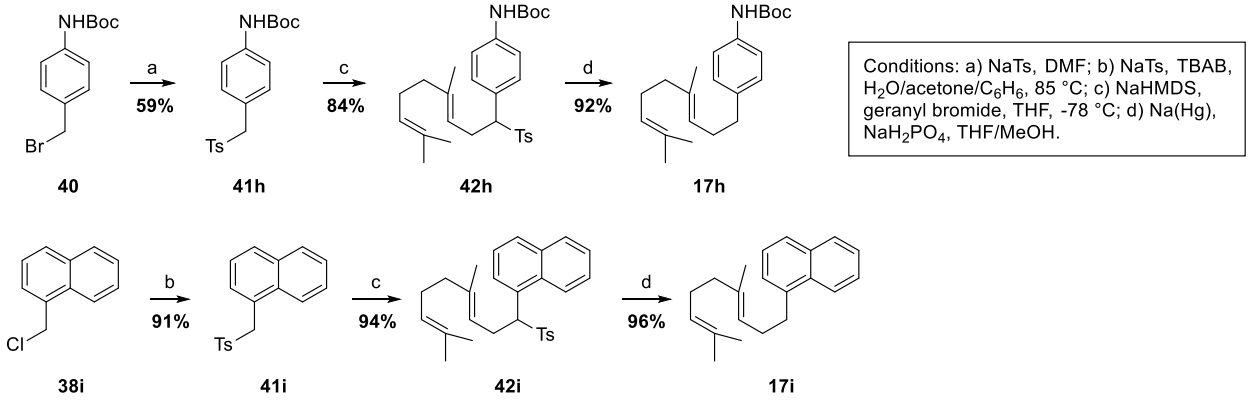
Phenol **17g** was conveniently accessed by octanethiolate-mediated demethylation of **17c** which was already on hand (Scheme 10). This protocol is preferred to the ethanethiolate-mediated method, as the longer-chain alkylthiols are significantly less malodorous. Silylation of **17g** under standard conditions afforded **17f**.

Scheme 10.



Finally, compounds **17h** and **17i** were accessed by the robust, three-step protocol outlined in Scheme 11. Displacement of benzyl bromide **40** or benzyl chloride **38i** with sodium 4-toluenesulfinate afforded sulfones **41** in good yield. Alkylation of the sodium salts (from treatment of **41** with sodium hexamethyldisilazide) with geranyl bromide afforded **42**, and reductive C–S cleavage afforded the desired polyenes **17h** and **17i**. This sequence has proven to be fairly general in cases in which preparation of a benzylic Grignard reagent is unsuccessful for whatever reason (see Section 2.4).

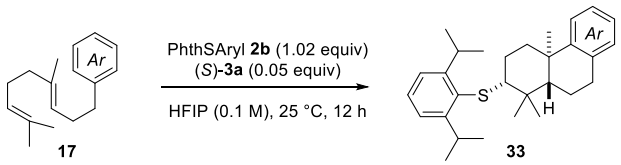
Scheme 11.



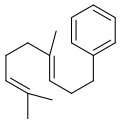
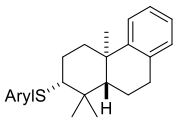
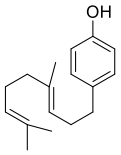
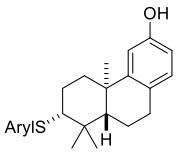
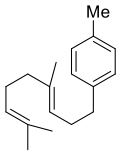
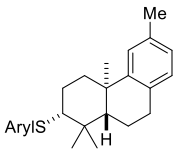
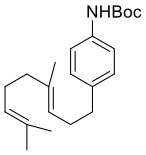
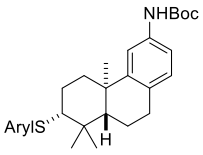
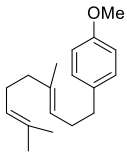
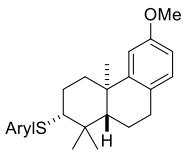
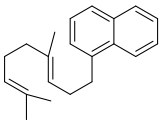
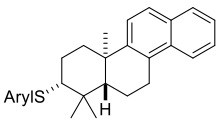
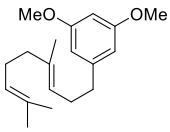
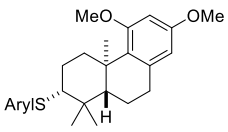
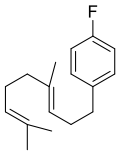
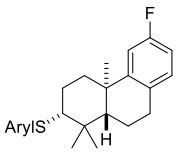
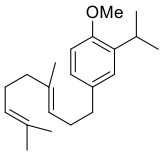
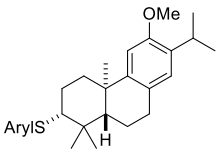
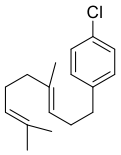
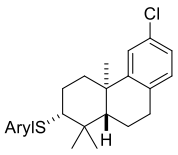
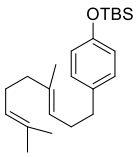
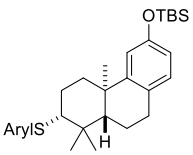
Most of the homogeranylarenes **17** underwent sulfenocyclization to afford products **33** in good yield and enantioselectivities (Table 3). In addition to the parent homogeranylbenzene **17a**, all substrates bearing at least one electron-donating substituent were competent. Certain entries merit special discussion. Sulfenocyclization of **17e** was desirable because the resulting tricycle **33e** is a late-stage intermediate for the total synthesis of two natural products (*vide infra*). Although two constitutional isomers were possible from the reaction of **17e**, which bears an unsymmetrically substituted arene, only a single isomer was observed (probably influenced by the steric bulk of the isopropyl group) in 68% yield and 92:8 e.r. In addition to silyl-protected phenol **17f**, free phenol **17g** also cyclized efficiently, albeit in more modest yield. The sulfenocyclization of *N*-Boc aniline **17h** is notable for two reasons. Not only is this the first example of a nitrogen-substituted terminal arene in an enantioselective polyene cyclization, but it also highlights tolerance of a functional group which is incompatible with mesic acid required for previous sulfenofunctionalization

methods. Using HFIP as a reaction solvent for sulfenofunctionalization chemistry has removed the need for mesic acid, allowing for an expansion of scope to include more acid-sensitive functional groups. Electron-poor substrates **17j** and **17k** did not cyclize efficiently and resulted in complex product mixtures. In the absence of a strong terminal nucleophile, the HFIP anion (hexafluoroisopropyl alkoxide) is known to intercept thiiranium ions[66-67] and other cationic intermediates.[68-69] This pathway is likely the case here, although the complexity of the ^{1}H NMR spectrum of the crude reaction mixtures obfuscates the analysis. The complete failure of **17j** and **17k** to react productively was a bit surprising, given that halogen-substituted arenes are competent terminal nucleophiles for other enantioselective polyene cyclizations in the literature. The position of substituents (*meta* vs. *para*) relative to the site of C-capture likely has a strong influence on the reaction outcome. This phenomenon is explored in more detail in Section 2.3. In addition to homogeranylarenes, 2-geranylphenols are also competent substrates, affording benzo-fused dihydropyran scaffolds as a result of O-capture rather than C-capture. Owing to the increased nucleophilicity of phenols relative to arenes, electron-withdrawing aromatic substituents were tolerated in addition to electron-donating substituents. Again, good yields and enantioselectivities were observed. Full details can be found in the manuscript.[70]

Table 3. Results for catalytic, enantioselective sulfenocyclization of homogeranylarenes.

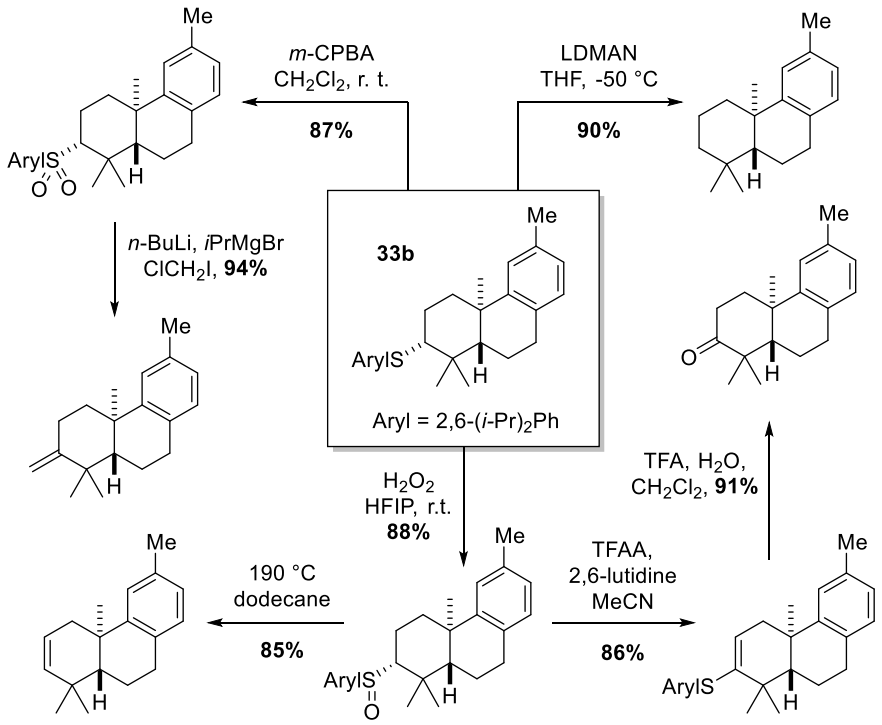


17 **33**

entry	substrate	product	yield (%)	e.r.	entry	substrate	product	yield (%)	e.r.
1	 **17a**	 **33a**	60%	90:10	7	 **17g**	 **33g**	50%	91:9
2	 **17b**	 **33b**	60%	90:10	8	 **17h**	 **33h**	78%	92:8
3	 **17c**	 **33c**	59%	92:8	9	 **17i**	 **33i**	59%	92:8
4	 **17d**	 **33d**	78%	90:10	10	 **17j**	 **33j**	n.d.	n.d.
5	 **17e**	 **33e**	68%	92:8	11	 **17k**	 **33k**	n.d.	n.d.
6	 **17f**	 **33f**	71%	93:7					

Employing the bulky sulfenylating agent **2b** afforded products **33** in good chemo- and enantio-selectivity. Indeed, **2b** is the optimal reagent for most alkene thiofunctionalization reactions catalyzed by (*S*)-**3a**, typically resulting in excellent enantioselectivities (>95:5) for reactions of *trans*-disubstituted alkene substrates. Nonetheless, the (2,6-diisopropyl)phenyl thioether motif is rarely (never) present in natural product targets or pharmaceutically relevant molecules, so the requirement to install this particular group in all products **33** represented a major limitation to an otherwise useful method. As such, a campaign was undertaken to diversify the products **33**, using the thioether moiety as precursor. In spite of the sterically crowded environment, the sulfide was readily transformed to carbon and oxygen functionality by oxidative, reductive, and isohypsic processes (Scheme 12). These transformations are described in detail in the corresponding manuscript,[70] but they are briefly illustrated here in the context of two total syntheses of natural products.

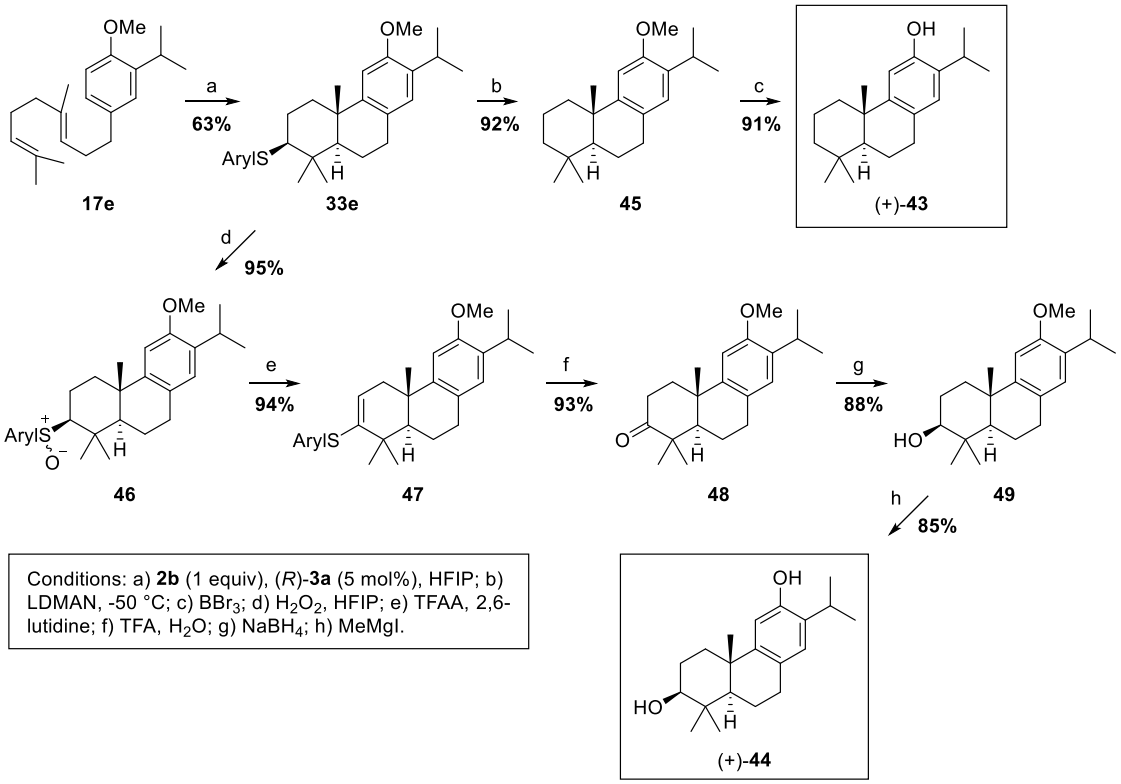
Scheme 12.



The tricyclic diterpenoids (+)-ferruginol **43** and (+)-hinokiol **44** were selected as synthetic targets. Both possess anti-fungal and anti-bacterial properties, and they have been isolated from

numerous plant species around the world.[71-72] Despite their abundance, isolation of **43** and **44** from natural sources is not trivial, and they have often been obtained as mixtures with other, structurally similar diterpenoids. Therefore, concise laboratory syntheses of **43** and **44** are desirable. While several syntheses of (+)-**43** have been reported, most of these utilize chiral pool staring materials, which may themselves be challenging to isolate. Additionally, the only reported total synthesis of (+)-**44** also begins from chiral pool starting material.[73] More ideal routes to these compounds would proceed by cyclization of an easily accessed polyolefinic compound. Tada et al. achieved a diastereoselective polyene cyclization in a key step of their synthesis of (+)-**43**.[74] Shortly before the present work was submitted, Zhao and co-workers published a highly enantioselective, Brønsted acid-catalyzed polyene cyclization initiated by iminium ion generation (see Scheme 6).[54] Within this work was the demonstration of an enantioselective total synthesis of non-natural (–)-**43**. As a consequence of the unique initiating group, the geminal dimethyl groups had to be installed post-cyclization which required a significant amount of laborious functional group interconversion (FGI). By contrast, a catalytic, enantioselective method which employs non-engineered, isoprene-derived substrates would require significantly less FGI post-cyclization, which is emphasized in the synthesis of (+)-**43** presented below (Scheme 13).

Scheme 13.



In the retrosynthetic analysis of (+)-**43** and (+)-**44**, compound (+)-**33e** was identified as a common intermediate. This tricycle was accessed from diene **17e** with the method previously described (Table 3), using the (*R*)-enantiomer of catalyst **3a** to obtain the correct absolute configuration of the product. The polyene sulfenocyclization was performed on a gram scale (greater than 3.0 mmol) with no appreciable decrease in yield, enantioselectivity, or isomeric purity relative to the smaller scale reaction. Reductive C–S cleavage of **33e** with lithium *N*,*N*-dimethylamino-1-naphthalenide (LDMAN) afforded compound **45** in 92% yield. Many one-electron reducing agents can achieve this transformation. The advantage of using LDMAN is the ease of removing this reagent from the product mixture with an aqueous acidic workup.[75] Subsequent demethylation of **45** using boron tribromide afforded the natural product (+)-**43** in 91% yield. The total synthesis of (+)-ferruginol from linear polyene **17e** was accomplished in just three steps and 53% overall yield.

To access (+)-**44**, common intermediate **33e** was first oxidized to sulfoxide **46** in 95% yield using hydrogen peroxide in HFIP.[76] These conditions reliably convert sulfides to sulfoxides without over-oxidation to sulfones. Unsurprisingly, a mixture of sulfoxide diastereomers was observed. Upon treatment with trifluoroacetic anhydride and 2,6-lutidine, both diastereomers of **46** underwent a Pummerer-type rearrangement within 15 minutes to afford vinyl sulfide **47** in 94% yield.[77-78] Acidic hydrolysis of **47** afforded ketone **48** in 93% yield. Substrate-controlled, diastereoselective reduction of **48** with sodium borohydride afforded alcohol **49** in a 12:1 epimeric ratio and 88% isolated yield of the desired epimer. Finally, a survey of demethylation reagents was carried out to identify appropriate conditions for conversion of **49** to (+)-**44**. Treatment with boron tribromide returned a complex product mixture resulting from ionization of the free secondary alcohol. Nucleophilic alkylthiolate reagents could achieve the desired transformation but at a very slow rate (days) with significant amounts of by-product formation. In their total synthesis of (–)-cylindrocyclophane A, Hoye and co-workers achieved clean demethylation of a phenol in the presence of a secondary benzylic alcohol using neat methylmagnesium iodide under vacuum at 160 °C.[79] These unusual conditions worked exceptionally well for the conversion of **49** to (+)-**44**, affording an 85% yield with only a trace of by-product formation. Although Hoye did not speculate on a mechanism, the reaction is presumed to proceed as follows. Initial deprotonation of the secondary alcohol under ambient conditions protects this reactive functionality as the magnesium alkoxide. Next, upon subjecting methylmagnesium iodide to elevated temperatures, this reagent is converted to magnesium iodide and ethane gas via the Schlenk equilibrium, which is driven forward by constant removal of ethane under vacuum conditions. Coordination of the Lewis basic ether moiety to the Lewis acidic MgI_2 occurs with concomitant displacement of iodide, which accomplishes the demethylation reaction via formation of iodomethane, which is also removed under vacuum. The reaction mixture is returned to ambient conditions and quenched with aqueous acid, which protonates both the magnesium alkoxide and newly formed magnesium phenoxide to afford product (+)-**44**. This method is a very clever way to perform a Lewis-acid mediated phenol demethylation in the presence of an ionizable functionality.

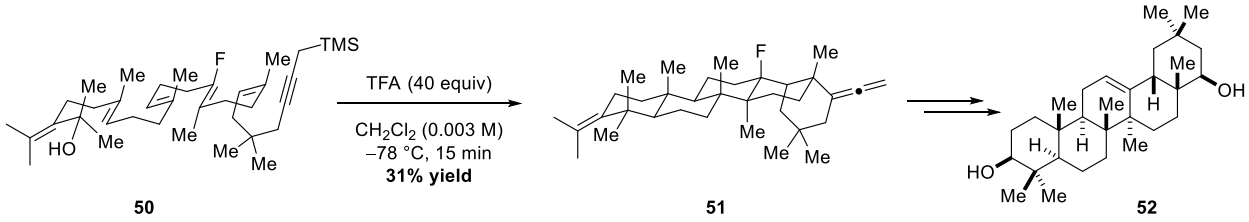
In summary, a catalytic, enantioselective sulfenocyclization of dienes was developed which satisfied all of the initial project goals. The reaction affords complex, tricyclic products in consistently good yields and good enantioselectivities (≥90:10 e.r.). The reaction is run at room temperature, and no special precautions need to be taken for exclusion of air or moisture. These

mild conditions enabled a broad functional group tolerance which includes acid-sensitive groups such as carbamates. Finally, the non-engineered diene substrates are easy to prepare, and in most cases are accessed in one step from inexpensive geranyl acetate. The utility of the products has been showcased in the concise, enantioselective total syntheses of (+)-ferruginol and (+)-hinokiol.

2.3. Investigations into Sulfenocyclization of Trienes

Given the initial success observed for sulfenocyclization of compounds containing two double bonds, the next logical step was to extend this method to include longer chain, tri-olefinic substrates. Many beautiful examples can be found in the literature of non-enzymatic polyene cyclizations of tri- and tetra-olefinic compounds, perhaps none more striking than the pentacarbocyclization first reported by W. S. Johnson (Scheme 14).[80] Linear polyene **50**, which bears no rings nor stereogenic centers, was converted to intermediate **51** as a single diastereomer, simply upon treatment with trifluoroacetic acid. In a mere three additional steps, the synthesis of *rac*-sophoradiol **52** was achieved. The ability to construct five rings and eight stereogenic centers in a single chemical step should be a source of pride and inspiration for every synthetic organic chemist.

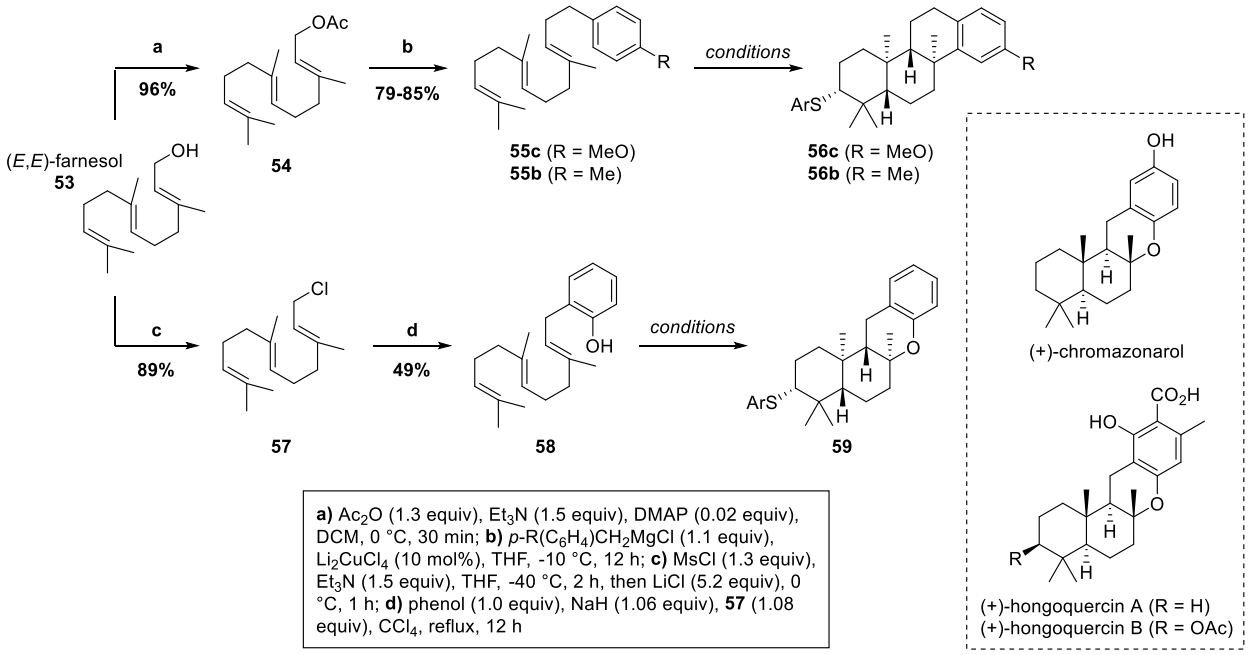
Scheme 14.



While this is no doubt an impressive example, substrate **50** was specifically engineered to maximize the likelihood of a successful polyene cyclization. First, the initial cation-generating event (ionization of a tertiary alcohol with strong acid) can only occur at a single site in **50**. Acid-mediated opening of a pre-installed oxirane is another classic method for site-selective initiation of polyene cyclizations. Second, substrate **50** contains a strategically positioned fluorine atom which functions as a stabilizing group for a cationic intermediate. These modifications improve the selectivity and yield of the desired polyene cyclization, but the obvious disadvantage is that

substrate **50** is difficult to access and cannot be easily derived from natural sources. Methods which employ non-engineered substrates such as **55** or **58** (Scheme 15) are more ideal from an accessibility standpoint, but selective cyclization of these simple, longer-chain polyenes remains a significant synthetic challenge.

Scheme 15.



The major hurdle to high-yielding sulfenocyclization of substrates **55** or **58** is achieving high site-selectivity in the initial cation generating event. As noted in the previous section, chemical differentiation of just two olefins posed a significant synthetic challenge, which was only solved by utilization of a highly polar reaction medium which favors a particular foldamer of the polyene in solution. In the case of trienes, this challenge is only exacerbated. Still, the literature provides a few examples of non-enzymatic, polyene cyclizations of non-engineered, farnesyl-derived trienes in synthetically useful yields. A highly relevant example was the report from Gulder and coworkers describing the beneficial effect of HFIP on racemic halocyclization of polyenes.[61] Included in this study is a single example of cyclization of a triene, homofarnesylbenzene, which proceeds in modest yield (40%). It is noted that the subsequent addition of a stronger acid was necessary to force the cascade cyclization to completion, after the

initial carbocation-generating event under the standard reaction conditions. Prior to this work, Qu and coworkers demonstrated the cyclization of pre-formed epoxy dienes, and one example of an epoxy triene, in HFIP with a high concentration of tetraphenylphosphonium tetrafluoroborate as a salt additive.[62] The products were isolated in synthetically useful yields as single diastereomers. In addition to enhancing the polarity of the reaction medium, the salt additive also depressed the melting point of HFIP, allowing the reactions to be run at lower temperatures. Several compelling examples of long chain, enantioselective, polyene cyclizations run in solvents other than HFIP are known. MacMillan and coworkers successfully cyclized a compound containing six double bonds by SOMO catalysis.[53] The substrate, however, is highly engineered, containing two strategically-placed nitrile moieties which help stabilize the radical intermediate.

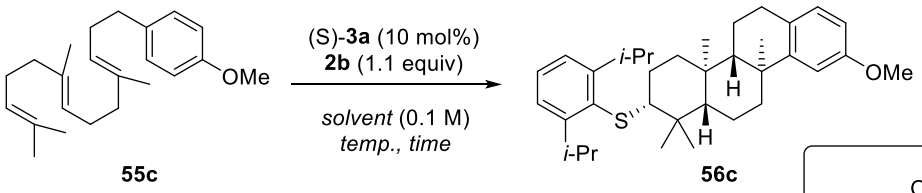
The preparation of **55** and **58** was straightforward (Scheme 15). Coupling benzylic Grignard reagents **35** with *trans*,*trans*-farnesyl acetate **54**, catalyzed by Li_2CuCl_4, afforded trienes **55** in good yield. Alkylation of phenol with *trans*,*trans*-farnesyl chloride **57**, using conditions optimized for the C-alkylation of phenols,[23, 60] afforded **58** in good yield. The sulfenocyclization of **58** is particularly desirable, as the resulting polycyclic core maps onto the structures of several natural products. Farnesyl acetate **54** and farnesyl chloride **57** were accessed in nearly quantitative yield from farnesol **53**. Commercial, technical grade farnesol **53** is inexpensive, but is generally sold as a 90:10 mixture of isomers (*E*,*E*:*E*,*Z*). This was considered insufficient for screening purposes, as even a highly selective sulfenocyclization would produce a mixture of diastereomeric compounds and obfuscate ^{1}H NMR analysis of the crude reaction mixtures. Isomerically pure farnesol (≥97:3 *E*,*E*:*E*,*Z*) can also be purchased from several suppliers at an increased price. Additionally, technical grade farnesol can be converted to the *N*,*N*-diphenyl carbamate, a derivative which is solid at room temperature, and recrystallized until the desired level of geometric purity is obtained.[81] The carbamate is readily hydrolyzed under basic conditions to return pure farnesol. This procedure was successful, returning farnesol in excellent (>99:1 *E*,*E*:*E*,*Z*) geometric purity, but the recovery was poor and the protocol was quite tedious, requiring four recrystallizations. For these reasons, purchasing the isomerically pure farnesol is recommended. On two separate occasions from two different suppliers, the purity of **53** was determined to be >99:1 *E*,*E*:*E*,*Z* by ^{1}H NMR analysis, much better than the advertised ratio.

Sulfenocyclization of trienes was anticipated to afford potentially more complex product mixtures than for the analogous reaction of dienes. The logic behind preparation of **55c** bearing a

4-methoxy substituent was that this would facilitate interpretation of the ^{1}H NMR spectra of crude mixtures during screening campaigns, because the number of methoxy signals would correspond to the number of unique products generated.

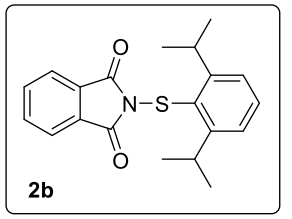
As a starting point for reaction development, **55c** was treated with sulfenylating agent **2b** and catalyst (*S*)-**3a** in a nitromethane/HFIP solvent system (Table 4, entry 1). Nitromethane, a common solvent for non-enzymatic polyene cyclizations, was selected as a co-solvent so that the reaction could be run below the freezing point of HFIP (–3 °C). It was hypothesized that lower temperatures may help bias the desired foldamer and lead to a cleaner reaction profile, but no conversion was observed at –20 °C after 4 h. Upon warming to 25 °C, full consumption of starting material occurred within 12 h to afford a highly complex mixture of products. Judging from the ^{1}H NMR spectrum of the crude material, at least eight unique species had formed, on the basis of the number of singlets in the 3.80 – 3.70 ppm range (arising from methoxy groups). By contrast, TLC analysis of the crude mixture revealed a single spot, suggesting that all of the products formed were of similar polarity. Consequently, chromatographic purification was not attempted. The reaction was repeated with different fluorinated, alcoholic solvents, which resulted in either complex mixtures (nonafluoro-*tert*-butanol, entry 2) or minimal conversion due to poor reagent solubility (2,2,3,3,4,4,4-heptafluoro-*n*-butanol, entry 3).

Table 4. Attempted sulfenocyclization of **55c**.

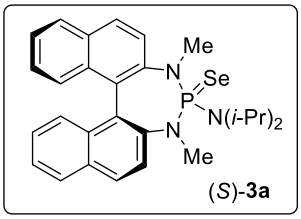


55c **56c**

entry	*solvent*	*temp.*	*time*	*result*
1	HFIP/$MeNO_2$ (1:1)	–20 °C	4 h	no conv.
		to 25 °C	12 h	complex mixture
2	$(F_3C)_3COH$	25 °C	12 h	complex mixture
3	$F_3C(CF_2)_2CH_2OH$	25 °C	12 h	~ no. conv.
4	HFIP	0 °C	2 h	no conv.
		to 25 °C	2 h	complex mixture
	+ *i*-$PrNO_2$, $ClSO_3H$	–25 °C	3 h	complex mixture no anisole



2b

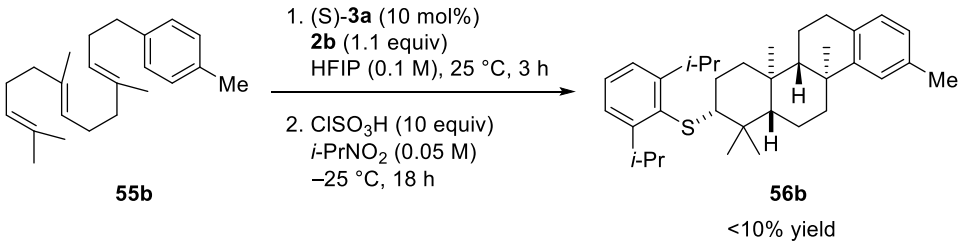


(*S*)-**3a**

Although the sheer complexity of the crude ^{1}H NMR spectra prevented their interpretation, one important feature was the presence of olefinic signals (in the region from 5.0 to 5.5 ppm), which should not be present in a successful sulfenocyclization. This observation implies the presence of species resulting from one or both of the following: (1) unselective thiiranium ion generation, or (2) incomplete cascade cyclization, which affords a mixture of early termination products. The latter phenomenon is quite common for non-enzymatic polyene cyclizations, and the typical remedy is to introduce a strong acid to the reaction mixture some time after the initial cation-forming event has taken place.[50, 61] It was hypothesized that the reaction of **55c** might also suffer from incomplete cyclization to some extent, so the 'acid-doping' strategy was explored (entry 4). Full consumption of **55c** occurred in HFIP within 2 h at 25 °C (no conversion was observed at 0 °C), at which point a solution of chlorosulfonic acid in 2-nitropropane was added to the reaction mixture. After 3 h of reaction time at –25 °C, a new, complex product mixture was isolated, which notably lacked any singlets in the 3.80 – 3.70 ppm range of the ^{1}H NMR spectrum. The lack of any methoxy groups indicates that the anisole ring was ionized under these strongly acidic conditions.

At this point, it was deemed prudent to reevaluate the substrate choice. Without a pure sample of the product **56c**, and given the uninterpretable outcome of the reactions in Table 4, it was impossible to confirm whether or not **56c** was forming at all. It was still hypothesized that chlorosulfonic acid treatment could provide access to the correct product, given the ample literature precedent, but the anisole moiety of **55c** was clearly incompatible with this reagent. Therefore, the cyclization of compound **55b** which bears a 4-methyl substituent was explored. Compound **55b** retains the beneficial aspect of **55c** (the presence of a diagnostic ^{1}H NMR signal), but is now compatible with chlorosulfonic acid. Indeed, when **55b** was subjected to the standard reaction conditions in HFIP at 25 °C (Scheme 16), followed by treatment with chlorosulfonic acid, a new species was detected whose spectral data were consistent with the structure of **56b**. The principal basis for this assignment is a specific ^{1}H NMR signal (δ 3.01 ppm, dd, J = 12.6, 3.7 Hz, 1H) which is diagnostic for the proton residing on the sulfur-bearing carbon. Still, **56b** was only isolated in roughly 60–70% purity after chromatography, which precluded any rigorous assignment or proof of structure.

Scheme 16.

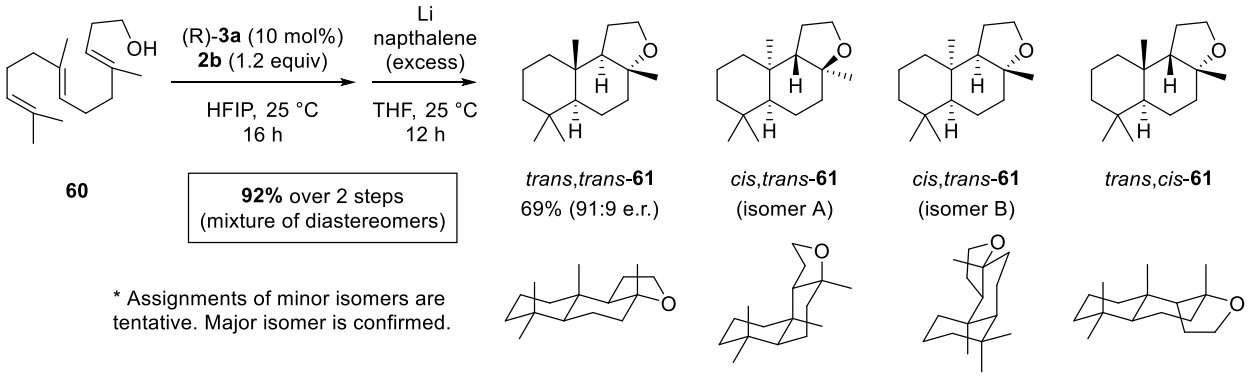


55b **56b**

<10% yield

With this encouraging hint of success, other substrate classes containing more nucleophilic terminating groups were examined, as these were considered more likely to cyclize without the requirement of strong acid. It had already been demonstrated in this laboratory that homofarnesol **60** was a competent substrate for the transformation (Scheme 17).[82] Treatment of **60** with catalyst (*R*)-**3a** and sulfenylating agent **2b** in HFIP, followed by reductive C–S cleavage, afforded tricyclic ether **61** in 92% yield over two steps as a mixture of four diastereomers. The major isomer, *trans,trans*-**61** comprised 69% of the diastereomeric mixture and is the natural product (–)-ambrox. In addition to primary alcohols, it has previously been empirically demonstrated that phenols are more effective terminal nucleophiles than simple arenes, at least in the case of sulfenocyclization of dienes. Therefore, the cyclization of 2-farnesylphenol **58** was investigated.

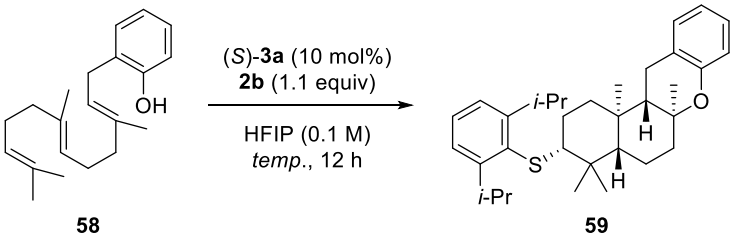
Scheme 17.



Subjecting **58** to standard conditions (HFIP, 25 °C) afforded a complex mixture of products (Table 5, entry 1), but a species consistent with the structure of **59** was identified as a minor (<10%)

component. Notably, this species was isolated without the 'acid-doping' step, confirming the original hypothesis. Reducing the temperature (entry 2) led to an improved yield of **59**. The less-nucleophilic substrate **55a**, by contrast, did not react at 0 °C (Table 4, entry 4). These experiments demonstrate the advantage of using the more nucleophilic 2-farnesylphenol **58** as a privileged substrate. A salt additive (entry 3) had no effect on the reaction profile. Although these experiments were certainly encouraging, the yield and purity of **59** still left much to be desired. Chromatographic purification of **59** was extremely challenging, as the various reaction by-products are non-polar and have very similar R_f values. In fact, the level of contamination in the isolated **59** precludes its definitive structural assignment.

Table 5. Sulfenocyclization of triene **58**.



58 59

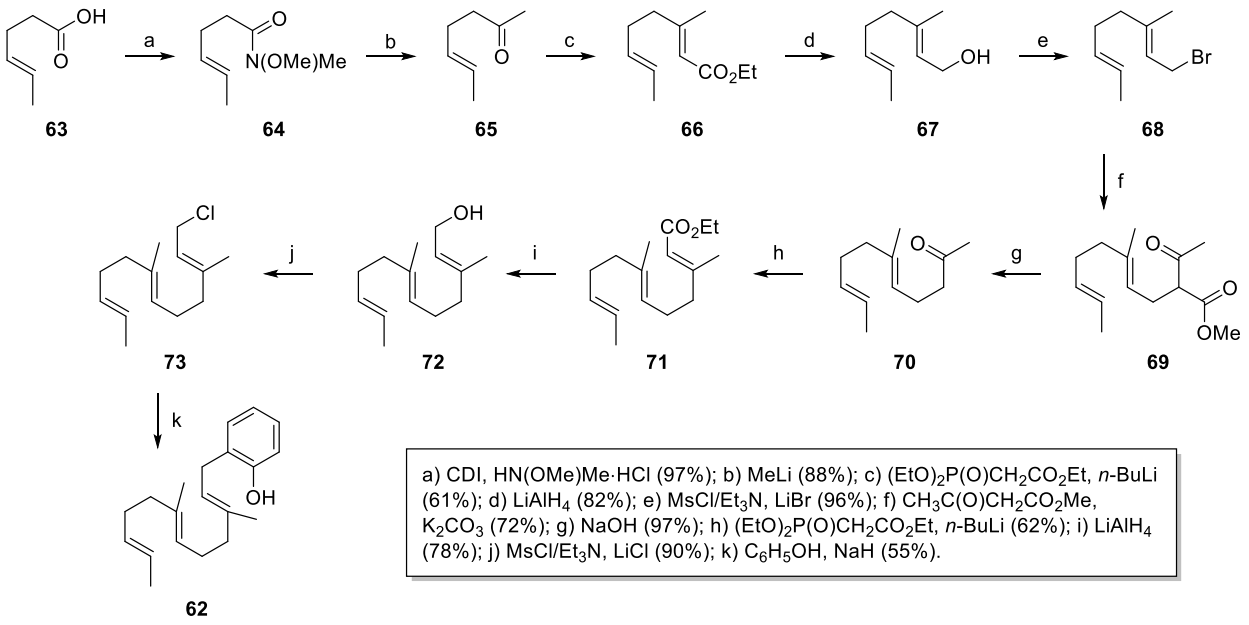
entry	temp.	additive	yield
1	25 °C	none	<10%
2	0 °C	none	<30%
3	0 °C	$(n\text{-Bu})_4N^+BF_4^-$	<30%

Evidently, the fortuitous solvophobic interaction which led to high chemoselectivity for sulfenocyclization of dienes was no longer having the same influence on triene substrates. The introduction of a third isoprenoid subunit dramatically increases both the degrees of freedom and the number of available conformers for the substrate. To attain the desired foldamer leading to site-selective thiiranium ion generation, the entropic barrier is simply too large, even in highly polar reaction media. Since the reactivity of the olefins could no longer be tuned exclusively by solvent effects, different methods of biasing the olefin reactivity had to be explored. Donor-acceptor adducts of catalyst **3a** are known to react faster with certain classes of olefins. Unsurprisingly, increasing the electron density of the alkene tends to increase the rate of thiiranium ion generation, with the fastest reactions observed for silyl enol ethers[83] and alkenyl boronate complexes.[84] In addition to electronic parameters, the bulky catalyst adduct is also sensitive to the steric environment of the alkene substrate. Toward that end, compound **62** was envisioned to result

in high chemoselectivity for thiiranium ion generation on the trans-disubstituted olefin compared to the two trisubstituted olefins, solely on the basis of steric arguments.

The preparation of **62** presented a formidable synthetic challenge, as this 'engineered' polyene could not be accessed from natural farnesol **53**. Ultimately, **62** was constructed by the robust, albeit lengthy, route outlined in Scheme 18. Carboxylic acid (*E*)-**63** was selected as a starting point, as this compound can be prepared on a huge scale as a single geometric isomer by a Johnson orthoester Claisen rearrangement.[85-86] Acid **63** was converted to the corresponding Weinreb amide **64** via a mixed anhydride with carbonyl diimidazole (CDI). Due to its low toxicity and ease of handling, CDI is preferred over other reagents commonly used to generate mixed anhydrides, such as ethyl chloroformate. However, it is important to realize that CDI hydrolyzes to an appreciable extent upon storage under air. Procedures which employ CDI often use this reagent in a substantial excess (1.20 equiv or more) for this reason, because commercial sources are typically contaminated with a significant amount of imidazole. The ideal stoichiometry for the pure reagent is, of course, 1.0 equiv, and any excess leads to the formation of by-products. Therefore, for the most consistent results in the conversion of **63** to **64**, CDI was first purified by recrystallization from THF and stored under argon, and only a very slight excess (1.05 equiv) was used in the reaction mixture. This led to the consistent isolation of **64** in very high yield and purity, without the need for chromatography. Subsequent addition of methyllithium afforded volatile ketone **65**.

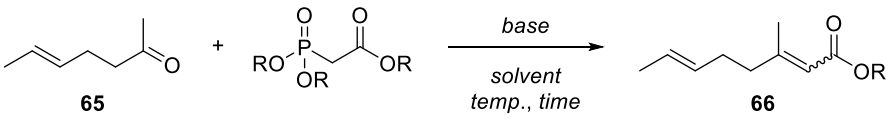
Scheme 18.



Horner-Wadsworth-Emmons olefination afforded unsaturated ester **66** as a mixture of geometric isomers. Obviously, a highly (*E*)-selective olefination would be desired, so a number of reaction conditions were explored (Table 6). The combination of sodium hydride in benzene (entry 1) was reported to give >20:1 (*E*:*Z*) selectivity for a similar compound,[87] but **66** was only isolated as a 4:1 (*E*/*Z*) mixture in 69% overall yield. The *E*/*Z* ratio is easily estimated from ^{1}H NMR by comparing the relative integrations of the signals arising from the methyl group on the trisubstituted olefin. In both isomers, this signal appears as a narrow doublet (J = 1.2 Hz) arising from long-range coupling, but the chemical shift is significantly farther downfield in (*E*)-**66** (2.15 ppm) than in (*Z*)-**66** (1.87 ppm).[88] Switching to sodium methoxide in THF (entry 2) afforded **66** in a slightly diminished 3:1 (E/Z) ratio. Using *n*-butyllithium in THF (entry 3) returned **66** in a comparable ratio to the original reaction conditions, albeit in a diminished overall yield. Nonetheless, these conditions were chosen for scale-up (entries 4 and 5) because of operational simplicity and safety reasons. Gratifyingly, the yield of **66** improved considerably on scale (77% overall), while maintaining the same isomeric ratio observed on a smaller scale. The isomers were easily separated by chromatography to afford 61% yield of (*E*)-**66** and 16% yield of (*Z*)-**66**, both

in >98:2 geometric purity. Although this step provided access to large quantities of (*E*)-**66** and was sufficient for the present purposes, it is duly noted that highly selective construction of trisubstituted olefins via Wittig-type chemistry remains a largely unsolved problem in organic synthesis.

Table 6. Survey of conditions for (*E*)-selective HWE olefination.



entry	*scale*	*R* =	*base*	*solvent*	*temp.*	*time*	*conv.*	*E/Z*	*yield*
1	9 mmol	Et	NaH (1.1 equiv)	C_6H_6	25 °C	12 h	>90%	4:1	69% total
2	1 mmol	Me	NaOMe (1.4 equiv)	THF	reflux	12 h	>90%	3:1	n.d.
3	1 mmol	Et	*n*-BuLi (1.0 equiv)	THF	–78 °C to 25 °C	12 h	>90%	4:1	39% (E) 10% (Z)
4	11 mmol	Et	*n*-BuLi (1.05 equiv)	THF	–78 °C to 25 °C	36 h	>85%	4:1	56% (E) 15% (Z)
5	22 mmol	Et	*n*-BuLi (1.05 equiv)	THF	–78 °C to 25 °C	48 h	>90%	4:1	61% (E) 16% (Z)

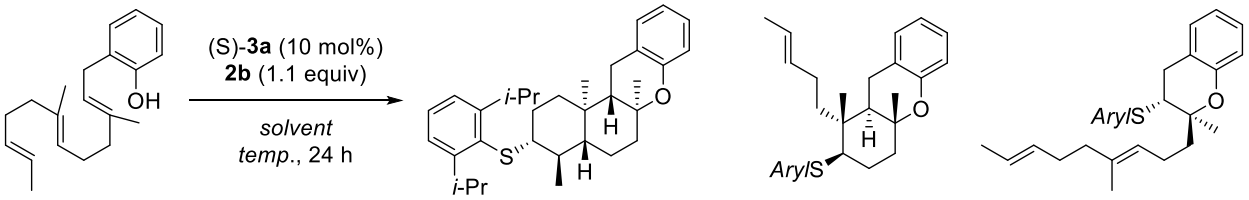
Reduction of (*E*)-**66** with lithium aluminum hydride afforded allylic alcohol **67** in good yield. Treatment of **67** with phosphorus tribromide afforded **68** as expected, but it was found that a two-step, one-pot approach (mesylation of **67** followed by displacement with lithium bromide) afforded allylic bromide **68** in consistently higher purity and yield. Alkylation of methyl acetoacetate with **68** afforded **69** in addition to a small amount of the dialkylation product, and decarboxylation under basic conditions afforded ketone **70** in high yield. This five-step sequence (olefination, reduction, bromination, alkylation, and decarboxylation) achieved the homologation of ketone **65** by a single isoprenoid unit to ketone **70**. A familiar sequence was used to install the final alkene. Horner-Wadsworth-Emmons olefination (same conditions as Table 6, entry 5 for the synthesis of **66**) afforded **71**, again in a 4:1 (*E*/*Z*) isomeric ratio. As **71** is even less polar than **66**, chromatographic separation of (*E*/*Z*) isomers was anticipated to be challenging. As such, two alternative olefination conditions were briefly investigated, which are purported to give excellent

(*E*) selectivity in the construction of disubstituted olefins from aldehydes. First, replacing *n*-butyllithium with a DBU/lithium chloride mixture afforded no conversion whatsoever. Likewise, replacing the phosphonate ester with the corresponding phosphonium bromide salt (using *n*-butyllithium to generate the ylide) also afforded no conversion. Clearly, these methods cannot be extended to less-reactive ketones for the stereoselective construction of trisubstituted olefins. The original Horner-Wadsworth-Emmons conditions were retained, and after careful chromatographic separation, (*E*)-**71** was isolated in 62% yield in >99:1 geometric purity. Subsequently, **71** was reduced with $LiAlH_4$, and the resulting alcohol **72** was chlorinated to afford **73**. C-Selective alkylation of phenol with **73** afforded the desired triene substrate **62** in moderate yield (55%). A host of minor by-products were generated in this reaction, including one resulting from *ortho*,*para*-bis(alkylation) of phenol. Nevertheless, **62** was isolated in high purity after a single chromatographic purification. Overall, the target compound **62** was prepared from (*E*)-**63** in 11 steps and 7% overall yield. This route highlights the difficulty of accessing non-natural polyolefinic molecules in a stereoselective fashion.

With the target substrate in hand, the sulfenocyclization of **62** to **74** was explored under a variety of reaction conditions (Table 7). Disappointingly, very complex product mixtures were again observed, and the site-selectivity for thiiranium ion generation on **62** was not improved relative to the parent compound **58**. In fact, in addition to **74**, products whose spectral data were consistent with **75** and **76** were identified in some of the reaction mixtures. This outcome disproves the hypothesis that the catalyst system reacts more rapidly with disubstituted alkenes than with trisubstituted alkenes on the same molecule, indicating that catalyst-substrate interactions are not influenced primarily by steric parameters. Interestingly, the reaction solvent continued to have a profound impact on the reaction outcome. Although complex mixtures were observed in every case, the desired product **74** was only identified when the reaction was run in HFIP (entries 1 and 7) or CH_2Cl_2 (entry 2). The decision to run the reaction in CH_2Cl_2 with a sub-stoichiometric amount of mesic acid (the "classic" conditions for Lewis base-catalyzed thiofunctionalization) was fortuitous, as this was the only entry in which all three products **74**, **75**, and **76** were generated in more than trace quantity (a host of other, unidentified by-products were also formed). Chromatographic separation afforded semi-pure, authentic samples of each product, which could be overlaid with the ^1H NMR spectra of crude reaction mixtures from other entries. In this manner, it was determined that **74** and **75** accounted for ~60% of the product mixture in HFIP (entry 1). A

survey of other polyfluorinated alcoholic solvents did not improve on this result. As expected on the basis of previous results, only partial conversion was observed in 2,2,3,3,4,4,4-heptafluoro-*n*-butanol (entry 3) due to poor solubility. Apart from unreacted **62**, both **75** and **76** could be identified in the crude product mixture, but not the desired **74**. The reaction in 2,2,2-trifluoroethanol (TFE, entry 4) afforded a complex product mixture containing **76** but neither **74** nor **75**. The most acidic solvents, nonafluoro-*tert*-butanol (entry 5) and dodecafluoropinacol (entry 6), both afforded highly complex mixtures containing nothing identifiable.

Table 7. Sulfenocyclization of **62**.



62 **74** **75** **76**

				species present?			
Entry	*Solvent*	*Temp.*	*Conv.*	**74**	**75**	**76**	*Yield* **74**
1	HFIP	25 °C	Full	yes	yes	no	n.d.
2	CH_2Cl_2 (w/ MsOH)	25 °C	Full	yes	yes	yes	~5%
3	$CF_3(CF_2)_2CH_2OH$	25 °C	Partial	no	yes	yes	0%
4	TFE	25 °C	Full	no	no	yes	0%
5	$(CF_3)_3COH$	25 °C	Full	no	no	no	0%
6	$[(CF_3)_2C(OH)]_2$	25 °C	Full	no	no	no	0%
7	HFIP	0 °C	Full	yes	yes	no	~30%

As HFIP had so far enabled the most selective reaction (entry 1), the temperature was reduced to 0 °C to explore whether the reaction profile would be improved (entry 7). Indeed, the reaction was noticeably cleaner, and this enabled the isolation of desired **74** in approx. 30% yield and >80% purity. Although these results were encouraging, they were not appreciably better than those observed for the sulfenocyclization of parent compound **58** in HFIP at 0 °C (Table 5, entries 2 and 3). Given the extreme synthetic overhead associated with preparing **62**, it was decided that this was not the best substrate to use in further screening campaigns. Instead, different strategies

were explored for biasing the reactivity of the three alkenes. Since catalyst **3a** appeared to be fairly insensitive to steric differences among the alkenes, at least in the context of this particular reaction, it was hypothesized that **3a** might be more selective to the electronic properties of the alkenes.

Specifically, it was envisioned that replacing the distal alkene with a more electron-rich silyl enol ether would direct thiiranium ion generation exclusively to this position. Enoxysilanes have already been shown to be favorable substrates for Lewis base-catalyzed thiofunctionalization, enabling access to enantiomerically enriched, α-sulfenylated ketones.[83] With this in mind, compounds **77** were selected as target substrates (Figure 15). Ideally, subjecting (*Z*)-**77** to the standard reaction conditions would initially form thiiranium ion **78** in high chemo- and enantioselectivity. This species would likely open spontaneously to afford silyloxocarbenium ion **79**, and subsequent cascade cyclization would ultimately generate polycyclic compound **80** bearing a silyl-protected, tertiary alcohol. Although epimer **81** could also be obtained, it is anticipated that nucleophilic attack on silyloxocarbenium ion **79** would be highly diastereoselective, for a number of reasons. First, for intramolecular capture of **79** to proceed via the optimal Bürgi-Dunitz angle, the silyloxy group must be pseudo-axial as drawn, which leads to product **80**. Second, the transition state leading to **80** is expected to be lower in energy because the substituent with the smaller A-value (trimethylsilyloxy, A = 0.74) occupies the axial position, while the substituent with the larger A-value (phenyl, A = 3) occupies the equatorial position. The opposite is true for the higher-energy transition state leading to **81**. Finally, along a similar line of reasoning, the large phenyl group and the adjacent, bulky sulfide enjoy a *trans* relationship in favored product **80**, while epimer **81** would place these groups in a *cis* orientation.

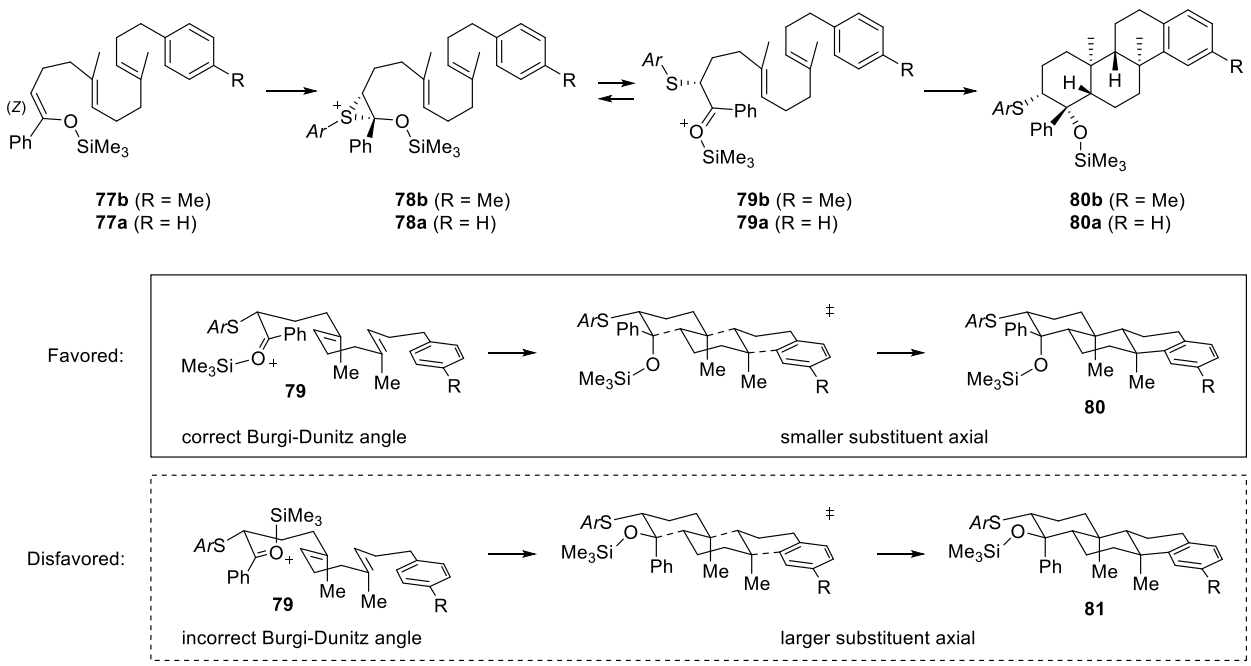
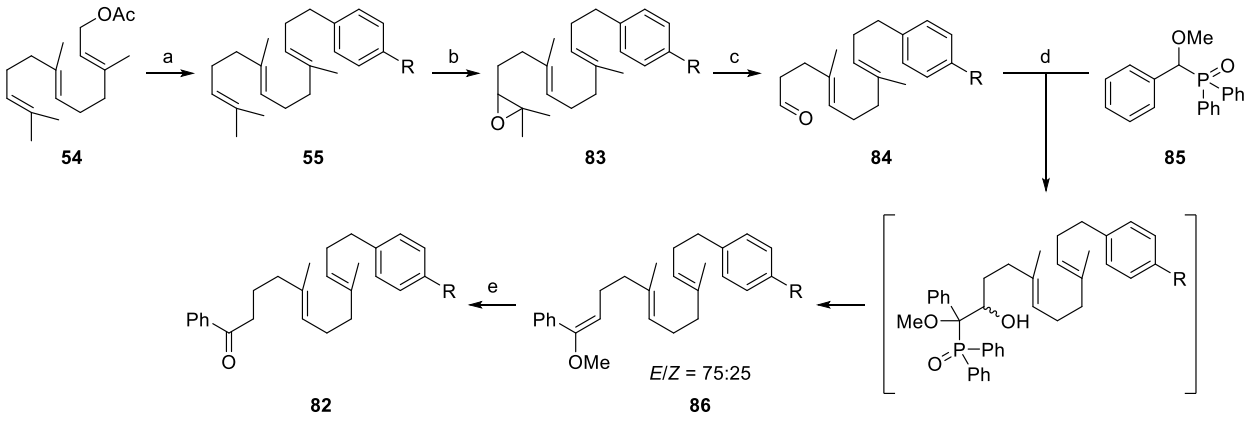


Figure 15. Proposed sulfenocyclization of enoxysilanes.

As noted earlier, phenols are more effective terminal nucleophiles than arenes, and their ability to react at 0 °C proved to be a major advantage during screening campaigns. Thus, the choice of target substrates **77** containing an arene nucleophile was not ideal, and was made solely on the basis of synthetic accessibility. A route to precursor ketones **82** was devised (Scheme 19) which took advantage of natural farnesol as the principal source of carbon atoms. Thus, this route was far more concise than the one required for **62**. Homofarnesylarenes **55** were prepared by coupling farnesyl acetate **54** with benzylic Grignard reagents **35** which proceeded in high yield (*vide supra*). Next, selective epoxidation of the most distal alkene (bearing geminal methyl groups) was accomplished in a one-pot, two-step procedure by treating a dilute solution of **55** in a THF/water mixture with *N*-bromosuccinimide followed by potassium carbonate in methanol. Presumably, a similar solvophobic effect is observed for **55** in THF/water as in HFIP, leading to high site selectivity for the initial bromination, but the insolubility of **55** in water necessitates a low reactant concentration. Oxidative cleavage of epoxide **83** afforded aldehyde **84** in good yield. Phosphine oxide **85** was prepared in quantitative yield by the reaction of chlorodiphenylphosphine with benzaldehyde dimethyl acetal. Subsequent Horner-Wittig olefination afforded methyl enol

ether **86** in a roughly 3:1 isomeric mixture. Ordinarily, the diastereomeric α-hydroxyphosphine oxides resulting from a Horner-Wittig reaction can be isolated as discrete intermediates, separated, and subjected to stereospecific elimination conditions to afford a single alkene isomer in a convergent fashion. Indeed, this is one of the chief advantages of this olefination method. In this instance however, the α-hydroxy phosphine oxide was not isolable and underwent elimination in the same pot to form **86**, presumably because of the thermodynamic driving force associated with the formation of a trisubstituted, conjugated alkene. This outcome was inconsequential, as **86** was simply hydrolyzed under acidic conditions to afford aromatic ketone **82**. It is noted that this two-step sequence is a convenient, high yielding method for the one-carbon homologation of aliphatic aldehydes to aryl ketones, which does not appear to be described in the literature. In summary, this robust, five-step synthesis worked equally well to prepare **82b** on a milligram scale and to prepare **82a** on a gram scale.

Scheme 19.



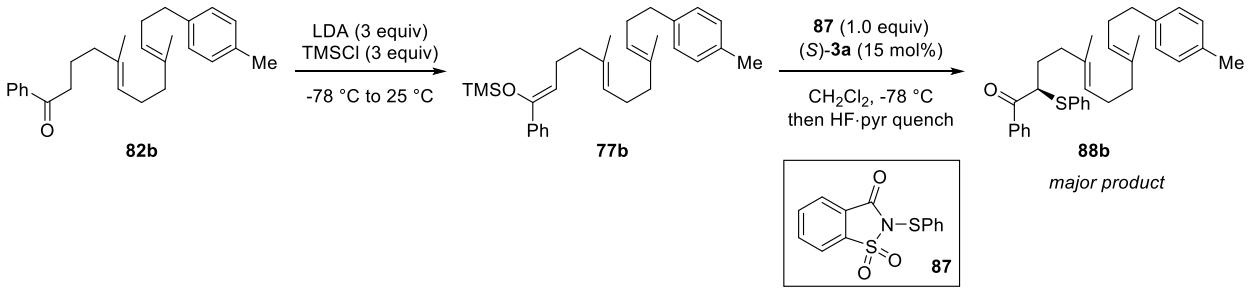
Conditions: a) *p*-R(C_6H_4)CH_2MgCl (1.1 equiv), Li_2CuCl_4 (10 mol%); b) NBS (1.1 equiv) in THF/H_2O, then K_2CO_3 (excess) in MeOH; c) $NaIO_4$ (0.6 equiv), H_6IO_5 (1.1 equiv); d) LDA (1.4 equiv); e) HCl (excess), acetone.

	mg scale (R = Me)		*gram scale* (R = H)	
Step	Compound	Yield	Compound	Yield
a	**55b**	79%	**55a**	95%
b	**83b**	49%	**83a**	55%
c	**84b**	85%	**84a**	85%
d	**86b**	88%	**86a**	86%
e	**82b**	95%	**82a**	93%

Treatment of aromatic ketone **82b** with LDA and trimethylsilyl chloride at –78 °C afforded silyl enol ether **77b** as a single geometric isomer, as expected (Scheme 20). This compound was

contaminated with some unidentifiable, silyl-containing species which could not be removed, as **77b** is neither stable to chromatography nor to distillation. Therefore, the crude mixture was directly subjected to conditions expected to initiate sulfenofunctionalization. Given the extreme sensitivity of trimethylsilyl enol ethers to acid, the more reactive sulfenyl transfer agent **87** was used, to circumvent the introduction of any acidic reagents (MsOH) or solvents (HFIP) to the reaction mixture. At –78 °C, full conversion of **77b** was observed, but upon quench and workup the desired product **80b** was not identified. Rather, α-sulfenylated ketone **88b** was isolated as the major species, presumably in enantiomerically enriched form, although this was not confirmed. Clearly, sulfenyl group transfer to generate thiiranium ion **78b** occurred as expected, but the stabilized silyloxocarbenium ion **79b** was not sufficiently electrophilic to initiate a polyene cyclization at –78 °C. Possible solutions were considered, including substituting the acid-labile trimethylsilyl group for a more stable TBDPS or TIPS group. Enol ethers of type **77** containing these bulkier silyl groups are amenable to chromatographic purification, and they are predicted to be more stable in HFIP and other polar, protic solvents compared to TMS enol ether **77b**. Three compounds of type **77**, derived from ketone **82a**, containing a TBS, TBDPS, and TIPS group were prepared and treated with sulfenylating agent **2b** and racemic catalyst tetrahydrothiophene in HFIP at room temperature. Unfortunately, these experiments resulted in highly complex product mixtures, and the α-sulfenylated ketone by-product (of type **88**) was identified as a component in every case. The exploration and optimization of catalytic sulfenocyclization of trienes (both engineered and non-engineered systems) is an ongoing area of research.

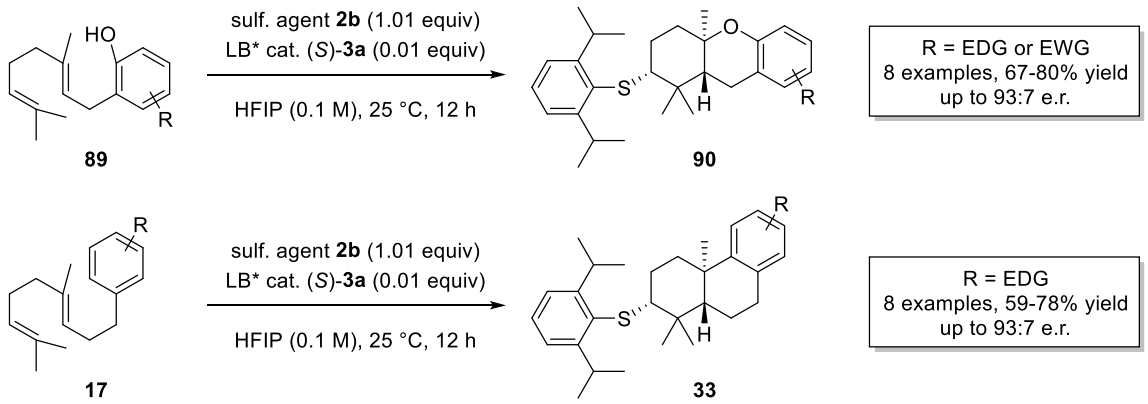
Scheme 20.



2.4. Kinetics and Mechanistic Studies

In the midst of continuing investigation into the sulfenocyclization of trienes, a mechanistic interrogation of the already successful sulfenocyclization of dienes (see Chapter 2.2) was undertaken. As previously noted, the sulfenocyclization of electronically diverse 2-geranylphenols **89**, as well as electron-rich homogeranylarenes **17**, proceeds in good yield and enantioselectivity using sulfenyl transfer agent **2b**, catalyst (*S*)-**3a**, and HFIP as a reaction solvent (Scheme 21).[70]

Scheme 21.



The mechanism for Lewis base-catalyzed sulfenofunctionalization of olefins has been extensively studied in these laboratories (see Chapter 1),[26-27] and the following catalytic cycle has been proposed by analogy (Figure 16), illustrated here for the sulfenocyclization of 2-geranylphenol **89**. Initially, HFIP-mediated sulfenyl group transfer from **2b** to (*S*)-**3a** generates a cationic, donor-acceptor complex **91**. This highly electrophilic complex reacts with diene substrate **89** to generate an enantiomerically enriched, thiiranium ion intermediate **92**. This thiiranium ion serves as the initiating group for a cationic, polyene cascade cyclization which is ultimately terminated by the pendent phenol nucleophile, forming tricyclic product **90**.

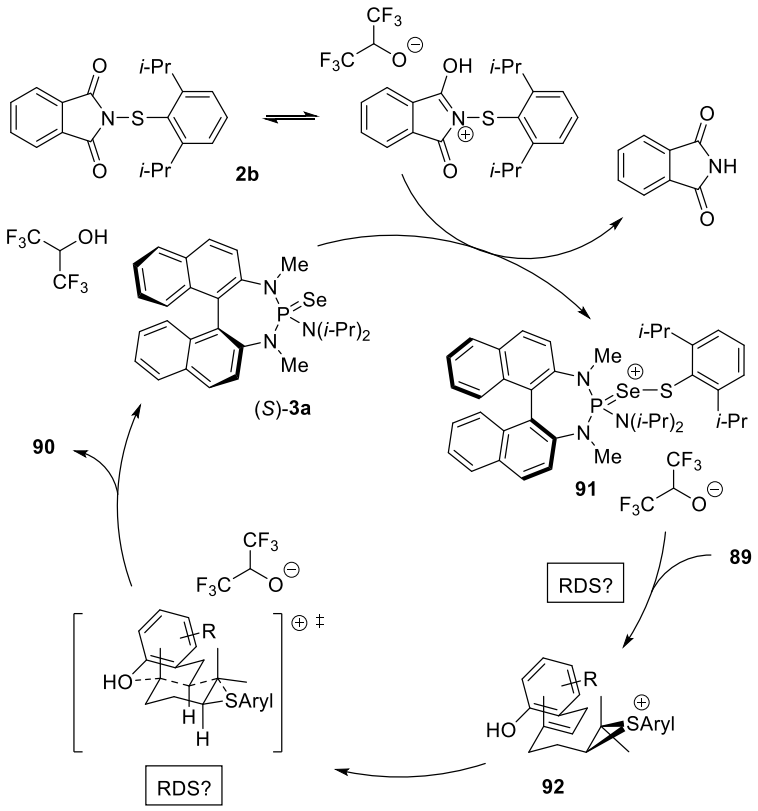


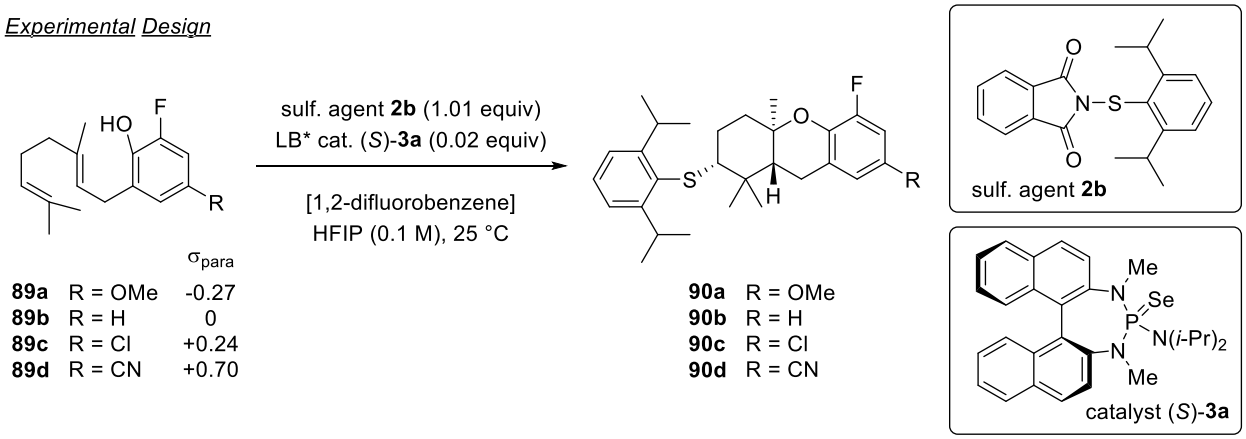
Figure 16. Proposed catalytic cycle for polyene sulfenocyclization.

In previous mechanistic studies on Lewis base-catalyzed, intramolecular oxysulfenylation (see Chapter 1, Figure 9),[26] the following kinetic profile was observed: the reaction is first order in both catalyst and olefin, and zeroth order in sulfenylating agent. This is consistent with a mechanism in which sulfenyl group transfer from the catalyst donor-acceptor complex to the olefin is the rate-determining step. While this mechanism is generally presumed to be operative regardless of the nucleophile employed, there was reasonable suspicion that this may not be case in the aforementioned polyene cyclization for two reasons. First, the reaction solvent is HFIP (highly polar, protic) rather than CH_2Cl_2 (relatively non-polar, aprotic). HFIP may participate in hydrogen-bonding interactions with all of the reaction components, which could impact the kinetic profile. Secondly, the nature of the nucleophilic, thiiranium-ion opening is quite different from previous systems because the transfer of electron density is propagated over the entire molecule as part of a cationic cascade process. Over forty years ago, William S. Johnson and co-workers first observed a pronounced dependence of the rate of acid-mediated cyclization of epoxy-polyenes on

the electronic nature of the terminal arene nucleophile.[89] Faster reaction rates were observed for substrates bearing electron rich arenes than for those containing electron poor ones, even though these motifs were located far away from the site of initiation. It was hypothesized that a similar phenomenon may exist in the present system (i.e. the rate-determining step has switched from thiiranium generation to thiiranium opening), in which case a strong rate dependence on the electronic character of the terminal arene (or phenol) nucleophile would be expected.

To test this hypothesis, the following experiments were carried out (Scheme 22). A series of 2-geranylphenols **89a** through **89d** bearing electronically diverse *para*-substituents were subjected to standard reaction conditions (see Chapter 2.2). All substrates were *ortho*-fluorinated so that reaction conversion could be monitored in real time by quantitative ^{19}F NMR (1,2-difluorobenzene was utilized as an internal standard). A solvent-suppression protocol was employed to decrease the intensity of the HFIP ^{19}F resonance, which allowed for more accurate integration of the ^{19}F resonances corresponding to **89** and **90**. Comparison of the reaction rates across the series provided valuable insight into the reaction mechanism.

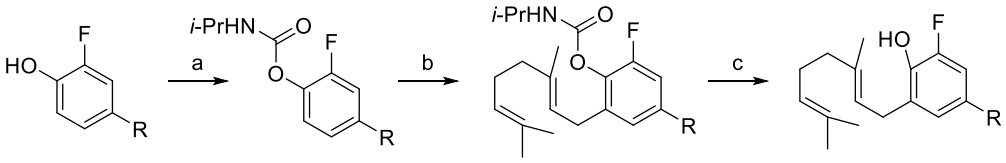
Scheme 22.



Synthesis of the fluorinated 2-geranylphenols proved to be a formidable synthetic challenge. It was envisioned that **89a** through **89d** could be obtained in one step from commercially available phenols **93** using conditions previously developed for C-selective phenol alkylation.[23, 60] Unfortunately, in the case of *ortho*-fluorinated phenols, this protocol afforded complex product mixtures and low yields of **89**. Additionally, chromatographic separation of pure **89** from the

various reaction by-products proved impossible. Alternative strategies were explored for more selective alkylation of **93** (Scheme 23). Hoppe and co-workers have developed a protocol for *ortho*-lithiation of 2-fluorophenols employing an *N*-isopropyl carbamate as a directing group.[90-91] The aryllithium species were trapped with diverse electrophiles in high yields, and while allylic halides were not included in the demonstrated scope, this appeared to be a promising route for installation of a geranyl side chain. Preparation of carbamates **94a** through **94d** from the corresponding phenols **93a** through **93d** was straightforward. Directed lithiation of the *in situ* generated, *N*-silylated carbamates and subsequent trapping with geranyl bromide afforded the desired alkylation products **95a** through **95c** in synthetically useful yields, and importantly, the isolated products were isomerically pure. Finally, the carbamates were hydrolyzed under basic, aqueous conditions to afford phenols **89a** through **89c**. An additional phenol **89e** (R = Me) was also prepared from **93e** in an analogous fashion, but it was discovered that the ^{19}F NMR resonances of **89e** and **90e** overlapped, so consequently, rate data could not be obtained for this substrate using the current experimental setup.

Scheme 23.



93a	R = OMe	**94a**	78%	**95a**	39%	**89a**	87%
93b	R = H	**94b**	78%	**95b**	40%	**89b**	88%
93c	R = Cl	**94c**	82%	**95c**	17%	**89c**	84%
93d	R = CN	**94d**	71%	**95d**	---	**89d**	---
93e	R = Me	**94e**	88%	**95e**	54%	**89e**	89%

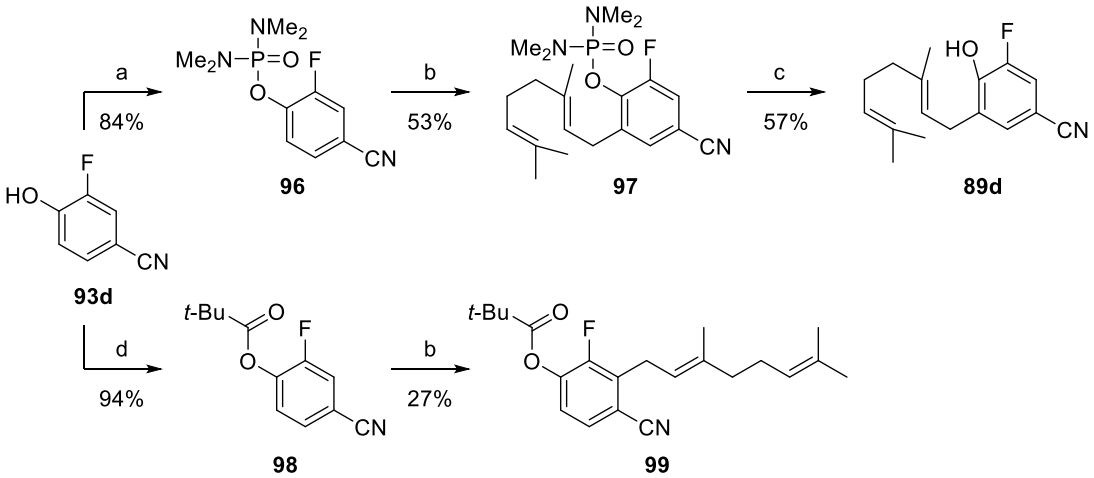
Conditions: a) i-PrCNO (1.1 equiv), DMAP (0.05 equiv), THF, 60 °C; b) TMEDA (1.1 equiv), TMSOTf (1.05 equiv), Et_2O, 25 °C, then TMEDA (2.0 equiv), *n*-BuLi (2.0 equiv), –78 °C, then geranyl bromide (1.25 equiv), –78 °C; c) aq. NaOH (2.5 equiv), EtOH, 25 °C

All values are isolated yields after recrystallization, chromatography, or distillation.

The synthetic sequence just described was not appropriate for the preparation of **89d**, as the nitrile moiety of **94d** was susceptible to nucleophilic addition by *n*-butyllithium during the directed lithiation step (*sec*-butyllithium returned a similar result). In the interest of retaining the

same synthetic strategy, the substitution of organolithium reagents with less nucleophilic magnesium amide bases was investigated (Scheme 24). Knochel and co-workers have reported methods for directed *ortho*-magnesiation of electron-deficient arenes, including those bearing fluorine atoms and nitrile groups. First, the directing group ability of *N,N,N',N'*-tetramethylphosphorodiamidate[92] was investigated with monobasic and dibasic magnesium amide bases. Treatment of **96** with dibasic $(tmp)_2Mg\cdot 2LiCl$ complex, followed by transmetalation and trapping with geranyl bromide, resulted in a dialkylated arene, but encouragingly, the nitrile moiety was untouched under these reaction conditions. To prevent over-metalation, the monobasic (tmp)MgCl·LiCl complex was substituted for the dibasic reagent, which led to the formation of desired *ortho*-alkylation product **97** in good yield. The phosphorodiamidate moiety is crucial for directing magnesiation to the correct position. When carbonate **98** was treated with monobasic (tmp)MgCl·LiCl under identical conditions, magnesiation occurred at the most acidic position leading to undesired isomer **99**, even though *tert*-butyl carbonate is known to be an effective directing group for magnesium amide bases.[93] Directing group removal was achieved by microwave-assisted, acidic hydrolysis to afford phenol **89d**.

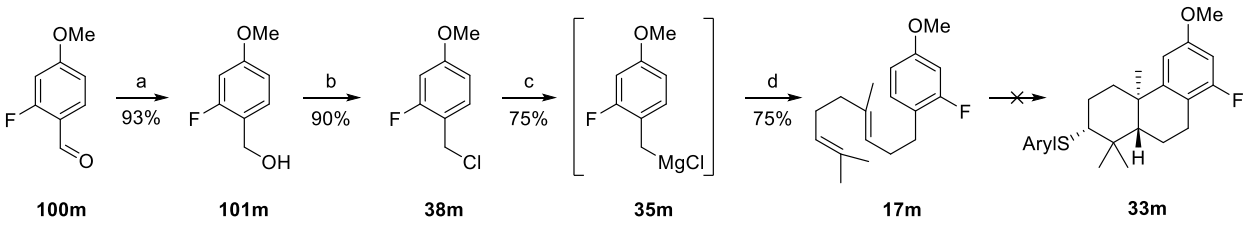
Scheme 24.



Conditions: a) $ClP(O)(NMe_2)_2$ (1.2 equiv), Et_3N (1.2 equiv), DMAP (0.1 equiv), THF, 25 °C; b) tmpMgCl·LiCl (1.1 equiv), THF, 0°C, then $ZnCl_2$ (1.2 equiv), THF, –40 °C, then CuCN·2LiCl (0.5 equiv), geranyl bromide (1.5 equiv), THF, –40 °C to 25 °C; c) HCO_2H/EtOH/H_2O 1:9:1 (0.9 M), μW, 120 °C; d) Boc_2O (1.5 equiv), Et_3N (2.2 equiv), DMAP (0.05 equiv), DCM, 25 °C.

Additionally, a fluorinated homogeranylarene was desired to ascertain whether any differences in the kinetic profile existed for the sulfenocyclizations of **89** and **17**. The challenge here was that electron-deficient homogeranylarenes were known to be incompatible with the sulfenocyclization method (see Chapter 2.2, Table 3, entries 10-11), affording complex mixtures due to their poor nucleophilicity. Consequently, it was anticipated that an *ortho*-fluorinated homogeranylarene would require a balancing electron-donating group for clean cyclization, so diene **17m** was targeted as a substrate. The synthesis of **17m** was straightforward (Scheme 25, see also Chapter 2.2). Reduction of commercially available aldehyde **100m** afforded alcohol **101m** in 93% yield. Treatment of **101m** with thionyl chloride and a catalytic amount of pyridine cleanly afforded benzyl chloride **38m** in 90% yield. The corresponding Grignard reagent **35m** was prepared in 75% yield (determined by titration), and subsequent coupling with geranyl acetate afforded target compound **17m**, also in 75% yield.

Scheme 25.

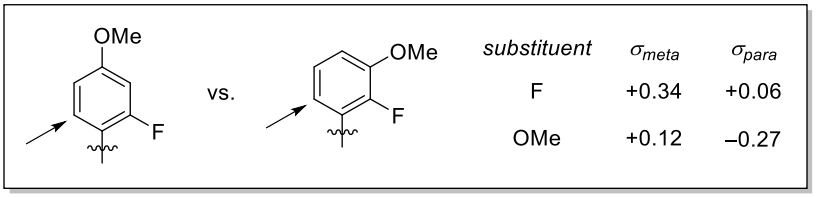


Conditions: a) $NaBH_4$ (1.5 equiv), MeOH, 0 °C, 30 min; b) $SOCl_2$ (1.2 equiv), pyridine (cat.), Et_2O, 0 °C to 25 °C, 3 h; c) Mg (1.3 equiv), THF, 0 °C to 25 °C, 2 h; d) geranyl acetate (1.0 equiv), **35m** (1.05 equiv), Li_2CuCl_4 (0.1 equiv), THF, -10 °C, 4 h.

Unfortunately, diene **17m** did not undergo clean sulfenocyclization under the standard reaction conditions, and a complex mixture of species was formed along with **33m**. Evidently, even with the added methoxy group, the nucleophilicity of the arene was still poor. This was somewhat surprising, given that a methyl ether is the archetypal example of an electron-donating group, but a careful reading of the physical organic literature reveals that such sweeping generalizations can lead to inaccurate predictions of reactivity (Figure 17). A methyl ether only increases the rate of electrophilic aromatic substitution when it is located *para* or *ortho* to the site of carbon-carbon bond formation ($\sigma_{para} = –0.27$). By contrast, a methyl ether located *meta* to the

site of bond formation actually serves to decrease the reaction rate (σ_{meta} = +0.12).[94] Therefore, in order to counterbalance the effect of the electron-withdrawing fluorine atom, the electron-donating methoxy group should actually be placed in the *para* position to provide the most beneficial effect.

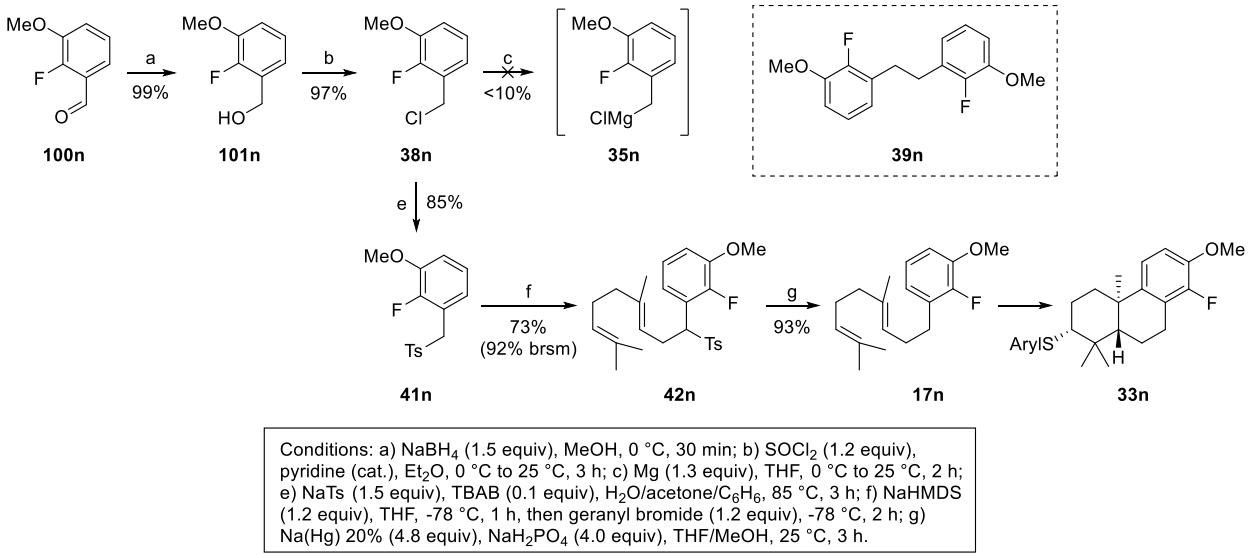
Figure 17. Hammett constants for methyl ethers.



substituent	σ_{meta}	σ_{para}
F	+0.34	+0.06
OMe	+0.12	–0.27

With this consideration in mind, modified diene substrate **17n** was targeted. Initial attempts to prepare **17n** followed the same route used for **17m**. Commercially available aldehyde **100n** was converted to alcohol **101n** and benzyl chloride **38n** without issue. Unfortunately, attempted conversion of **38n** to Grignard reagent **35n** resulted in almost exclusive formation of homocoupling by-product **39n**. Therefore, an alternative route was followed (Scheme 26, see also Chapter 2.2). Benzyl chloride **38n** was converted to sulfone **41n** in 85% yield by a phase transfer-catalyzed nucleophilic displacement. Alkylation with geranyl bromide afforded intermediate **42n** in 73% yield (92% based on recovered starting material). Finally, reductive C–S cleavage using sodium amalgam cleanly afforded the target diene **17n**. Gratifyingly, **17n** underwent clean sulfenocyclization using the standard reaction conditions to afford desired tricycle **33n** as the major product, confirming the original hypothesis.

Scheme 26.



Conditions: a) $NaBH_4$ (1.5 equiv), MeOH, 0 °C, 30 min; b) $SOCl_2$ (1.2 equiv), pyridine (cat.), Et_2O, 0 °C to 25 °C, 3 h; c) Mg (1.3 equiv), THF, 0 °C to 25 °C, 2 h; e) NaTs (1.5 equiv), TBAB (0.1 equiv), H_2O/acetone/C_6H_6, 85 °C, 3 h; f) NaHMDS (1.2 equiv), THF, -78 °C, 1 h, then geranyl bromide (1.2 equiv), -78 °C, 2 h; g) Na(Hg) 20% (4.8 equiv), NaH_2PO_4 (4.0 equiv), THF/MeOH, 25 °C, 3 h.

With all of the desired substrates **89a** through **89d** and **17n** in hand, the kinetics experiments outlined in Scheme 22 were performed. To determine the order in each reaction component, the loadings of catalyst (*S*)-**3a**, sulfenylating agent **2b**, and substrate **89** (or **17n**) were varied from run to run, and the data was processed according to the variable time normalization analysis (VTNA) method described by Burés.[95-97] The VTNA method can be used directly on raw rate data (i.e. [**90**] vs. time) and works by replacing the time axis with the *time integral* (Equation 1) of the concentrations of each reactant (labeled [*A*], [*B*], and [*C*] in Equation 1). The rate plots from different runs will only overlay when the reactant concentrations within the time integral are raised to a certain power (*a*, *b*, and *c*), which corresponds to the order in that reactant. The time integral is approximated by the trapezoid rule (right side of equation 1), so it is easy to calculate from raw rate data using a computer spreadsheet package. The correct values for *a*, *b*, and *c* are simply arrived at by trial and error until, from a visual approximation, a nice overlay of the time-normalized rate plots is observed.

Equation 1.

$$\int_{t=0}^{t=n} [A]^a [B]^b [C]^c dt = \sum_{i=1}^{n} \left(\frac{[A]_i + [A]_{i-1}}{2}\right)^a \left(\frac{[B]_i + [B]_{i-1}}{2}\right)^b \left(\frac{[C]_i + [C]_{i-1}}{2}\right)^c (t_i - t_{i-1})$$

This semi-quantitative data treatment allows the user to extract more information from fewer data points, compared to RPKA and other data analysis methods, at the cost of slightly diminished accuracy (e.g. the treatment can easily differentiate between reaction orders of 2.0, 1.0, and 0.5, but perhaps not between 1.1, 1.0, and 0.9). For example, in the conversion of **89c** to **90c**, the time-normalized rate plots from four different experiments (run at variable concentrations of each reactant) only overlay when the exponent terms within the time integral are equal to 1.0, 0.5, and 0.5 (Figure 18). Nearly identical behavior was likewise observed for all other substrates **89**.

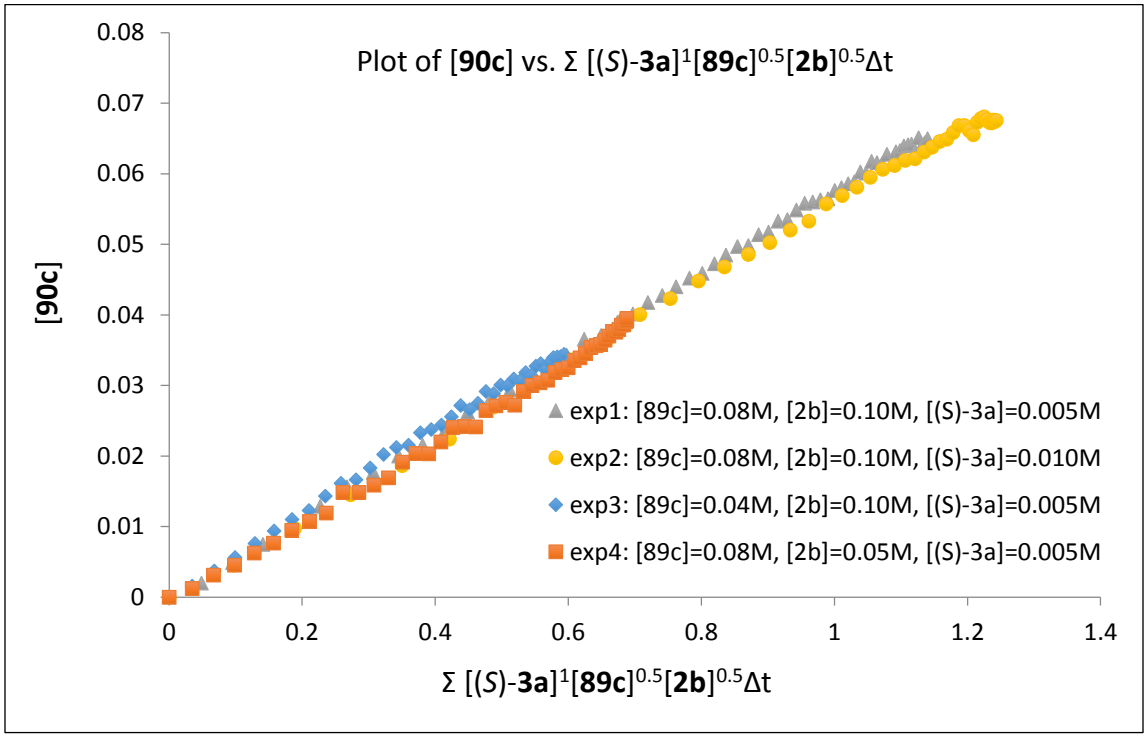
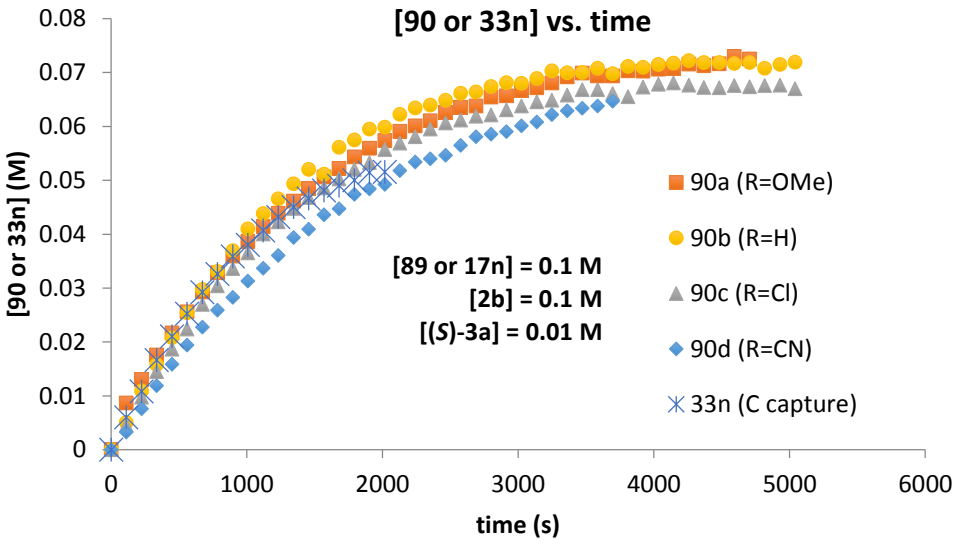


Figure 18. VTNA of the conversion of **89c** to **90c**.

The results of these experiments were quite surprising, and a much different kinetic profile was observed compared to earlier kinetic studies performed in this laboratory for related systems (see Chapter 1). For the sulfenocyclization of **89** to **90**, the reaction was first-order in catalyst (*S*)-**3a** and fractional order in both substrate **89** (~0.5 order) and sulfenylating agent **2b** (also ~0.5 order). The same result was obtained for all substrates, regardless of the *para*-substituent contained in the phenol (Table 8). Complete details can be found in the corresponding manuscript.[98]

Table 8. Calculated rate equations for the sulfenocyclization of **89a** through **89d**.

substrate	*rate equation*	k_{obs}
89a R = OMe	$k_{obs}[(S)\text{-}\mathbf{3a}]^{1}[\mathbf{89a}]^{0.6}[\mathbf{2b}]^{0.5}$	0.062 ± 0.004
89b R = H	$k_{obs}[(S)\text{-}\mathbf{3a}]^{1}[\mathbf{89b}]^{0.5}[\mathbf{2b}]^{0.4}$	0.051 ± 0.003
89c R = Cl	$k_{obs}[(S)\text{-}\mathbf{3a}]^{1}[\mathbf{89c}]^{0.5}[\mathbf{2b}]^{0.5}$	0.055 ± 0.001
89d R = CN	$k_{obs}[(S)\text{-}\mathbf{3a}]^{1}[\mathbf{89d}]^{0.5}[\mathbf{2b}]^{0.6}$	0.075 ± 0.001



A catalyst order of 1.0 is consistent with sulfenyl group transfer (thiiranium ion formation) as the rate-determining step, and is consistent with previous mechanistic studies, but the fractional orders observed for both **89** and **2b** were unexpected. In particular, the presence of any non-zero order for sulfenylating agent **2b** is surprising, because catalyst (*S*)-**3a** is presumed to be saturated at all times (the donor-acceptor complex **91** is presumed to be the resting state of the catalyst). In the present system, the reaction rate is obviously influenced by the concentration of **2b**, but the nature of this influence remains unclear. The observation of fractional order for substrate **89** was also surprising, as an order of 1.0 is expected for a rate-determining step which involves sulfenyl group transfer between **91** and one molecule of olefinic substrate **89**. It was hypothesized that in

HFIP, the phenolic substrate **89** may preferentially exist as a hydrogen-bonded dimer, and dissociation would be required for sulfenyl group transfer to take place. If true, this behavior would result in an observed order of ~0.5 for **89**. This hypothesis was tested by preparing substrate **17n**, which is incapable of forming hydrogen-bonded homodimers, and subjecting it to the same reaction conditions. For the sulfenocyclization of **17n** to **33n**, the exact same kinetic profile was observed as for the conversion of **89** to **90** (1^{st} order in (*S*)-**3a**, ~0.5 order in **2b**, and ~0.5 order in **17n**), which rules out this hypothesis. To ascertain whether this intriguing kinetic profile is an innate property of the polyene sulfenocyclization reaction, or whether it is induced by solvent effects, a previously studied oxysulfenylation reaction[26] was performed in HFIP. The results of this experiment (1^{st} order in catalyst (*S*)-**3a**, 1^{st} order in alkene substrate, and 0^{th} order in sulfenylating agent **2b**) match those obtained previously when the reaction was carried out in CH_2Cl_2 with mesic acid. This result confirms that the unusual reaction orders observed in the conversion of **89** to **90** cannot solely be due to solvent effects. Rather, the polyene sulfenocyclization appears to be unique in its kinetic behavior (compared to other Lewis base-catalyzed transformations studied in these laboratories), which warrants further investigation.

As for the relative rates of reaction of **89a** through **89d**, the k_{obs} seemed relatively immune to changes in the electronic properties of the terminating phenol (Table 8). From a qualitative assessment of the raw rate data (below Table 8), one might conclude that the reaction of electron-deficient **89d** is marginally slower compared to **89a** through **89c**, but this difference is quite small compared to the over 6-fold rate difference between electron-rich and electron-poor substrates originally reported by Johnson.[89] Furthermore, the rate of C-capture (substrate **17n**) appears essentially identical to the rate of O-capture (substrates **89a** through **89d**). These data are more consistent with thiiranium ion generation as the rate-determining step, where electronic perturbations in the terminating group are not expected to exert a large influence. Still, it is noted that a Hammett plot of the rate data from Johnson's study indicates two, distinct mechanistic regimes. For the electron-poor terminating arenes in Johnson's study, the rate of cyclization was strongly influenced by the electronic nature of the substrate ($\rho = -1.4$). But for electron-rich terminating arenes, this dependence was weaker ($\rho = -0.2$), which implies a potential change in the rate-determining step from capture (for electron-deficient terminators) to initiation (for electron-rich groups). In the present study, it is possible that all of the phenols **89a** through **89d** are sufficiently electron-rich such that all four cyclizations are contained within the latter

mechanistic regime. In a similar line of reasoning, it is possible that **89a** through **89d** are too similar (i.e. the *para*-substituent exerts little electronic influence compared to the other three substituents, which are preserved across the series), which would result in similar reaction rates in either mechanistic regime. However, the fact that a comparable reaction rate was measured for **17n** (predicted to be markedly less nucleophilic than any of the phenols **89**) *strongly* suggests that the rate-determining step is *not* the nucleophilic capture of a thiiranium ion, which is consistent with previous mechanistic proposals.

Although this mechanistic picture is still incomplete, these experiments represent an important and necessary step in understanding Lewis base-catalyzed transformations, and may someday provide insight on optimization of sulfenocyclization to include more diverse polyene substrates (e.g. those containing three or more olefins, or containing poorly nucleophilic terminating groups). Based on the data collected so far, it seems reasonable to conclude that the rate-determining step does not involve nucleophilic capture of a thiiranium ion, but as of yet, there is no satisfying explanation for the observed fractional orders in substrate and sulfenylating agent, and this project remains an intriguing area of research.

2.5. Conclusion and Outlook

In summary of this chapter, a method for catalytic, enantioselective polyene cyclization has been developed involving chiral, Lewis base-catalyzed activation of electron-deficient sulfenyl transfer agents. The method is complementary to existing catalytic, enantioselective methods and works exceptionally well for the polycyclization of dienes. Currently, an efficient polycyclization of trienes and longer-chain polyenes remains elusive for this method, despite intensive research in this area. The key barrier to success for this project is identifying highly site-selective conditions for thiiranium ion generation (which ideally do not involve the lengthy synthesis of engineered substrates). The high selectivity observed for dienes is attributed to the lowest-energy, solution-state conformation of the substrate in HFIP which renders one alkene more accessible to the donor-acceptor complex on the basis of folding. Consequently, the identification of ideal solvent blends and temperatures for a selective sulfenocyclization of trienes could be aided greatly by computational chemistry. Performing energy minimization calculations on a triene substrate in a matrix of solvent molecules (chosen from a wide variety of solvents and solvent blends) should

result in a variety of different conformations depending on the reaction medium. Using chemist's intuition, it may be possible to identify promising solvent blends for the transformation simply upon visual inspection of these lowest-energy conformations.

A second major hurdle to the expansion of the sulfenocyclization method was simply the analysis of complex mixtures resulting from substrates which did not cyclize cleanly. It is difficult to optimize a reaction if one cannot even begin to identify the by-products, and this was by far the greatest source of frustration for this project. The development and implementation of new methods for analysis, structure determination, and separation of complex mixtures will almost certainly be necessary if this project is to succeed. A newly developed NMR method called SCALPEL is a promising candidate for the deconvolution of highly complex product mixtures frequently obtained from sulfenocyclization of trienes.[99] The successful application of this method is a promising avenue of future research for this project.

Chapter 3. Enantioselective, Lewis Base-Catalyzed Carbosulfenylation of Alkenylboronates Enabled by a 1,2-Boronate Migration

3.1. Background and Research Objectives

Chiral, non-racemic, secondary and tertiary alkylboronic esters are useful synthetic intermediates in modern organic chemistry.[100-101] Their utility stems from their ability to engage in stereospecific, functional group interconversions (FGIs) to forge new carbon-carbon, carbon-hydrogen, or carbon-heteroatom bonds (Figure 19).[102] Stereoretentive FGIs of boronic esters include oxidation to secondary[103] and tertiary[104] alcohols, amination,[105-106] one-carbon homologation,[107] alkenylation,[108-110] and alkynylation.[111] These methods all proceed with perfect enantiospecificity on account of their shared mechanism, the 1,2-boronate migration. Alkylboronic esters also engage in stereoretentive cross-coupling reactions with aryl halides, which proceed with high enantiospecificity.[112] Additionally, some highly enantiospecific, stereoinvertive processes are known, such as the conversion of alkylboronic esters to alkyl halides.[113-114] Consequently, the development of new methods for constructing enantiomerically enriched secondary and tertiary alkylboronic esters has been an active area of research.[115]

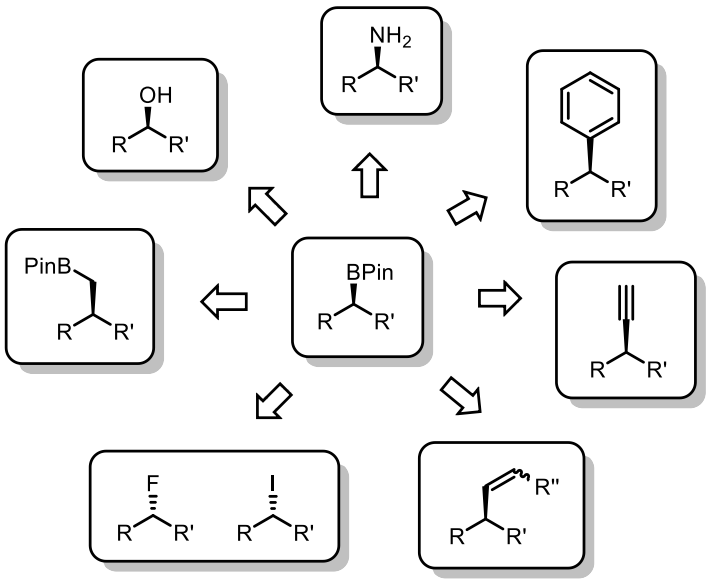
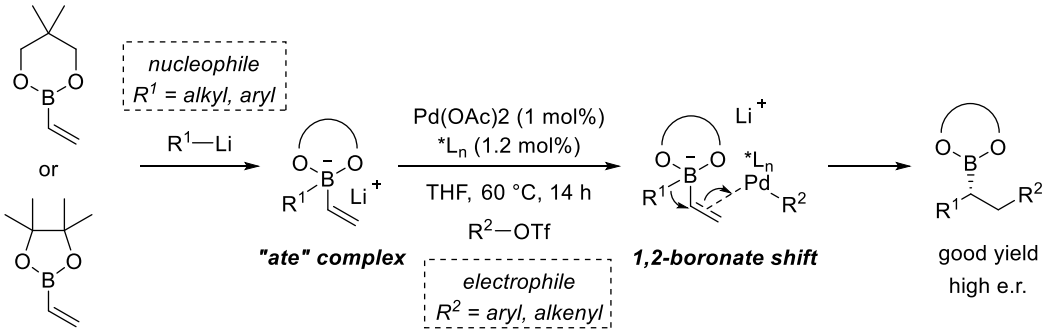


Figure 19. Stereospecific transformations of chiral, non-racemic, alkylboronic esters.

Among the many methods available for preparing chiral, non-racemic alkylboronic esters, the "conjunctive" coupling methods disclosed by Morken and co-workers (Scheme 27) have generated much attention.[116-122] The phrase "conjunctive" was coined by Morken to describe cross-coupling reactions in which the carbon electrophile (e.g. an aryl halide) and the carbon nucleophile (e.g. an organolithium species) are not directly bonded in the product, but rather conjoined by a two-carbon linker. Synthetically, such transformations are quite powerful because they forge two carbon-carbon bonds and create up to two stereogenic centers in a single step. The general mechanism for conjunctive coupling begins with addition of an organometallic reagent to a neutral, electron-deficient boronic ester, which generates an anionic, tetracoordinate, alkenylboronate (8-B-4)[123] complex. This is followed by the key 1,2-metalate shift, an elementary step which is very common for tetracoordinate boron "ate" complexes.[124-125] The 1,2-migration of the nucleophile converts an sp^2-hybridized carbon atom to an sp^3-hybridized stereogenic center, and an arylpalladium (or arylnickel) species, formed by concomitant oxidative addition of the carbon electrophile, serves as the "electron sink" for the electrons displaced from the π-bond. The net result is a secondary or tertiary alkylboronic ester, and the process is rendered highly enantioselective by a chiral ligand.

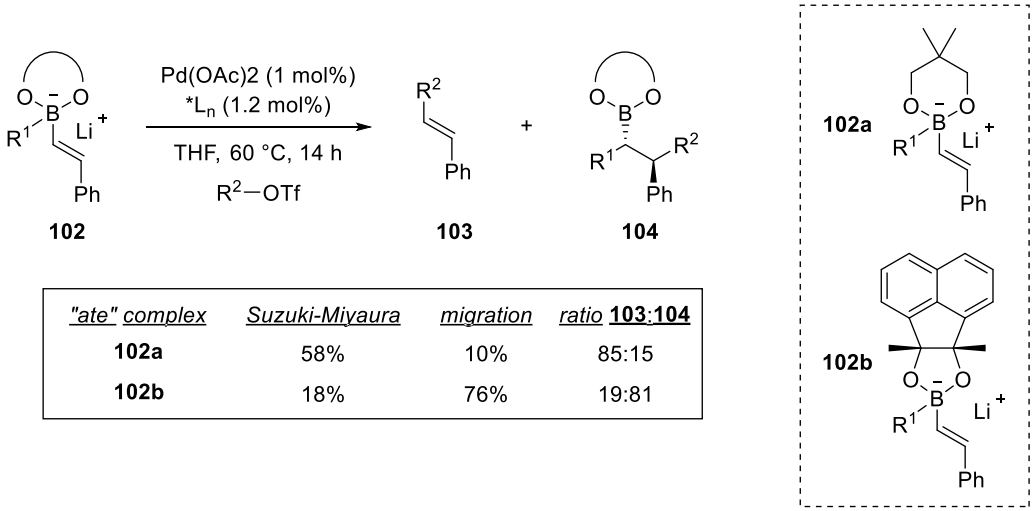
Scheme 27.



Until recently, conjunctive coupling had only been used to prepare compounds bearing one stereogenic center. Boronate migration and carbopalladation proceed at a slower rate for *trans*-disubstituted alkenylboronates compared to monosubstituted vinylboronates; this process was slower than direct Suzuki-Miyaura coupling of the "ate" complex **102** to form **103** (Scheme 28).

Morken and co-workers ultimately solved this problem by employing sterically encumbered, acenaphthoquinone-derived boronic esters to disfavor direct Suzuki-Miyaura coupling.[122] This modification enabled access to a wide range of products **104** containing two vicinal stereogenic centers with a high degree of enantio- and diastereoselectivity.

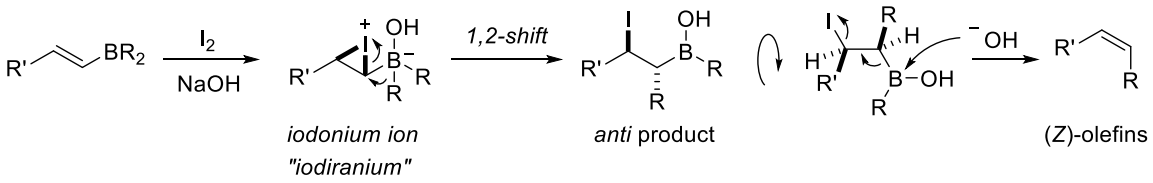
Scheme 28.



"ate" complex	*Suzuki-Miyaura*	*migration*	*ratio* **103**:**104**
102a	58%	10%	85:15
102b	18%	76%	19:81

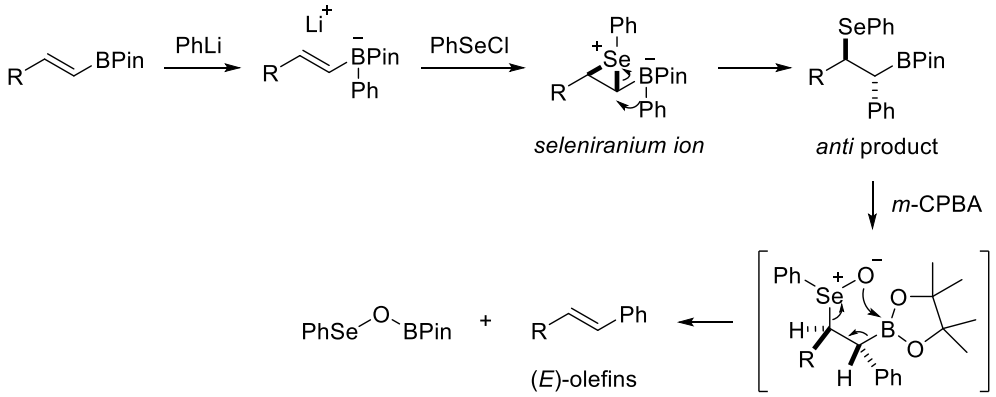
For the diastereoselective, conjunctive coupling shown in Scheme 28, the reported diastereomeric ratios were >20:1 for all products **104**. Under conditions of palladium catalysis, it is reasonable to assume that the migration-carbopalladation is a concerted process, which explains why only *anti* products are observed. This metal-induced, 1,2-metalate migration to an sp^2-hybridized carbon atom appears to be a diastereospecific process, and not merely a diastereoselective one. In fact, the analogous diastereospecific boronate migration to an sp^3-hybridized carbon atom has been known for many decades. The phenomenon was first identified by Zweifel in his eponymous olefination reaction (Scheme 29).[126-127] The reaction of *trans*-disubstituted alkenylboranes with iodine and aqueous base generates a zwitterionic, iodonium-boronate complex. Subsequent 1,2-migration of an alkyl group from the boronate complex opens the iodonium ion in stereospecific fashion, affording an α-iodinated secondary borane as a single *anti* diastereomer. Under the reaction conditions, this intermediate is not isolable and undergoes base-mediated *anti* elimination to form exclusively (*Z*)-olefins.

Scheme 29.



More recently, Aggarwal and co-workers described the synthesis of α-selenylated secondary boranes which proceeds through an analogous mechanism (Scheme 30).[128] The reaction of *trans*-disubstituted alkenylboronic esters with organolithium reagents generates a tetracoordinate, boronate complex. Treating the "ate" complex with phenylselenyl chloride forms a transient, zwitterionic seleniranium ion. Subsequent 1,2-migration opens the seleniranium ion, affording stable, isolable seleno-ethers with >95:5 diastereomeric ratios. A broad substrate scope was demonstrated for this transformation, although an enantioselective variant was not reported. The products are still useful synthetic intermediates, because treatment with a mild oxidant results in spontaneous *syn* selenoxide elimination, reliably affording (*E*)-olefins in high geometric purity.[110]

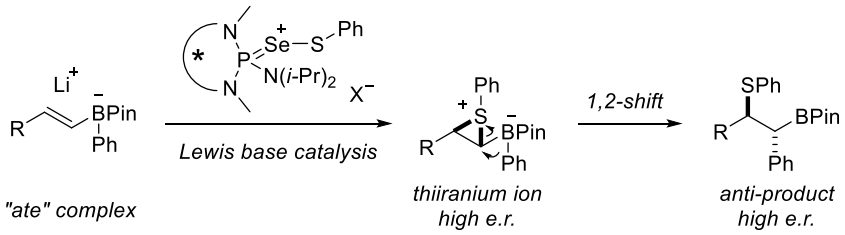
Scheme 30.



It follows that an enantioselective synthesis of α-functionalized, alkylboronic esters, analogous to the racemic syntheses disclosed by Zweifel and Aggarwal, could be achieved if the

initial generation of an “iranium” ion was rendered enantioselective. The enantioselective, electrophilic thiofunctionalization of alkenes using Lewis base catalysis has been extensively developed in the Denmark laboratory (see Chapters 1 and 2).[19] It was hypothesized that sulfenyl group transfer from a chiral, cationic donor-accepter complex (see Chapter 1, Figure 9) to an alkenylboronate would generate an enantiomerically enriched, zwitterionic, thiiranium “ate” complex (Scheme 31). Subsequent, diastereospecific 1,2-boronate migration would open the thiiranium ion and afford chiral, non-racemic alkylboronic esters bearing two vicinal stereogenic centers with a high degree of stereochemical control. This method was envisioned to be complementary to those previously disclosed by Morken, and to expand the chemical space of chiral, non-racemic boronic esters accessible through the 1,2-metalate shift.

Scheme 31.



The research objectives for this project are summarized as follows: (1) demonstration of a Lewis base-catalyzed, enantioselective carbosulfenylation of alkenylboronates, proceeding by the mechanism just described, which is characterized by (a) good yields, (b) good enantioselectivities, and (c) broad functional group tolerance; (2) thorough analysis of reaction scope, in particular the effect of alkene substitution on reaction outcome; and (3) demonstration of useful FGIs of both the thioether and boronic ester moieties present in the products.

3.2. Reaction Development and Scope

Despite the apparent simplicity of the proposal outlined above, alkenylboronates were anticipated to be quite challenging substrates for enantioselective, electrophilic thiofunctionalization using the traditional Denmark catalyst system, for a number of reasons. First,

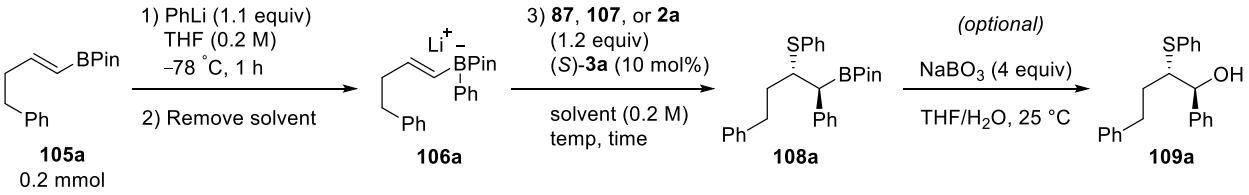
alkenylboronates are significantly more nucleophilic than simple, unactivated alkenes or even styrenes. As such, background conversion was expected to be a substantial problem, and one which would lead to drastic reductions in obtainable enantioselectivity. Second, alkenylboronates were anticipated to be incompatible with the acidic reaction conditions typically required to generate the cationic, donor-acceptor complex (see Chapter 1, Figure 9). Third, it was envisioned that the key zwitterionic thiiranium "ate" complex may exist in equilibrium with an open-chain carbocation stabilized by an adjacent (8-B-4) center through hyperconjugation, which could lead to an erosion in the obtainable diastereospecificity for the 1,2-boronate migration event.

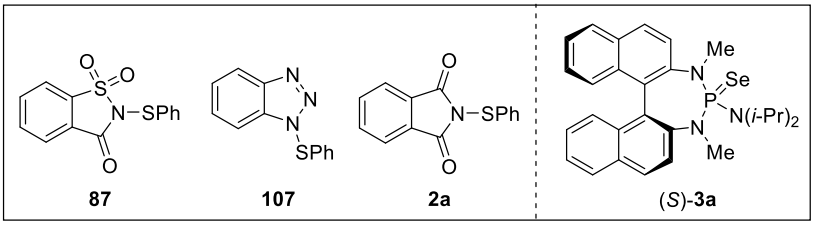
As a starting point for reaction development, boronate complex **106a**, generated from boronic ester **105a** and phenyllithium, was treated with saccharin-derived sulfenylating agent **87** and catalyst (*S*)-**3a** in CH_2Cl_2 at cryogenic temperatures (Table 9). Because of the anticipated incompatibility of **106a** with acidic reagents, the more reactive **87** was selected for its ability to transfer its sulfenyl group to catalyst (*S*)-**3a** without the assistance of acid, unlike phthalimide-derived **2a**. In fact, these reaction conditions are very similar to those employed for the catalytic, enantioselective thiofunctionalization of silyl enol ethers,[83] a class of alkenes which also exhibit enhanced nucleophilicity and acid sensitivity. Encouragingly, the desired product **109a** (from oxidation of immediate product **108a**) was isolated after 3 hours in good yield and perfect diastereospecificity. Unfortunately, **109a** was nearly racemic, which was indicative of rapid background reactivity between **106a** and **87** (Table 9, entries 1-2). Background reactivity was effectively suppressed with the less-reactive sulfenylating reagents **107** or **2a** (entries 3-6), but unsurprisingly, in the absence of an acidic environment, adding catalyst (*S*)-**3a** did not improve conversion.

Inspired by recent studies on the Lewis base-catalyzed, enantioselective polyene sulfenocyclization, in which using HFIP as a reaction solvent obviated the requirement for strongly acidic additives (see Chapter 2.2),[70] various polar protic solvents were surveyed in the present system. Employing methanol or ethanol ($pK_a = 16$)[129] as a reaction solvent with **87** and (*S*)-**3a** led to a remarkable improvement in enantioselectivity, while yield of **109a** remained high (entries 7-10). Evidently, the background reaction was dramatically attenuated in these solvents. No conversion was observed when the less active sulfenyl transfer reagents **107** and **2a** were employed, except when the more acidic alcohols TFE ($pK_a = 12$)[64] or HFIP ($pK_a = 9$)[64] were used as reaction solvents (entries 11-16). In these latter cases, observed enantiomeric ratios for **109a**

were still high, indicating a similar suppression of background reactivity, but yields were sharply diminished, likely due to acid-mediated decomposition of the boronate complex. These results reveal an interesting "balancing act" between the solvent pK_a and the activity of the sulfenylating reagent which enables a productive reaction of **106a**. Although all of the polar protic solvents successfully attenuated the background reaction, the boronate **106a** is only stable in the higher pK_a solvents ethanol and methanol, and only the most active reagent **87** is capable of transferring a sulfenyl group in this non-acidic environment. Therefore, the optimized conditions in entry 10 were selected to explore the scope of the transformation. The suppression of background reactivity in polar protic solvents is attributed to hydrogen bonding interactions between the solvent and the pinacolate complex **106a**, which serves to stabilize the anionic character and decrease the nucleophilicity of **106a**. This feature ensures that sulfenyl group transfer occurs only from the highly electrophilic, cationic, donor-accepter complex, and not from the mildly electrophilic **87**.

Table 9. Optimization of Sulfenylating Agent, Solvent, and Temperature.



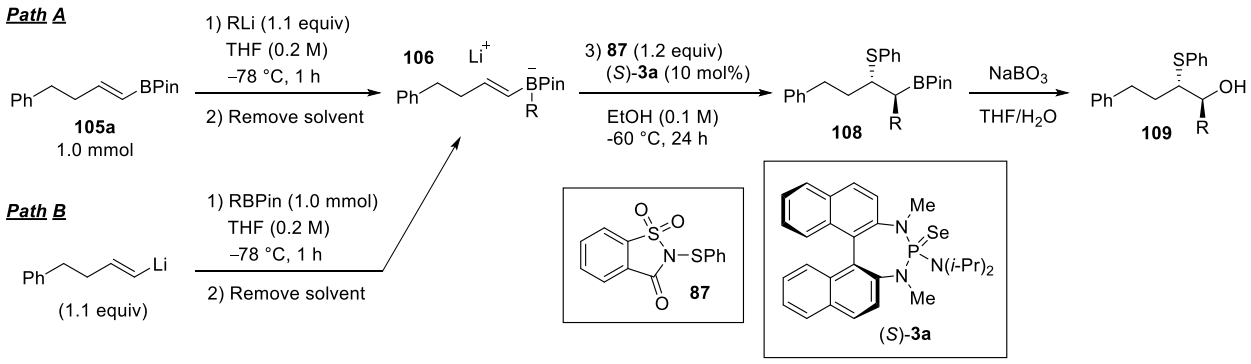


entry	S.A.	cat	solvent	temp (°C)	time (h)	yield(%)	e.r.
1	**87**	--	CH_2Cl_2	-78	3	56[a]	--
2	**87**	(*S*)-**3a**	CH_2Cl_2	-78	3	68[a]	55:45
3	**107**	--	CH_2Cl_2	-78	18	11[b]	--
4	**107**	(*S*)-**3a**	CH_2Cl_2	-78	18	16[b]	57:43
5	**2a**	--	CH_2Cl_2	-20	36	31[b]	--
6	**2a**	(*S*)-**3a**	CH_2Cl_2	-20	36	37[b]	53:47
7	**87**	--	MeOH	-60	24	10[b]	--
8	**87**	(*S*)-**3a**	MeOH	-60	24	47[a]	94:6
9	**87**	--	EtOH	-60	24	14[b]	--
10	**87**	(*S*)-**3a**	EtOH	-60	24	80[a]	98:2
11	**107**	--	EtOH	-20	24	7[b]	--
12	**107**	(*S*)-**3a**	EtOH	-20	24	10[b]	--
13	**107**	--	TFE	-20	2	10[b]	--
14	**107**	(*S*)-**3a**	TFE	-20	2	32[b]	85:15
15	**2a**	--	HFIP	0	2	0[c]	--
16	**2a**	(*S*)-**3a**	HFIP	0	2	27[a,c]	83:17

a) Yield of isolated alcohol **109a** from oxidation. b) ^{1}H NMR yield of pinacolborane **108a.** c) Extensive decomposition of boronate **106a** observed.

With the optimized conditions in hand, the substrate scope of the reaction was examined, beginning with the migrating groups. Operationally, the "ate" complex **106** is prepared in THF by the reaction between an organolithium reagent and an alkenylboronic ester (Path A). Alternatively, the roles of the reacting partners can be reversed (Path B) to form **106** with equal efficacy, for cases in which functional group liabilities preclude conversion of the migrating group to an organolithium reagent. In either case, THF is removed in vacuo and **106** is redissolved in ethanol. The solution of **106** is then transferred to a second, pre-cooled flask containing a suspension of **87** and (S)-**3a** in ethanol in which the sulfenylation-migration reaction takes place (Scheme 32). The resulting chiral, non-racemic boronic esters **108** can be isolated and are generally stable to chromatographic purification, but in most cases they were oxidized to the corresponding alcohols **109** to aid purification and characterization.

Scheme 32.



A selection of the compatible migrating groups and the resulting products **109** are illustrated in Figure 20. The complete scope can be found in the manuscript.[84] Generally speaking, electronically diverse aryl groups, including those bearing *ortho* substituents, migrated efficiently to afford products **109** in high yields, high enantioselectivity, and perfect diastereospecificity. A drop in yield and enantioselectivity was observed for heteroaryl and alkyl migrating groups, exposing a current limitation of this method. Intriguingly, the absolute configuration of **108** (determined by X-ray crystallography) was found to be (*S*,*S*), *opposite* to what was expected from catalyst (*S*)-**3a** on the basis of previous studies in the Denmark laboratory and existing models for

facial selectivity.[26] Clearly, the modes of interaction between pinacolboronates **106** and the cationic, donor-acceptor complex are much different than those which exist for simple olefins. That the observed enantiomeric ratio is still very high, just in the opposite direction, is a remarkable outcome whose origin is still an object of active speculation.

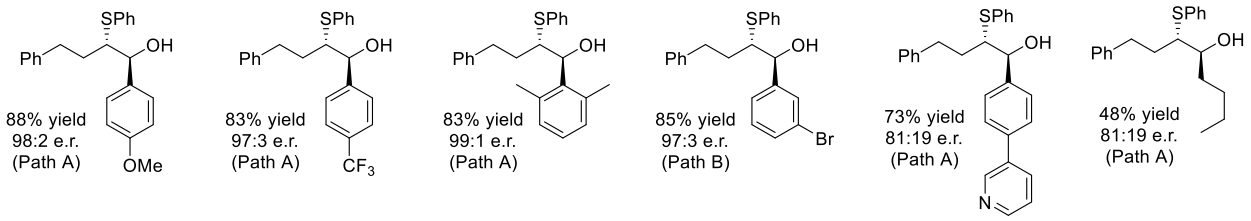
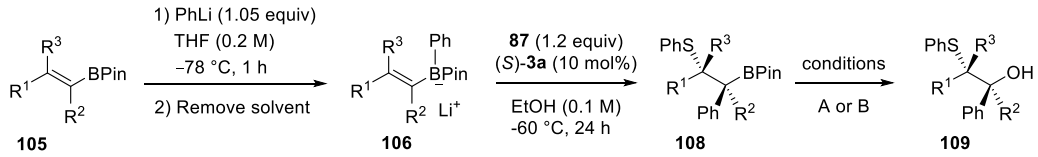


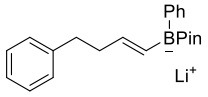
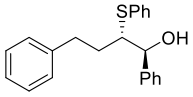
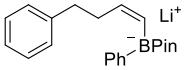
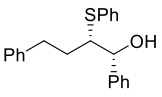
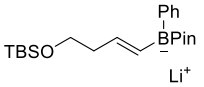
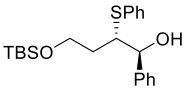
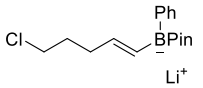
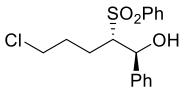
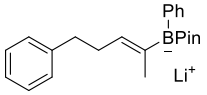
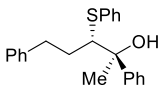
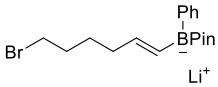
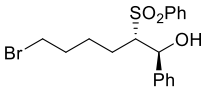
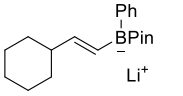
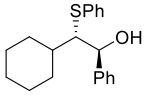
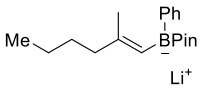
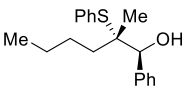
Figure 20. Representative scope of migrating groups.

With the survey of migrating groups completed, the examination of scope turned to focus on the substitution pattern of the alkenyl fragment (Table 10). As the key mechanisms for facial discrimination were likely different for alkenylboronates compared to simple olefins (*vide supra*), a thorough survey of differentially substituted alkenylboronates in the presence of (*S*)-**3a** was deemed necessary. In agreement with all previous work, *trans*-1,2-disubstituted alkenylboronates **106a** through **106e** were excellent substrates for the present transformation, affording products **109a** through **109e** with consistently high enantiomeric ratios using catalyst (*S*)-**3a**. Functional groups compatible with the transformation include silyl ethers and primary alkyl halides. All attempts to rigorously purify **109c** and **109d** resulted in intra- and/or intermolecular halide displacement to form alkylsulfonium salts. Therefore, the crude thioethers were oxidized to the stable sulfones **110c** and **110d** for isolation and purification. Also in agreement with previous work, a *cis*-1,2-disubstituted alkenylboronate **106f** was not well-recognized by (*S*)-**3a** and afforded **109f** in poor enantiomeric ratio (68:32).[20] Although geminal 1,1-disubstituted alkenes are traditionally poor substrates for (*S*)-**3a**, that was not true in the present case. Both 1,1-disubstituted alkenylboronate **106g** and 1,1,2-trisubstituted alkenylboronate **106h** reacted efficiently to form products **109g** and **109h** in high yield and high enantioselectivity. Unfunctionalized vinylboronate **106i** reacted to form **109i** in good yield but more modest enantioselectivity (84:16). Finally, 1,2,2-trisubstituted alkenylboronate **106j** was a poor substrate for this transformation. Product **109j** was isolated in poor yield and nearly racemic form. This result was analogous to that observed by

Aggarwal and co-workers for the selenofunctionalization of a similar compound.[128] This phenomenon results from premature opening of the thiiranium (or seleniranium) ion to form a stabilized, tertiary carbocation which is highly susceptible to elimination.

Table 10. Survey of alkenylboronates in enantioselective sulfenylation-1,2-migration.



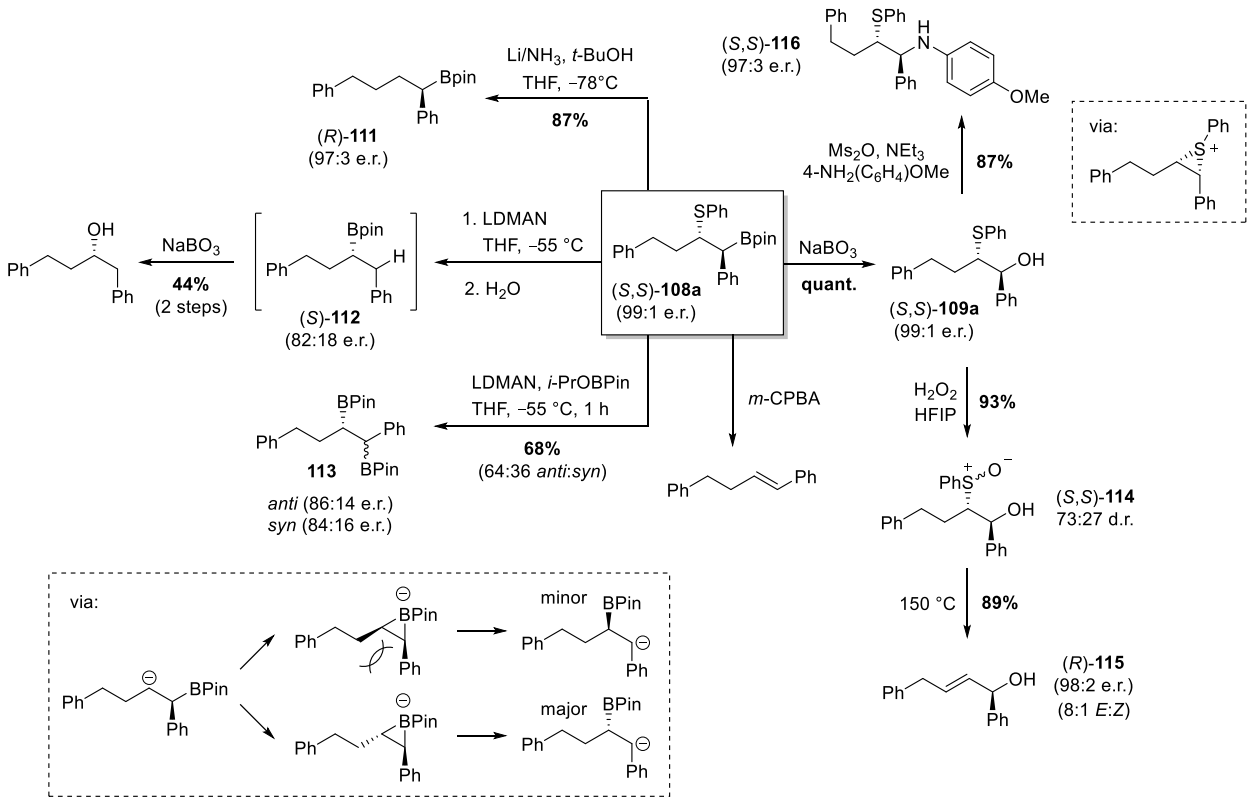
substrate 106	product 109	yield	e.r.	substrate 106	product 109	yield	e.r.
 **106a**	 **109a**	85%[a]	98:2	 **106f**	 **109f**	61%[a]	69:31
 **106b**	 **109b**	65%[a]	96:4	 **106g**	 **109g**	74%[b]	95:5
 **106c**	 **110c**	85%[a,c]	99:1	 **106h**	 **109h**	76%[b]	96:4
 **106d**	 **110d**	80%[a,c]	99:1	 **106i**	 **109i**	60%[a]	84:16
 **106e**	 **109e**	90%[a,c]	99:1	 **106j**	 **109j**	27%[b,d]	54:46

a) Conditions A for oxidation of **108** to **109**: $NaBO_3$ (4 equiv), THF/H_2O, 25 °C; b) Conditions B for oxidation of **108** to **109**: NaOH, H_2O_2, THF, 0 °C; c) **109** oxidized to sulfone **110** with *m*-CBPA prior to isolation; d) Tentative absolute configuration shown.

As alluded to previously, the chiral sulfenyl boronic esters **108** are stable intermediates, and both functional groups engage in a number of synthetically useful FGIs (Scheme 33). Treating enantiomerically enriched **108a** with one set of reducing conditions (lithium, ammonia, *tert*-

butanol) afforded the expected C–S cleavage product **111** in good yield. Alternatively, when LDMAN was used as the reductant, an interesting rearrangement occurred (likely via a cyclic boratirane ion) to form the more stabilized, benzylic carbanion. The carbanion can be trapped with a proton source or other electrophiles. Owing to the kinetic preference for *anti* (vs. *syn*) boratirane formation, only a modest erosion in e.r. (82:18) was observed for **112** or for either diastereomer of **113**. All attempts to selectively oxidize the sulfenyl group of **108a** simply resulted in elimination to form a *trans*-alkene (see Scheme 30).[110] After first oxidizing boronic ester **108a** to alcohol **109a**, the sulfenyl group could then be oxidized to afford stable intermediate **114**. Thermal sulfoxide elimination formed allylic alcohol **115**. This sequence serves as a useful method for the preparation of secondary (and tertiary) allylic alcohols with a high degree of stereochemical control. Mesylation of **109a** reforms the thiiranium ion, which can be re-opened with diverse nucleophiles and overall retention of configuration. This protocol was used to access α-stereogenic secondary amine **116** in high yield.

Scheme 33.



3.3. Conclusion and Outlook

In summary, a catalytic, enantioselective, and diastereospecific carbosulfenylation of alkenylboronates has been demonstrated. The reaction proceeds by enantioselective, Lewis base-catalyzed sulfenyl group transfer to an electron-rich alkene, followed by a 1,2-boronate migration to open the resulting thiiranium ion. The reaction is performed under mild conditions and displays reasonable functional group tolerance. A wide variety of aryl groups were demonstrated to migrate efficiently, while the migration of alkyl groups is not yet optimized. Most alkene substitution patterns are tolerated in the reaction, although *cis* alkenylboronates are not optimal substrates for the transformation. The products of the reaction are chiral, non-racemic alkyl boronic esters bearing two vicinal stereogenic centers, which are useful intermediates in organic synthesis. The versatility of these compounds was highlighted by several robust FGIs.

The reversal in absolute configuration for sulfenylation products derived from alkenylboronates compared to simple olefins is a phenomenon which warrants future investigation, which would be primarily computational in nature. Elucidation of key transition state substrate-catalyst interactions which influence facial selectivity would provide valuable information regarding structure-activity relationships of the Denmark catalyst. This knowledge could be used to inform catalyst optimization for substrates which are more challenging, e.g. those which involve migration of an alkyl group, and would thus expand the chemical space accessible by the boronate sulfenylation-migration method.

Alkenylboronate sulfenylation-migration and polyene sulfenocyclization are the latest two (published!) examples from the Denmark laboratory of Lewis base-catalyzed reactions which have been enabled by polar protic solvents, albeit for very different reasons. In recent years, it has become more reasonable to suggest that provided the appropriate reaction conditions, the Denmark catalyst system is capable of generating a thiiranium ion on *any* alkene, regardless of its steric or electronic properties, and that this thiiranium ion may be opened by *any* reasonably nucleophilic group. The number of novel, truly imaginative transformations which the Lewis base subgroup has brought to fruition within just the past year alone is quite exciting. The key, overarching challenge which remains to be solved is the development of a catalyst scaffold which can more effectively recognize *cis* alkenes. Highly enantioselective functionalization has remained well out of reach for this broad substrate class. Perhaps machine learning methods for computer-guided

catalyst optimization, another active area of research within the Denmark laboratory, could one day provide a solution to this problem.

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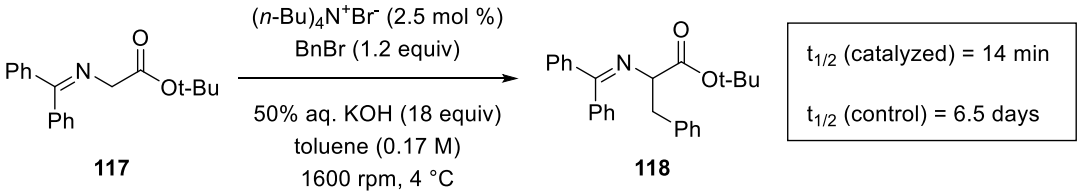
Appendix A. The Phase Transfer Catalyzed, Anionic oxy-Cope Rearrangement

A.1. Introduction

Phase transfer catalysis (PTC) is a form of catalysis in which a transfer reagent facilitates the transport of ionic intermediates between immiscible phases.[130] Often, these immiscible phases are two liquid layers, one aqueous and the other an organic solvent like toluene, although solid-liquid PTC systems are known. The transfer reagent is typically a quaternary ammonium or phosphonium salt which is sufficiently lipophilic to have affinity for both aqueous and organic phases. The hydroxide-mediated α-alkylation of glycine imine Schiff bases in the presence of a tetraalkylammonium salt is a classic example of a PTC reaction (Scheme 34). In the presence of an ammonium catalyst, this reaction reaches full conversion in a few hours, but takes days in the absence of catalyst.[131]

Scheme 34.



Two general theories exist as to the exact mechanism of a phase transfer catalyzed reaction: the extraction model, proposed by Starks,[132] and the interfacial model, proposed by Makosza.[133] A brief comparison of these models is appropriate. In the extraction model (Figure 21), illustrated for the base-mediated *O*-alkylation of alkoxides (Williamson ether synthesis), the role of the catalyst is to extract inorganic ions from the aqueous phase. Once the ammonium salt diffuses into the aqueous layer, it undergoes salt metathesis (exchange) with potassium hydroxide to form an ammonium hydroxide species. This species diffuses back into the organic layer, where hydroxide deprotonates the substrate to form an ammonium alkoxide ion pair. Subsequent reaction with an electrophile forms the product and regenerates the catalyst. Reactions which operate by the extraction mechanism are intrinsically (organic) rate-limited and therefore stir rate-independent.

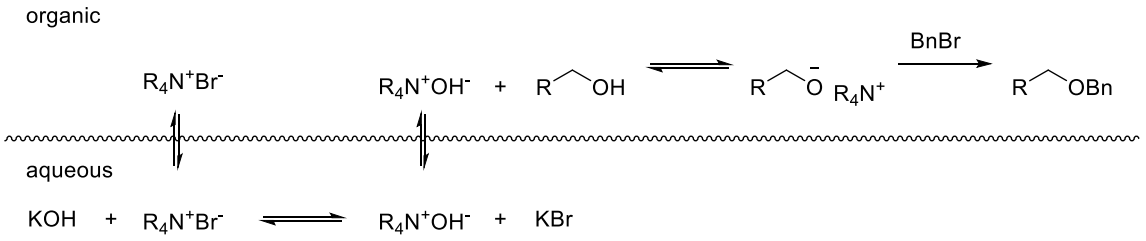


Figure 21. Starks extraction model.

The extraction model is commonly invoked for reactions with unstabilized, anionic intermediates (e.g. alkoxide ions), or when the anion being transported has somewhat higher affinity for the organic layer, as in the S_N2 displacement of an alkyl halide by cyanide ion under biphasic conditions.[130] For base-mediated PTC reactions involving stabilized anions (e.g. enolates), it is far more likely that the Makosza interfacial mechanism (Figure 22) is operating, as illustrated in Scheme 34 for the α-alkylation of a glycine imine Schiff base. The principal difference between the extraction and interfacial mechanisms is that in the interfacial model the ammonium salt is not directly involved in transporting inorganic ions from the aqueous layer to the organic layer. Both the inorganic hydroxide base and the acidic substrate are assumed to be present in small amounts in the "interfacial" region, a water-rich organic layer where the two phases meet. Deprotonation occurs to form the sodium or potassium enolate, followed by ion exchange with the catalyst to generate an ammonium enolate ion pair.

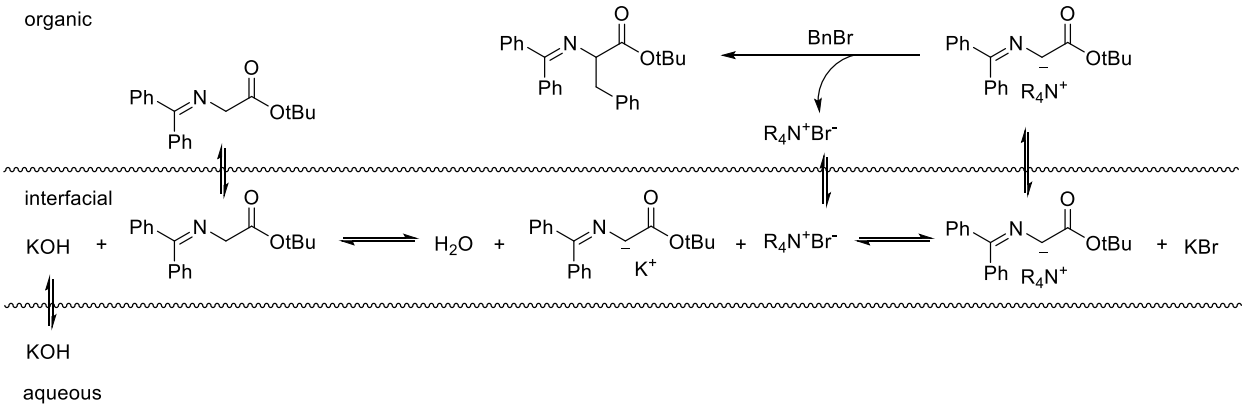


Figure 22. Makosza interfacial mechanism.

Alternatively, the formation of the ammonium hydroxide species in the interfacial region could occur first, followed by deprotonation to form the ammonium enolate (Figure 23, Liotta modification). In either case, the ammonium enolate ion pair then diffuses from the interfacial region to the organic layer in a process called *desolvation*. The primary role of the catalyst is this transfer of an organic anion (e.g. an enolate) from the interfacial region to the organic phase. The remainder of the mechanism mirrors that of the extraction model: attack on an electrophile to form the product and regenerate the catalyst. Reactions which operate by the interfacial mechanism are transport rate-limited, and therefore stir rate-dependent.

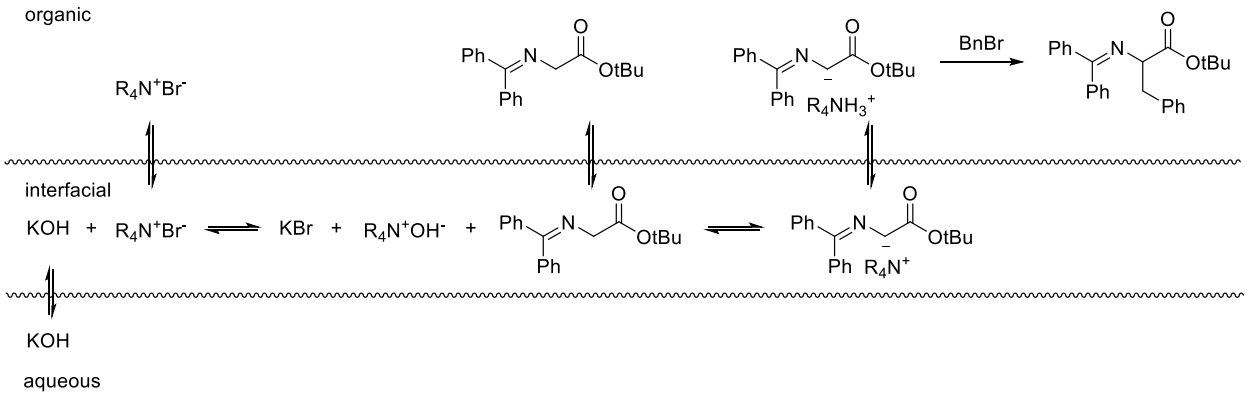


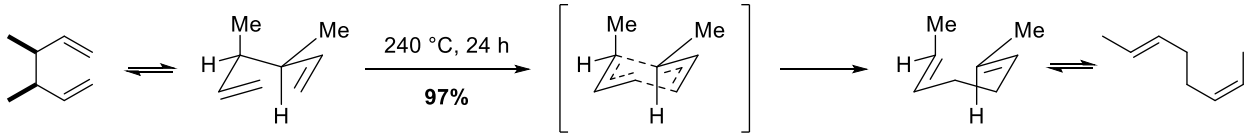
Figure 23. Liotta modification of the Makosza interfacial mechanism.

Replacing the tetraalkylammonium salt with a chiral ammonium catalyst opens up the possibility of asymmetric phase transfer catalysis (APTC) by differentiating the two faces of the ammonium enolate. This concept was first exploited by the Merck Corporation for the enantioselective α-methylation of indanone derivatives, and later by O'Donnell and co-workers for the enantioselective mono-alkylation of glycine imine Schiff bases.[134-135] The latter example continues to be a premier method for the enantioselective synthesis of non-natural, α-amino acids (see Appendix C). The ability to form new carbon-carbon bonds stereoselectively under exceptionally mild conditions has made PTC a powerful force in organic synthesis for the past several decades. Phase transfer catalysis affords several advantages over traditional, homogeneous reaction conditions; namely, a reduction in the volume of organic solvent required, and the ability to use more environmentally benign reagents (e.g. hydroxide and carbonate bases) which are

poorly soluble in organic media. The development of novel phase transfer-catalyzed transformations is therefore relevant from both an industrial and an academic standpoint.

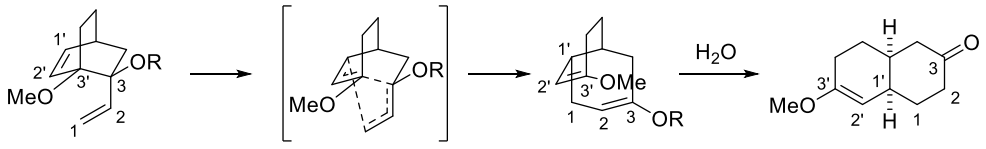
Pericyclic reactions have long been recognized as powerful tools in the synthesis of complex organic molecules, due to their highly predictable nature and ability to set multiple stereogenic centers in a single step.[136] Pericyclic reactions may be bimolecular, as is the case with many cycloadditions, but a large number, including sigmatropic rearrangements and electrocyclizations, are unimolecular in nature. The Cope rearrangement, the thermal [3,3]-sigmatropic rearrangement of 1,5-dienes, is one such transformation (Scheme 35). Unless the 1,5-diene is part of a particularly strained carbon skeleton, the Cope rearrangement proceeds through a chair-like transition state, leading to predictable configurations and double bond geometries in the products formed. Traditional Cope reactions often require high temperatures unless there exists a significant thermodynamic driving force which favors the product side of the equilibrium (e.g. release of strain).[137]

Scheme 35.



Evans and Golob discovered that an oxyanion substituent on one of the C(sp^3) carbons of a 1,5-diene leads to dramatic rate enhancement of the Cope rearrangement, often allowing these reactions to be run at room temperature or lower. Presumably, the electron density of the oxyanion helps to stabilize the transition state, leading to the observed rate enhancement. Additionally, the formation of an enolate in the product is a thermodynamic driving force for the reaction, rendering the rearrangement irreversible. The rearrangement of 1,5-dien-3-ols in the presence of a strong base has been termed the anionic oxy-Cope rearrangement (Scheme 36).[138]

Scheme 36.



Alcohol **119** (R = H)
Alkoxide **120** (R = K)

Substrate	*Ea* (kcal/mol)	Temp. (°C)
119	35.9 ± 1.8	175-215
120	19.4 ± 0.7	10-55

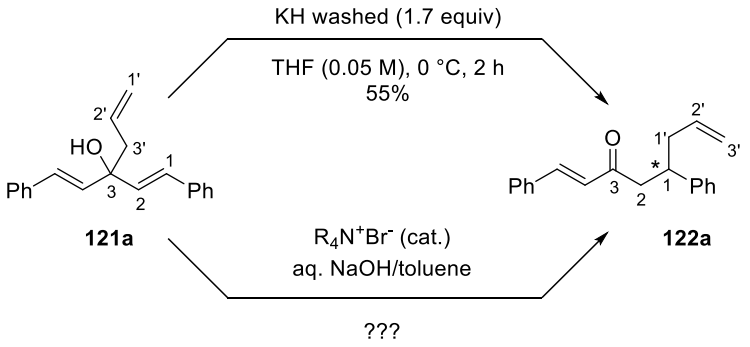
Most examples of the anionic oxy-Cope rearrangement in the literature are carried out in a polar aprotic solvent like THF, HMPT, or diglyme. Although some allylic alcohols are significantly acidic to be deprotonated by hydroxide bases, sodium and potassium hydroxide are incompatible with the typical reaction conditions due to their poor solubility in these organic solvents. Potassium hydride is used instead, and although this strong base also exhibits poor solubility in THF, the deprotonation step is irreversible due to the generation of H_2. Often, anionic oxy-Cope rearrangements also benefit from the addition of 18-crown-6, which suggests that a solvent-separated ion pair rearranges more quickly. Not all anionic oxy-Cope rearrangements can be carried out at temperatures at low as 0 °C, but in general the conditions are far less forcing than those required for Cope rearrangements.

Since this rearrangement proceeds via an anionic intermediate, it was considered a potential candidate for a phase transfer-catalyzed reaction. While the most common application of PTC is in the α-alkylation of carbonyl compounds, in theory, PTC may be applied to any reaction that involves an anionic intermediate, including unimolecular rearrangements.[139] While the vast majority of known PTC reactions are bimolecular, there are scattered reports in the literature of intramolecular reactions involving ionic intermediates being run under PTC conditions.[140-142]

Performing the anionic oxy-Cope rearrangement under PTC conditions (Scheme 37) offers potential advantages over the traditional reaction conditions. Inorganic hydroxide bases could be compatible with the rearrangement under liquid-liquid PTC conditions, eliminating the need for handling reactive hydride bases. The ammonium alkoxide generated as an intermediate under PTC conditions is a more separated ion pair than a sodium or potassium alkoxide and thus more likely to undergo rearrangement. This eliminates the need for costly crown ethers as reaction additives.

Most importantly, if there are substituents on either double bond of the starting material, a new stereogenic center will be generated in the reaction, and the use of a chiral ammonium salt as a transfer reagent may induce some degree of enantioselectivity in the product.

Scheme 37.



The system chosen for initial study (Scheme 37) is a desymmetrization reaction of achiral, tertiary alcohol **121a**. The product of rearrangement is conjugated ketone **122a** which bears a β-stereogenic center. The conversion of **121a** to **122a** has already been demonstrated in racemic form under classical anionic oxy-Cope conditions.[143] However, if the reaction is amenable to PTC conditions, a chiral ammonium counterion may bias one reactive conformer over the other, leading to non-racemic product. There are limited reports in the literature of asymmetric phase transfer catalyzed rearrangements.[140-142] Many of these have a limited substrate scope, but nevertheless they are proof that a chiral ammonium counterion can influence the stereochemical outcome of a unimolecular PTC reaction. Thus, the enantioselective, desymmetrization of tertiary alcohols such as **121a** may be possible via a phase transfer catalyzed anionic oxy-Cope rearrangement. This would help to further expand the utility of pericyclic reactions in organic synthesis. The research objectives for this project were: (1) to establish the viability of a phase transfer catalyzed anionic oxy-Cope rearrangement (i.e. demonstrate catalytic activity as well as no background conversion) and (2) investigate the application of asymmetric PTC to this rearrangement using chiral ammonium salts for the desymmetrization of tertiary alcohols

A.2. Development and Scope

In order to study the desymmetrization of achiral tertiary alcohols via a phase transfer-catalyzed, anionic oxy-Cope rearrangement, four substrate classes were envisioned for the initial scope (Figure 24). All are 1,5-dien-3-ols with an additional vinylic or allylic substituent, with varying patterns of substitution. The retrosynthesis of all four substrate classes involves the addition of allylic or vinylic Grignard reagents into substituted ketones or esters. Members of the first three classes were synthesized, including several novel compounds. The synthesis and subsequent reactivity studies of each class will be presented in the order in which they appear in the figure.

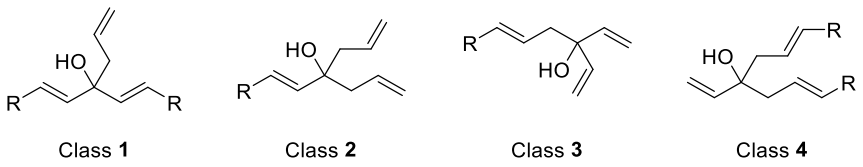
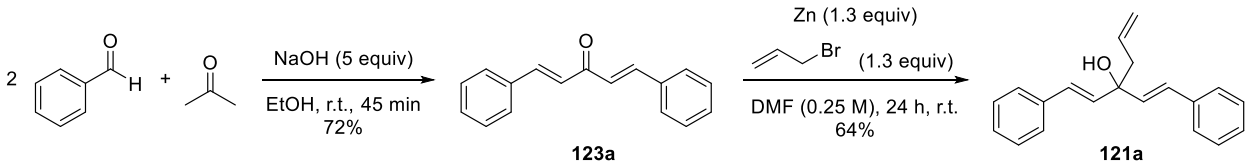


Figure 24. Target substrates for anionic, oxy-Cope rearrangement.

Compounds in Class 1 proved to be the most successful for undergoing rearrangement and were also rather easy to access. Dicinnamyl alcohol **121a** was synthesized through a known route (Scheme 38). The precursor to **121a** is dibenzylidene acetone (DBA) **123** which is commercially available but also easily synthesized by the condensation of benzaldehyde with acetone.[144] Addition of an allylzinc reagent into **123** was accomplished using a published procedure.[143]

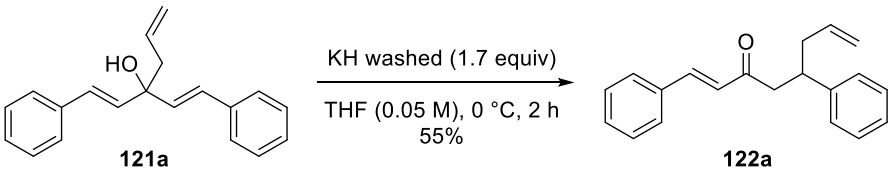
Scheme 38.



Before investigating the rearrangement under PTC conditions, **121a** was treated with potassium hydride to determine its competency for rearrangement under traditional conditions

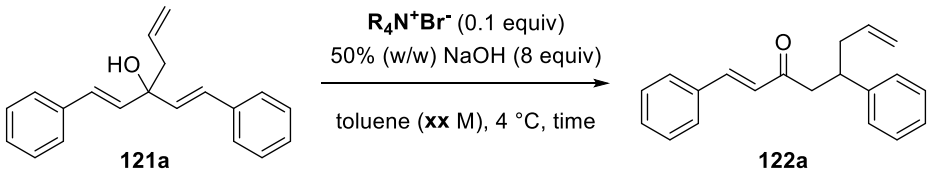
(Scheme 39). The desired rearrangement product **122a** was isolated in modest yield without the need for a crown ether, in concordance with literature precedent.[143]

Scheme 39.



Encouragingly, in the next stage of experimentation, **121a** was treated with tetra-*n*-butylammonium bromide (TBAB) and aqueous sodium hydroxide and was found to successfully rearrange under PTC conditions (Table 11, entry 1). Additionally, no background conversion was observed (entry 2). Unfortunately, the catalyzed reaction did not go to completion, and extended reaction times led to a decreased yield of **122a** and a significant amount of polymeric side products. It is thought that the enolate ion resulting from the rearrangement can react with the product enone in a competing self-condensation process. It was hypothesized, then, that diluting the reaction volume would favor the desired rearrangement and disfavor the bimolecular self-condensation pathway. By decreasing the substrate concentration to 0.03 M in toluene (entry 3), the polymerization pathway was sufficiently suppressed to afford a maximum yield of 51% for desired product **122a** after 5h, after which point the yield of **122a** began to decrease. Further lowering the concentration (entry 4) continued to improve the maximum obtainable yield of **122a** but required much longer reaction times and solvent volumes which were impractical for the reaction set-up. Accordingly, a substrate concentration of 0.03 M was concluded to be optimal for this transformation. Replacement of TBAB with the less lipophilic tetraethylammonium bromide (TEAB) resulted in a slower reaction (entry 5), while the more lipophilic tetra-*n*-octylammonium bromide resulted in faster conversion and a higher maximum yield of **122a** (entry 6). These results indicate that seemingly minor changes in catalyst lipophilicity (cLogP value) have a significant influence on reaction conversion, which will be a recurring theme in this section (see also Appendix B).

Table 11. Rearrangement of **121a** to **122a** under PTC conditions.



entry	PTC catalyst	conc. of **121a** (in toluene)	time	yield*
1	R = *n*-Bu (TBAB)	0.060 M	3h	43%
2	none	0.060 M	72h	0%
3	R = *n*-Bu (TBAB)	0.030 M	5h	51%
4	R = *n*-Bu (TBAB)	0.015 M	12h	62%
5	R = Et (TEAB)	0.030 M	7h	32%
6	R = *n*-Oct (TOAB)	0.030 M	3h	52%
			7h	66%

* Yield determined by HPLC integration against an internal standard (biphenyl).

With the suitable reaction conditions in hand, the activity and selectivity of a number of chiral, non-racemic quaternary ammonium salts were investigated (Figure 25). Unfortunately, most chiral catalysts showed absolutely no conversion, and only two catalysts showed any activity at all. The Maruoka-type catalyst **124a** displayed poor conversion (31% maximum product yield after 9 days) and the product formed was racemic. The reaction employing the aza-propellane catalyst **125** reached a product HPLC yield of 10% within two hours but then stalled. The product formed was also racemic within the experimental margin of error. All other catalysts, including several *Cinchona* alkaloid-derived catalysts **126**, showed no conversion even after extended reaction times at elevated temperatures.

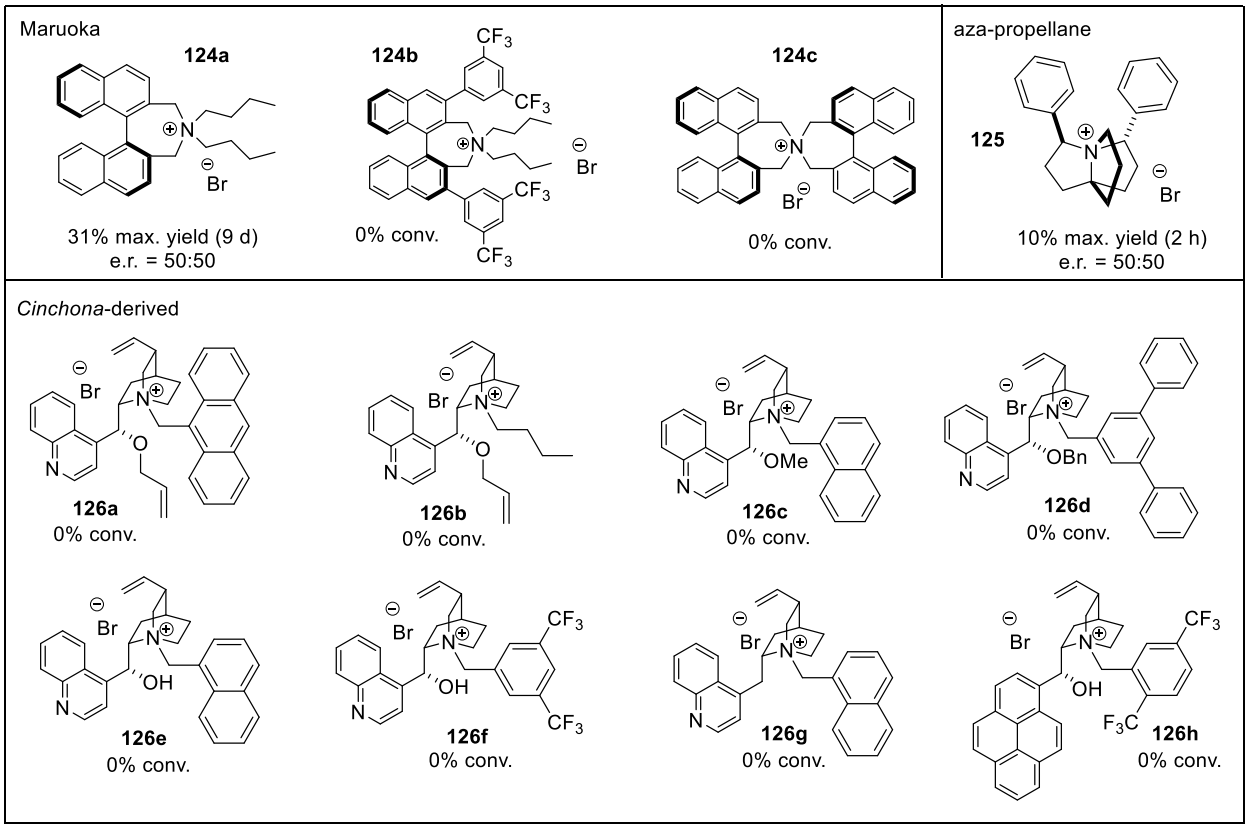
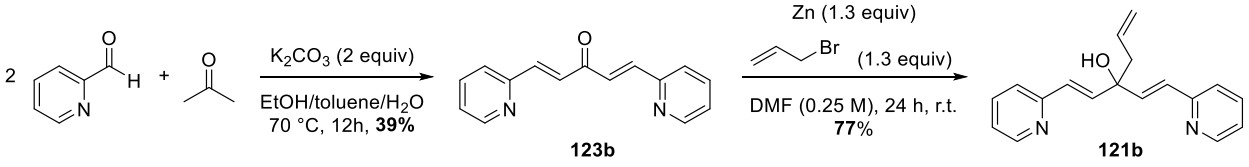


Figure 25. Survey of chiral, non-racemic PTCs in the rearrangement of **121a** to **122a**.

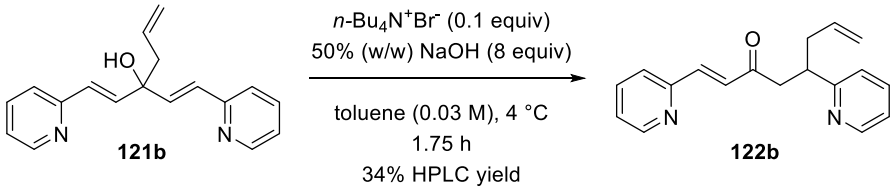
In addition to dicinnamyl alcohol **121a**, compound **121b** containing two pyridinyl moieties was synthesized to probe the effects of changing the electronic properties of the substrate. (Scheme 40). The synthetic route chosen for **121b** was analogous to the one used for **121a**. Condensation of pyridine-2-carboxaldehyde with acetone yielded the intermediate dienone **123b**.[145] The desired (*E*,*E*) isomer could be isolated by careful column chromatography or by recrystallization. Addition of an allylzinc reagent yielded novel alcohol **121b**.

Scheme 40.



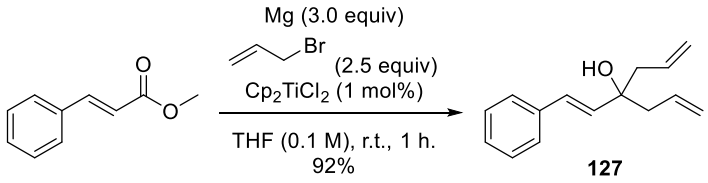
The rearrangement of alcohol **121b** did proceed under PTC conditions to afford novel enone **122b** (Scheme 41). The rearrangement of **121b** is faster compared to **121a**. The yield of **122b** peaks after roughly 1.75 hours and then begins to drop off due to competing self-condensation pathways. The maximum yield of **122b** was only 34% and so further investigations into the rearrangement of **121b** were abandoned, as this was not perceived to be synthetically useful.

Scheme 41.



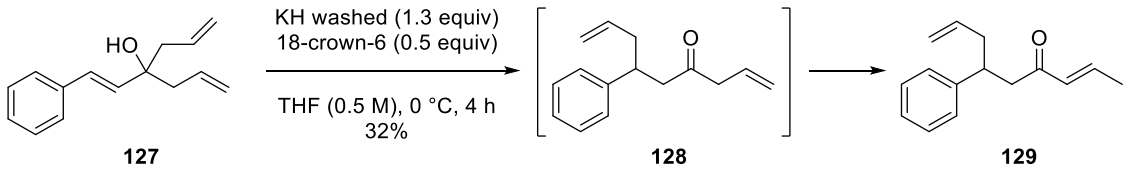
Members of substrate Class 2 (see Figure 24) were the easiest to synthesize and purify. Cinnamyl alcohol **127** was chosen as the target substrate and was synthesized from methyl cinnamate according to a literature procedure (Scheme 42).[146]

Scheme 42.



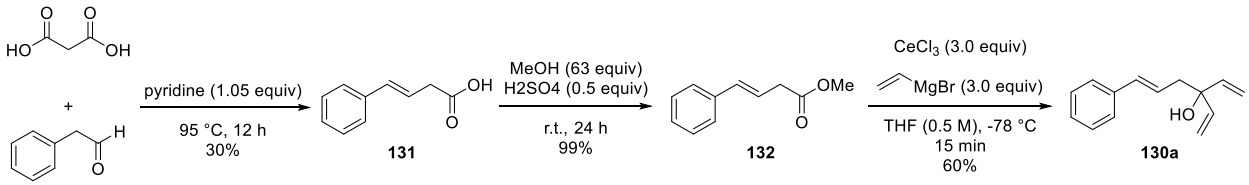
The rearrangement of alcohol **127** to **128** (isolated as isomer **129**) did proceed under traditional anionic oxy-Cope conditions, a transformation which was previously unknown for this compound (Scheme 43). However, the reaction did not proceed under PTC conditions. A number of tetraalkylammonium salts (of varying chain length: C_4, C_6, C_8, C_{10}, C_{12}, and C_{16}), solvents (toluene, trifluorotoluene, TBME, and DCE), and bases (aq. KOH, solid KOH, aq. K_2CO_3, aq. NaOH, and aq. CsOH) were surveyed but no conversion was observed in any case. For this reason, further investigations into this substrate class were abandoned.

Scheme 43.



The preparation of alcohols in Class 3 (see Figure 24) presented a more formidable synthetic challenge. Alcohol **130a** was chosen as the target substrate for this class and was synthesized in three steps from commercially available precursors (Scheme 44). First, a condensation between phenylacetaldehyde and malonic acid afforded the β,γ-unsaturated carboxylic acid **131**.[147] Isolation of the desired *E*-isomer is non-trivial but can be accomplished through successive recrystallizations. Formation of the methyl ester **132** via a Fischer esterification proceeded without incident in nearly quantitative yield.[148] Initial attempts to add two equivalents of vinylmagnesium bromide to **132** resulted in complex product mixtures and low isolated yields of desired alcohol **130a**. One of the by-products identified was the butenyl ketone resulting from continuous 1,2- and 1,4-addition.[149] Fortunately, the inclusion of anhydrous cerium(III) chloride in the Grignard addition[150] led to a dramatic improvement in the reaction profile and allowed for the isolation of alcohol **130a** in 60% yield. The two-stage protocol for the dehydration of cerium(III) chloride heptahydrate[151] (first to the monohydrate, then ultimately to the anhydrous salt) must be followed exactly for the reaction to be successful.

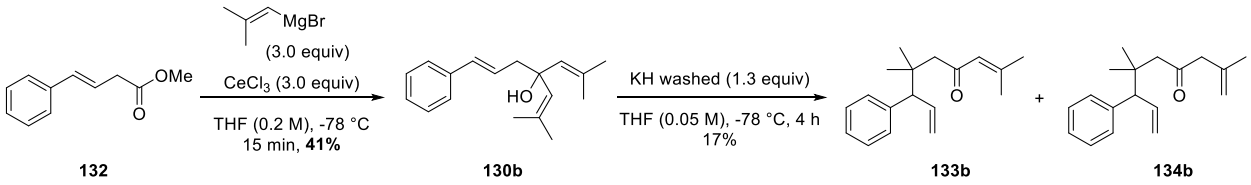
Scheme 44.



Unfortunately, compound **130a** was a poor candidate for rearrangement under both traditional and PTC conditions. The unsubstituted vinyl ketone resulting from the rearrangement is an excellent Michael acceptor and competitive self-condensation pathways prevailed. It was hypothesized that increasing the steric bulk around the vinyl groups would disfavor Michael

addition and allow the rearrangement product to be isolated in reasonable yields. With this in mind, an alternative substrate **130b** was synthesized in analogous fashion, containing isobutenyl groups rather than terminal vinyl moieties (Scheme 45). This substrate does rearrange to the desired enone (isolated as a mixture of tautomers **133b** and **134b**) under traditional conditions (potassium hydride in THF). However, the low yield and difficult purification of **133b** precluded further studies on the rearrangement of substrate **130b**.

Scheme 45.



A.3. Discussion and Outlook

The phase transfer catalyzed anionic oxy-Cope rearrangement was realized for a limited substrate scope. This provides a proof-of concept for a new intramolecular PTC reaction, but unfortunately the yields of these transformations were not synthetically useful, as the reactions suffered from competitive self-condensation processes. Furthermore, the transformation could not be performed asymmetrically, which was another goal of the project. There are several results from this project which merit discussion. Under PTC conditions, none of the alcohols rearranged in the absence of a quaternary ammonium salt, even after multiple weeks of reaction time. This is somewhat unusual for a PTC reaction, as the background conversions for a wide variety of hydroxide-mediated PTC reactions (both bimolecular and unimolecular) are slow but nonzero. Dicinnamyl alcohol **121a** successfully rearranged to enone **122b** in the presence of tetrabutylammonium bromide (TBAB) and other tetraalkylammonium salts. However, low or no conversion was observed in the presence of any other ammonium salt tested. Cinnamyl alcohol **127** did not rearrange at all under PTC conditions, even in the presence of TBAB, despite being structurally very similar to **121**.

To facilitate discussion of these results, it will be useful to refer to a general mechanistic proposal. There is evidence that PTC reactions which involve the generation of alkoxides do

proceed through the extraction mechanism, the most famous example being the synthesis of ethers under PTC conditions.[130, 152] To this end, the results of this project will first be interpreted within the context of an extraction mechanism (Figure 26).

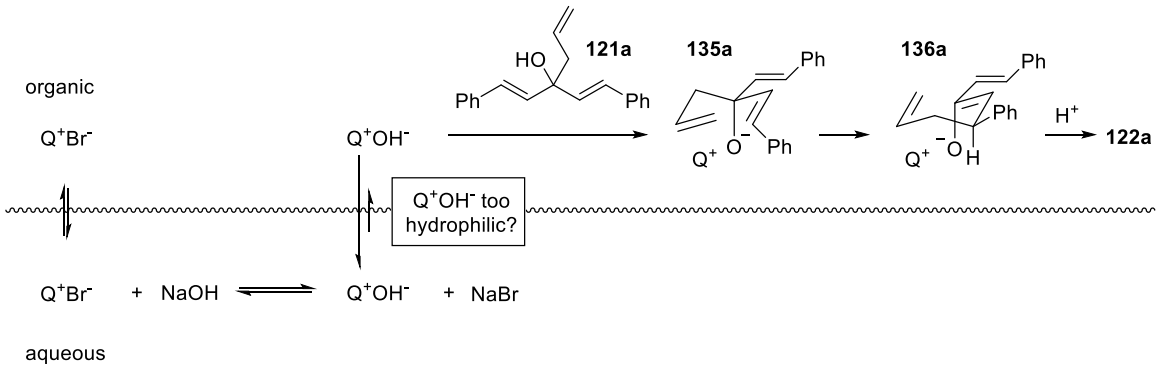


Figure 26. Proposed mechanism for the anionic oxy-Cope rearrangement (extraction model).

In the extraction model, the quaternary ammonium catalyst is directly responsible for transporting hydroxide from the aqueous phase to the organic phase (see above). In the absence of a catalyst, the hydroxide ion concentration in the toluene layer would be negligible, which does explain the complete lack of background conversion for this reaction. One would expect the rate of the extraction step, the diffusion of the ammonium hydroxide ion pair from the aqueous phase to the organic phase, to be largely dependent on the structure of the quaternary ammonium counterion. Tetraalkylammonium compounds like TBAB have substantial affinity for nonpolar solvents like toluene owing to the presence of several straight-chain alkyl groups. As a result, when these catalysts exchange with sodium hydroxide, the resulting ammonium hydroxide ion pairs are sufficiently lipophilic to enter the organic layer, in spite of the low affinity of hydroxide for this phase, which allows the reaction to proceed. In the case of an even more lipophilic catalyst, TOAB (Table 11, entry 6), the rate of conversion increased accordingly. By contrast, the *Cinchona*-derived phase transfer catalysts **126** (Figure 25) are significantly more hydrophilic due the presence of nitrogen- and oxygen-containing functional groups. Apparently, when one of these catalysts is used in place of TBAB, the resulting ammonium hydroxide ion pair is not sufficiently lipophilic to enter the organic phase, so the extraction step proceeds either very slowly or not at all. For every example of an ether synthesis under PTC conditions described in the literature,

without exception, the catalyst used is either a tetrabutylammonium salt or Aliquat-336 ®, another straight-chain tetraalkylammonium salt.[152] For hydroxide-mediated PTC reactions where the extraction mechanism is operating, it appears that only tetraalkylammonium salts are capable of catalyzing the reaction.

Alternatively, it is also possible that the phase transfer catalyzed, anionic oxy-Cope rearrangement proceeds through an interfacial mechanism, so this is also presented for discussion (Figure 27). This proposal is analogous to the one drawn for the phase transfer catalyzed [2,3]-Wittig rearrangement, also of interest to the Denmark laboratory.[142] This mechanism for a unimolecular PTC reaction is significantly more complex and nuanced than those which are drawn either for a bimolecular PTC reaction (as in Figures 22 and 23) or for the extraction mechanism just described (Figure 26). This is because the deprotonation event occurs early, and there are several subsequent pathways for rearrangement which could be operative.

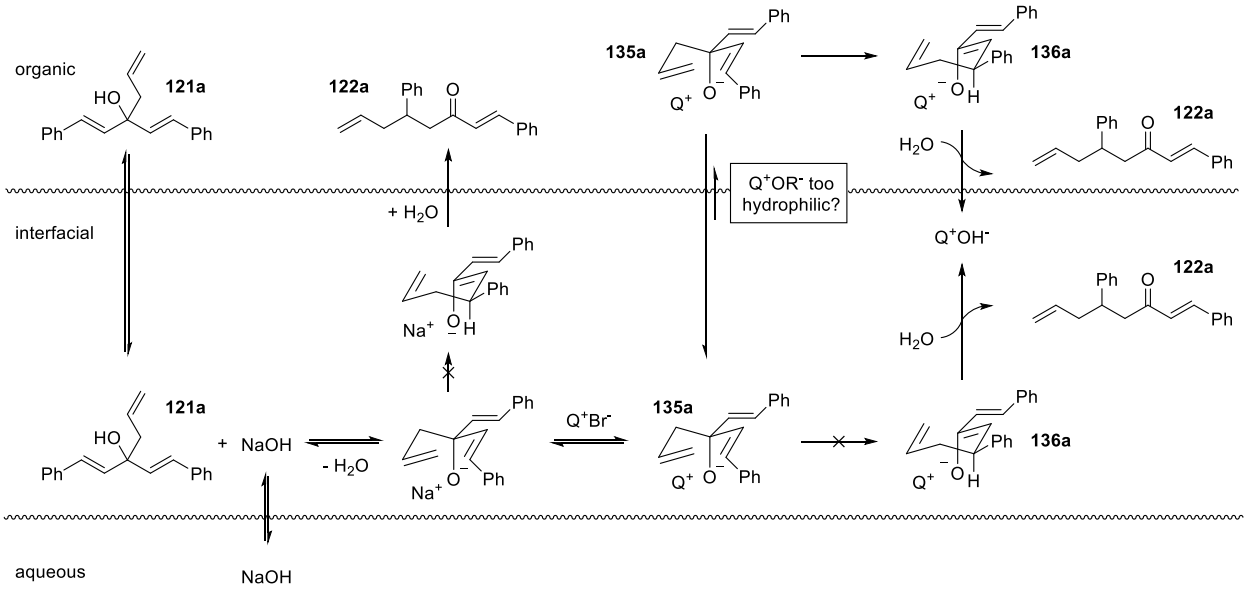


Figure 27. Proposed mechanism for the anionic oxy-Cope rearrangement (interfacial model).

Deprotonation of **121a** by sodium hydroxide in the interfacial region forms a sodium alkoxide ion pair. One pathway which could be drawn is immediate rearrangement without the involvement of an ammonium catalyst. However, this pathway can be ruled out because no background conversion was observed for any of the substrates studied. Clearly, a sodium alkoxide

is not a sufficiently separated ion pair to undergo rearrangement on its own. The alternative pathway, ion exchange with the catalyst to form ammonium alkoxide **135a**, must be the next step. From here, there are two possibilities. Either **135a** undergoes immediate rearrangement in the interfacial region, or it must first desolvate before rearranging. Rearrangement is expected to be more facile in the organic phase than in the interfacial region because the lack of water molecules would destabilize the ammonium alkoxide ion pair. It seems unlikely that the structure of the quaternary ammonium counterion would have a large effect on the rate of rearrangement of **135a** to **136a** within the interfacial region. However, as noted above when discussing the extraction model, the structure of the counterion would be expected to have a significant impact on the rate of desolvation of **135a** into the organic phase. Given this consideration and the fact that only some quaternary ammonium salts display catalytic activity, desolvation into the organic phase would appear to be a necessary step. Following rearrangement of **135a** to ammonium enolate **136a** within the organic phase, the addition of a water molecule regenerates the catalytically competent ammonium hydroxide and releases the enone **122a**.

The catalyst is serving two roles in this mechanism. First, it must be able to exchange with a sodium alkoxide to form **135a**. Second, this newly formed ion pair must be sufficiently lipophilic to be transported back to the organic phase. The success or failure of an ammonium salt in catalyzing this reaction must be linked to one of these two key steps. It is unlikely that the equilibrium in the initial exchange step is sufficiently altered depending on the ammonium salt used (i.e. there appears to be no reason why a tetrabutylammonium cation could undergo exchange and a cinchonidinium cation could not). More likely, the issue arises in the desolvation step. In the vast majority of hydroxide-mediated PTC reactions which proceed through an interfacial mechanism, the species undergoing desolvation is an enolate, not an alkoxide (refer to Figures 22 and 23). These species have quite different chemical properties and do not necessarily behave the same way in solution. Generally speaking, stabilized, charge-delocalized anions (e.g. enolates) display better solubility in organic solvents than do unstabilized anions (e.g. alkoxides). So while ammonium enolates are typically lipophilic enough to re-enter the organic phase, the same is probably not true for ammonium alkoxides, and whether or not ammonium alkoxide **135a** is capable of desolvation likely depends heavily on the lipophilicity of the catalyst itself. This factor could explain why only the linear tetraalkylammonium species were really effective catalysts. Regardless of whether an interfacial or extraction mechanism is operating, the same conclusion is

drawn concerning the relative activities of different quaternary ammonium salts in catalyzing this reaction. The success of a catalyst is tied to its lipophilicity and how well it is able to extract an alkoxide or hydroxide ion into the organic phase.

The inability of cinnamyl alcohol **127** to undergo phase transfer catalyzed rearrangement in the presence of TBAB, despite being quite similar in structure to dicinnamyl alcohol **121a** was initially quite puzzling. However, a reasonable explanation for this difference in reactivity can be offered invoking some of the same principles outlined above. While the two substrates have comparable lipophilicities, a key difference is that the hydroxyl group in **121a** is doubly allylic, while the hydroxyl group in **127** is only singly allylic. The electron density of an alcohol (or alkoxide) is slightly delocalized by an allylic double bond due to hyperconjugation. Since this effect is additive for doubly allylic alcohols, one would expect that **121a** is more acidic than **127** and forms a more stabilized (charge-delocalized) alkoxide. Considering the mechanisms outlined above, these expectations have important ramifications. Alcohol **127**, being a weaker acid, would be less easily deprotonated by a hydroxide base, and the corresponding alkoxide may not be lipophilic enough to desolvate, regardless of the structure of the ammonium counterion. The stabilizing effect of an allylic double bond is not very large, but it may be enough to affect the reactivity of alcohols in this scenario. Again, this same conclusion can be drawn in the context of either the interfacial or the extraction mechanism.

For the rearrangement of **121a** to **122b** under PTC conditions, most chiral catalysts were not effective at promoting the rearrangement (Figure 25). Two chiral catalysts did show modest levels of conversion, but the product isolated from the reaction was racemic. This outcome indicates that the ammonium counterion is unable to bias the preferred conformer of the alkoxide in the stereodetermining step and that both enantiomeric transition states are equal in energy. Whether this is a result of the ammonium counterion being too weakly bound to the alkoxide, or the catalyst not bearing bulky enough substituents in the proper orientation to bias the conformation remains to be seen.

To summarize, a phase transfer catalyzed anionic oxy-Cope rearrangement has been reported. This is a rare example of an intramolecular reaction being carried out under PTC conditions and serves as a nice proof-of-concept for this methodology. However, the limited substrate and catalyst scope, competitive side reactions, and lack of stereoselective induction severely hinder the synthetic utility of this process.

Appendix B. Investigation of Azahelicene-Derived Scaffolds for APTC

B.1. Introduction and Rationale

The success of asymmetric, phase transfer catalysis depends heavily on the nature of the chiral ammonium salt used as a catalyst. In theory, any quaternary ammonium compound could be active as a phase transfer catalyst, but in reality there are several factors that must be taken into consideration. These include the cross-sectional area of the catalyst, the lipophilicity of the catalyst (cLogP), and whether the catalyst is stable under PTC conditions (e.g. stable to high concentrations of hydroxide). As a result, there are strikingly few unique scaffolds commonly employed for APTC. In fact, the field is dominated by only two: those derived from the *Cinchona* alkaloids and the binaphthol-derived compounds developed by Maruoka et al. (Figure 28).

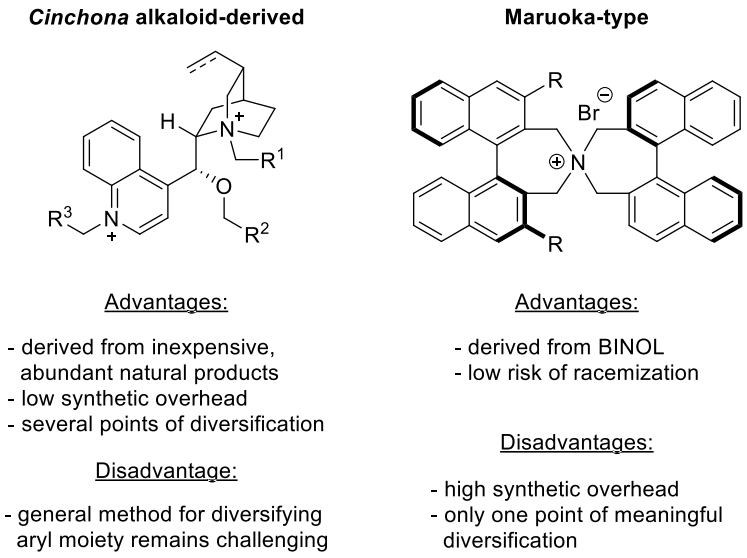


Figure 28. Most common scaffolds for APTC.

The ubiquitous nature of *Cinchona*-derived catalysts in APTC is due to a number of factors. The *Cinchona* alkaloids are cheap and readily available, chiral-pool, natural products.[153] Conversion of any *Cinchona* alkaloid to a phase transfer catalyst is accomplished in a single step, N-quaternization, which proceeds under mild conditions with a large number of benzyl or alkyl

halides. The various functional groups present in the cinchona alkaloids also present opportunities for further diversification. A common manipulation is O-alkylation of the C(9)-hydroxyl group. The terminal vinyl group of the quinuclidine moiety is readily converted to a terminal alkyne which can then be coupled to a variety of aryl halides via the Sonogashira reaction.[154] While *N*-quaternization occurs first at the quinuclidine nitrogen, the quinoline nitrogen will also alkylate in the presence of an excess of alkylating agent, leading to the so-called "diquat" catalysts originally developed by Merck Research Laboratories.[155] Thus, hundreds of derivatives can be generated in just a few steps from a common readily available precursor, allowing easy access to a library of phase transfer catalysts. However, there are still no truly general methods for replacing the quinoline ring with a different aryl or heteroaryl group stereoselectively, which has substantially hampered efforts to access diverse chemical space in this region of the catalyst.

The phase transfer catalyst scaffold introduced by Maruoka et al. was a response to the difficulties of accessing diverse chemical space in the cinchona-derived catalysts. Rather than beginning from a natural product, Maruoka envisioned the design of chiral, C_2-symmetric ammonium salts derived from commercially available (*R*) and (*S*) binaphthols. The resulting spiro compounds were structurally rigid and highly selective phase transfer catalysts, particularly when a bulky or electron-deficient aryl group was installed at the 3,3' position of one subunit.[156-157] Of course, these catalysts also suffer from high synthetic overhead, which has somewhat limited their widespread use in APTC.

The Denmark group has a long-standing interest in developing new scaffolds for asymmetric phase transfer catalysis. A series of cyclopentylpyrrolizidine (CPP) catalysts developed in these laboratories have also been used effectively in phase transfer catalyzed reactions (Figure 29).[158-159]

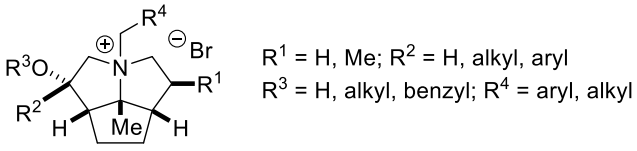


Figure 29. The cyclopentylpyrrolizidine (CPP) catalyst scaffold.

The three catalyst scaffolds just described have all been employed for highly enantioselective, intermolecular, phase transfer catalyzed reactions (e.g. for bimolecular enolate

alkylations). By contrast, the development of phase transfer catalysts which enable highly enantioselective *intra*molecular transformations (e.g. unimolecular, anionic rearrangements) has historically been far more challenging (see Appendix A). The classic "steric screening" models that have been used to rationalize the high enantioselectivities observed in enolate alkylations with *Cinchona*-derived catalysts,[160-161] for example, no longer apply in the case of unimolecular rearrangements. Depending on the nature of the substrate-catalyst interaction at the time of rearrangement, the substrate may be located far away from the chiral information contained within the catalyst. It was hypothesized, then, that the best catalyst for unimolecular APTC may be one which displays helical chirality, such that a chiral environment will be present regardless of the binding mode within the catalyst-substrate ion pair. Helicenes are molecules consisting of five or more *ortho*-fused aryl or heteroaryl rings which adopt a three-dimensional helical structure (Figure 30). Despite not containing any stereogenic centers, helicenes possess helical chirality and can be resolved into (+) and (–) enantiomers.

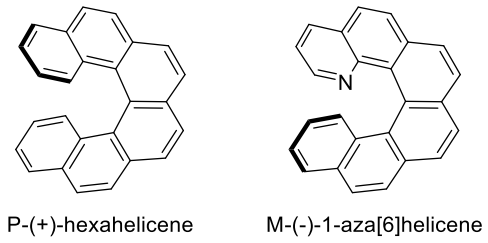
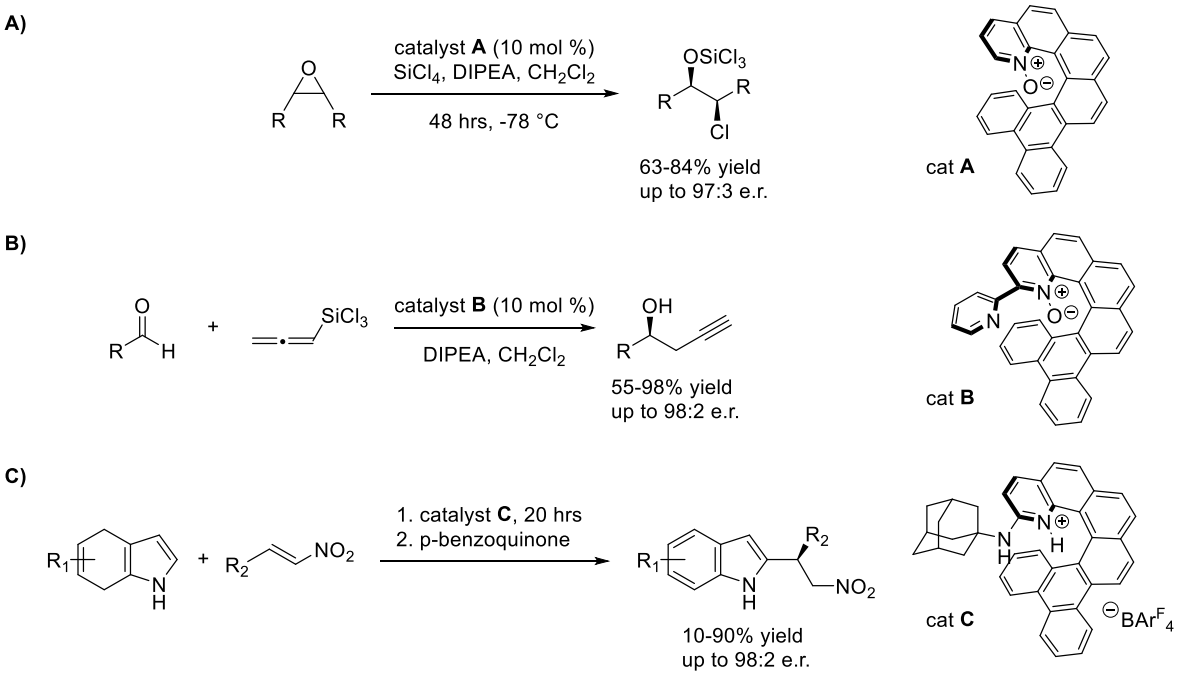


Figure 30. Representative examples of helicenes.

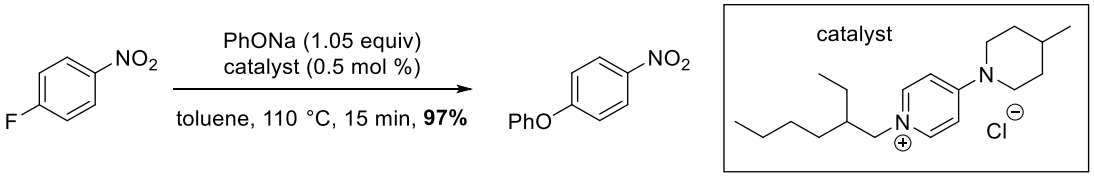
For helicenes containing six or more rings, the inversion barrier is large, as significant bond distortion would be required for the terminal aryl rings to move past one another. In addition to possessing a unique spatial chirality and displaying high rigidity and thermal stability, helicenes are also highly polarizable and are amenable to charge-transfer complexation. For these reasons, there has been considerable interest in the past twenty years in developing helicene-based catalyst systems for asymmetric transformations.[162] In particular, helicenes containing at least one nitrogen atom in the ring system itself (azahelicenes) have been recently explored by Takenaka et al. for a variety of applications in Lewis base and hydrogen-bonding catalysis (Scheme 46).[163-165]

Scheme 46.



One area which has remained unexplored is the possibility of using *N*-quaternized azahelicenes as phase transfer catalysts. There are limited examples of using substituted pyridinium salts as phase transfer catalysts. In particular, such salts have found a niche application in catalyzing aromatic nucleophilic substitution reactions under anhydrous conditions, as they are stable at elevated temperatures (Scheme 47).[166-167]

Scheme 47.



These 4-aminopyridinium catalysts decompose in the presence of aqueous sodium hydroxide, forming pyridones following displacement of dialkylamine. It follows that a pyridinium salt lacking the 4-amino substituent should be more stable under these conditions. Indeed, the very success of the "diquat" catalysts, which contain an *N*-quaternized quinoline moiety, in hydroxide-

mediated PTC reactions suggests that this motif must be at least somewhat stable in the presence of aqueous hydroxide. Therefore, it seemed plausible that a quaternized azahelicene could be stable under similar conditions, and thus possible that azahelicenes could be developed into a generally applicable phase transfer catalyst scaffold. With the goal of generating a catalyst library, the azahelicene scaffold was assessed for potential points of easy diversification. All of the published syntheses of 1-aza[6]helicene **137** (see below) are at least somewhat modular, which allows one to bring in differentially substituted fragments and generate azahelicenes containing various substituents on the backbone. But even considering just the manipulations which parent azahelicene **137** may undergo, there are still at least two promising opportunities for diversification (Figure 31). First, it was expected that a number of alkylating agents could be used to quaternize the pyridine nitrogen, including alkyl halides and functionalized benzyl bromides. Again, this is often the only synthetic manipulation performed on the cinchona alkaloids to obtain a catalyst library. Second, several methods exist for installing arenes and other groups at the 2-position of pyridines.[168] It was expected that azahelicenes would behave similarly, allowing for the late-stage installation of groups at this position. Additionally, the resolution of azahelicene **7** is known, which would allow access to enantiopure catalysts. The O'Donnell alkylation (Appendix A, Scheme 34) could serve as an initial benchmark reaction for evaluating the performance of azahelicene-derived catalysts in a hydroxide-mediated PTC reaction.

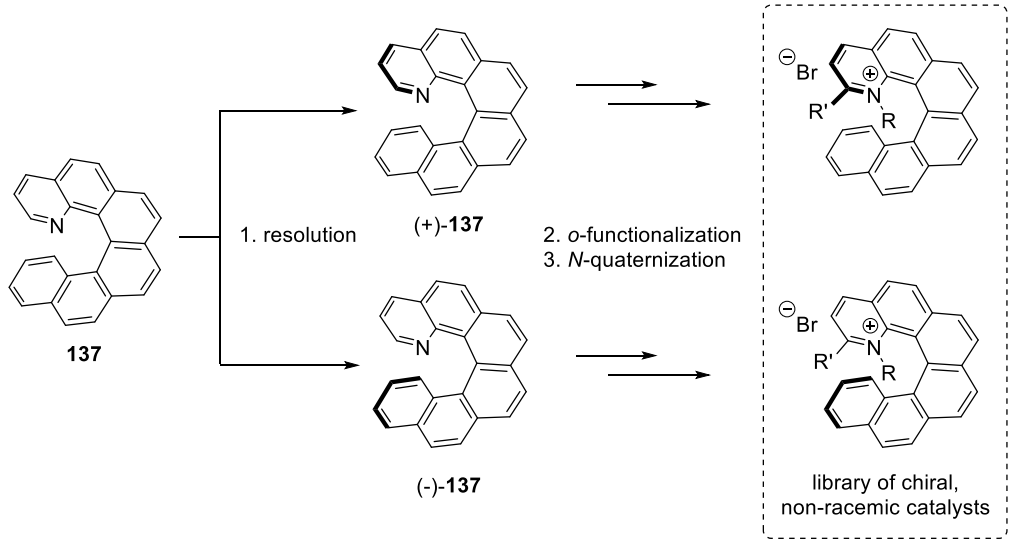
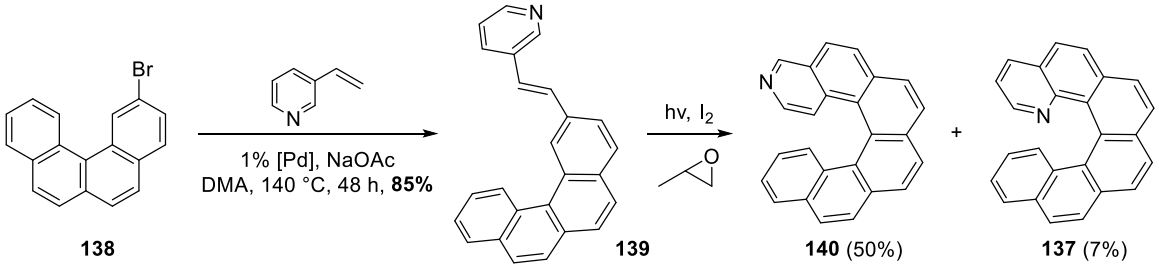


Figure 31. General plan for a library synthesis of azahelicene-derived APTCs.

Several synthetic routes to (rac)-1-aza[6]helicene **137** have been described and are summarized briefly here. The first reported synthesis of **137** was in 2008 from Hassine and co-workers (Scheme 48).[169] A Heck reaction between aryl bromide **138** and 3-vinylpyridine catalyzed by Herrmann's palladacycle afforded *trans*-olefin **139**. Oxidative photocyclization (Mallory conditions) yielded a mixture of constitutionally isomeric products **140** and **137**.

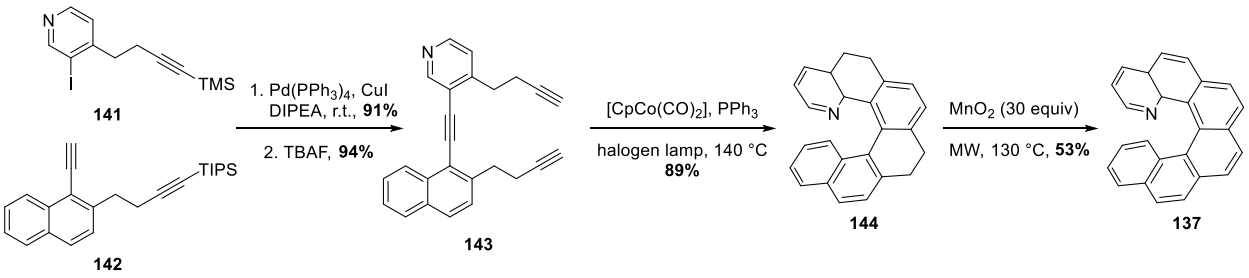
Scheme 48.



Historically, the Mallory oxidative photocyclization was one of the first strategies broadly applied for carbohelicene synthesis, owing to the generality of the reaction and the fact that the olefin geometry in the precursor is not important.[170-172] However, the photochemical route is not optimal here since the desired product **137** is the minor constitutional isomer formed. Another drawback is that Mallory photocyclizations must be run at extremely dilute concentrations to avoid byproduct formation, which is incompatible with large scale synthesis.

An alternative approach developed by Stará and Starý involves the union of iodopyridine **141** and alkynylnaphthalene **142** via a Sonogashira reaction (Scheme 49).[173] The resulting triyne **143** then undergoes a [2+2+2] cyclization in the presence of a cobalt catalyst to form three rings of the helicene in a single step.

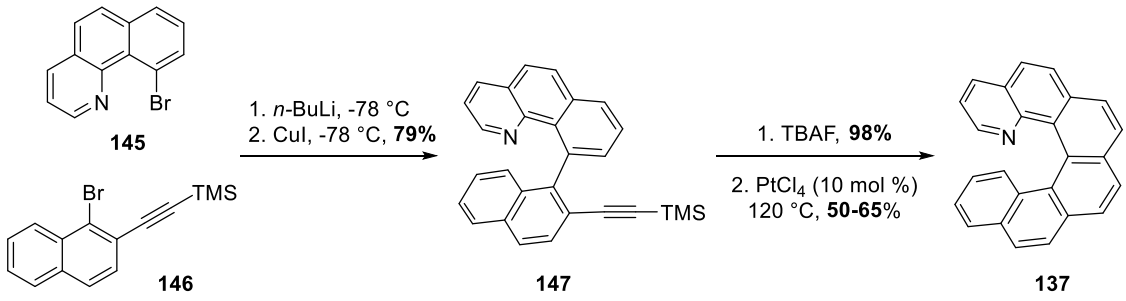
Scheme 49.



Subsequent oxidation of **144** with manganese dioxide affords azahelicene **137**. An enantioselective variant has recently been developed allowing absolute stereocontrol over the resulting helicene.[174] However, achieving high enantioselectivity requires that *p*-tolyl groups must be present at the alkyne termini in **143**. As these cannot be cleaved off the backbone following cyclization, this poses a severe limitation. More concerning is the final oxidation step, which required forcing conditions and proceeded in a disappointing 53% yield.

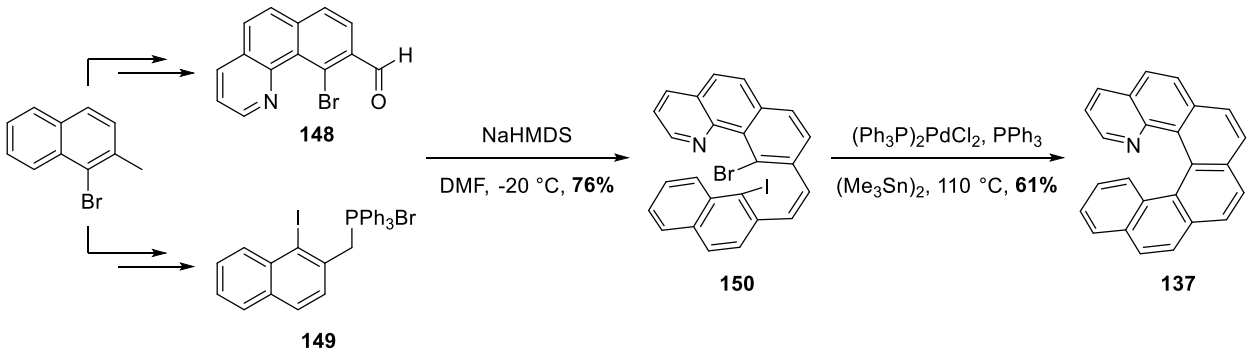
An expedient route to **137** developed by Fuchter and co-workers involves an intramolecular cross coupling between benzo[h]quinoline **145** and bromonapthalene **146** to afford axially chiral species **147** (Scheme 50).[175] Subsequent deprotection and platinum-catalyzed cycloisomerization affords desired product **137**. This route is attractive for its brevity, but the final ring-forming step required forcing conditions and afforded variable yields of **137**.

Scheme 50.



A similar approach developed by Takenaka et al. unites aldehyde **148** and phosphonium salt **149** in a *Z*-selective Wittig olefination to form **150**, followed by an intramolecular Stille-Kelly cross coupling to form the final ring (Scheme 51). The syntheses of several derivatives of **137** were also accomplished by introducing structural changes to the southern Wittig partner **149**. The variety of synthetic methods which exist for accessing azahelicenes makes these compounds attractive starting points for building a diverse catalyst library.

Scheme 51.

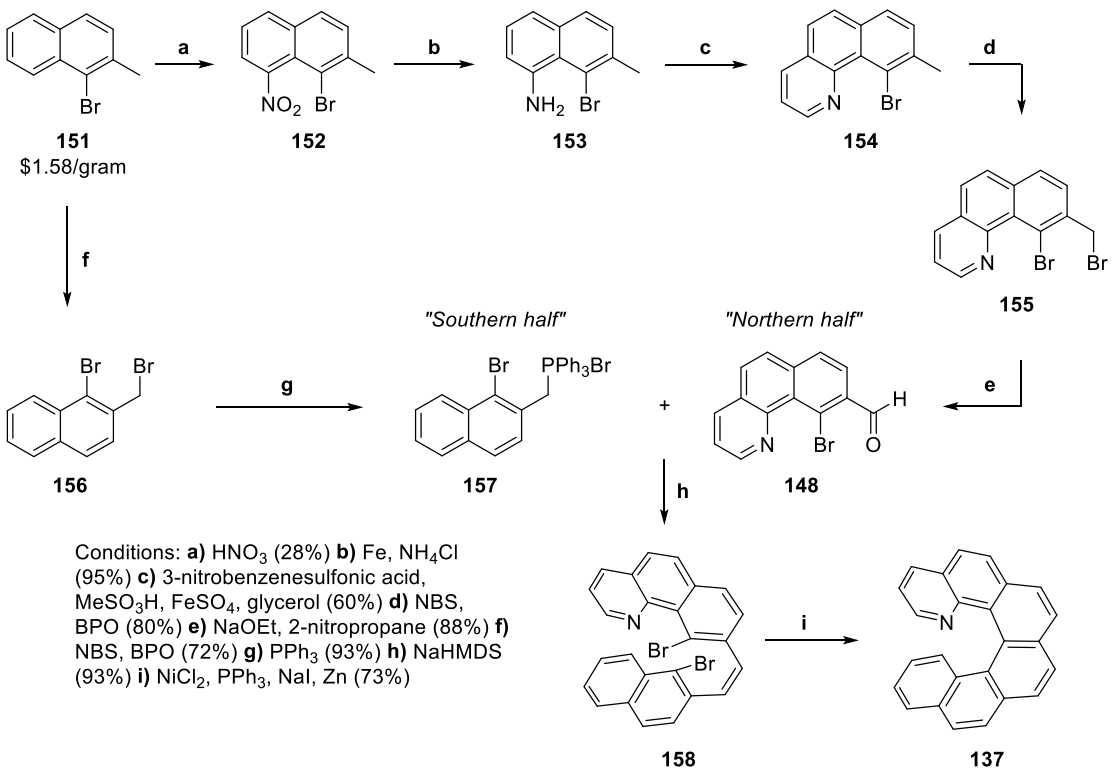


The research objectives for this project were: (1) to generate a new library of phase transfer catalysts via *N*-quaternization of azahelicenes, (2) establish the viability of these salts as catalysts in a known benchmark reaction (the O'Donnell alkylation), and (3) test these catalysts for activity in other interesting PTC reactions, including the anionic oxy-Cope rearrangement, the [2,3]-Wittig rearrangement, and the vinylcyclopropanation of glycine imine Schiff bases.

B.2. Catalyst Synthesis and Performance

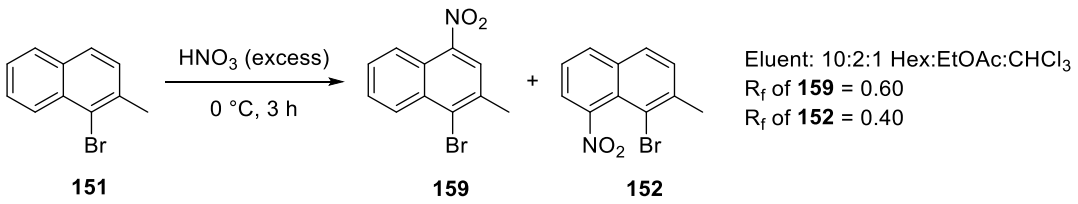
The route chosen for the synthesis of azahelicene **137** (Scheme 52) closely mirrors the one published by Takenaka et al. with a few important modifications (see below).[163] This route is a convergent synthesis with nine total steps (seven steps in the longest linear sequence). All nine reactions are amenable to large scale and most proceed in good to excellent yield (seven of the nine steps proceed in greater than 70% yield). As the initial goal was to access gram quantities of **137** as quickly as possible, this route appeared to be the best choice.

Scheme 52.



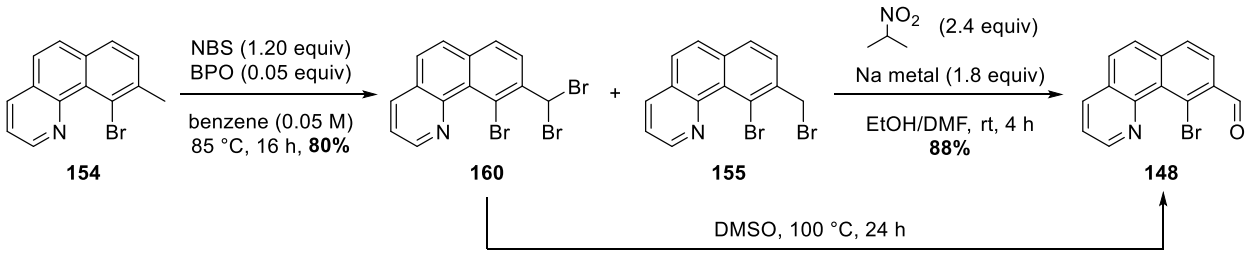
The synthesis of aldehyde **148** (northern half) was accomplished in five steps from 1-bromo-2-methylnaphthalene **151** which is an inexpensive and readily available starting material. Technical grade **151** (90% or even 85% purity) could be used as received in the initial nitration step without incident. Aromatic nitration using HNO_3/H_2SO_4 leads to a complex mixture of polynitrated products. Using neat nitric acid leads to selective nitration at the two most activated positions, affording mononitrated naphthalenes **152** and **159** in approximately a 1:1 ratio (Scheme 53). These products have very different polarities and are easily separated by column chromatography. Subsequent recrystallization afforded highly pure **152** in a 28% yield (on a 50 gram scale).

Scheme 53.



The second step is a heterogeneous reduction of nitronaphthalene **152** to aminonapthalene **153** via transfer hydrogenation. The rate of this reaction was highly variable depending on the scale, but in every case nearly quantitative yields of the desired product were obtained without the need for further purification. The construction of the terminal pyridine ring was achieved by a modified Skraup quinoline synthesis and afforded **154** in 60% yield. Radical bromination of **154** afforded **155**. An excess of *N*-bromosuccinimide is used which leads to the isolation of some dibrominated product **160** in addition to the desired monobrominated **155**. The conversion of both products to aldehyde **148** is possible using operationally simple conditions (Scheme 54).

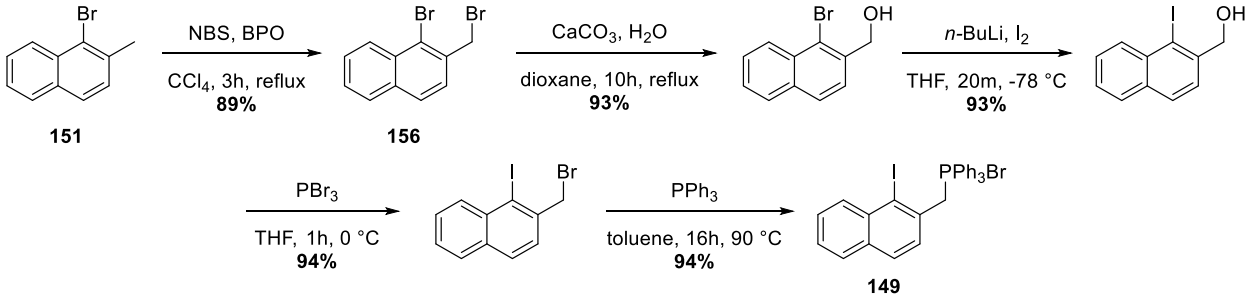
Scheme 54.



The conversion of **155** to aldehyde **148** is accomplished by a Hass-Bender oxidation which proceeds cleanly (88% yield) and the product, typically isolated by filtration, requires no further purification. It is necessary to use a large excess of 2-nitropropane relative to sodium ethoxide when generating the nitronate *in situ*. If any residual ethoxide is present when **155** is added, a competitive S_N2 reaction forms a benzylic ether which is difficult to separate from the desired product. Geminal dibromide **160** is converted to the desired aldehyde by heating in DMSO, and this reaction also proceeds cleanly.[176] The overall yield of the northern half is 11 % over five steps and all reactions are easily scalable.

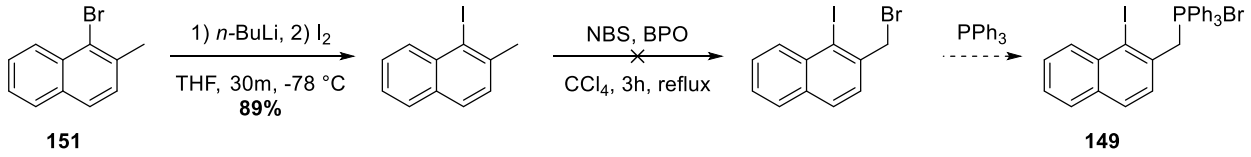
The published synthesis of the phosphonium salt **149** (southern half) for the key Wittig reaction requires five steps from **151** (Scheme 55).[163, 177-179]

Scheme 55.



A more direct three-step synthesis was envisioned from the same starting material (Scheme 56). The conversion of aryl bromide **151** to the corresponding aryl iodide proceeded without incident (89%), but this compound did not survive the radical bromination step. The carbon-iodine bond is sufficiently weak to be cleaved under these conditions, and the major isolated product of the reaction was 1-bromo-2-methylnaphthalene **151**.

Scheme 56.



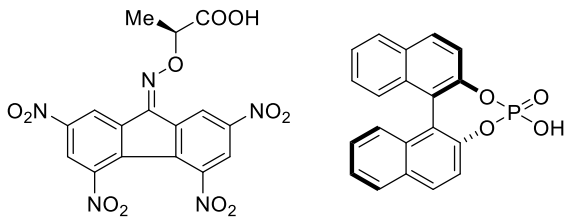
While there appeared to be no simpler route to iodonaphthalene **149**, it became apparent that converting the bromide to the iodide was probably not necessary. Intramolecular couplings between two aryl bromides under Stille-Kelly conditions are known, and these conditions are typically the same used for couplings between an aryl iodide and aryl bromide.[180] Additionally, other methods exist for coupling two aryl bromides, such as the Ullmann reaction.[181] Phosphonium

bromide **157** is a known compound prepared in two steps from commercially available **151**, which simplified the synthesis of the southern fragment tremendously (Scheme 52).[182-183] With the northern and southern fragments in hand, the (*Z*)-selective Wittig reaction proceeded without incident using the conditions developed by Takenaka et al. to afford olefin **158** (*Z*:*E* ratio = 10:1). Nominal improvements in the *Z*:*E* ratio are possible through recrystallization, but it was determined that enrichment beyond 10:1 is not necessary for the subsequent cross-coupling reaction, as the (*E*)-alkene is not reactive under the conditions used. Another aspect of Takenaka's synthetic route which offered an opportunity for improvement was the frequent employment of the Stille-Kelly coupling. These conditions require stoichiometric amounts of highly toxic hexamethylditin, which poses a significant health and safety risk on a large scale. Several methods of intramolecular coupling of aryl halides are known which do not require organotin reagents. The most notable is the copper-mediated Ullmann coupling.[181] Thus, alternative reaction conditions were explored for the ring closing of dibromide **158** to azahelicene **137**. Under classical Ullmann conditions (activated copper powder, refluxing DMF), the reaction converted cleanly to a single species whose spectroscopic data did not match that of **137**. Rather, the mass spectrum indicated that dimerization took place rather than the desired intramolecular reaction. It is likely that under the forcing reaction conditions, double bond isomerization was faster than cross-coupling which would lead to the observed result.

Since the high temperatures required for classical Ullmann couplings led to unproductive reaction pathways, a milder coupling protocol was sought. The Semmelhack modification of the Ullmann coupling employs zerovalent nickel species to effect similar ring closings at much lower temperatures.[184] Following a procedure developed by Rawal et al., the active nickel(tetrakis(triphenylphosphine)) catalyst was generated in situ from nickel(II) chloride, triphenylphosphine, sodium iodide, and zinc powder.[185] The dibromide **137** was added to the cocktail and heated at 75 °C overnight. Under these conditions full conversion to the desired helicene was observed (Scheme 52). Yields as high as 70% for this transformation were observed, which is better than could be achieved with the Stille-Kelly conditions reported by Takenaka. This completed the total synthesis of 1-aza[6]helicene **137** from 1-bromo-2-methylnaphthalene **151** in nine total steps. The longest linear sequence contained seven steps with an overall yield of 7%.

In order to access enantiomerically pure catalysts, it was necessary to obtain enantiopure azahelicenes prior to *N*-quaternization. The asymmetric synthesis of azahelicenes is still in its

infancy[174] and to date only racemic syntheses have been reported for the target compound **137**. Procedures for resolving 1-aza[6]helicene **137** have been described. One method involves an *m*-CPBA oxidation to the corresponding *N*-oxide, the enantiomers of which can be separated using preparative HPLC.[163] Heterocyclic *N*-oxides can be converted back to the corresponding aromatic amines by a number of means, including hydride reducing agents, heterogeneous reductions (transfer hydrogenation), and trivalent phosphorus compounds.[186] A more desirable method of resolution, also described in the literature, is the formation of a diastereomeric complex with an enantiomerically pure tartaric acid and subsequent recrystallization.[173] It was determined that the basified sample (free helicene) can be resolved analytically using normal-phase HPLC. Selective recrystallization is more amenable to large scale separation than preparative HPLC, so this was the approach taken. The procedure reported by Stará and Starý, which uses di-*O*-benzoyltartaric acid as the resolving agent, allows for isolation of about 20% of the theoretical maximum amount of enantiopure compound. The azahelicene resolution is apparently highly sensitive to minor changes in the resolving agent, as several carboxylic acids commonly used for resolution of chiral amines, including malic, mandelic, 10-camphorsulfonic, tartaric, and di-*O*-tolyltartaric acids were unsuccessful in this case.[173] Due to the discouraging yields reported for this resolution, a brief screen of other resolving agents was considered (Figure 32). The first compound reported as a chiral resolving agent for helicenes was 2-(2,4,5,7-tetranitro-9-fluorenylideneaminooxy)propionic acid (TAPA) **161**. This reagent has been demonstrated to form crystalline complexes with carbohelicenes to effect resolution, so one would expect even greater success when the helicene actually contains a basic nitrogen atom.[187]

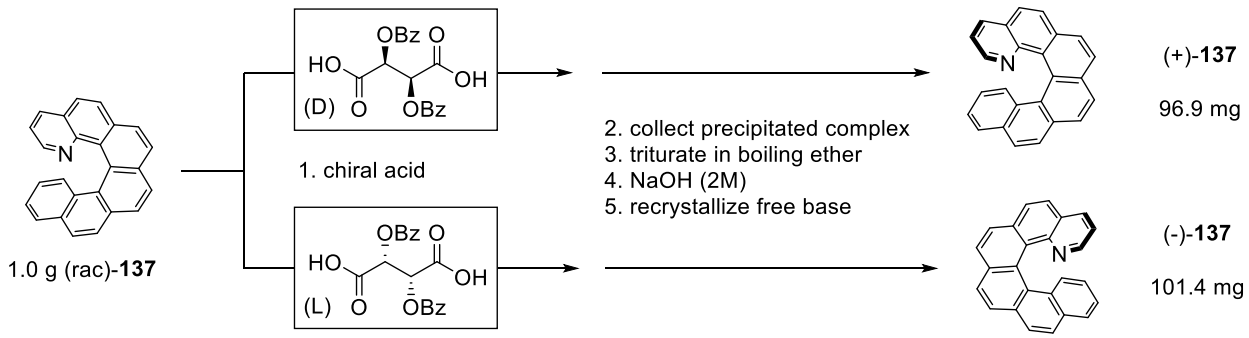


161 **162**

Figure 32. Chiral acids previously used for resolutions.

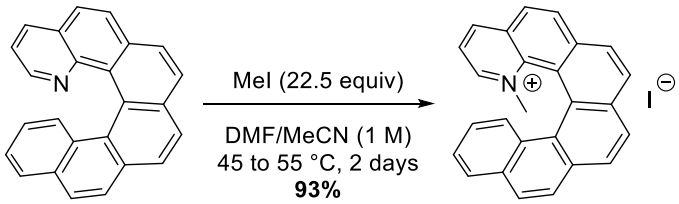
The synthetic route to access TAPA is prohibitively long to justify preparing a compound for screening purposes. However, chiral binaphtholphosphoric acids are easily prepared in one step from BINOL and have been shown to be effective resolving agents for weakly basic amines.[188] As such, this was considered to be a good screening candidate and enantiomerically pure **162** was prepared from (*R*)-BINOL and phosphorus oxychloride in 42% yield. However, this compound did not form a crystalline diastereomeric complex with **137** in a variety of solvents (using the method recommended by Jacques et al.)[189] and this agent was quickly abandoned. The original published procedure by Stará and Starý was followed (Scheme 57) which at least has the benefit of using inexpensive and commercially available resolving agents. Additionally, the yield of isolated enantiopure helicene can also be improved somewhat by scaling up the resolution. Nevertheless, this is a tedious process which is not high yielding, and the field of azahelicene resolution still has room for improvement.

Scheme 57.



The *N*-quaternization of cinchona alkaloids can typically be accomplished under mild conditions using a variety of alkyl and benzyl bromides. The quaternization of **137** was expected to be somewhat more challenging due to the more congested environment around the nitrogen atom. Thus, the first agent chosen for *N*-quaternization was methyl iodide. *N*-Methylation occurred under relatively mild reaction conditions (55 °C) in excellent yield (Scheme 58). Iodide salt **163a** is a brilliant orange compound, stable to silica gel chromatography, and can be recrystallized from methanol.

Scheme 58.



The ^{1}H-NMR spectrum of **163a** in CDCl3 (Figure 33) has one feature worth mentioning. The chemical shift of the methyl group is δ2.93. For comparison, the reported chemical shift of the methyl group in *N*-methylquinolinium iodide is δ3.71, which is nearer what would be expected for a methyl group attached to an electronegative element.[190] The substantial upfield shift for the methyl group in **163a** is explained by anisotropic shielding as a result of this group being directly situated over an extended aromatic system. The larger magnetic field generated by the spectrometer induces a *ring current* within the aromatic system, which in turn generates its own, smaller magnetic field. Outside of the ring, these fields have an additive effect, and contribute to the large, downfield chemical shifts observed for most aromatic protons. But within the ring (including directly above and below the center of the ring), these fields oppose each other, resulting in substantial upfield shifts for any protons in this vicinity.[191]

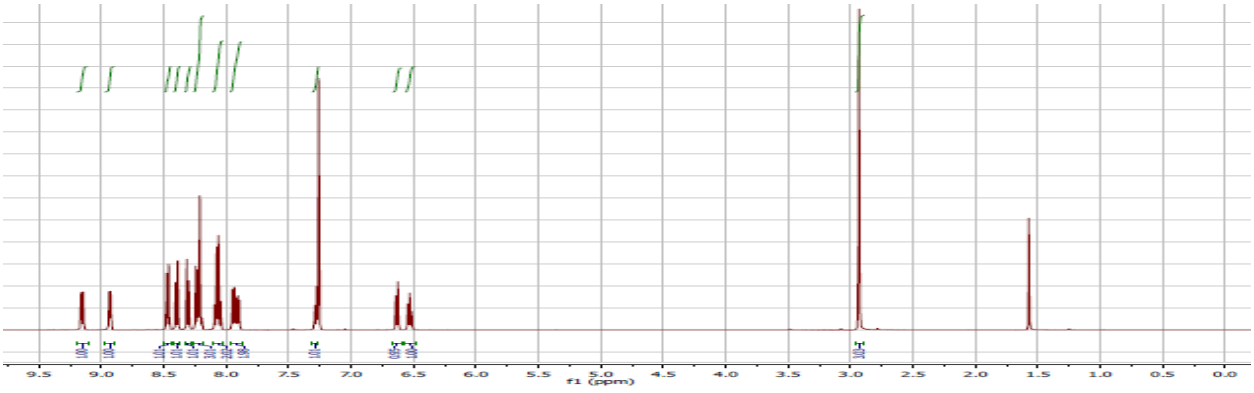
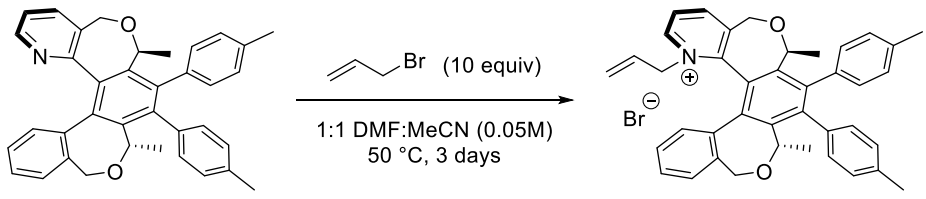


Figure 33. ^{1}H-NMR spectrum of **163a** in CDCl3.

Since quaternization is performed after the enantiomeric resolution, the amount of heat required to effect the quaternization was not without concern. The inversion barrier for helicenes is large, but racemization could occur at sufficiently high temperatures. An inversion barrier of 134.8 kJ/mol (or 32.2 kcal/mol) for **137** has been reported, and it was noted that enantiomerically pure samples of **137** will racemize quickly at 140 °C ($t_{1/2}$ = 72 minutes).[173] While the temperatures required for quaternization with methyl iodide were far below this value (55 °C), it was still considered prudent to perform an experiment which would detect any erosion in e.r. In the quaternization of (+)-**137** with methyl iodide (a slow reaction taking up to two days), aliquots were taken periodically and HPLC was used to measure the e.r. of the starting material not yet consumed in the reaction. At no point in the reaction was any erosion in the e.r. of the starting material observed. Since the product **163a** must have a substantially greater barrier to inversion than **137** owing to the *N*-methyl group, this was taken as sufficient evidence that the quaternization procedure is compatible with enantiopure material.

Concerns about the accessibility of the nitrogen atom in **137** were not unfounded. After the initial success with methyl iodide, attempts to install any other electrophiles at this position were unsuccessful, including allyl bromide, ethyl bromide, benzyl bromide, and *in situ* generated benzyl triflate. This was a major impediment to constructing a catalyst library, since the electrophile chosen for *N*-quaternization is often the only source of diversity (in the cinchona scaffold, for example). In a brief follow-up to this project, heavily modified azahelicene **164** containing a partially saturated backbone underwent facile *N*-allylation to afford salt **165** in high yield (Scheme 59). This result suggests that the nitrogen atom is more accessible in azahelicenes which are less planar, which is consistent with chemical intuition. Therefore, species like **164** might serve as better starting points for construction of diverse catalyst libraries compared to **137**.

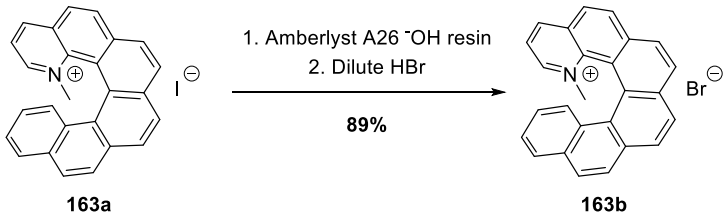
Scheme 59.



164 **165**

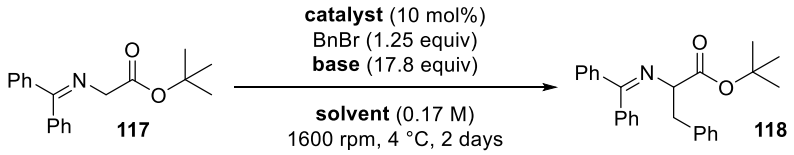
Nevertheless, iodide salt **163a** was tested as a phase transfer catalyst using the O'Donnell alkylation as a benchmark reaction. Unfortunately, this compound showed very poor performance as a phase transfer catalyst. Only nominal rate enhancement above background was observed, and the reaction stalled after two days with no further conversion (Table 12, entries 1-2). Knowing that quaternary ammonium bromide salts are typically more effective catalysts than the corresponding iodide salts, ion exchange of salt **163a** was explored (Scheme 60). Exchange of iodide with hydroxide using Amberlyst A26 resin was facile. Completeness of this first ion exchange was assessed using a qualitative silver nitrate test for halide ions. Following the first ion exchange, dilute hydrobromic acid was added to solution to form the bromide salt **163b**. This compound is typically a rusty orange color and, again, it is stable to silica gel chromatography.

Scheme 60.



Compound **163b** was an effective phase transfer catalyst for the O'Donnell alkylation (Table 12, entry 3), providing rates of conversion significantly above background levels (62% after two days vs. 6% for the control reaction). A significant and as yet unexplained aspect of this reaction is the induction period observed for the catalyzed reaction in the first eight hours. Optimization studies were carried out to determine the effects of different solvents (toluene vs. trifluorotoluene) and bases (saturated potassium carbonate, sodium hydroxide, and potassium hydroxide) on reaction rate, yield, and the presence/absence of an induction period (Table 12, entries 4-9). The results indicated that changing these parameters did not have a significant effect on the reaction outcome, with the exception of potassium carbonate, for which no conversion was observed. Thus, the original conditions employing aqueous potassium hydroxide and toluene were used in future studies with enantiopure catalysts.

Table 12. Optimization studies for the alkylation of **117**.

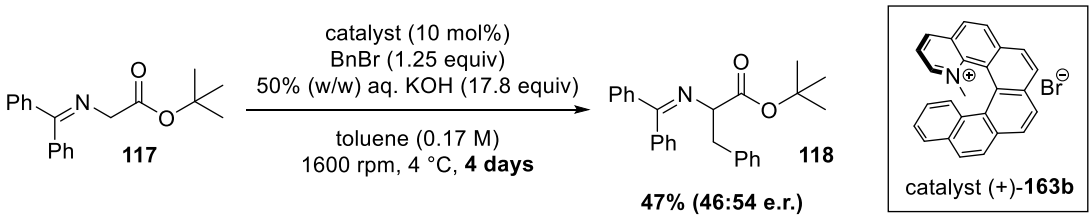


entry	*catalyst*	*base*	*solvent*	*additive*	*yield of* **118**	*induction period*
1	**163a**	KOH (50% w/w aq)	toluene	none	13%	n.d.
2	**none**	KOH (50% w/w aq)	toluene	none	6%	no
3	**163b**	KOH (50% w/w aq)	toluene	none	62%	yes
4	**163b**	KOH (50% w/w aq)	toluene	KBr (0.5 equiv)	29%	yes
5	**163b**	KOH (50% w/w aq)	TFT	none	66%	yes
6	**163b**	CsOH (80% w/w aq)	toluene	none	57%	yes
7	**163b**	CsOH (80% w/w aq)	TFT	none	64%	yes
8	**163b**	K_2CO_3 (sat aq)	toluene	none	0%	--
9	**163b**	K_2CO_3 (sat aq)	TFT	none	0%	--

TFT = α,α,α-trifluorotoluene. Yields determined by HPLC using biphenyl as an internal standard.

Enantiopure catalyst (+)-**163b** was accessed from helicene (+)-**137** using the route already described for preparation of racemic catalyst **163b** (see Schemes 58 and 60). Spectroscopic data for the enantiopure and racemic catalysts were identical. However, when (+)-**163b** was used as a phase transfer catalyst in the O'Donnell alkylation, the reaction rate was significantly slower than that observed for the racemic catalyst (Scheme 61). After two days the reaction catalyzed by (+)-**47** had barely reached 18% yield, while the reaction catalyzed by racemic **47** reaches 62% yield in the same amount of time. After four days the reaction had reached 47% yield and at this point the reaction was worked up in order to determine the e.r. of the product. An e.r. of 46:54 was observed, which was confirmed by two separate runs.

Scheme 61.



The rate difference observed for the asymmetric reaction was puzzling. Also of concern were some reproducibility issues occasionally seen among the alkylations run with racemic **163b**. Specifically, while the majority of runs gave very consistent results, occasionally large differences in reaction rate were observed among catalyzed runs depending on which batch of racemic catalyst **163b** was used. This observation had no obvious explanation, as the purity of every batch of catalyst was assessed by ^{1}H-NMR analysis. Completeness of the iodide to bromide ion exchange was also unequivocally proven by elemental halide analysis. The possibility was considered whether the observed inconsistencies were due to catalyst decomposition. Quaternary pyridinium salts are known to be susceptible to reversible and regioselective hydroxide attack at the 2-position, followed by oxidation to the corresponding pyridone in the presence of a mild oxidant.[168] For this reason, there was concern about the stability of **163b** in hydroxide-mediated PTC. To address this issue, 2-phenyl substituted compound **166b** was chosen as a new synthetic target, the hope being that a bulky group in this position would prevent unwanted reactivity with hydroxide in solution (Figure 34).

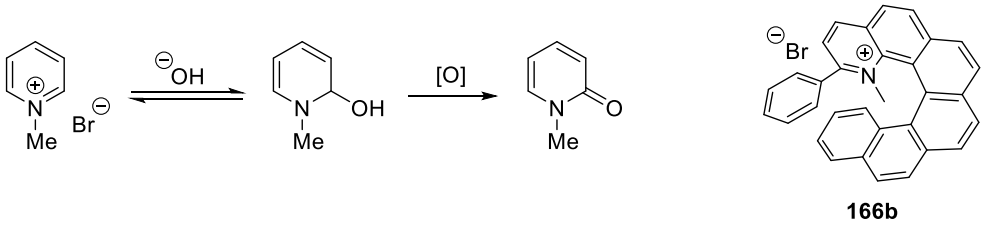
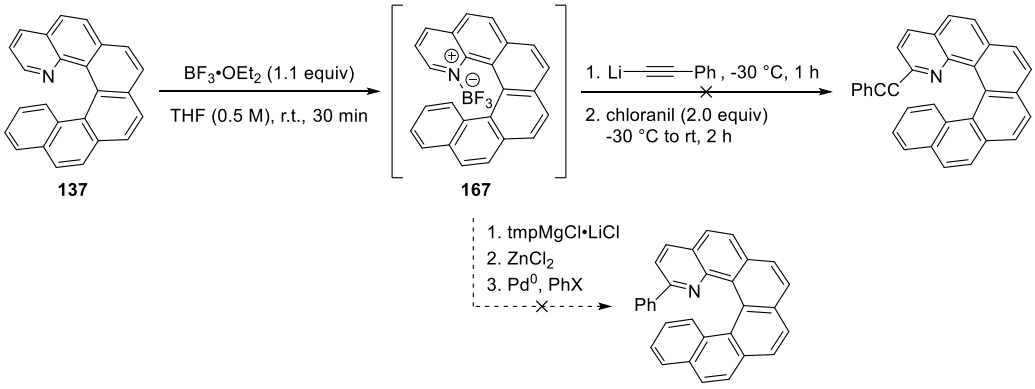


Figure 34. Hydroxide-mediated decomposition of pyridines.

It was envisioned that salt **166b** could be arrived at through two general approaches for *ortho*-arylation of pyridines. The first approach involves formation of the BF_3-pyridine adduct, which is known to activate the substrate towards *ortho*-arylation. Knochel et al. have recently

described a one-pot procedure for BF_3-adduct formation, *ortho*-deprotonation using a bulky magnesium amide base, transmetalation, and Csp^2-Csp^2 bond formation via a Negishi coupling.[192] Alternatively, organolithium reagents will add regioselectively to the 2-position of pyridine-BF_3 adducts, affording *ortho*-arylated pyridines after subsequent rearomatization.[193-194] A number of 2-substituted pyridines and quinolines have been prepared in this manner, and it was thought that the same approach could be applicable to azahelicenes. First, it was confirmed that **137** readily forms an adduct **167** when reacted with BF_3 etherate at room temperature. While the adduct was not rigorously purified (**167** is not stable to silica gel chromatography), the downfield shifts observed in the ^{1}H-NMR relative to the parent helicene, as well as a characteristic signal in the ^{19}F-NMR were highly indicative of azahelicene-BF_3 adduct formation. However, attempts to introduce groups at the 2-position were not successful (Scheme 62). Specifically, when **167** was treated with the bulky base tmpMgCl·LiCl and quenched with deuteroacetic acid, no deuterium incorporation was observed. This indicated that adduct **167** did not undergo *ortho*-metalation under these conditions, so the one-pot transmetalation and Negishi coupling was not attempted. Likewise, the addition of alkynyllithium reagents to pyridine-BF_3 adducts has been described, but no reaction was observed between lithium phenylacetylide and azahelicene adduct **167**.

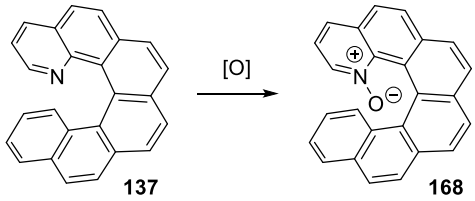
Scheme 62.



The second general approach for the synthesis of *ortho*-arylated pyridines involves an initial oxidation to the pyridine *N*-oxide, followed either by organolithium addition and rearomatization or by direct Csp^2-H activation. The *N*-oxidation of **137** with *m*-CPBA has been published by Takenaka et al. and under these conditions the desired N-oxide **168** was obtained in

38% yield.[163-164] Although some unreacted starting material could be recovered from the reaction, this was a disappointing yield for a late-stage transformation, and a number of oxidizing agents commonly used for *N*-oxidation of pyridines were tested for conversion of the free helicene to the *N*-oxide (Table 13).[195-197] These reactions all proceeded sluggishly or not at all, with the best yield still obtained by using *m*-CPBA.

Table 13. Survey of conditions for *N*-oxidation.

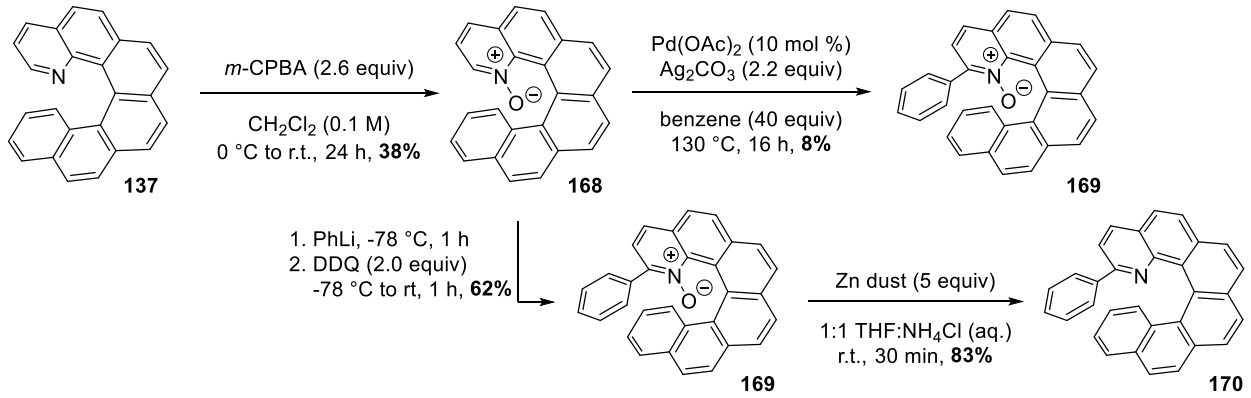


Oxidant	*Yield of* **168**
m-CPBA [a]	38%
trifluoroperacetic acid (TFPAA) [b]	12%
dimethyldioxirane (DMDO) [c]	0%
TMO/H_2O_2 [d]	0%

Conditions: **a)** m-CPBA (2.6 equiv), CH_2Cl_2, 0 °C to 25 °C; **b)** TFAA (10 equiv), UHP (10 equiv), K_2CO_3 (20 equiv), dioxane, 12 °C to 25 °C; **c)** Oxone ® (10 equiv), acetone (25 equiv), buffer (pH = 8), 25 °C; **d)** H_2O_2 (2 equiv), $MeRhO_3$ (0.04 equiv), CH_2Cl_2, 25 °C.

Attempts to arylate the *N*-oxide via direct C-H activation were successful, but this method is low yielding, forms a complex mixture of products, and requires forcing conditions.[198] Aryllithium addition followed by rearomatization with DDQ had been used previously by Takenaka et al. for the synthesis of 2-pyridyl-azahelicene-*N*-oxides, and this approach was also successful here to form novel 2-phenyl-azahelicene-*N*-oxide **169** in 62% yield (Scheme 63).[164]

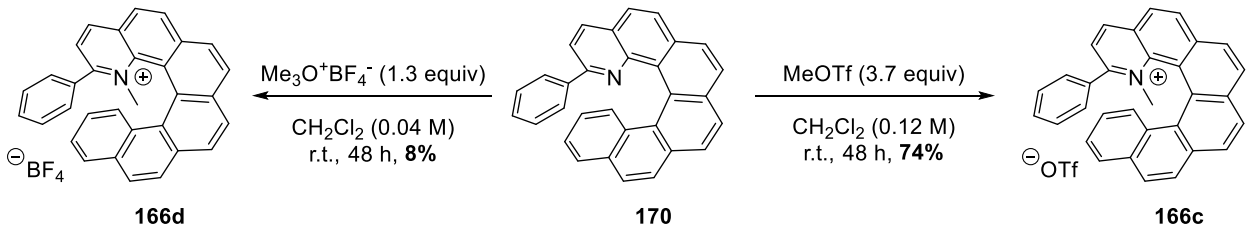
Scheme 63.



Next, it was necessary to find conditions for the reduction of the functionalized *N*-oxide back to the free pyridine. Traditionally, this is done using trivalent phosphorus reagents (PPh_3 or PCl_3), although heterogeneous conditions employing palladium, iron, or zinc with a proton source have also been reported.[168, 196] Conveniently, *N*-oxide **169** was converted to free helicene **170** by stirring with zinc powder in a 1:1 mixture of THF and saturated aqueous ammonium chloride. This reaction is typically complete within half an hour and is high-yielding (83%). Synthesis of enantiopure 2-phenylazahelicene (-)-**170** was accomplished in three steps from parent helicene (-)-**137** using the same sequence.

With functionalized helicene **170** in hand, *N*-quaternization was attempted using the usual conditions. Unfortunately, with the introduction of additional steric bulk around the nitrogen atom, methylation no longer occurred in the presence of methyl iodide, even at elevated temperatures. Therefore, the transformation was attempted using more reactive electrophiles. *N*-Methylation was achieved using methyl triflate at room temperature, yielding triflate salt **166c** in good yield (Scheme 64). Trimethyloxonium tetrafluoroborate (methyl Meerwein reagent) was a much less effective methylating agent, resulting in a low level of conversion to the tetrafluoroborate salt **166d**.

Scheme 64.

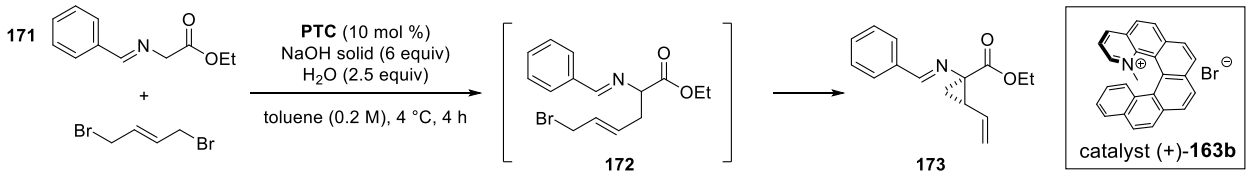


The triflate salt was determined to be inactive as a catalyst, so ion exchange to the bromide salt **166b** was accomplished in 59% yield using the same protocol outlined previously for iodide salt metathesis (see Scheme 60). However, when tested as a phase transfer catalyst, compound **166b** displayed a negligible rate enhancement above the background reaction. This likely indicates that **166b**, while perhaps better engineered against known decomposition pathways, is now so lipophilic that it is not present at the interfacial region in appreciable quantities.

The issues already discussed of catalyst stability and reproducibility notwithstanding, it was clear that at least some success had been achieved in the benchmark reaction (O'Donnell alkylation) using catalyst **163b**. This catalyst was subsequently screened for activity in several known hydroxide-mediated intramolecular PTC reactions. The results of these studies are summarized here.

The cyclopropanation of (*E*)-*N*-phenylmethyleneglycine ethyl ester **171** under PTC conditions developed by the Merck Research Laboratories is one of the few examples of an enantioselective intramolecular PTC reaction (Scheme 65). In contrast to substrate **1** used in the O'Donnell alkylation, which only undergoes monoalkylation, the α-methylene position in glycine imine **171** is sufficiently accessible to allow dialkylation.

Scheme 65.

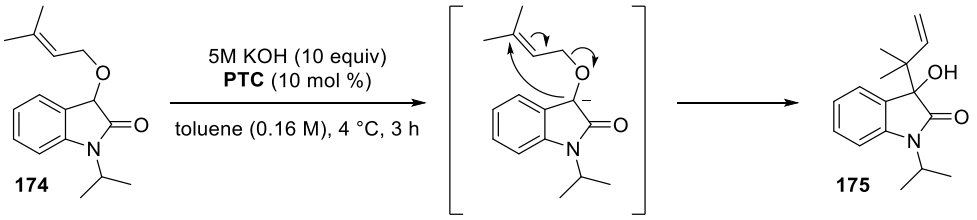


Initial S_N2 displacement of 1,4-dibromobutene yields transient intermediate **172**, which then undergoes intramolecular S_N2' displacement to yield vinylcyclopropane **173**. A large number of cinchona-derived catalysts have been previously screened in this reaction, and unlike the O'Donnell alkylation (which can already be performed asymmetrically with an enantiomeric ratio greater than 99:1), the maximum stereoselectivity which has been observed for the cyclopropanation reaction is 92:8 on a high-throughput scale and 89:11 on a process scale.[140] It was thought possible that azahelicene-derived catalyst (+)-**163b** could be active in this transformation. Unfortunately, no rate enhancement was observed above the background reaction.

The phase transfer catalyzed [2,3]-Wittig rearrangement of allyloxy-oxindoles (Scheme 66) has been extensively studied in these laboratories. The use of chiral, non-racemic cinchona-derived catalysts leads to some degree of asymmetric induction in the product. To date, the best e.r. observed for this transformation is 73:27.[142] As this appeared to be the upper limit accessible by cinchona-derived catalysts, it was considered worthwhile to test other unique catalyst scaffolds

for activity in this rearrangement. Unfortunately, no rate enhancement for the [2,3]-Wittig rearrangement was observed above the background level of conversion using either **163b** or (+)-**163b**.

Scheme 66.



Likewise, no catalytic activity was observed in the anionic oxy-Cope rearrangement (Appendix A, Scheme 37) using catalyst **163b**. No conversion was observed after several days using this quaternary pyridinium salt. The modified *N*-allylpyridinium salt **165** also displayed no catalytic activity in this transformation.

B.3. Discussion and Outlook

In the course of this research, significant amounts of time and effort were spent accessing gram quantities of azahelicene **137**. While this high synthetic overhead severely hindered rapid access to a catalyst library, it also provided an opportunity to make meaningful contributions to the field of azahelicene synthesis. The route developed by Takenaka et al. was streamlined from twelve to nine total steps by changing the target precursor olefin from **150** to **158**. Additionally, the conversion of **158** to azahelicene **137** represents the first example of an azahelicene synthesis employing a nickel-mediated intramolecular cross coupling.

At the outset of this project, it was largely unclear how well the known chemistry of pyridines would translate to the chemistry of azahelicenes. It was expected that the nitrogen atom of **137** would be sufficiently less nucleophilic than a pyridine nitrogen owing to the additional steric bulk, and indeed this seemed to be the case. While a number of electrophiles were unsuccessful at effecting the *N*-quaternization of **137**, this transformation was accomplished under mild conditions using methyl iodide to afford salt **163a** (Scheme 58). This report represents the first synthesis of an *N*-alkylated azahelicene. In addition to reacting with small, highly activated

electrophiles, azahelicene **137** was also shown to be capable of forming an adduct **167** with boron trifluoride, although **167** does not undergo subsequent *ortho*-functionalization chemistry which is known for pyridine-BF_3 adducts. The increased steric bulk around the nitrogen atom in **137** relative to an unsubstituted pyridine or quinoline also proved to be severely detrimental to attempts at *N*-oxide formation (Table 13). By contrast, aryllithium addition to **168** and subsequent rearomatization to form **169** was high yielding (and well-precedented), and the reduction of helicene *N*-oxide **169** to **170** was also quite facile.

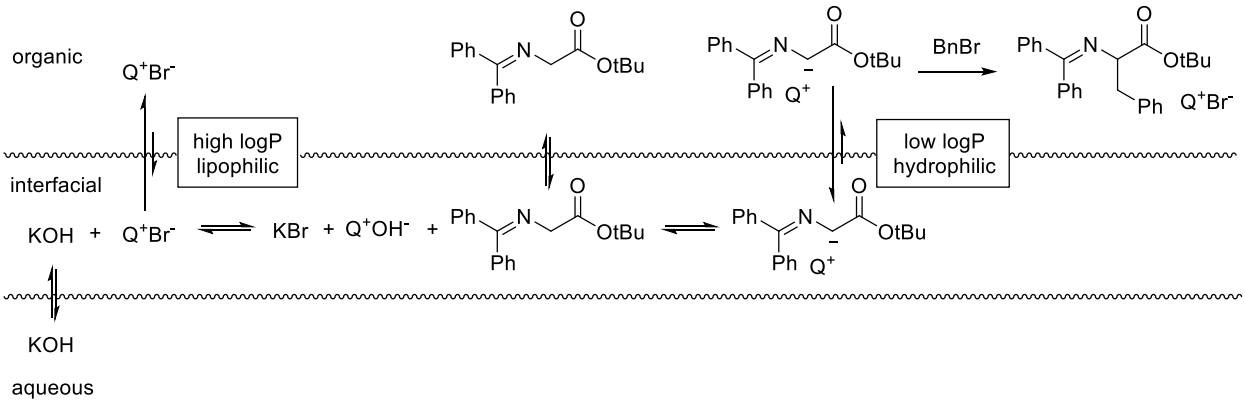


Figure 35. Interfacial model for phase transfer catalyzed enolate alkylation.

Azahelicene-derived salt **163b** was modestly successful at catalyzing the O'Donnell alkylation of **117** under PTC conditions (Table 12). The catalyzed reaction did proceed significantly faster than the background reaction, but was still substantially slower than the reaction catalyzed by TBAB under the same conditions (Appendix A, Scheme 34). Additionally, the maximum yield of **118** leveled off at slightly above 60% when **163b** was used as a catalyst, while nearly quantitative yields of **118** can be obtained with tetraalkylammonium salts. The presence of an induction period is also concerning, as it suggests that the catalytically active species might not be **163b** as drawn. These results, in conjunction with the occasionally observed reproducibility issues, seem to suggest some level of catalyst decomposition *in situ*. The synthesis of **166b** was intended to circumvent the decomposition problem (Figure 34), but reactions run in the presence of **166b** displayed no rate enhancement for the conversion of **117** to **118**. It is possible that **166b** could still undergo decomposition, but a more likely explanation is that due to its

increased lipophilicity relative to **163b**, catalyst **166b** is simply not present in appreciable quantities in the interfacial region to help desolvate the enolate (Figure 35). This conclusion is supported by cLogP calculations which show a 100-fold increase in the (o/w) partition coefficient for **166b** relative to **163b** (Figure 36). The synthesis of less lipophilic derivatives of **163b** and **166b** which are predicted to have more appropriate cLogP values is a potential future direction of this project.

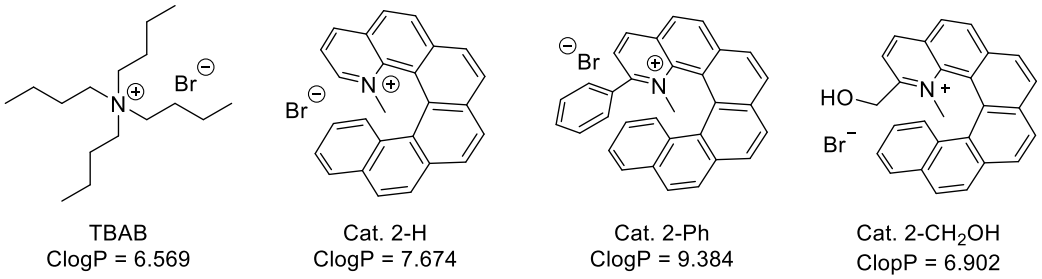


Figure 36. Calculated ClogP values for some ammonium and pyridinium salts.

The low enantiomeric ratio of **118** observed when the alkylation reaction is run in the presence of (+)-**163b** suggests that the azahelicene-derived counterion is not well suited to differentiate the two faces of the enolate. This was not too surprising in light of the "steric screening" models for enantioselective enolate alkylations using *Cinchona*-derived catalysts.[160-161] Stereochemical models posit an interaction between the quinoline ring of the catalyst and the aryl groups of the benzophenone imine **117**. The *N*-benzyl group creates a pocket in which one face of the enolate is effectively shielded such that alkylation preferentially occurs on the opposite face. It is unclear exactly how the helicene-derived catalysts would provide a similar bias for direction of approach, at least in the context of this model. Nevertheless, the product formed is non-racemic which indicates that the catalyst is somehow capable of differentiating the two faces, if only to a small degree. Actually, the azahelicene-derived catalysts were never intended to provide high enantioselectivity for bimolecular alkylation reactions. Rather, it was hypothesized that these catalysts would afford superior enantioselectivity for unimolecular, anionic rearrangements. It is unfortunate that no catalytic activity (rate enhancement) was observed for these species in any of the unimolecular reactions surveyed, so this hypothesis remains untested.

To summarize, the synthesis of several novel azahelicene-based *N*-methylpyridinium halide salts has been reported. These compounds may be accessed in racemic and enantiopure form and display catalytic activity in the α-alkylation of carbonyl compounds under PTC conditions. However, the high synthetic overhead, difficulty of late-stage diversification, suspected decomposition under hydroxide-mediated PTC, and poor asymmetric induction preclude the use of quaternized azahelicenes as a general phase transfer catalyst scaffold.

Appendix C. Synthesis of Diverse Bisoxazoline (BOX) Ligands

C.1. Strategies for Stereoselective Amino Alcohol Synthesis

As part of a broader initiative to apply chemoinformatics and machine learning toward catalyst and ligand optimization,[159, 199] the Denmark laboratory became interested in the preparation of a number of diverse bisoxazoline ligands. This highly cooperative effort provided the opportunity to validate the state-of-the-art methods available for enantioselective construction of amino acids and amino alcohols, and also highlighted the limitations and challenges associated with the preparation of these compounds. This appendix serves to provide a brief overview of synthetic efforts towards some novel bisoxazolines (Figure 37). Given the prevalence of bisoxazolines as a privileged ligand scaffold in asymmetric catalysis,[200] this discussion should prove useful.

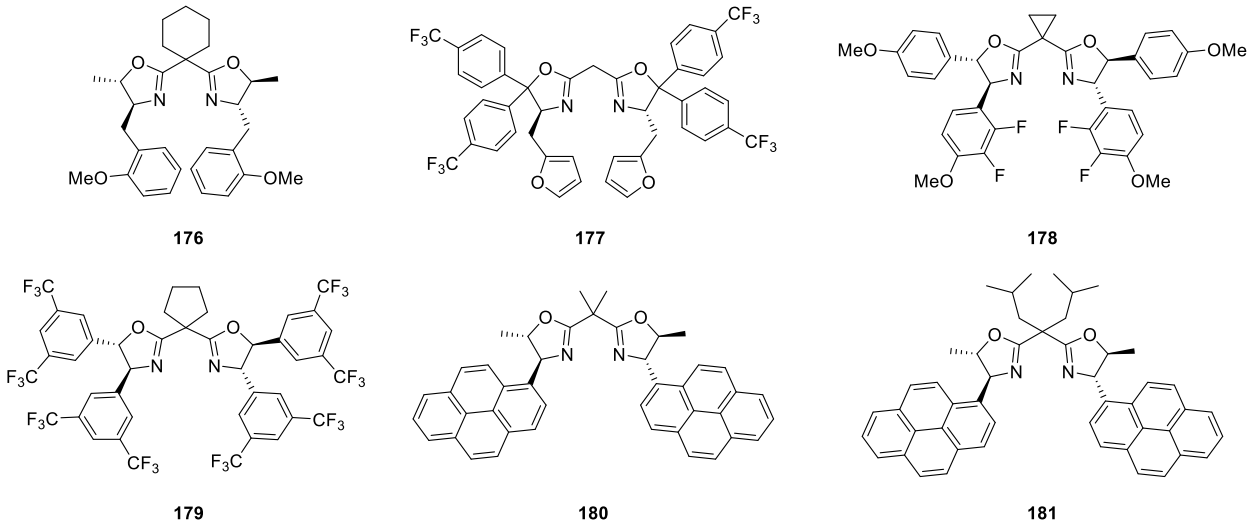


Figure 37. Novel, chiral, non-racemic, C_2-symmetric bisoxazoline ligands.

Bisoxazolines are generally constructed by either invertive or retentive cyclization of bis(hydroxyamide) intermediates, which are derived from two equivalents of an amino alcohol and

a diacyl chloride (Figure 38). Therefore, the principal challenge of synthesizing the ligand is identifying a stereoselective approach to the requisite amino alcohol.

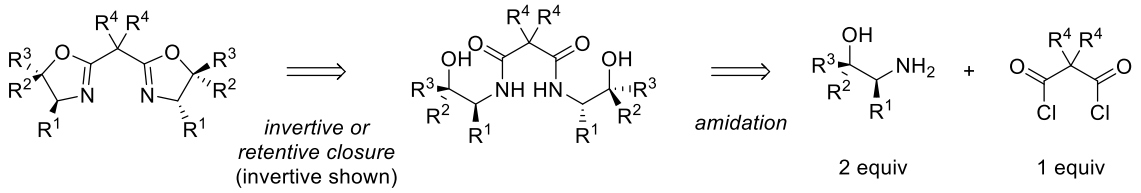


Figure 38. Preparation of bisoxazolines from 1,2-amino alcohols.

Depending on the identity of the carbinol substituents (R^2 and R^3), the amino alcohol is accessed by either reduction of an amino acid ($R^2 = R^3 = H$), addition of an organometallic reagent (two equivalents) to an amino ester ($R^2 = R^3 \neq H$), or diastereoselective reduction of an α-amino ketone ($R^2 = H$ or $R^3 = H$) derived from addition of an organometallic reagent (one equivalent) to an α-amino Weinreb amide. In all three scenarios, the ultimate progenitor is an enantiomerically enriched, mono-substituted α-amino acid/ester (Figure 39). The most successful, general routes identified for accessing these precursors were enantioselective, phase transfer catalyzed enolate alkylation[201] (R^1 = benzyl) or enantioselective, organocatalyzed Strecker reaction[202] (R^1 = aryl).

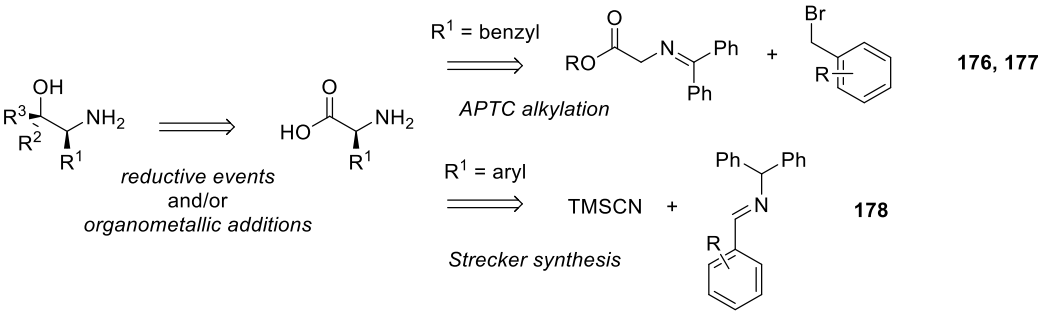


Figure 39. Preparation of chiral, non-racemic, 1,2-amino alcohols.

Alternatively, in some cases the requisite 1,2-amino alcohols were derived from enantiomerically enriched 1,2-diols. These could be prepared in generally high yield and selectivity by Sharpless asymmetric dihydroxylation of stilbene and styrene derivatives (Figure 40).[203] Although this was an excellent method for the introduction of stereocenters, the number of

library bisoxazolines which could be prepared in this manner was limited, owing to the substrate requirements for enantioselective dihydroxylation.

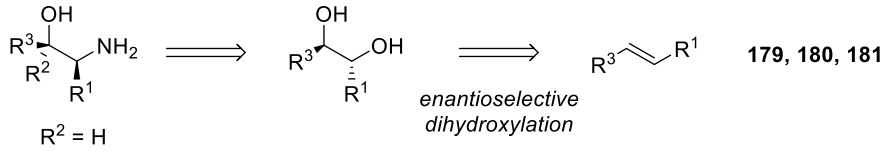


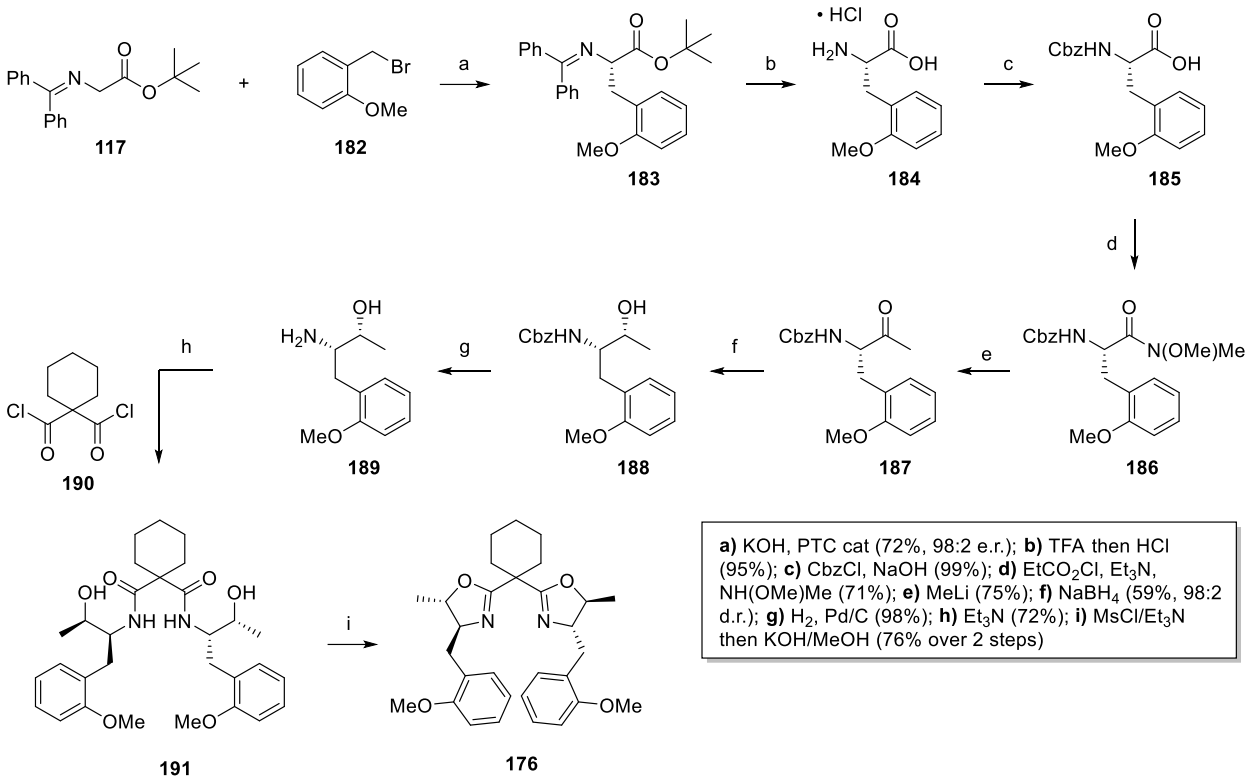
Figure 40. Preparation of non-racemic amino alcohols by enantioselective dihydroxylation.

C.2. Forward Syntheses of BOX Ligands

176: The forward synthesis of bisoxazoline ligand **176** is outlined in Scheme 67. This route began with an enantioselective, phase-transfer-catalyzed alkylation of *tert*-butyl glycine benzophenone imine **117** with 2-anisyl bromide **182** to afford intermediate **183**. The reaction was performed on >20 mmol scale, and afforded **183** in >60% yield and excellent enantioselectivity (>98:2 e.r.). The absolute configuration of the major enantiomer was presumed to be (*S*) on the basis of literature precedent.[204] The phase transfer catalyst was accessed in two steps from inexpensive, chiral pool starting material.[204-205] Next, global hydrolysis of **183** under acidic conditions afforded amino acid **184** as the hydrochloride salt in nearly quantitative yield. Subsequently, the *N*-terminus was protected as the benzyl carbamate (Cbz) **185**, and the free carboxylic acid was converted to Weinreb amide **186** via the mixed anhydride. Addition of methyllithium to **186** afforded ketone **187** in high yield without epimerization of the nitrogen-bearing stereogenic center. Titanium tetrachloride-mediated reduction of **187** with triethylsilane was facile but afforded a mixture of diastereomers, which was quite unexpected on the basis of the close literature precedent.[206] Even at cryogenic temperatures, the highest obtainable d.r. was 77:23 in favor of the desired *erythro*-**188**. In an effort to improve this ratio, a survey of various reductants was undertaken. Treatment of **187** with lithium tri-*sec*-butyl borohydride (L–Selectride) or lithium triethylborohydride (Super hydride) afforded complex mixtures, whereas treatment with lithium tri-*tert*-butoxyaluminum hydride resulted in low conversion. Sodium borohydride, lithium aluminum hydride, and the original triethylsilane/$TiCl_4$ system all afforded **188** in similar yields and diastereoselectivity. Ultimately, sodium borohydride was selected as the reductant solely

because of operational simplicity, and *erythro*-**188** and *threo*-**188** were separated by chromatography. The *N*-Cbz group was cleanly cleaved by hydrogenolysis to afford amino alcohol **189** in nearly quantitative yield.

Scheme 67.



At this point, it was important to prove the relative configuration of the two vicinal stereogenic centers following reduction of **187** to **188** (up to this point, *erythro*-**188** was assumed to be the major diastereomer on the basis of literature precedent).[206] The most straightforward approach was to convert acyclic **188** (or **189**) to the corresponding 5-membered oxazolidinones, in which the vicinal substituents are locked in either a *cis* or *trans* configuration. Treatment of amino alcohol *erythro*-**189** with carbonyldiimidazole (CDI) afforded *cis*-**192** in 72% yield. Although this procedure works well, it is not necessary to use the free amino alcohol to access the oxazolidinone. Treatment of *N*-Cbz carbamate *threo*-**188** with sodium hydride afforded *trans*-**192** directly with concomitant production of benzyl alcohol. With the diastereomeric oxazolidinones

in hand, the ^{1}H NMR spectra were carefully examined. Ordinarily, *cis*-**192** and *trans*-**192** would be easily differentiated on the basis of the magnitude of the coupling constant between the two ring protons.[207] Unfortunately, both signals were split by their exocyclic substituents, resulting in rather complex multiplets which obfuscated a simple *J*-value measurement. Consequently, both compounds were subjected to ^{1}H 2–D NOESY analysis, which provided the necessary information on the spatial relationship between the methyl group and the *ortho*-anisyl group (Figure 41). Specifically, in the oxazolidinone derived from *erythro*-**189**, a NOESY cross peak was observed between the benzylic protons and the methyl group, which is expected if these ring substituents are indeed in a *cis* relationship. By contrast, in the oxazolidinone derived from *threo*-**188**, no cross peak was observed between these groups, confirming the *trans* relationship between the ring substituents. In conclusion, the original, tentative assignments were correct, and the major diastereomer resulting from ketone reduction is indeed the desired *erythro*-**188**.

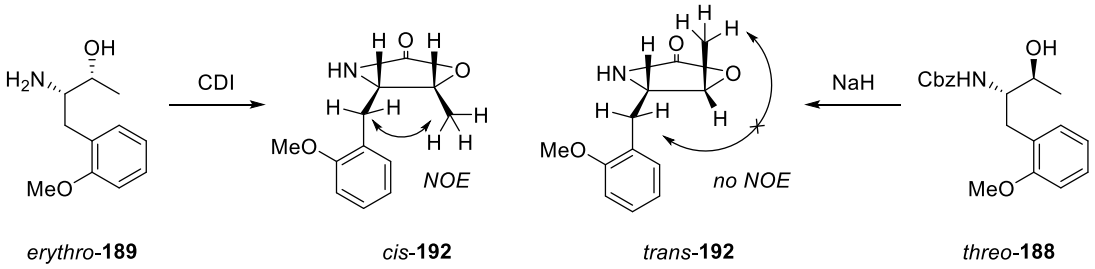


Figure 41. Establishment of relative configuration.

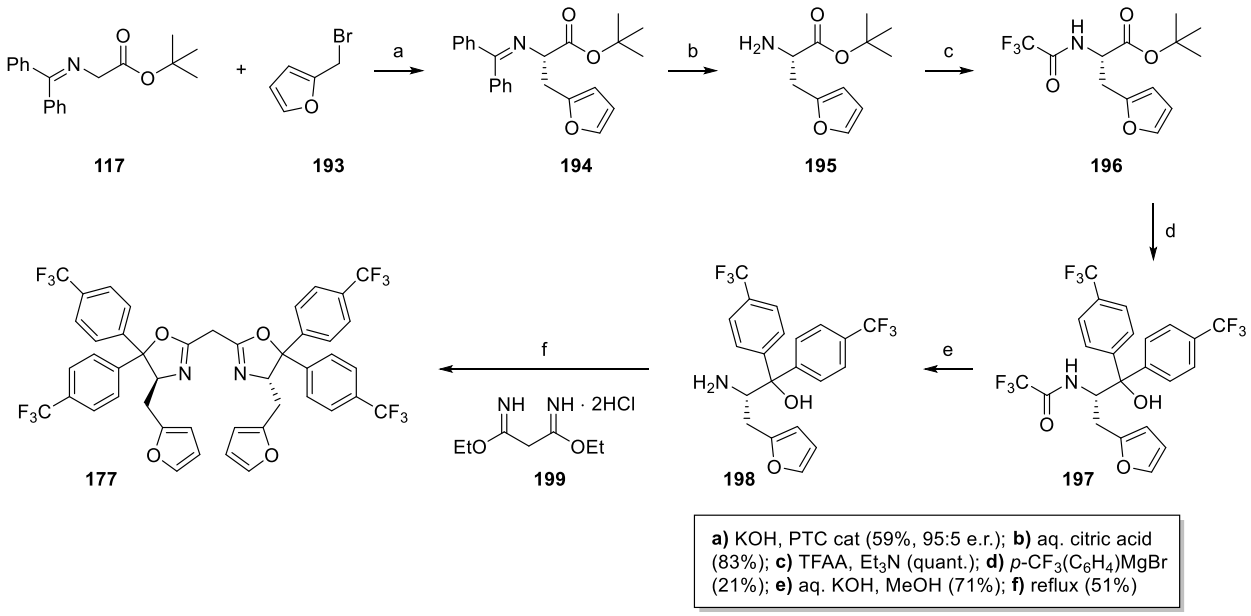
Having developed a robust route to requisite amino alcohol **189**, the synthesis of bisoxazoline **176** was finally in sight. Reacting two equivalents of **189** with cyclohexane-1,1-dicarbonyl dichloride **190** afforded variable yields of bis(hydroxyamide) **191** when **190** was generated *in situ*. It was eventually discovered that when **190** was prepared on a large scale and purified by distillation, a higher, more consistent yield of **191** was obtainable. Subsequent mesylation and invertive displacement afforded the target bisoxazoline **176** in 76% yield over two steps.

177: The forward synthesis of bisoxazoline ligand **177** is outlined in Scheme 68. Like **176**, the requisite amino acid was prepared by an enantioselective, phase-transfer-catalyzed enolate alkylation of compound **117**. The preparation of furfuryl bromide **193** from furfuryl alcohol is a

delicate procedure and must be performed immediately before the alkylation reaction. Only freshly distilled furfuyl alcohol should be used, and the procedure of Zanetti[208] should be followed exactly. Bromide **193** is quite unstable and prone to rapid decomposition; black, polymeric residues were frequently observed on all glassware used to prepare **193**. The alkylation itself works nicely, affording imino ester **194** in good yield and high enantioselectivity (95:5) using the dimeric Jew–Park catalyst.[204] Again, the absolute configuration of the major enantiomer was presumed to be (*S*) on the basis of literature precedent. Selective hydrolysis of the imine moiety in the presence of the *tert*-butyl ester was accomplished with dilute aq. citric acid to afford amine **195**, which was subsequently protected as the *N*-trifluoroacetamide **196**. The addition of two equivalents of *para*-trifluoromethylphenylmagnesium bromide to **196** proved to be a formidable synthetic challenge. First, the Grignard reagent itself is highly prone to homocoupling. The best results were obtained when the reagent was generated at 25 °C (initiation was essentially instantaneous) and used immediately. The formation of active Grignard reagent was confirmed/monitored by GCMS analysis of a reaction aliquot quenched into methanol. At all timepoints, a mixture of α,α,α-trifluorotoluene (product of quenched reagent), *p*-(trifluoromethyl)bromobenzene, and 4,4'-(trifluoromethyl)biphenyl was observed, but the most favorable ratio of α,α,α-trifluorotoluene was observed at 15 min and decreased at longer reaction times. The addition of Grignard reagent to ester **196** was rapid, reaching full conversion within 2 hours. Unfortunately, the quenched reaction mixture formed intractable emulsions during workup, which likely hurt the obtainable recovery of crude **197**. Additionally, the product was only semi-stable to silica gel chromatography and in all cases, **197** was isolated in low yield with trace amounts of an unidentified, inseparable impurity. The optimization of this step is a standing challenge. Gratifyingly at least, no epimerization of the α-stereogenic center was observed during the addition. Alcohol **197** was isolated with a 94:6 enantiomeric ratio, essentially unchanged from imino ester **194**. Removal of the *N*-trifluoroacyl group under basic conditions (no conversion was observed under reductive conditions) afforded amino alcohol **198**. Bisoxazoline **177** was prepared in 51% yield by condensing two equivalents of **198** with diethyl malonimidate dihydrochloride **199**.[209] This reaction proceeded at a painfully slow rate, affording roughly 80% conversion to **177** after eight days in refluxing CH_2Cl_2. Similarly sluggish rates have been previously documented in the literature for other secondary and tertiary alcohols.[210] Switching to higher-boiling dichloroethane as the reaction solvent did not improve the

yield. Purification of **177** was also a challenge, with substantial impurities remaining after chromatography, but the level of purity was sufficient for initial screening campaigns.

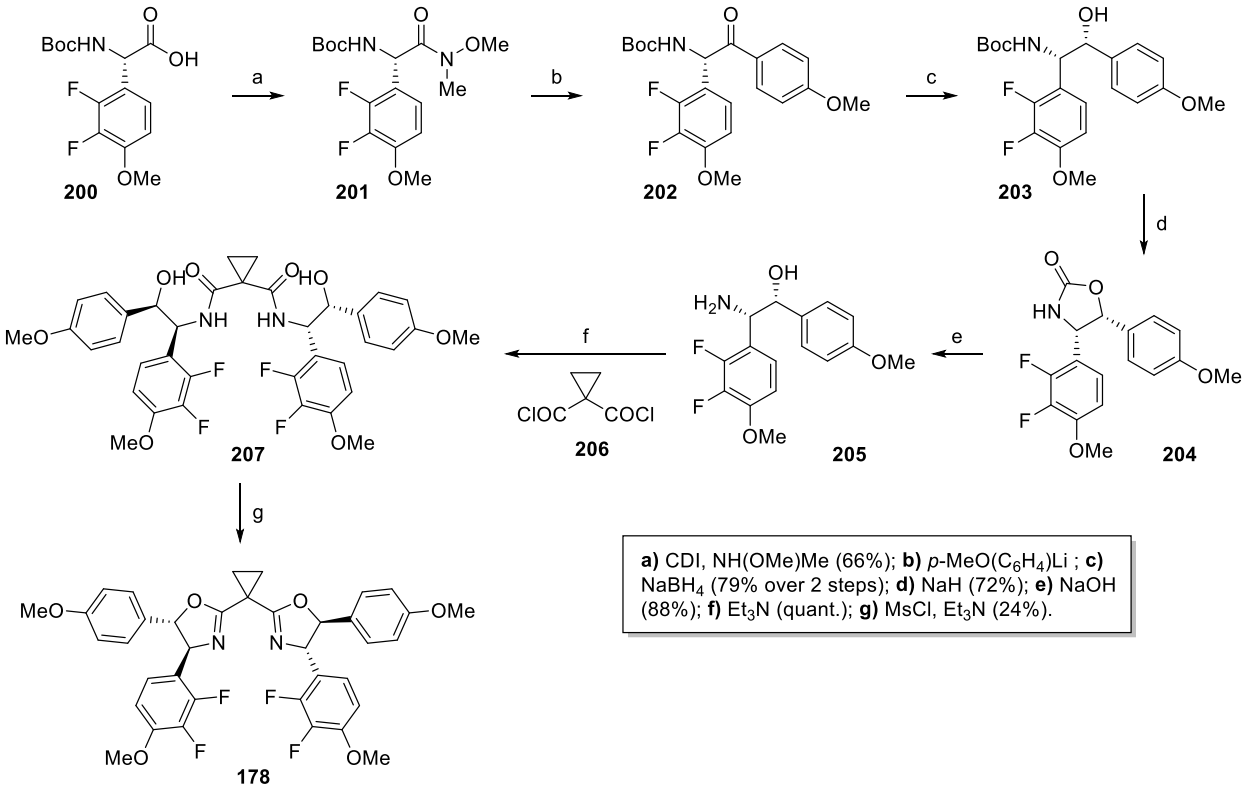
Scheme 68.



178: The forward synthesis of bisoxazoline ligand **178** is outlined in Scheme 69. Amino acid **200** was accessed in enantiomerically enriched form by an asymmetric, organocatalyzed Strecker reaction.[211] Regrettably, the enantiomeric ratio of **200** could not be accurately determined by the analytical methods available at the time of synthesis, but it was presumed to be ≥90:10 based on concurrent results for similar compounds. The absolute configuration of **200** was also presumed to be (*S*) on the basis of literature precedent. This compound was prepared by a colleague as part of a collaborative research effort, so only the forward transformation of **200** to **178** will be outlined here. Amino acid **200** was converted via mixed anhydride to Weinreb amide **201**, and subsequent addition of 4-methoxyphenyllithium afforded ketone **202**. After workup, ketone **202** was isolated as a mixture with anisole and several minor impurities. An enantiomeric ratio of 92:8 was measured for **202**, implying that the original assumption concerning the fidelity of the asymmetric Strecker synthesis was correct. Ketone **202** is susceptible to epimerization under basic conditions, so maintenance of a buffered environment during workup is crucial. In an earlier, non-optimized synthesis of **202**, the compound was accidentally exposed to basic conditions during the

workup step. The enantiomeric ratio measured for **202** after chromatography was 88:12, a small but significant decrease from the 92:8 ratio observed in the optimized synthesis. Given this known liability toward epimerization, crude **202** was immediately treated with sodium borohydride to afford amino alcohol **203** which has no such liability. The reduction proceeded in high diastereoselectivity to afford *erythro*-**203** as a single isomer.

Scheme 69.



At this point in the synthesis, it was necessary to confirm the relative configuration of the vicinal stereogenic centers. Treatment of **203** with sodium hydride proceeded with retention of configuration to afford oxazolidinone *cis*-**204**, whereas treatment of **203** with mesyl chloride and triethylamine proceeded with inversion of configuration to afford diastereomeric oxazolidinone *trans*-**204** (Figure 42). Unlike the scenario encountered during the synthesis of **176**, the assignment of the two diastereomeric oxazolidinones in the present case was easily accomplished by comparison of the coupling constants between the two vicinal ring protons. The coupling constant

for *cis*-**204** (J = 8.5 Hz) was larger than observed for *trans*-**204** (J = 6.0 Hz), which is consistent with the general trend documented in the literature.[207] Additionally, both ring proton signals in *trans*-**204** are shifted upfield relative to *cis*-**204**, which is also consistent with literature trends.[207] Therefore, the original assignment was correct, and the sodium borohydride reduction does indeed afford *erythro*-**203** as the major product.

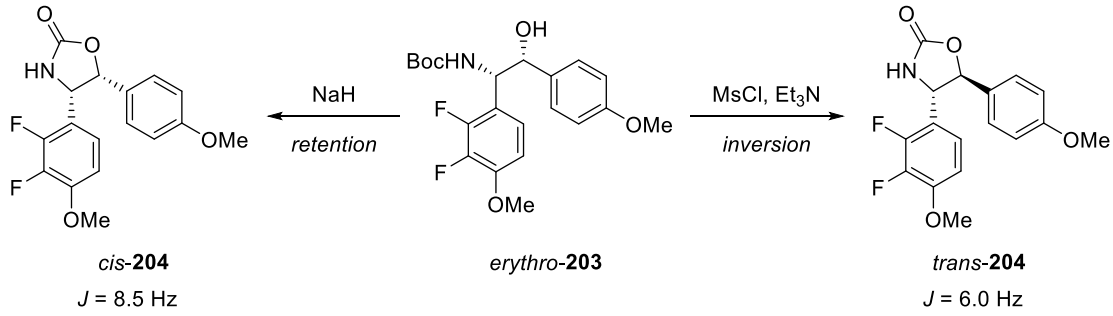
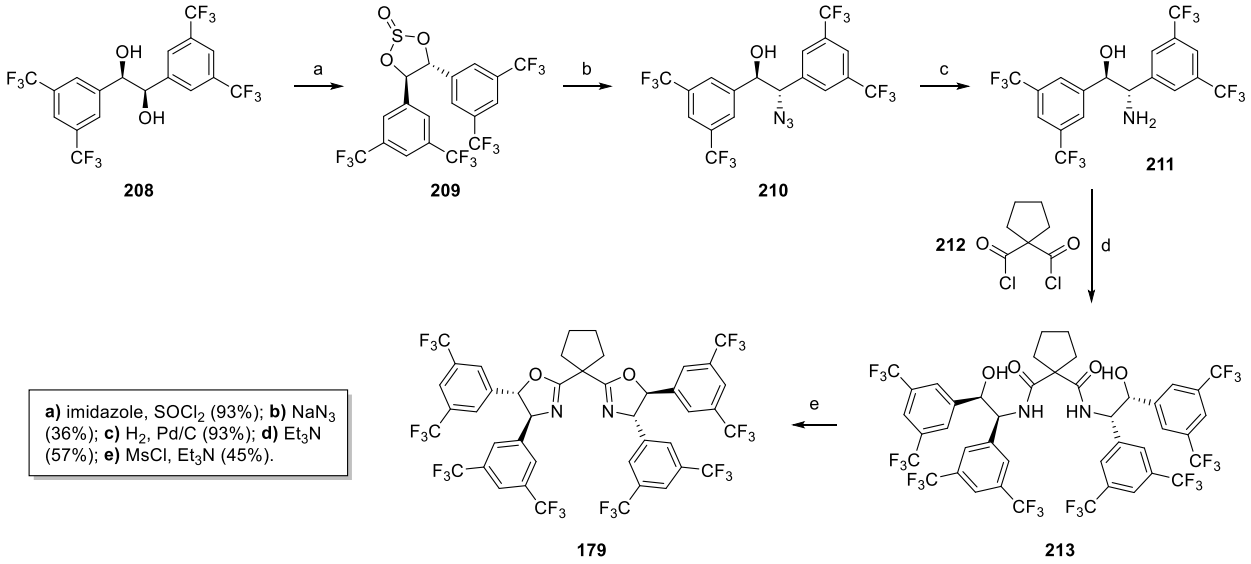


Figure 42. Assignment of relative configuration.

Retentive formation of *cis*-**204** offered a convenient, mild method for deprotection of the *N*-Boc moiety, so all material in the pipeline was funneled to this intermediate, which was then hydrolyzed with sodium hydroxide to generate the enantiomerically enriched, free 1,2-amino alcohol **205**. Reacting two equivalents of **205** with one equivalent of freshly distilled cyclopropane-1,1-dicarbonyl dichloride **206** cleanly afforded bis(hydroxyamide) **207** as expected. To prepare **178** via invertive ring closure, **207** was treated with mesyl chloride and triethylamine. Unlike the analogous step in the synthesis of **176**, in which the bis(mesylate) was isolated as a semi-stable intermediate, the more activated benzylic bis(mesylate) generated from **207** underwent spontaneous ring-closing displacement in the same pot to afford **178**. The purification of **178** is not optimized. Unexpectedly, this compound was only semi-stable to silica gel chromatography, which led to a low isolated yield of **178** in less than desirable purity. Still, this was sufficient for initial screening campaigns. The instability of **178** relative to the other library members (Figure 37) is best rationalized by the presence of the strained, cyclopropane motif, which is a liability under mildly acidic conditions. Special care should be taken during the chromatographic purification of such derivatives.

179: The forward synthesis of bisoxazoline ligand **179** is outlined in Scheme 70. Diol **208** was accessed in enantiomerically pure form (>99:1 e.r.) by Sharpless asymmetric dihydroxylation of a symmetrically substituted stilbene.[212] The absolute configuration of **208** was presumed to be (*R*,*R*) on the basis of literature precedent. This compound was prepared by a colleague as part of a collaborative research effort, so only the forward elaboration of **208** to **179** will be outlined here. Diol **208** was converted to cyclic sulfite **209** in good yield using *N*,*N*'-thionyldiimidazole prepared *in situ*. Opening the cyclic sulfite with sodium azide resulted in multiple by-products and a modest isolated yield of azido alcohol **210**. One suggestion for improvement is to further oxidize **209** to the corresponding cyclic sulfate prior to treatment with sodium azide. Cyclic sulfates undergo nucleophilic opening more readily at lower temperatures, which may suppress by-product formation and lead to higher yields of **210**, at the cost of introducing an additional synthetic step.

Scheme 70.

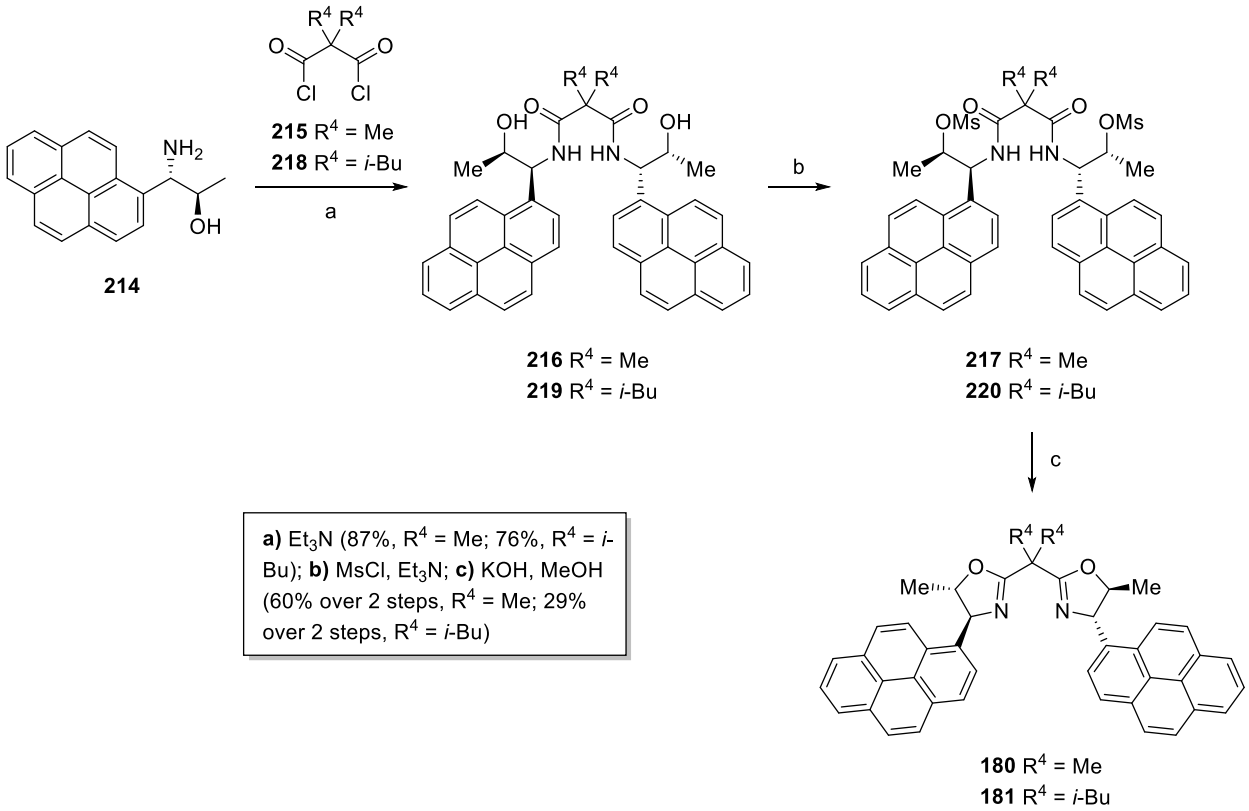


Azide **210** was easily reduced to amino alcohol **211** in high yield. Bis(hydroxyamide) **213** was prepared in the usual way from two equivalents of **211** and one equivalent of cyclopentane-1,1-dicarbonyl dichloride **212**. Again, it is crucial to synthesize **212** on a large scale and purify by distillation in order to obtain the best results in the amidation reaction. Treatment of **213** with triethylamine and mesyl chloride directly afforded **179**. The success of this invertive closure hinges on the purity of bis(hydroxyamide) **213**. When **213** was not rigorously purified, a low yield of **179**

was observed. When **213** was first purified by column chromatography, a 45% yield of **179** could be consistently obtained.

180 and **181:** These two compounds differ only in the substituents present at the bridging position (R^4). The forward syntheses of these two ligands are outlined in Scheme 71. Amino alcohol **214** was accessed in enantiomerically enriched form by Sharpless asymmetric dihydroxylation of (*E*)-1-crotylpyrene, followed by a three-step sequence analogous to the one described for the preparation of **179** (*vide supra*).[212-213] This compound was prepared by a colleague as part of a collaborative research effort, so only the forward transformation of **214** to **180** and **181** will be outlined here.

Scheme 71.



Conversion of **214** to **180** and **181** was performed using the same sequence of steps previously outlined for the synthesis of **176** (*vide supra*). First, reaction of **214** with either 2,2-dimethylpropanedioyl dichloride **215** or 2,2-diisobutylpropanedioyl dichloride **218** afforded

bis(hydroxyamides) **216** or **219**, respectively, both in good yields. Again, using freshly distilled diacyl chlorides afforded the best, most consistent results. Next, treatment with mesyl chloride and triethylamine afforded semi-stable bis(mesylates) **217** or **220**, respectively. These compounds did not undergo spontaneous ring closure, and they were observed by ^{1}H NMR to be the major species present in the crude reaction mixtures. As they were not expected to be stable to column chromatography, the bis(mesylates) were treated with KOH in methanol to effect the displacement and ring closure. Bisoxazoline **180** (R^4 = Me) was isolated in 60% yield over two steps from **216**. By contrast, the yield of **181** (R^4 = *i*-Bu) was markedly lower, only 29% over two steps from **219**. Although all of the bis(mesylate) **220** had been consumed after 12 h (determined by TLC), multiple products containing a single oxazoline ring were isolated from the reaction mixture along with bisoxazoline **181**. This suggests that the second ring closing event is far slower than the first, and this rate of closure is evidently influenced by the geminal isobutyl groups at the bridging position. Allowing the displacement reaction to run for a longer period of time and/or at elevated temperatures may improve the obtainable yield of **181**.

General Experimental

Reaction solvents tetrahydrofuran (Fisher, HPLC grade, BHT stabilized), diethyl ether (Fisher, ACS grade, BHT stabilized), and dichloromethane (Fisher, HPLC grade, not stabilized) were dried by percolation through two columns packed with neutral alumina under positive pressure of argon. Toluene (Fisher, ACS grade) was dried by percolation through one column packed with neutral alumina and one column packed with Q5 reactant under positive pressure of argon. *N*,*N*-dimethylformamide (Fisher, ACS grade) was dried by percolation though two columns packed with molecular sieves. Methanol and ethanol were distilled from magnesium turnings under a nitrogen atmosphere. Pyridine, triethylamine, DIPA, DIPEA, and acetonitrile were distilled from calcium hydride under a nitrogen atmosphere. Solvents for filtration, transfers, chromatography, and recrystallizations were purchased from commercial sources and used as received. "Brine" refers to a saturated solution of sodium chloride in distilled water. Column chromatography was performed using Merck grade 9385, 60 Å silica gel. Visualization was accomplished by UV light, potassium permanganate solution, ceric ammonium molybdate solution, or phosphomolybdic acid solution. Analytical TLC was performed on Merck silica gel plates with F_{254} indicator. R_f values reported were measured using a 10 x 2 cm plate. All reactions were conducted under an atmosphere of dry argon unless stated otherwise. Microwave reactions were performed in an Anton Parr Monowave 400 Microwave Synthesis Reactor.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker 500 MHz (500 MHz, ^{1}H; 126 MHz, ^{13}C) spectrometer. Spectra are reference to residual chloroform (δ = 7.26 ppm, ^{1}H; 77.16 ppm, ^{13}C) or residual benzene (δ = 7.16 ppm, ^{1}H; 128.06 ppm, ^{13}C). ^{31}P NMR spectra were recorded on a Varian 400 MHz (162 MHz, ^{31}P) spectrometer and referenced to an external standard (85% H_3PO_4 in H_2O). For characterization of pure, novel compounds, ^{19}F NMR spectra were recorded on a Bruker 500 MHz (471 MHz, ^{19}F) spectrometer and referenced to a hexafluorobenzene internal standard (δ = –161.64 ppm, in $CDCl_3$) according to the method recommended by Togni and co-workers. For quantitative kinetic experiments, ^{19}F NMR spectra were recorded on a Varian 600 MHz (565 MHz, ^{19}F) spectrometer equipped with a 5 mm AutoTuneX probe. Chemical shifts are reported in parts per million. Assignments were obtained by reference to COSY, HMQC, HMBC, TOCSY, and NOESY correlations. Elemental analysis was performed by the University of Illinois Microanalysis Laboratory. Mass spectrometry (MS) was performed by the University of Illinois Mass Spectrometry Laboratory. Electron Impact (EI) spectra were performed at 70 eV using

methane as the carrier gas on a Finnagin-MAT C5 spectrometer. Electrospray Ionization (ESI) spectra were performed on a Micromass Q-Tof Ultima spectrometer. Data are reported in the form of m/z (intensity relative to the base peak = 100). Infrared spectra (IR) were recorded neat on a Perkin-Elmer FT-IR system and peaks were reported in cm^{-1} with indicated relative intensities: s (strong, 0-33% T); m (medium, 34-66% T); w (weak, 67-100% T). Melting points (mp) were determined on a Thomas-Hoover or Büchi capillary melting point apparatus in sealed tubes and are corrected.

Commercial Reagents

The following commercial reagents were used as received: 1-(chloromethyl)-4-methylbenzene, 1-(chloromethyl)-4-methoxybenzene, 1-(chloromethyl)-4-fluorobenzene, magnesium turnings, geranyl acetate, copper(II) chloride (anhydrous), thionyl chloride, potassium tert-butoxide (anhydrous), 1-octanethiol, tert-butyldimethylsilyl chloride, imidazole, sodium *p*-toluenesulfinate (hydrate), tetrabutylammonium bromide, sodium hexamethyldisilazide (1.0 M solution in THF), sodium dihydrogen phosphate (monohydrate), sodium amalgam (20% w/w sodium), hexafluoroisopropyl alcohol (Oakwood), tetrahydrothiophene, tetra(*n*-butyl)ammonium fluoride trihydrate, hydrogen peroxide (30% w/w aq.), trifluoroacetic anhydride, 2,6-lutidine, trifluoroacetic acid, sodium borohydride, lithium (granules), *N*,*N*-dimethyl-1-aminonaphthalene, boron tribromide (Sigma), *trans*,*trans*-farnesol, phenol, *N*,*O*-dimethylhydroxylamine hydrochloride, methyllithium (solution in Et_2O), triethyl phosphonoacetate, lithium aluminum hydride (Alfa-Aesar), methanesulfonyl chloride, anhydrous lithium bromide, potassium carbonate, sodium periodate, periodic acid, 2-fluoro-4-methoxyphenol **93a**, 2-fluorophenol **93b**, 2-fluoro-4-chlorophenol **93c**, 3-fluoro-4-hydroxybenzonitrile **93d**, 2-fluoro-4-methoxybenzaldehyde **100m** (Sigma), 2-fluoro-3-methoxybenzaldehyde **100n** (Sigma), 4-(dimethylamino)pyridine, isopropyl isocyanate (Sigma), trimethylsilyl trifluoromethanesulfonate (Oakwood), sodium hydroxide, bis(dimethylamino)phosphoryl chloride (Strem), anhydrous zinc chloride, anhydrous copper(I) cyanide, formic acid 97% (Sigma), 1,1,1,2-tetrachloroethane, sodium perborate tetrahydrate, hydrogen peroxide (Sigma, 30% w/w aq.), tetra-*n*-butylammonium chloride (Alfa-Aesar), allyl bromide, zinc dust (Sigma), 18-crown-6, tetra-*n*-butylammonium bromide (Sigma), *n*-butyl bromide, 1-bromo-2-methylnaphthalene, nitric acid, iron powder, glycerol, methanesulfonic acid, sodium 3-nitrobenzenesulfonate salt (Alfa-Aesar), iron(II) sulfate heptahydrate, *N*-bromosuccinimide, benzoyl peroxide, 2-nitropropane, sodium metal, anhydrous nickel(II)

chloride, triphenylphosphine, sodium iodide, methyl iodide, hydrobromic acid, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, methyl trifluoromethanesulfonate, (+)-dibenzoyl-D-tartartic acid, (–)-dibenzoyl-L-tartartic acid, benzophenone, *tert*-butyl bromoacetate, benzyl bromide, potassium hydroxide, benzyl chloroformate, palladium on carbon (5% Pd w/w), phosphorus tribromide, citric acid monohydrate, and sodium azide.

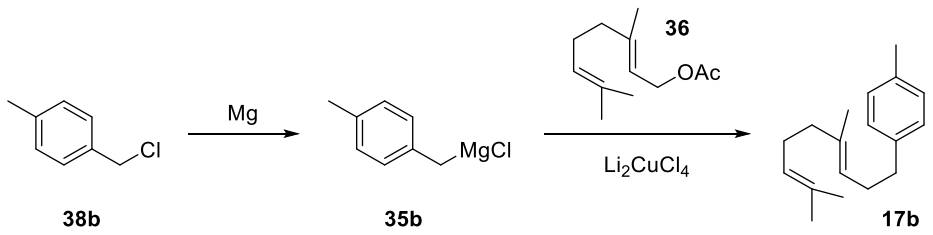
1-Naphthaldehyde was purchased from commercial sources and purified as described by Denmark et al.[214] Lithium chloride was purchased from commercial sources and dried (130 °C, 0.1 torr) for 12 h before use.[215] *meta*-Chloroperbenzoic acid was purchased from commercial sources and washed with phosphate buffer before use.[215] Commercial benzylmagnesium chloride solution **35a** was titrated in the manner described for **35b** (*vide infra*). Commercial *n*-butyllithium solution (2.5 M in hexanes) and phenyllithium solution (1.9 M in Bu_2O) were titrated before use.[216] Potassium hydride and sodium hydride were purchased from commercial sources (as dispersion in mineral oil) and washed with hexanes inside of the glovebox prior to use. Carbonyl diimidazole (CDI) was purchased from commercial sources, recrystallized from boiling THF under inert atmosphere, and dried under inert atmosphere prior to use.

Experimental for Chapter 2

Literature Preparations

The following compounds from Chapter 2 were prepared by literature methods and characterization matched the data previously reported: *tert*-butyl (4-(bromomethyl)phenyl)carbamate **40**,[217] *N*-((2,6-diisopropylphenyl)thio)-phthalimide **2b**,[26] catalyst (*R*)-**3a**,[83] catalyst (*S*)-**3a**,[24] (*E*)-(4,8-dimethylnona-3,7-dien-1-yl)benzene **17a**,[218] (*E*)-1-(4,8-dimethylnona-3,7-dienyl)-3,5-dimethoxybenzene **17d**[185], geranyl bromide,[219] (*E*)-hex-4-enoic acid **63**,[85-86] *trans*,*trans*-farnesyl acetate **54**,[220] (methoxy(phenyl)methyl)diphenylphosphine oxide **85**,[221] 2-fluorophenyl isopropyl carbamate **94b**,[90-91] and tmpMgCl·LiCl (solution in THF).[222]

(*E*)-1-(4,8-Dimethylnona-3,7-dien-1-yl)-4-methylbenzene (17b)



A flame-dried, 50-mL, three-necked, round-bottomed flask equipped with a stir bar, argon inlet, two septa, and temperature probe was charged with magnesium turnings (182 mg, 7.50 mmol, 1.25 equiv). The turnings were mechanically activated immediately before use by grinding with a mortar and pestle for 10 min. The flask was again evacuated, flame-dried, and placed under argon. Once cool, the flask was charged with THF (10 mL) and a single drop of 1,2-dibromoethane. The mixture was stirred at 25 °C for 15 min and then cooled to 0 °C using an ice bath. A second, flame-dried flask was charged with 1-(chloromethyl)-4-methylbenzene **38b** (0.794 mL, 6.00 mmol) and THF (5 mL). The resulting solution was taken up in a 10-mL plastic Leur-Lock syringe and added dropwise to the reaction flask at 0 °C over 30 min using a syringe pump. The external ice bath is maintained throughout, but a slight exotherm (approx. 3 °C) is observed over the course of addition along with a slight darkening of the color. Once the addition was complete, the ice bath was removed and the mixture was allowed to warm to 25 °C. Stirring was continued for 1 h at 25 °C, and then the Grignard reagent was titrated in the following manner. An oven-dried, dram-sized vial equipped with a Teflon stir bar was charged with a small amount (roughly 1 mg) of 1,10-

phenanthroline as an indicator. The vial was fitted with a Teflon-lined cap, evacuated, and placed under argon. A precise amount (300 μL) of the Grignard reagent was added to the vial. The contents of the vial turned a deep purple color. A 1.0 M solution of *sec*-butanol in xylenes was added dropwise to the vial with a syringe with rapid stirring until a yellow endpoint was reached. The exact amount of *sec*-butanol solution added to each vial was used to calculate the concentration of the Grignard reagent (the reaction is a 1:1 molar ratio). In this manner, the concentration of (4-methylbenzyl)magnesium chloride **35b** was determined to be 0.36 M (average of two runs; expected 0.40 M). The reagent was used immediately.

Compound **17b** was synthesized by an analogous procedure to the one described by Surendra and Corey.[218] A flame-dried, 5-mL, Schlenk flask was charged with anhydrous lithium chloride (38.8 mg, 0.92 mmol, 0.2 equiv) and anhydrous copper(II) chloride (61.6 mg, 0.46 mmol, 0.1 equiv) inside of the glove box. The flask was sealed, removed from the box, charged with THF (2.4 mL), and sonicated at 25 °C under argon for 15 min. An orange solution resulted, indicating formation of the desired Li_2CuCl_4 complex. A separate, flame-dried, 100-mL, three-necked, round-bottomed flask equipped with a stir bar, temperature probe, two septa, and argon inlet was charged with geranyl acetate **36** (0.98 mL, 0.89 g, 4.58 mmol, d = 0.916 g/mL) and THF (8.4 mL). The resulting clear, colorless solution was cooled to 0 °C using an ice bath. The orange solution of the Li_2CuCl_4 complex was added dropwise to the solution of geranyl acetate **36**. The homogenous mixture was stirred at 0 °C for 10 min and then cooled to an internal temperature of -10 °C using an ice/salt bath. The Grignard reagent **35b** prepared previously (14 mL, 0.36 M, 5.04 mmol, 1.1 equiv) was added dropwise to the reaction flask via cannula transfer over 20 min. The rate of addition was adjusted as needed such that the internal temperature did not exceed -3 °C. During the course of addition, the initially orange reaction mixture turned colorless, then yellow and eventually brown. Stirring was continued (below 0 °C) for 2 h. Full conversion was observed by TLC (hexanes/CH_2Cl_2, 90:10). The cold bath was removed, and the reaction was quenched by the addition of sat. aq. NH_4Cl (10 mL). The resulting biphasic mixture was stirred vigorously for 5 min and then partitioned between diethyl ether (50 mL) and water (50 mL). The layers were separated, and the aqueous phase was extracted with diethyl ether (2 x 25-mL). The combined organic layers were washed with 1 M HCl (25 mL), sat. aq. $NaHCO_3$ (25 mL), and brine (25 mL), and then were dried over sodium sulfate, filtered, and concentrated (30 °C, 15 mmHg) to afford 1.1425 g of crude product as a hazy, pale yellow oil. The product was purified by chromatography

(silica gel, 3 cm x 18 cm, dry load on Celite, 25 mL fractions, hexanes/CH_2Cl_2 gradient elution: 95:5 (300 mL) to 90:10 (300 mL)) to afford 887.9 mg (80%) of **17b** as a clear, colorless oil. Spectroscopic data for **17b** matched the literature values.[223]

Data for **17b**:

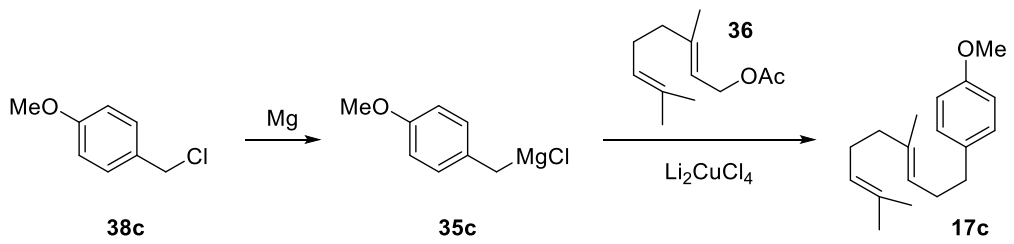
^{1}H NMR: (500 MHz, $CDCl_3$)

7.08 (app. s, 4H), 5.21-5.16 (m, 1H), 5.12-5.06 (m, 1H), 2.62-2.57 (m, 2H), 2.32 (s, 3H), 2.28 (q, *J* = 7.4 Hz, 2H), 2.06 (q, *J* = 7.0 Hz, 2H), 2.00-1.96 (m, 2H), 1.69 (s, 3H), 1.60 (s, 3H), 1.56 (s, 3H).

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

139.50, 135.77, 135.19, 131.47, 129.04, 128.47, 124.50, 123.88, 39.86, 35.85, 30.25, 26.87, 25.85, 21.16, 17.84, 16.14.

(*E*)-1-(4,8-Dimethylnona-3,7-dien-1-yl)-4-methoxybenzene (17c)



38c **35c** **17c**

A flame-dried, 100-mL, three-necked, round-bottomed flask equipped with a stir bar, argon inlet adapter, 25-mL addition funnel, temperature probe, and septum was charged with magnesium turnings (540.1 mg, 22.2 mmol, 1.25 equiv). The turnings were mechanically activated immediately before use by grinding with a mortar and pestle for 10 min. The flask was again evacuated, flame-dried, and placed under argon. Once cool, the flask was charged with THF (30 mL) and a single drop of 1,2-dibromoethane. The mixture was stirred at 25 °C for 15 min and then cooled to 0 °C using an ice bath. The addition funnel was charged with 1-(chloromethyl)-4-methoxybenzene **38c** (2.41 mL, 2.78 g, 17.8 mmol) and THF (15 mL). This solution was added dropwise to the reaction flask at 0 °C over 30 min. The external ice bath was maintained throughout, but a slight exotherm (approx. 3 °C) was observed over the course of addition. The internal temperature was monitored, and it should not exceed 5 °C during the addition. A brown-

black solution resulted over the course of addition. Once the addition was complete, the ice bath was removed and the mixture was allowed to warm to 25 °C. Stirring was continued for 1 h at 25 °C, and then the Grignard reagent **35c** was titrated in the manner described previously for **35b**. The concentration of (4-methoxybenzyl)magnesium chloride was determined to be 0.29 M (average of two runs; expected 0.40 M). The reagent was used immediately.

Compound **17c** was synthesized by an analogous procedure to the one described by Surendra and Corey.[218] A flame-dried, 10-mL, Schlenk flask was charged with anhydrous lithium chloride (100.5 mg, 2.37 mmol, 0.2 equiv) and anhydrous copper(II) chloride (159.3 mg, 1.19 mmol, 0.1 equiv) inside a dry box. The flask was sealed, removed from the box, charged with THF (6 mL), and sonicated at 25 °C under argon for 15 min. An orange solution resulted, indicating formation of the desired Li_2CuCl_4 complex. A separate, flame-dried, 200-mL, Schlenk flask equipped with a stir bar and temperature probe was charged with geranyl acetate **36** (2.54 mL, 2.33 g, 11.9 mmol, D = 0.916 g/mL) and THF (20 mL). The resulting clear, colorless solution was cooled to 0 °C using an ice bath. The orange solution of the Li_2CuCl_4 complex was added dropwise to the solution of geranyl acetate **36**. The homogenous mixture was stirred at 0 °C for 10 min and then cooled to an internal temperature of -10 °C using an ice/salt bath. The Grignard reagent **35c** prepared previously (43 mL, 0.29 M, 12.5 mmol, 1.05 equiv) was added dropwise to the reaction flask via cannula transfer over 20 min. The rate of addition was adjusted as needed such that the internal temperature did not exceed -3 °C. During the course of addition, the initially orange reaction mixture turned colorless, then yellow and eventually brown. Stirring was continued (below 0 °C) for 3 h. Full conversion was observed by TLC (hexanes/EtOAc, 80:20). The cold bath was removed, and the reaction was quenched by the addition of sat. aq. NH_4Cl (30 mL). The resulting biphase was stirred vigorously for 5 min and then partitioned between diethyl ether (100 mL) and water (100 mL). The layers were separated, and the aqueous phase was extracted with diethyl ether (2 x 50-mL). The combined organic layers were washed with 1 M HCl (50 mL), sat. aq. $NaHCO_3$ (50 mL), and brine (50 mL), and then were dried over sodium sulfate, filtered, and concentrated (30 °C, 15 mmHg) to afford 3.99 g of crude **17c**. The product was purified by chromatography (silica gel, 5 cm x 18 cm, 50-mL fractions, hexanes/Et_2O gradient elution: 98:2 (500 mL) to 96:4 (500 mL) to 94:6 (500 mL)) to afford **17c** contaminated with 4-methylanisole (from quenched Grignard reagent). This by-product was removed by drying the sample (120 °C,

0.1 mmHg) for 30 min to afford 2.9569 g (97%) of pure **17c** as a clear, colorless oil. Spectroscopic data for **17c** matched the literature values.[223]

Data for **17c**:

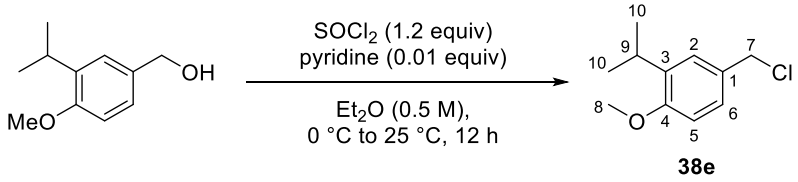
^{1}H NMR: (500 MHz, $CDCl_3$)

7.11 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 5.21-5.13 (m, 1H), 5.12-5.05 (m, 1H), 3.79 (s, 3H), 2.58 (app. t, 2H), 2.27 (q, *J* = 7.4 Hz, 2H), 2.10-2.03 (m, 2H), 2.01-1.94 (m, 2H), 1.69 (s, 3H), 1.61 (s, 3H), 1.55 (s, 3H).

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

157.66, 135.67, 134.55, 131.32, 129.33, 124.36, 123.67, 113.62, 55.26, 39.72, 35.21, 30.20, 26.72, 25.71, 17.70, 15.99.

3-Isopropyl-4-methoxybenzyl Chloride (**38e**)



38e

A flame-dried, 200-mL, three-necked, round-bottomed flask equipped with a stir bar, argon inlet adapter, temperature probe, and two septa was charged with 3-isopropyl-4-methoxybenzyl alcohol[224] (4.92 g, 27.3 mmol) and diethyl ether (55 mL, 0.5 M) to form a pale yellow solution. Pyridine (22 μL, 0.273 mmol, 0.01 equiv) was added to the flask, and the solution was cooled to an internal temperature of –3 °C using an ice/salt bath. Neat thionyl chloride (2.39 mL, 32.8 mmol, 1.2 equiv) was added dropwise to the flask over 15 min, making sure to maintain the internal temperature below 0 °C, resulting in a thin, white suspension. After addition was complete, the mixture was allowed to slowly warm to 25 °C, and then stirring was continued at 25 °C for 10 h. A turbid, colorless solution resulted. Full conversion was observed by TLC (hexanes/EtOAc, 80:20). The reaction was quenched by the addition of water (50 mL) and was stirred vigorously for 2 min. The resulting biphasic mixture was transferred to a 500-mL separatory funnel and the layers were separated. The aqueous layer was extracted with diethyl ether (2 x 50 mL). The combined organic layers were washed with sat. aq. sodium bicarbonate (1 x 100 mL – *caution* gas

evolution observed) and brine (1 x 100 mL), then dried over sodium sulfate, filtered, and concentrated (30 °C, 15 mmHg) to afford a thin yellow oil (4.88 g). The product was further purified by Kugelrohr distillation (110 °C, 0.1 mmHg) to afford 4.34 g (80%) of **38e** as a clear, colorless liquid.

Data for **38e**:

b.p.: 110 °C (ABT, 0.1 mmHg)

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

7.22 (d, *J* = 2.3 Hz, 1H, HC(2)), 7.19 (dd, *J* = 8.3, 2.3 Hz, 1H, HC(6)), 6.81 (d, *J* = 8.3 Hz, 1H, HC(5)), 4.58 (s, 2H, $H_2C(7)$), 3.83 (s, 3H, $H_3C(8)$), 3.30 (hept, *J* = 6.9 Hz, 1H, HC(9)), 1.21 (d, *J* = 6.9 Hz, 6H, $H_3C(10)$).

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

157.1 (C(4)), 137.6 (C(3)), 129.6 (C(1)), 127.2 (HC(6)), 126.9 (HC(2)), 110.5 (HC(5)), 55.6 ($H_3C(8)$), 47.0 ($H_2C(7)$), 26.9 (HC(9)), 22.7 ($H_3C(10)$).

IR: (neat)

2960 (w), 2869 (w), 2837 (w), 1608 (w), 1498 (m), 1463 (m), 1443 (w), 1383 (w), 1362 (w), 1348 (w), 1293 (w), 1246 (s), 1187 (w), 1171 (m), 1158 (w), 1116 (w), 1089 (m), 1032 (m), 941 (w), 893 (w), 866 (w), 812 (m), 750 (w), 688 (m), 597 (m), 472 (m)

LRMS: (EI, 70 eV)

51.0 (2), 74.0 (3), 77.0 (4), 78.0 (2), 79.0 (2), 91.0 (5), 103.0 (3), 105.0 (2), 115.0 (5), 116.0 (2), 117.0 (9), 131.0 (2), 133.0 (10), 134.0 (2), 147.0 (9), 148.0 (6), 149.0 (2), 163.0 (100), 164.1 (13), 183.0 (30), 184.0 (3), 185.0 (10), 198.0 (25), 199.0 (3), 200.0 (8).

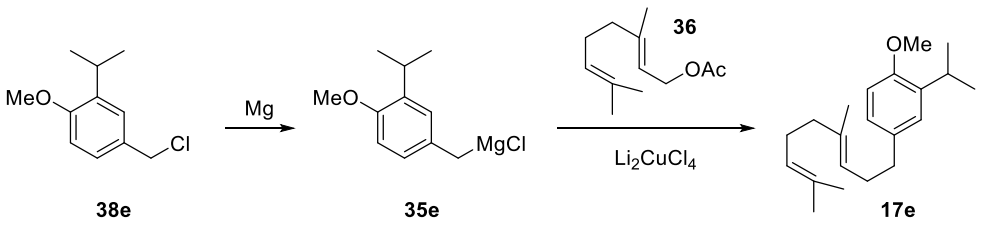
Analysis: $C_{11}H_{15}ClO$ (198.69)

Calcd: C, 66.50%; H, 7.61%

Found: C, 66.41%; H, 7.43%

TLC: R_f 0.54 (silica gel, hexanes/EtOAc, 80:20, UV)

(*E*)-4-(4,8-Dimethylnona-3,7-dien-1-yl)-2-isopropyl-1-methoxybenzene (**17e**)



38e **35e** **17e**

A flame-dried, 50-mL, two-necked, round-bottomed flask equipped with a stir bar, temperature probe, septum, and argon inlet adapter was charged with magnesium turnings (177.8 mg, 7.32 mmol, 1.23 equiv). The turnings were mechanically activated immediately before use by grinding with a mortar and pestle for 10 min. The flask was charged with THF (10 mL) and 1 drop of 1,2-dibromoethane as initiator. The mixture was stirred at 25 °C for 15 min and then cooled to 0 °C. A flame-dried, 15-mL, tear-drop flask was charged with 4-(chloromethyl)-2-isopropyl-1-methoxybenzene **38e** (1.18 g, 5.93 mmol) and THF (5 mL) to form a colorless solution. The solution was taken up in a 10-mL Leur-Lock plastic syringe and added dropwise to the reaction flask over 30 min using a syringe pump. The internal temperature was monitored throughout, and the temperature was observed to rise from 0.5 °C to nearly 3.0 °C over the course of addition (external ice bath was maintained throughout). A pale orange color resulted. The ice bath was removed and the mixture was stirred at 25 °C for 1 h. The Grignard reagent **35e** was titrated as described previously for **35b**. The concentration of **35e** was determined to be 0.33 M (average of two runs, theoretical = 0.395 M).

A flame-dried, 5-mL, Schlenk flask was charged with anhydrous lithium chloride (32.0 mg, 0.77 mmol, 0.2 equiv) and anhydrous copper(II) chloride (51.0 mg, 0.38 mmol, 0.1 equiv) inside of a glove box. The flask was sealed, removed from the glove box, and charged with THF (2 mL). The resulting mixture was sonicated for 15 min under argon at 25 °C, resulting in an orange solution indicative of the Li_2CuCl_4 complex. A separate, flame-dried, 100-mL, three-necked round-bottomed flask equipped with a stir bar, thermocouple probe, argon inlet adapter, and two septa was charged with geranyl acetate **36** (0.82 mL, 0.75 g, 3.83 mmol) and THF (7 mL) and was cooled to 0 °C. The Li_2CuCl_4 solution prepared previously was added to the solution of **36** at 0 °C in one portion. The orange solution was stirred at 0 °C for 10 min and then was cooled further to an internal temperature of –7 °C using an ice/salt bath. The previously prepared solution

of (3-isopropyl-4-methoxybenzyl)magnesium chloride **35e** (14 mL of 0.33 M solution, 4.6 mmol, 1.2 equiv) was added dropwise over 15 min to the reaction mixture via cannula transfer, taking care to maintain the internal temperature of the reaction flask below –5 °C. Over the course of the addition, the initially orange solution briefly became colorless, then gradually turned yellow and finally brown. Stirring was continued at 0 °C for 1 h, at which point the reaction was judged to be complete by TLC (hexanes/Et_2O, 9:1). The reaction was quenched by the addition of sat. aq. ammonium chloride (approx. 25 mL) in one portion. The mixture was poured into a 125-mL separatory funnel (rinsing with small amounts of ether and water) and the layers were separated. The aqueous layer was extracted with ether (2 x 25 mL). The combined organic layers were washed with 1 M aq. HCl (25 mL), sat. aq. $NaHCO_3$ (25 mL), and brine (25 mL), then dried over sodium sulfate, filtered, and concentrated (30 °C, 15 mmHg) to afford the crude product (1.39 g). The product was first purified by chromatography (silica gel, 4 x 18 cm, dry load on Celite, 25-mL fractions, hexanes/CH_2Cl_2 gradient elution: 97.5:2.5 (300 mL) to 95:5 (300 mL) to 92.5:7.5 (300 mL) to 90:10 (300 mL) to 87.5:12.5 (300 mL) to 85:15 (300 mL) to 82.5:17.5 (300 mL) to 80:20 (300 mL)) to afford **17e** as a clear oil (1.10 g) which is contaminated with 4-methyl-2-isopropylanisole (resulting from quenched Grignard reagent). The product was further purified by Kugelrohr distillation in two stages. Initially, the bulk material was heated to 95 °C (0.1 mmHg) without cooling for 30 min. All of the more volatile 4-methyl-2-isopropylanisole was removed under these conditions. Subsequently, the collection bulb was changed and the desired product was distilled at 180 °C (0.1 mmHg) to afford 1.00 g (87%) of analytically pure **17e** as a clear, colorless oil.

Data for **17e**:

b.p.: 180 °C (ABT, 0.1 mmHg)

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

7.02 (d, J = 2.2 Hz, 1H, HC(3)), 6.97 (dd, J = 8.2, 2.2 Hz, 1H, HC(5)), 6.76 (d, J = 8.2 Hz, 1H, HC(6)), 5.24-5.16 (m, 1H, HC(12)), 5.15-5.05 (m, 1H, HC(17)), 3.80 (s, 3H, H_3C(7)), 3.29 (hept, J = 6.9 Hz, 1H, HC(8)), 2.63-2.53 (m, 2H, H_2C(10)), 2.28 (q, J = 7.4 Hz, 2H, H_2C(11)), 2.07 (q, J = 7.1 Hz, 2H, H_2C(16)), 2.01-1.93 (m, 2H, H_2C(15)), 1.69 (s, 3H, H_3C(19)), 1.60 (s, 3H, H_3C(20)), 1.56 (s, 3H, H_3C(14)), 1.21 (d, J = 6.9 Hz, 6H, H_3C(9)).

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

155.02 (C(1)), 136.79 (C(2)), 135.67 (C(13)), 134.50 (C(4)), 131.46 (C(18)), 126.36 (HC(3)), 126.24 (HC(5)), 124.53 (HC(17)), 123.99 (HC(12)), 110.40 (HC(6)), 55.65 (H_3C(7)), 39.88 (H_2C(15)), 35.65 (H_2C(10)), 30.42 (H_2C(11)), 26.92 (H_2C(16)), 26.85 (HC(8)), 25.86 (H_3C(19)), 22.92 (H_3C(9)), 17.84 (H_3C(20)), 16.18 (H_3C(14)).

IR: (neat)

2961 (m), 2923 (m), 1609 (w), 1497 (s), 1443 (m), 1381 (w), 1361 (w), 1348 (w), 1290 (w), 1243 (s), 1170 (m), 1154 (w), 1090 (m), 1037 (m), 888 (w), 807 (m), 744 (w), 633 (w), 583 (w).

LRMS: (EI, 70 eV)

69.1 (7), 91.0 (4), 115.0 (3), 117.1 (5), 133.1 (8), 147.1 (4), 148.1 (7), 149.1 (4), 161.1 (3), 163.1 (100), 164.1 (35), 176.1 (20), 177.1 (4), 300.2 (12), 301.2 (3)

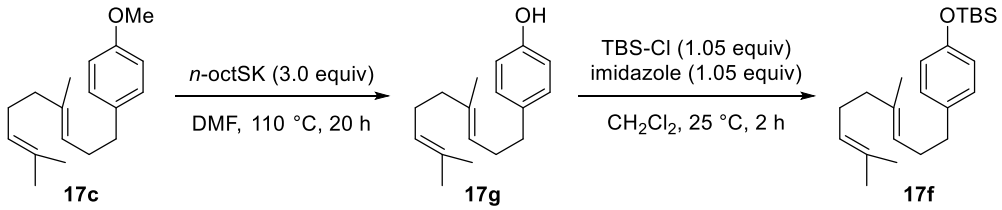
Analysis: $C_{21}H_{32}O$ (300.49)

Calcd: C, 83.94%; H, 10.73%

Found: C, 83.78%; H, 10.52%

TLC: R_f 0.29 (silica gel, hexanes/CH_2Cl_2, 90:10, UV/CAM)

Preparation of Compounds 17g and 17f



(*E*)-4-(4,8-Dimethylnona-3,7-dien-1-yl)phenol (17g)

A flame-dried, 50-mL, two-necked, round-bottomed flask equipped with a stir bar and two septa was charged with potassium *tert*-butoxide (0.65 g, 5.82 mmol, 3.0 equiv) inside of a dry box and sealed with a septum. The flask was removed from the dry box and fitted with a reflux condenser and argon inlet adapter. The system was briefly evacuated and then placed under argon.

The flask was charged with DMF (6.5 mL) through the septum. The potassium *tert*-butoxide dissolved with stirring to afford a pale yellow solution. To this solution, 1-octanethiol (1.0 mL, 0.85 g, 5.82 mmol, 3.0 equiv) was added dropwise over 5 min at 25 °C using a syringe. A thick, white suspension resulted, and a slight exotherm was observed. The suspension was stirred at 25 °C for 20 min. Next, (*E*)-4-homogeranylanisole **17c** (501.0 mg, 1.94 mmol) was added dropwise over 5 min at 25 °C using a syringe. The suspension was heated to 110 °C (oil bath) for 20 h. Conversion was assessed periodically by TLC (hexanes/EtOAc, 80:20). Upon completion, the reaction mixture was cooled to 25 °C and poured into water (25 mL), which resulted in a white suspension. The mixture was acidified by the dropwise addition of 6 M HCl (1 mL), transferred to a 125-mL separatory funnel, and extracted ether (3 x 25 mL). The combined ethereal extracts were washed with a 5% (w/v) aq. lithium chloride solution (4 x 25 mL) and then dried over sodium sulfate, filtered, and concentrated (30 °C, 15 mmHg) to afford the crude product as a yellow liquid (1.28 g). The product was purified by chromatography (silica gel, 4 x 17 cm, dry load on Celite, 25-mL fractions, hexanes/EtOAc gradient elution: 95:5 (400 mL) to 90:10 (300 mL) to 85:15 (300 mL)) to afford 391.5 mg (83% yield) of **17g** as a pale yellow oil. Spectroscopic data were identical to those reported by Yamamoto et al. using sodium ethanethiolate for the demethylation.[225] The procedure described above, while slower, is preferred as 1-octanethiol is far less odorous than ethanethiol and is more easily separated from the desired product.

Data for **17g**:

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

7.05 (d, J = 8.5 Hz, 2H), 6.74 (d, J = 8.5 Hz, 2H), 5.19-5.14 (m, 1H), 5.11-5.06 (m, 1H), 4.51 (s, 1H), 2.59-2.54 (m, 2H), 2.26 (q, J = 7.5 Hz, 2H), 2.08-2.02 (m, 2H), 2.00-1.95 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.54 (s, 3H).

(*E*)-*tert*-Butyl(4-(4,8-dimethylnona-3,7-dien-1-yl)phenoxy)dimethylsilane (17f)

A flame-dried, two-necked, 25-mL, round-bottomed flask equipped with a stir bar, septum, and argon inlet adapter was charged with 4-homogeranylphenol **17g** (388.4 mg, 1.59 mmol) and dichloromethane (5 mL, 0.3 M). The resulting pale yellow solution was cooled to an internal temperature of 0 °C using an external ice bath. Imidazole (115.2 mg, 1.67 mmol, 1.05 equiv) was added as a solid all at once at 0 °C, immediately followed by *tert*-butyldimethylsilyl chloride

(253.9 mg, 1.67 mmol, 1.05 equiv) as a solid all at once. The imidazole dissolved, but addition of *tert*-butyldimethylsilyl chloride resulted in a white/off-white suspension. The ice bath was removed and the reaction was allowed to warm gradually to 25 °C. Stirring was continued for 2 h at 25 °C. Conversion was followed by TLC (hexanes/Et_2O, 90:10). After 2 h, essentially full conversion was observed, and the reaction was quenched by the addition of water (10 mL) which resulted in a clear biphasic mixture. The mixture was transferred to a 60-mL separatory funnel, and the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 10 mL). The combined organic layers were washed with brine (1 x 20 mL), dried over sodium sulfate, filtered, and concentrated (30 °C, 15 mmHg) to afford the crude product (0.56 g) as a yellow oil. The product was purified by chromatography (silica gel, 3 x 18 cm, dry load on Celite, 25-mL fractions, hexanes/Et_2O gradient elution: 98:2 (300 mL) to 96:4 (300 mL)) to afford 490.9 mg (86%) of **17f** as a clear, colorless oil. The product was purified to an analytical standard by Kugelrohr distillation (180 °C ABT, 0.1 mmHg) to afford 470.8 mg (83%) of **17f** as a clear, colorless oil.

Data for **17f**:

b.p.: 180 °C (ABT, 0.1 mmHg)

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

7.03 (d, *J* = 8.4 Hz, 2H, HC(13)), 6.74 (d, *J* = 8.4 Hz, 2H, HC(14)), 5.20-5.14 (m, 1H, HC(9)), 5.09 (tt, *J* = 7.0, 1.3 Hz, 1H, HC(4)), 2.56 (t, *J* = 7.4 Hz, 2H, H_2C(11)), 2.26 (q, *J* = 7.4 Hz, 2H, H_2C(10)), 2.05 (q, *J* = 7.0 Hz, 2H, H_2C(5)), 2.01-1.93 (m, 2H, H_2C(6)), 1.69 (s, 3H, H_3C(1)), 1.60 (s, 3H, H_3C(3)), 1.53 (s, 3H, H_3C(8)), 0.98 (s, 9H, H_3C(18)), 0.18 (s, 6H, H_3C(16)).

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

153.7 (C(15)), 135.8 (C(7)), 135.3 (C(12)), 131.5 (C(2)), 129.4 (HC(13)), 124.5 (HC(4)), 123.8 (HC(9)), 119.9 (HC(14)), 39.9 (H_2C(6)), 35.4 (H_2C(11)), 30.3 (H_2C(10)), 26.9 (H_2C(5)), 25.9 (H_3C(18)), 25.8 (H_3C(1)), 18.4 (C(17)), 17.8 (H_3C(3)), 16.1 (H_3C(8)), -4.3 (H_3C(16)).

IR: (neat)

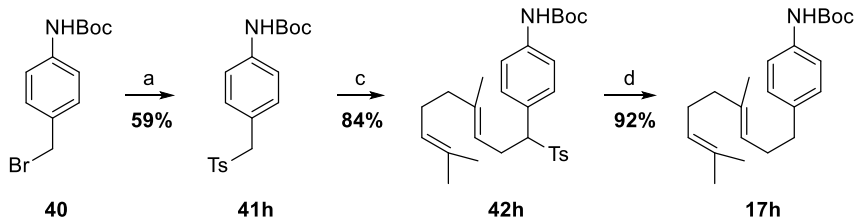
2958 (w), 2929 (m), 2857 (w), 1609 (w), 1509 (s), 1472 (w), 1463 (w), 1376 (w), 1362 (w), 1251 (s), 1168 (w), 1101 (w), 1006 (w), 913 (s), 836 (s), 809 (m), 779 (s), 688 (w), 657 (w), 546 (w)

LRMS: (EI, 70 eV)
69.1 (7), 73.1 (15), 91.1 (4), 107.1 (3), 149.0 (7), 163.1 (3), 164.1 (10), 165.1 (21), 166.1 (4), 177.1 (2), 205.1 (2), 221.1 (100), 222.1 (34), 223.1 (9), 234.1 (9), 235.1 (2), 358.3 (7), 359.3 (2)

Analysis: $C_{23}H_{38}OSi$ (358.64)
Calcd: C, 77.03%; H, 10.68%
Found: C, 76.69%; H, 10.61%

TLC: R_f 0.82 (silica gel, hexanes/Et_2O, 90:10, $KMnO_4$)

Multistep Synthesis of Compound 17h



40 **41h** **42h** **17h**

***tert*-Butyl (4-(4-Methylphenylsulfonylmethyl)phenyl)carbamate (41h)**

A flame-dried, 10-mL, round-bottomed flask equipped with a stir bar and argon inlet adapter was charged with *tert*-butyl (4-(bromomethyl)phenyl)carbamate **40** (429.5 mg, 1.50 mmol) and DMF (3 mL, 0.5 M). A pale-yellow solution resulted. Sodium *p*-toluenesulfinate (321.7 mg, 1.81 mmol, 1.2 equiv) was added in one portion at 25 °C. The heterogeneous mixture was stirred at 25 °C for 30 min, during which time most of the solid dissolved, ultimately resulting in a turbid, yellow solution. Consumption of starting material was confirmed by TLC (hexanes/EtOAc, 50:50). The solution was poured into a 125-mL separatory funnel containing water (50 mL). Residual material in the flask was rinsed in with ethyl acetate (25 mL). This initially resulted in an emulsion, but the layers separated upon standing. The aqueous phase was extracted with ethyl acetate (2 x 25 mL). The combined organic layers were washed with a 5% (w/v) aq. lithium chloride solution (3 x 25 mL), then dried over sodium sulfate, filtered, and concentrated (30 °C, 15 mmHg) to afford the crude product (482.9 mg) as an off-white solid. The product was purified by trituration as follows. The crude material was suspended in a mixture of 1:1

EtOAc:hexanes (10 mL) and sonicated for 30 min at 25 °C. Vacuum filtration of this suspension yielded 225.5 mg (42%) of analytically pure **41h** as a fine white solid. Yields are variable, ranging from 42% to 59%.

Data for **41h**:

m.p.: 203–204 °C (d)

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

8.44 (bs, 1H, NH), 7.57 (d, J = 8.2 Hz, 2H, HC(10)), 7.47 (d, J = 8.6 Hz, 2H, HC(5)), 7.37 (d, J = 8.2 Hz, 2H, HC(11)), 7.06 (d, J = 8.6 Hz, 2H, HC(6)), 4.40 (s, 2H, H_2C(8)), 2.42 (s, 3H, H_3C(13)), 1.48 (s, 9H, H_3C(1)).

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

153.58 (C(3)), 145.25 (C(12)), 140.87 (C(4)), 137.10 (C(9)), 132.24 (HC(6)), 130.30 (HC(11)), 129.38 (HC(10)), 123.52 (C(7)), 118.54 (HC(5)), 80.15 (C(2)), 62.15 (H_2C(8)), 28.50 (H_3C(1)), 21.49 (H_3C(13)).

IR: (neat)

3383 (w), 2982 (w), 1707 (m), 1615 (w), 1595 (w), 1522 (m), 1508 (m), 1416 (m), 1372 (w), 1314 (m), 1301 (m), 1259 (w), 1234 (m), 1146 (s), 1084 (m), 1056 (m), 1019 (w), 910 (w), 834 (m), 818 (m), 771 (w), 744 (m), 712 (m), 666 (s), 643 (m), 629 (w), 590 (w), 549 (s), 519 (s), 503 (w).

LRMS: (EI, 70 eV)

55.1 (11), 56.1 (6), 57.1 (39), 60.1 (8), 69.1 (18), 71.1 (8), 73.0 (10), 77.0 (7), 81.1 (8), 83.1 (7), 85.1 (6), 91.0 (14), 97.1 (6), 105.1 (6), 106.1 (73), 107.1 (6), 129.1 (8), 132.0 (36), 133.0 (6), 141.1 (8), 150.0 (100), 151.0 (10), 163.1 (65), 164.1 (7), 206.1 (66), 207.1 (11), 256.2 (7), 361.1 (2).

Analysis: $C_{19}H_{23}NO_4S$ (361.46)

Calcd: C, 63.13%; H, 6.41%; N, 3.88%

Found: C, 62.80%; H, 6.38%; N, 3.90%

TLC: R_f 0.46 (silica gel, hexanes/EtOAc, 50:50, UV)

Preparation of *tert*-Butyl (*E*)-(4-(4,8-Dimethyl-1-(4-methylphenylsulfonyl) nona-3,7-dien-1-yl)phenyl)carbamate (42h)

A flame-dried, 50-mL, three-necked, round-bottomed flask equipped with a stir bar, argon inlet adapter, temperature probe, and two septa was charged with *tert*-butyl (4-(4-methylphenylsulfonylmethyl)phenyl)carbamate **41h** (452.0 mg, 1.25 mmol) and THF (12 mL). The resulting clear, colorless solution was cooled to –78 °C using a dry ice/acetone bath. Sodium hexamethyldisilazide (1.0 M solution in THF, 3.0 mL, 3.00 mmol, 2.40 equiv) was added dropwise over 5 min at –78 °C. **Note:** Two equivalents of base are required in this case, due to the presence of the acidic N-H proton. The solution immediately turned bright yellow, and some orange precipitate was observed to form. Approximately halfway through the addition, more orange precipitate was observed, such that the appearance of the reaction was a bright-orange suspension. Stirring was continued at –78 °C for 1 h. Subsequently, a solution of geranyl bromide (333.6 mg, 1.54 mmol, 1.23 equiv) in THF (5 mL) was added dropwise at –78 °C over 20 min. The internal temperature was monitored throughout, and the rate of addition was maintained such that the internal temperature did not exceed -70 °C. The reaction mixture lightened to an orange/yellow solution. Stirring was continued at –78 °C for 3 h. Full conversion was observed by TLC (hexanes/EtOAc, 80:20). The reaction was quenched by the addition of sat. aq. sodium bicarbonate (25 mL) all at once with rapid stirring. The cold bath was removed, and the resulting pale-yellow suspension was allowed to warm to 25 °C. The mixture was transferred to a 125-mL separatory funnel, rinsing with water (25 mL) and ethyl acetate (25 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (2 x 25 mL). The combined organic phases were washed with brine (25 mL), dried over sodium sulfate, filtered, and concentrated (30 °C, 15 mmHg) to afford the crude product (0.62 g). The crude mixture was purified by chromatography (silica gel, 3 x 17 cm, dry load on Celite, 25-mL fractions, hexanes/EtOAc gradient elution: 90:10 (300 mL) to 80:20 (300 mL) to 70:30 (300 mL) to 60:40 (300 mL)) to afford 521.5 mg (84%) of **42h** as an off-white solid. At this point, the level of purity is sufficient for the next step. But to obtain an analytically pure sample, the product was recrystallized from ethyl acetate/hexanes. The product was dissolved in a minimal amount of hot ethyl acetate (10 mL) and subsequently treated with hot hexanes (10 mL). The pale yellow solution was allowed to cool slowly to 25 °C. A seed crystal was added (these are typically obtained by allowing the column fractions to stand

uncovered for several hours and then collecting the resulting crystals by vacuum filtration), and the flask was capped and placed in a –20 °C freezer for 12 h. The resulting white crystals were collected by vacuum filtration, rinsing with cold hexanes/EtOAc 50:50 (5 mL). The crystals were air-dried for 1 h and then dried under high vacuum (0.1 mmHg) for 12 h to afford 235.5 mg (38%) of analytically pure **42h**.

Data for **42h**:

m.p.: 145–146 °C (d)

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

7.43 (d, *J* = 8.1 Hz, 2H, HC(10)), 7.23 (d, *J* = 8.6 Hz, 2H, HC(5)), 7.18 (d, *J* = 8.1 Hz, 2H, HC(11)), 7.02 (d, *J* = 8.6 Hz, 2H, HC(6)), 6.47 (bs, 1H, NH), 4.92-4.86 (m, 1H, HC(20)), 4.84-4.75 (m, 1H, HC(15)), 3.95 (dd, *J* = 11.7, 3.7 Hz, 1H, HC(8)), 3.10 (ddd, *J* = 14.4, 6.9, 3.7 Hz, 1H, H_2C(14)), 2.76 (ddd, *J* = 14.4, 11.7, 6.9 Hz, 1H, H_2C(14)), 2.39 (s, 3H, H_3C(13)), 1.99-1.86 (m, 2H, H_2C(19)), 1.85-1.80 (m, 2H, H_2C(18)), 1.59 (s, 3H, H_3C(22)), 1.54 (s, 3H, H_3C(17)), 1.51 (s, 12H, H_3C(23) and H_3C(1)).

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

152.58 (C(3)), 144.45 (C(12)), 138.84 (C(4)), 138.75 (C(16)), 134.65 (C(9)), 131.56 (C(21)), 130.83 (HC(6)), 129.43 (HC(11)), 129.22 (HC(10)), 126.68 (C(7)), 123.98 (HC(20)), 118.86 (HC(15)), 117.96 (HC(5)), 80.88 (C(2)), 71.01 (HC(8)), 39.66 (H_2C(18)), 28.47 (H_3C(1)), 26.59 (H_2C(14)), 26.51 (H_2C(19)), 25.76 (H_3C(22)), 21.77 (H_3C(13)), 17.79 (H_3C(23)), 16.38 (H_3C(17)).

IR: (neat)

3388 (w), 2983 (w), 2918 (w), 1698 (m), 1614 (w), 1592 (w), 1523 (m), 1507 (m), 1447 (w), 1417 (m), 1392 (w), 1367 (w), 1315 (m), 1299 (m), 1269 (w), 1235 (m), 1143 (s), 1084 (m), 1057 (m), 1020 (m), 945 (w), 902 (w), 841 (m), 814 (m), 776 (w), 754 (w), 732 (w), 711 (m), 667 (s), 598 (s), 572 (s), 554 (m), 517 (m).

LRMS: (ESI, $[M+Na]^+$)

138.6 (2), 235.8 (7), 285.9 (6), 342.0 (7), 498.0 (2), 515.1 (4), 520.0 (100), 521.0 (33), 522.0 (10), 536.0 (4), 577.9 (2).

Analysis: $C_{29}H_{39}NO_4S$ (497.69)

Calcd: C, 69.99%; H, 7.90%; N, 2.81%

Found: C, 69.87%; H, 7.84%; N, 2.81%

TLC: R_f 0.22 (silica gel, hexanes/EtOAc 80:20, UV/CAM)

tert-Butyl (_E_)-(4-(4,8-Dimethylnona-3,7-dien-1-yl)phenyl)carbamate (17h)

A flame-dried, 100-mL, three-necked, round-bottomed flask equipped with a stir bar, argon inlet adapter, and two septa was charged with *tert*-butyl (*E*)-(4-(4,8-dimethyl-1-tosylnona-3,7-dien-1-yl)phenyl)carbamate **42h** (1.01 g, 2.03 mmol), sodium dihydrogen phosphate (2.47 g, 20.3 mmol, 10.0 equiv), and THF (36 mL). A colorless suspension resulted, as the sodium dihydrogen phosphate is insoluble in THF. The suspension was cooled to 0 °C using an ice bath. Sodium amalgam (1.87 g, 16.2 mmol Na, 8.0 equiv Na) was added all at once. Immediately following, ethanol (4 mL) was added dropwise over 1 min resulting in a grayish suspension. The mixture was stirred at 0 °C for 3 h but was incomplete (monitored by TLC, hexanes/EtOAc, 80:20). The ice bath was removed and the mixture was stirred at 25 °C for 3 h but was still incomplete. The mixture was again cooled to 0 °C and an additional portion of sodium amalgam (1.87 g, 16.2 mmol Na, 8.0 equiv Na) was added all at once. The mixture was warmed to 25 °C and an additional portion of sodium dihydrogen phosphate (2.44 g, 20.3 mmol, 10.0 equiv) was added all at once. Stirring was continued for 18 h at 25 °C, over which time the mixture lightened to a very pale gray suspension. Full conversion was observed by TLC (hexanes/EtOAc, 80:20). The suspension was filtered through a pad of Celite (6 cm wide x 1 cm deep) to remove mercury, and the pad was rinsed with ethyl acetate (50 mL). The filtrate was transferred to a separatory funnel along with water (75 mL) and additional ethyl acetate (75 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate, filtered, and concentrated (30 °C, 15 mmHg) to afford the crude product (0.72 g). The product was purified by chromatography (silica gel, 3 x 15 cm, dry load on Celite, 25-mL fractions, hexanes/EtOAc gradient elution: 95:5 (300 mL) to 90:10 (300 mL) to 85:15 (300 mL) to 80:20 (300 mL)) to afford 644.0 mg (92% yield) of **17h** as a viscous oil, which crystallized to an analytically pure white solid upon standing.

Data for **17h**:

m.p.: 50–52 °C

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

7.25 (d, *J* = 8.5 Hz, 2H, HC(5)), 7.10 (d, *J* = 8.5 Hz, 2H, HC(6)), 6.39 (bs, 1H, NH), 5.20-5.13 (m, 1H, HC(10)), 5.12-5.06 (m, 1H, HC(15)), 2.62-2.54 (m, 2H, H_2C(8)), 2.26 (q, *J* = 7.4 Hz, 2H, H_2C(9)), 2.05 (q, *J* = 7.0 Hz, 2H, H_2C(14)), 2.00-1.93 (m, 2H, H_2C(13)), 1.68 (s, 3H, H_3C(17)), 1.60 (s, 3H, H_3C(18)), 1.55 (s, 3H, H_3C(12)), 1.51 (s, 9H, H_3C(1)).

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

153.00 (C(3)), 137.35 (C(7)), 136.12 (C(4) or C(11)), 135.87 (C(4) or C(11)), 131.46 (C(16)), 129.06 (HC(6)), 124.49 (HC(15)), 123.71 (HC(10)), 118.73 (HC(5)), 80.46 (C(2)), 39.85 (H_2C(13)), 35.58 (H_2C(8)), 30.16 (H_2C(9)), 28.52 (H_3C(1)), 26.86 (H_2C(14)), 25.85 (H_3C(17)), 17.85 (H_3C(18)), 16.14 (H_3C(12)).

IR: (neat)

3385 (w), 2977 (w), 2923 (m), 2855 (w), 1700 (s), 1593 (m), 1523 (s), 1508 (s), 1444 (w), 1411 (m), 1384 (m), 1366 (m), 1319 (m), 1306 (m), 1232 (s), 1159 (s), 1110 (m), 1053 (s), 1019 (m), 930 (w), 907 (w), 848 (m), 822 (s), 796 (m), 771 (m), 748 (m), 605 (s), 516 (s), 494 (w).

LRMS: (ESI, $[M+Na]^+$)

112.3 (2), 112.6 (2), 121.7 (2), 149.8 (16), 163.9 (4), 196.1 (3), 196.8 (2), 198.8 (2), 254.8 (3), 256.8 (4), 282.3 (3), 288.2 (12), 289.2 (2), 304.3 (4), 320.2 (15), 321.2 (3), 360.4 (3), 361.4 (3), 366.2 (100), 367.2 (36), 368.2 (6), 424.1 (2).

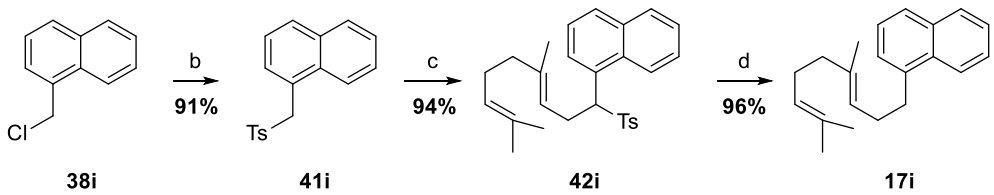
Analysis: $C_{22}H_{33}NO_2$ (343.51)

Calcd: C, 76.92%; H, 9.68%; N, 4.08%

Found: C, 76.65%; H, 9.51%; N, 4.25%

TLC: R_f 0.49 (silica gel, hexanes/EtOAc, 80:20, UV/CAM)

Multistep Synthesis of Compound 17i



38i **41i** **42i** **17i**

1-(4-Methylphenylsulfonylmethyl)naphthalene (41i)

A 25-mL, round-bottomed flask equipped with a stir bar and reflux condenser was charged with 1-(chloromethyl)naphthalene[226] **38i** (2.17 g, 12.28 mmol), sodium *p*-toluenesulfinate (3.28 g, 18.43 mmol, 1.50 equiv), tetra-*n*-butylammonium bromide (0.40 g, 1.23 mmol, 0.10 equiv), water (4.4 mL), acetone (3.3 mL), and benzene (3.3 mL). The biphasic mixture was heated to 85 °C (oil bath temperature) with vigorous stirring for 3 h. The stir rate was set high enough such that the reaction appearance was that of a peach-colored suspension. After 3 h, the oil bath was removed, stirring was stopped, and the layers were allowed to separate. The upper layer (organic phase) had the appearance of an orange solution, while the lower layer (aqueous phase) had the appearance of a thin, cloudy, colorless suspension. Full consumption of starting material was observed by TLC (hexanes/EtOAc, 80:20). The reaction mixture was partitioned between water (25 mL) and diethyl ether (25 mL) in a 125-mL separatory funnel. The layers were separated, and the aqueous layer was extracted with diethyl ether (2 x 25-mL). The combined organic extracts were washed with brine (25 mL), dried over magnesium sulfate, filtered, and concentrated (30 °C, 15 mmHg) to afford 3.79 g of crude **41i** as a yellow, oily solid. The product was purified by chromatography (silica gel, 5 cm x 16 cm, dry load on Celite, 50 mL fractions, hexanes/EtOAc gradient elution: 90:10 (500 mL) to 80:20 (500 mL) to 70:30 (500 mL) to 60:40 (500 mL) to 50:50 (500 mL)) to afford 3.31 g (91% yield) of **41i** as an off-white solid. At this point, the level of purity of the bulk material is sufficient for the next reaction. An analytically pure sample was obtained by two recrystallizations from a minimal amount (20 mL) of hot diethyl ether (affording 818.5 mg, or 22% overall yield), followed by sublimation (90 °C, 0.1 mmHg). The product sublimes very slowly and this is not a practical method for harvesting large quantities of material. The product is soluble

in CDCl3 but many of the ^{1}H-NMR signals overlap in this solvent. For this reason, the spectral data reported below were collected in benzene-d_6.

Data for **41i**:

m.p.: 108–109 °C

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

7.80-7.71 (m, 1H, HC(9)), 7.55-7.50 (m, 1H, HC(6)), 7.48 (d, *J* = 8.2 Hz, 1H, HC(4)), 7.39 (d, *J* = 8.2 Hz, 2H, HC(13)), 7.19-7.16 (m, 1H, HC(8)), 7.16-7.13 (m, 1H, HC(7)), 7.03-6.97 (m, 1H, HC(3)), 6.97-6.90 (m, 1H, HC(2)), 6.51 (d, *J* = 8.2 Hz, 2H, HC(14)), 4.44 (s, 2H, H_2C(11)), 1.74 (s, 3H, H_3C(16)).

^{13}C NMR: (126 MHz, C_6D_6)

143.9 (C(15)), 136.4 (C(12)), 134.2 (C(5)), 132.7 (C(10)), 130.7 (HC(2)), 129.5 (HC(4)), 129.3 (HC(14)), 129.1 (HC(13)), 128.7 (HC(6)), 126.5 (HC(8)), 126.03 (C(1)), 126.00 (HC(7)), 125.1 (HC(3)), 124.6 (HC(9)), 59.9 (H_2C(11)), 21.1 (H_3C(16)).

IR: (neat)

3050 (w), 2924 (w), 1597 (w), 1512 (w), 1494 (w), 1418 (w), 1398 (w), 1289 (m), 1216 (w), 1184 (w), 1155 (m), 1141 (m), 1129 (m), 1086 (m), 1018 (w), 946 (w), 890 (w), 855 (w), 803 (m), 774 (m), 746 (m), 728 (m), 672 (m), 643 (m), 626 (m), 561 (s), 515 (s), 498 (m), 486 (m), 460 (m)

LRMS: (EI, 70 eV)

63.0 (2), 65.0 (4), 89.0 (3), 91.1 (10), 115.1 (21), 116.1 (2), 124.0 (3), 139.1 (8), 140.1 (2), 141.1 (100), 142.1 (13), 296.1 (9), 297.1 (2)

Analysis: $C_{18}H_{16}O_2S$ (296.38)

Calcd: C, 72.94%; H, 5.44%

Found: C, 72.71%; H, 5.31%

TLC: R_f 0.20 (silica gel, hexanes/EtOAc, 80:20, UV)

(*E*)-1-(4,8-Dimethyl-1-(4-methylphenylsulfonyl)nona-3,7-dien-1-yl)naphthalene (42i)

A flame-dried, 100-mL, three-necked, round-bottomed flask equipped with a stir bar, argon inlet adapter, temperature probe, and two septa was charged with 1-((4-

methylphenylsulfonyl)methyl)naphthalene **41i** (600.7 mg, 2.03 mmol) and THF (16.5 mL). The resulting colorless solution was cooled to an internal temperature of –78 °C using a dry ice/acetone bath. Sodium hexamethyldisilazide (1 M solution in THF, 2.43 mL, 2.43 mmol, 1.20 equiv) was added dropwise over 10 min at –78 °C. Immediately, a bright yellow solution resulted. No significant exotherm was observed, and the internal temperature did not exceed –70 °C during the addition. The yellow solution was stirred at –78 °C for 1 h. A solution of geranyl bromide (530.3 mg, 2.43 mmol, 1.20 equiv) in THF (7.8 mL) was added dropwise at –78 °C over 20 min. Addition of this reagent does result in a slight exotherm, so the rate of addition was kept slow enough to maintain the internal temperature below –70 °C. The solution remained yellow but did become somewhat turbid. Stirring was continued at –78 °C for 2 h, at which point full conversion was observed by TLC (hexanes/EtOAc, 80:20). The reaction was quenched at –78 °C by adding (25 °C) sat. aq. sodium bicarbonate solution (40 mL). The cold bath was removed, and the off-white suspension was allowed to warm to 25 °C. The mixture was transferred to a 500-mL separatory funnel, rinsing with water (75 mL) and ethyl acetate (25 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 x 50 mL) The combined organic phases were washed with brine (50 mL), dried over sodium sulfate, filtered, and concentrated (30 °C, 15 mmHg) to afford 0.99 g crude **42i**. The product was purified by chromatography (silica gel, 4 cm x 20 cm, dry load on Celite, 25-mL fractions, hexanes/EtOAc gradient elution: 95:5 (300 mL) to 90:10 (300 mL) to 85:15 (300 mL) to 80:20 (300 mL)) to afford 737.0 mg (84% yield) of **42i** as a highly-viscous, pale-yellow oil (analytically pure). The oil is not amenable to purification by distillation.

Data for **42i**:

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

7.79 (d, *J* = 8.1 Hz, 1H, HC(4)), 7.76 (d, *J* = 7.9 Hz, 1H, HC(6)), 7.71-7.67 (m, 1H, HC(2)), 7.69-7.65 (m, 1H, HC(9)), 7.50-7.45 (m, 1H, HC(3)), 7.39-7.36 (m, 1H, HC(7)), 7.36 (d, *J* = 8.1 Hz, 2H, HC(13)), 7.34-7.29 (m, 1H, HC(8)), 6.99 (d, *J* = 8.1 Hz, 2H, HC(14)), 5.06 (dd, *J* = 11.3, 4.0 Hz, 1H, HC(11)), 4.80 (t, *J* = 6.9 Hz, 1H, HC(18)), 4.78-4.72 (m, 1H, HC(23)), 3.30 (ddd, *J* = 14.5, 6.9, 4.0 Hz, 1H, H_2C(17)), 2.99 (ddd, *J* = 14.5, 11.3, 6.9 Hz, 1H, H_2C(17)), 2.24 (s, 3H, H_3C(16)), 1.79-1.74 (m, 2H, H_2C(22)), 1.76-1.71 (m, 2H, H_2C(21)), 1.57 (s, 3H, H_3C(20)), 1.46 (s, 3H, H_3C(26)), 1.39 (s, 3H, H_3C(25)).

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

144.35 (C(15)), 138.91 (C(19)), 134.65 (C(12)), 133.63 (C(5)), 133.02 (C(10)), 131.50 (C(24)), 129.32 (HC(4)), 129.18 (HC(14)), 129.16 (HC(13)), 128.90 (HC(6)), 128.76 (C(1)), 127.11 (HC(2)), 126.39 (HC(8)), 125.44 (HC(7)), 125.18 (HC(3)), 123.85 (HC(23)), 122.36 (HC(9)), 118.73 (HC(18)), 64.66 (HC(11)), 39.59 (H_2C(21)), 27.82 (H_2C(17)), 26.40 (H_2C(22)), 25.60 (H_3C(26)), 21.57 (H_3C(16)), 17.66 (H_3C(25)), 16.42 (H_3C(20)).

IR: (neat)

3050 (w), 2966 (w), 2917 (w), 1597 (w), 1513 (w), 1494 (w), 1445 (w), 1399 (w), 1376 (w), 1312 (m), 1300 (m), 1289 (m), 1214 (w), 1183 (w), 1142 (s), 1084 (s), 1019 (w), 982 (w), 948 (w), 801 (m), 778 (s), 762 (m), 728 (m), 716 (m), 666 (s), 645 (w), 576 (s), 520 (s)

LRMS: (EI, 70 eV)

115.0 (12), 123.1 (23), 128.0 (15), 135.1 (24), 139.0 (19), 141.1 (100), 142.1 (44), 152.0 (25), 153.1 (70), 154.1 (25), 165.1 (53), 166.1 (18), 167.1 (35), 178.1 (35), 179.1 (37), 180.1 (10), 181.1 (32), 191.1 (17), 192.1 (18), 193.1 (83), 194.1 (16), 195.1 (39), 207.1 (49), 208.1 (23), 209.1 (13), 221.1 (32), 235.1 (16), 276.2 (35), 277.2 (100), 278.2 (72), 432.2 (1), 433.2 (1).

Analysis: $C_{28}H_{32}O_2S$ (432.62)

Calcd: C, 77.74%; H, 7.46%;

Found: C, 77.38%; H, 7.21%

TLC: R_f 0.35 (silica gel, hexanes/EtOAc, 80:20, UV/CAM)

(*E*)-1-(4,8-Dimethylnona-3,7-dien-1-yl)naphthalene (17i)

A flame-dried, 100-mL, three-necked, round-bottomed flask equipped with a glass-coated stir bar, argon inlet adapter, and two septa was charged with (*E*)-1-(4,8-dimethyl-1-tosylnona-3,7-dien-1-yl)naphthalene **42i** (509.4 mg, 1.18 mmol), sodium dihydrogen phosphate (0.85 g, 7.06 mmol, 6.0 equiv), and THF (24 mL). The resulting thin, white suspension was cooled to 0 °C using an ice bath. Sodium amalgam (20% w/w sodium, 0.42 g, 3.53 mmol, 3.0 equiv) was quickly added in one portion. Methanol (1.2 mL) was added dropwise at 0 °C over 1 min. The mixture was

allowed to slowly warm to 25 °C over 3 h, and stirring was continued for 9 h at 25 °C. While the suspension did become thicker over time, the reaction appeared incomplete by TLC (hexanes/EtOAc, 80:20). The mixture was again cooled to 0 °C and another portion of sodium amalgam (20% w/w sodium, 0.42 g, 3.53 mmol, 3.0 equiv) was quickly added, followed by an additional portion of methanol (1.2 mL). The reaction was stirred for 3 h at 0 °C. Full conversion was observed by TLC (hexanes/EtOAc, 80:20). The mixture was filtered through Celite (to remove elemental mercury) and the filter case was rinsed with ethyl acetate. The filtrate was transferred to a separatory funnel with water (50 mL) and additional ethyl acetate (50 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate, filtered, and concentrated (30 °C, 15 mmHg) to afford the crude product (324.9 mg). The product was purified by chromatography (silica gel, 2 x 16 cm, dry load on Celite, 10-mL fractions, hexanes/CH_2Cl_2 gradient elution: 97.5:2.5 (200 mL) to 95:5 (200 mL) to 92.5:7.5 (200 mL)) to afford **17i** as a clear, colorless oil (314.1 mg, 96%). Spectroscopic data matched those reported by Snyder et al. for this product accessed through a different method.[227]

Data for **17i**:

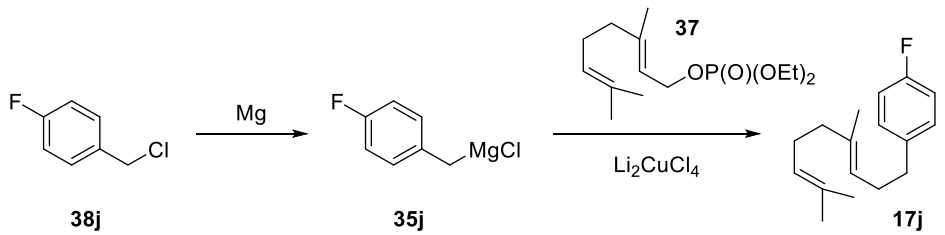
^{1}H NMR: (500 MHz, $CDCl_3$)

8.07 (d, *J* = 8.4 Hz, 1H), 7.87-7.82 (m, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.53-7.44 (m, 2H), 7.40 (dd, *J* = 8.1, 7.1 Hz, 1H), 7.33 (d, *J* = 6.7 Hz, 1H), 5.31-5.26 (m, 1H), 5.14-5.08 (m, 1H), 3.10 (dd, *J* = 8.7, 7.1 Hz, 2H), 2.45 (q, *J* = 7.3 Hz, 2H), 2.07 (q, *J* = 7.3 Hz, 2H), 2.03-1.97 (m, 2H), 1.70 (s, 3H), 1.61 (s, 3H), 1.54 (s, 3H).

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

138.6, 136.0, 134.0, 132.1, 131.5, 128.9, 126.6, 126.1, 125.8, 125.7, 125.5, 124.5, 124.0, 123.9, 39.9, 33.4, 29.4, 26.9, 25.9, 17.9, 16.2

(*E*)-1-(4,8-Dimethylnona-3,7-dien-1-yl)-4-fluorobenzene (17j)



38j **35j** **17j**

Grignard reagent **35j** was prepared by the method of Nugent and co-workers.[228] The procedure is excellently described and should be followed exactly. A 50-mL, flame-dried, Schlenk flask equipped with a stir bar was charged with magnesium turnings (1.5 g, 60 mmol, 6.0 equiv). The turnings were mechanically activated by dry stirring, under argon, for two days at 25 °C. THF (12 mL) was added, and 1-(chloromethyl)-4-fluorobenzene **38j** (1.4 g, 10 mmol) was added dropwise over 1.5 h using a syringe pump. The internal temperature was monitored with a thermocouple probe, and a slight exotherm was observed upon initiation. The internal temperature was maintained between 25 °C and 30 °C by briefly surrounding the flask with a reservoir of cool water when necessary. Once the addition was complete, the resulting dark grey solution was aged for 1 h, and then the Grignard reagent **35j** was titrated in the manner described previously for **35b**. The concentration of **35j** was determined to be 0.68 M (average of two runs; expected 0.83 M). The reagent was used immediately.

Grignard reagent **35j** (5.9 mL, 0.68 M, 4.0 mmol, 2.0 equiv) was transferred to a 10-mL, flame-dried flask and cooled to –40 °C using an acetonitrile/dry ice slush bath. A separate, flame-dried, 25-mL, two-necked, round-bottomed flask equipped with a stir bar was charged with THF (2 mL) and geranyl diethyl phosphate **37** (0.58 g, 2.0 mmol). The resulting colorless solution was also cooled to –40 °C using an acetonitrile/dry ice slush bath. The Grignard reagent **35j** was added in one portion to the flask containing **37** via cannula transfer. The reaction mixture was allowed to warm slowly to 25 °C over 4 h, and stirring was continued at this temperature for 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 80:20). The reaction was quenched by the addition of sat. aq. NH4Cl, and the biphasic mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over Na2SO4, filtered, and concentrated to afford 0.63 g of crude **17j**. The product was purified by chromatography (silica gel, hexanes/EtOAc gradient elution: 99:1 to 98:2) to afford 0.37 g (75%) of **17j**.

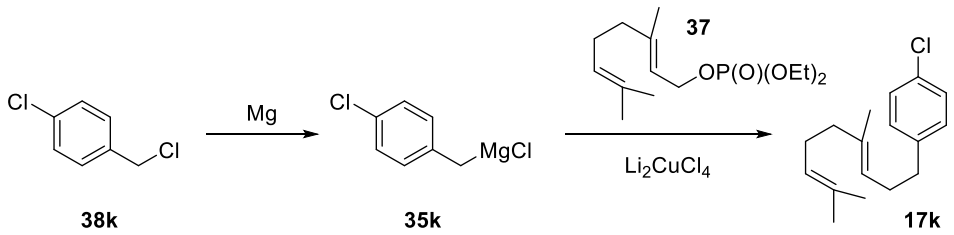
Data for **17j**:

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

7.15 – 7.10 (m, 2H), 6.98 – 6.92 (m, 2H), 5.18 – 5.12 (m, 1H), 5.11 – 5.05 (m, 1H), 2.61 (t, J = 7.7 Hz, 2H), 2.27 (q, J = 7.4 Hz, 2H), 2.08 – 2.02 (m, 2H), 2.00 – 1.95 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.53 (s, 3H).

TLC: R_f 0.88 (silica gel, hexanes/EtOAc, 80:20, UV/$KMnO_4$)

(*E*)-1-(4,8-Dimethylnona-3,7-dien-1-yl)-4-chlorobenzene (17k)



A 50-mL, flame-dried, Schlenk flask equipped with a stir bar was charged with magnesium turnings (1.5 g, 60 mmol, 6.0 equiv). The turnings were mechanically activated by dry stirring, under argon, for two days at 25 °C. THF (12 mL) was added, and a solution of 1-(chloromethyl)-4-chlorobenzene **38k** (1.6 g, 10 mmol) in THF (2 mL) was added dropwise over 1.5 h using a syringe pump. The internal temperature was monitored with a thermocouple probe, and a slight exotherm was observed upon initiation. The internal temperature was maintained between 25 °C and 30 °C by briefly surrounding the flask with a reservoir of cool water when necessary. Once the addition was complete, the resulting dark grey solution was aged for 1 h, and then the Grignard reagent **35k** was titrated in the manner described previously for **35b**. The concentration of **35k** was determined to be 0.25 M (average of two runs; expected 0.71 M). The reagent was used immediately.

The Grignard reagent **35k** (14 mL, 0.25 M, 3.5 mmol, 1.75 equiv) was cooled to –40 °C using an acetonitrile/dry ice slush bath. A separate, flame-dried, 25-mL, two-necked, round-bottomed flask equipped with a stir bar was charged with THF (2 mL) and geranyl diethyl phosphate **37** (0.58 g, 2.0 mmol). The resulting colorless solution was also cooled to –40 °C using an acetonitrile/dry ice slush bath. The Grignard reagent **35k** was added in one portion to the flask containing **37** via cannula transfer. The reaction mixture was allowed to warm slowly to 25 °C

over 4 h, and stirring was continued at this temperature for 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 80:20). The reaction was quenched by the addition of sat. aq. NH4Cl, and the biphasic mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over Na2SO4, filtered, and concentrated to afford 1.22 g of crude **17k**. The product was purified by chromatography (high porosity silica gel, hexanes/Et_2O gradient elution: 100:0 to 99:1) to afford 0.10 g (20%) of pure **17k**, along with mixed fractions contaminated with **39k**.

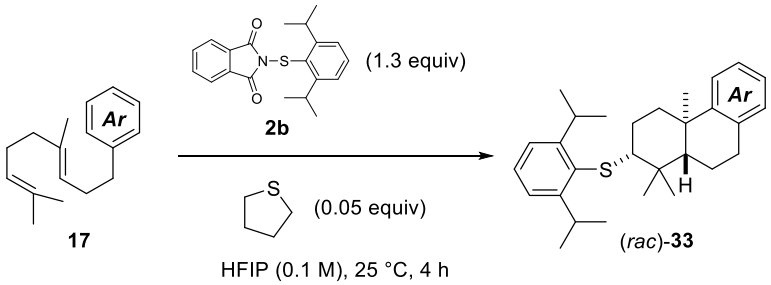
Data for **17k**:

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

7.25 – 7.21 (m, 2H), 7.13 – 7.09 (m, 2H), 5.17 – 5.11 (m, 1H), 5.11 – 5.05 (m, 1H), 2.60 (t, *J* = 7.7 Hz, 2H), 2.27 (q, *J* = 7.3 Hz, 2H), 2.08 – 2.02 (m, 2H), 2.00 – 1.94 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.53 (s, 3H).

TLC: R_f 0.91 (silica gel, hexanes/EtOAc, 80:20, UV/$KMnO_4$)

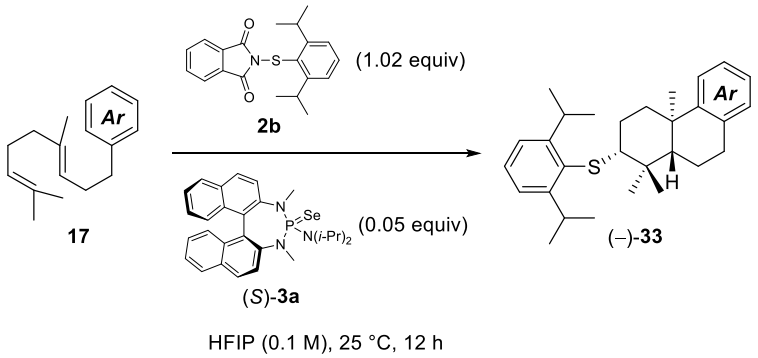
General Procedure: Catalytic, Racemic Sulfenocyclization of 17 to 33



A 100-mL, round-bottom flask equipped with a stir bar was charged with *N*-(2,6-diisopropylphenylthio)phthalimide **2b** (1.10 mmol, 1.10 equiv), hexafluoroisopropyl alcohol (10 mL, 0.1 M), and **17** (1.00 mmol) resulting in a yellow solution. Tetrahydrothiophene (0.05 equiv) was added in one portion and the mixture was stirred at 25 °C. After 2 h, the reaction was charged with additional *N*-(2,6-diisopropylphenylthio)phthalimide **2b** (0.20 mmol, 0.20 equiv) and stirring was continued for 2 h. [**Note:** unproductive consumption of **2b** is observed as a minor reaction pathway, which necessitates the additional charge of **2b** to reach full conversion.] Conversion was monitored by TLC. Once full conversion was reached, the colored suspension was diluted with

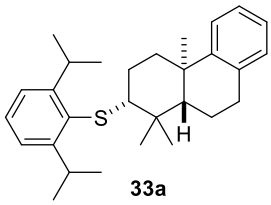
CH_2Cl_2 (10 mL). Volatiles were removed by rotary evaporation (30 °C, 15 mmHg) to afford crude (±)-**33**. Chromatography and subsequent recrystallization or trituration afforded pure (±)-**33**.

General Procedure: Catalytic, Enantioselective Sulfenocyclization of 17 to 33



A 100-mL, round-bottomed flask equipped with a stir bar was charged with *N*-(2,6-diisopropylphenylthio)phthalimide **17** (1.02 mmol, 1.02 equiv), hexafluoroisopropyl alcohol (10 mL, 0.1 M), and **2b** (1.00 mmol) resulting in a yellow solution. Catalyst (*S*)-**3a** (0.05 equiv) was added in one portion and the mixture was stirred at 25 °C for 12 h. Conversion was monitored by TLC. Once full conversion was reached, the colored suspension was diluted with CH_2Cl_2 (10 mL). Volatiles were removed by rotary evaporation (30 °C, 15 mmHg) to afford crude (–)-**33**. Chromatography and subsequent recrystallization or trituration afforded pure (–)-**33**.

Compound 33a



Data for (±)-**33a**:

m.p.: 160–162 °C (hexanes)

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

7.31 (t, *J* = 7.7 Hz, 1H, HC(21)), 7.16 (d, *J* = 7.7 Hz, 2H, HC(20)), 7.16-7.13 (m, 1H, HC(14)), 7.11-7.07 (m, 1H, HC(16) or HC(15)), 7.07-7.05 (m, 1H, HC(15) or

HC(16)), 7.05-7.02 (m, 1H, HC(17)), 4.01 (hept, *J* = 6.9 Hz, 2H, HC(22)), 3.02-2.94 (m, 1H, $H_2C(11^{eq})$), 2.88 (ddd, *J* = 17.5, 11.5, 7.3 Hz, 1H, $H_2C(11^{ax})$), 2.62 (dd, *J* = 12.5, 3.5 Hz, 1H, HC(4)), 2.23 (dt, *J* = 13.3, 3.4 Hz, 1H, $H_2C(6^{eq})$), 2.01-1.93 (m, 1H, $H_2C(10^{eq})$), 1.93-1.84 (m, 1H, $H_2C(5^{ax})$), 1.84-1.74 (m, 1H, $H_2C(10^{ax})$), 1.57 (dq, *J* = 10.2, 3.6 Hz, 1H, $H_2C(5^{eq})$), 1.39 (s, 3H, $H_3C(2)$), 1.38 (dd, *J* = 2.0 Hz, 1H, HC(9)), 1.26 (d, *J* = 6.9 Hz, 6H, $H_3C(23)$), 1.28-1.23 (m, 1H, $H_2C(6^{ax})$), 1.22 (s, 3H, $H_3C(8)$), 1.18 (d, *J* = 6.9 Hz, 6H, $H_3C(23')$), 1.12 (s, 3H, $H_3C(1)$).

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

154.18 (C(19)), 149.47 (C(13)), 135.09 (C(12)), 130.95 (C(18)), 129.11 (HC(17)), 128.91 HC(21)), 125.91 (HC(16) or HC(15)), 125.54 (HC(15) or HC(16)), 124.48 (HC(14)), 123.70 (HC(20)), 61.89 (HC(4)), 52.44 (HC(9)), 39.27 ($H_2C(6)$), 39.05 (C(3)), 37.95 (C(7)), 31.49 (HC(22)), 30.85 ($H_2C(11)$), 29.77 ($H_3C(2)$), 26.20 ($H_2C(5)$), 25.04 ($H_3C(23')$), 24.98 ($H_3C(8)$), 24.13 ($H_3C(23)$), 19.68 ($H_2C(10)$), 17.75 ($H_3C(1)$).

IR: (neat)

2961 (m), 2864 (w), 2837 (w), 1575 (w), 1489 (w), 1449 (m), 1391 (w), 1375 (m), 1360 (m), 1307 (w), 1267 (w), 1245 (w), 1198 (w), 1160 (w), 1052 (m), 995 (w), 967 (w), 939 (w), 879 (w), 835 (w), 798 (s), 771 (m), 758 (s), 752 (s), 731 (m), 722 (s), 702 (w), 559 (w), 486 (w).

LRMS: (EI, 70 eV)

55.1 (36), 57.1 (22), 69.1 (62), 73.0 (11), 83.1 (25), 91.1 (24), 97.1 (23), 115.1 (23), 117.1 (43), 123.0 (12), 128.1 (27), 129.1 (42), 131.1 (100), 132.1 (11), 141.1 (15), 142.1 (12), 143.1 (67), 144.1 (16), 145.1 (20), 149.0 (22), 151.1 (25), 157.1 (44), 169.1 (13), 171.1 (22), 179.1 (12), 194.1 (52), 211.1 (30), 227.2 (62), 228.2 (12), 420.3 (61), 421.3 (20).

Analysis: $C_{29}H_{40}S$ (420.70)

Calcd: C, 82.79%; H, 9.58%;

Found: C, 82.59%; H, 9.70%;

TLC: R_f 0.33 (silica gel, hexanes/CH_2Cl_2, 90:10, UV/CAM or PMA)

HPLC: t_R 7.4 min (50%); t_R 9.1 min (50%) (Supelco Astec, hexanes/*i*-PrOH, 99:1, 0.5 mL/min, 220 nm, 24 °C)

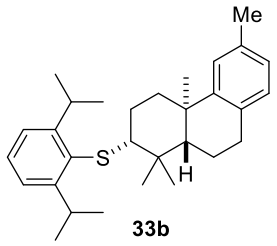
Data for (–)-**33a**:

HPLC: t_R 7.8 min (90%); t_R 10.6 min (10%) (Supelco Astec, hexanes/*i*-PrOH, 99:1, 0.5 mL/min, 220 nm, 24 °C)

after recrystallization: t_R 7.6 min (91%); t_R 9.7 min (9%)

Opt. Rot: $[\alpha]_D^{25}$ –10.2 (*c* = 1.06 in $CHCl_3$)

Compound 33b



33b

Data for (±)-**33b**:

m.p.: 197–199 °C (hexanes)

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

7.30 (t, *J* = 7.7 Hz, 1H, HC(22)), 7.16 (d, *J* = 7.7 Hz, 2H, HC(21)), 6.96 (bs, 1H, HC(14)), 6.94 (d, *J* = 7.7 Hz, 1H, HC(17)), 6.91-6.86 (m, 1H, HC(16)), 4.01 (hept, *J* = 6.8 Hz, 2H, HC(23)), 2.93 (dd, *J* = 16.9, 6.2 Hz, 1H, $H_2C(11^{eq})$), 2.83 (ddd, *J* = 17.5, 11.5, 7.4 Hz, 1H, $H_2C(11^{ax})$), 2.61 (dd, *J* = 12.5, 3.8 Hz, 1H, HC(4)), 2.24 (s, 3H, $H_3C(18)$), 2.23 (dt, *J* = 3.5 Hz, 1H, $H_2C(6^{eq})$), 2.00-1.92 (m, 1H, $H_2C(10^{eq})$), 1.87 (qd, *J* = 13.8, 3.4 Hz, 1H, $H_2C(5^{ax})$), 1.83-1.72 (m, 1H, $H_2C(10^{ax})$), 1.56 (dq, *J* = 14.0, 3.5 Hz, 1H, $H_2C(5^{eq})$), 1.38 (s, 3H, $H_3C(2)$), 1.36 (dd, *J* = 12.5, 2.0 Hz, 1H, HC(9)), 1.26 (d, *J* = 6.9 Hz, 6H, $H_3C(24)$), 1.28-1.23 (m, 1H, $H_2C(6^{ax})$), 1.22 (s, 3H, $H_3C(8)$), 1.18 (d, *J* = 6.9 Hz, 6H, $H_3C(24')$), 1.11 (s, 3H, $H_3C(1)$).

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

154.16 (C(20)), 149.34 (C(13)), 135.16 (C(15)), 131.94 (C(12)), 130.99 (C(19)), 129.02 (HC(17)), 128.88 (HC(22)), 126.44 (HC(16)), 125.04 (HC(14)), 123.69 (HC(21)), 61.94 (HC(4)), 52.55 (HC(9)), 39.31 (H_2C(6)), 39.07 (C(3)), 37.87 (C(7)), 31.48 (HC(23)), 30.44 (H_2C(11)), 29.79 (H_3C(2)), 26.19 (H_2C(5)), 25.04 (H_3C(24')), 24.94 (H_3C(8)), 24.12 (H_3C(24)), 21.39 (H_3C(18)), 19.75 (H_2C(10)), 17.75 (H_3C(1)).

IR: (neat)

2962 (s), 2929 (m), 2861 (m), 1573 (w), 1500 (m), 1457 (m), 1386 (m), 1375 (m), 1361 (m), 1305 (w), 1269 (w), 1248 (w), 1177 (m), 1161 (m), 1051 (m), 991 (w), 967 (m), 881 (m), 836 (w), 808 (s), 800 (s), 768 (m), 754 (s), 745 (m), 713 (w), 582 (w), 513 (w), 461 (s).

LRMS: (EI, 70 eV)

55.2 (16), 69.1 (46), 83.1 (14), 91.1 (15), 97.1 (13), 105.1 (15), 115.1 (17), 123.1 (11), 128.1 (18), 129.1 (19), 131.1 (40), 141.1 (16), 142.1 (17), 143.1 (33), 145.1 (100), 146.1 (12), 149.1 (19), 151.1 (28), 155.1 (12), 156.1 (11), 157.1 (68), 158.1 (17), 159.1 (21), 171.1 (48), 179.1 (12), 183.1 (11), 185.1 (23), 194.1 (38), 199.2 (11), 225.2 (34), 240.2 (11), 241.2 (97), 242.2 (19), 434.3 (66), 435.3 (24).

Analysis: $C_{30}H_{42}S$ (434.73)

Calcd: C, 82.89%; H, 9.74%

Found: C, 82.55%; H, 9.82%

TLC: R_f 0.33 (silica gel, hexanes/CH_2Cl_2, 90:10, UV/CAM or PMA)

HPLC: 10.2 min (50%); t_R 11.3 min (50%) (Supelco Astec, hexanes/*i*-PrOH, 99:1, 0.3 mL/min, 220 nm, 24 °C)

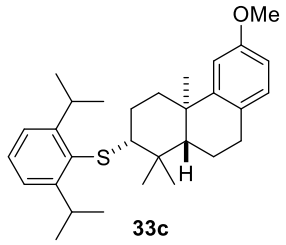
Data for (–)-**33b**:

HPLC: **Note:** The e.r. cannot be measured accurately prior to recrystallization due to overlapping signals arising from trace impurities. It is measured as **90:10** on the alkane derivative resulting from reductive C–S cleavage.

After recrystallization: t_R 10.3 min (93%); t_R 11.5 min (7%) (Supelco Astec, hexanes/*i*-PrOH, 99:1, 0.3 mL/min, 220 nm, 24 °C)

Opt. Rot: $[\alpha]_D^{25}$ –32.3 (*c* = 1.07 in $CHCl_3$)

Compound 33c



33c

Data for (±)-**33c**:

m.p.: 194–196 °C (hexanes)

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

7.31 (t, *J* = 7.7 Hz, 1H, HC(22)), 7.16 (d, *J* = 7.7 Hz, 2H, HC(21)), 6.96 (d, *J* = 8.4 Hz, 1H, HC(17)), 6.70 (d, *J* = 2.6 Hz, 1H, HC(14)), 6.65 (dd, *J* = 8.4, 2.6 Hz, 1H, HC(16)), 4.01 (hept, *J* = 6.9 Hz, 2H, HC(23)), 3.73 (s, 3H, $H_3C(18)$), 2.96-2.87 (m, 1H, $H_2C(11^{eq})$), 2.80 (ddd, *J* = 17.0, 11.5, 7.0 Hz, 1H, $H_2C(11^{ax})$), 2.62 (dd, *J* = 12.5, 3.8 Hz, 1H, HC(4)), 2.18 (dt, *J* = 13.0, 3.3 Hz, 1H, $H_2C(6^{eq})$), 1.98-1.92 (m, 1H, $H_2C(10^{eq})$), 1.92-1.83 (m, 1H, $H_2C(5^{ax})$), 1.82-1.72 (m, 1H, $H_2C(10^{ax})$), 1.56 (dq, *J* = 13.5, 3.5 Hz, 1H, $H_2C(5^{eq})$), 1.39 (s, 3H, $H_3C(2)$), 1.36 (dd, *J* = 12.5, 2.0 Hz, 1H, HC(9)), 1.29-1.23 (m, 1H, $H_2C(6^{ax})$), 1.26 (d, *J* = 6.9 Hz, 6H, $H_3C(24)$), 1.22 (s, 3H, $H_3C(8)$), 1.18 (d, *J* = 6.9 Hz, 6H, $H_3C(24')$), 1.11 (s, 3H, $H_3C(1)$).

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

157.87 (C(15)), 154.16 (C(20)), 150.73 (C(13)), 130.93 (HC(19)), 129.89 (HC(17)), 128.92 (HC(22)), 127.27 (C(12)), 123.70 (HC(21)), 111.28 (HC(16)), 110.08 (HC(14)), 61.86 (HC(4)), 55.36 ($H_3C(18)$), 52.47 (HC(9)), 39.30 ($H_2C(6)$), 39.06 (C(3)), 38.15 (C(7)), 31.49 (HC(23)), 30.02 ($H_2C(11)$), 29.79 ($H_3C(2)$), 26.19 ($H_2C(5)$), 25.04 ($H_3C(24')$), 24.87 ($H_3C(8)$), 24.13 ($H_3C(24)$), 19.80 ($H_2C(10)$), 17.77 ($H_3C(1)$).

IR: (neat)

2963 (s), 2930 (m), 1607 (m), 1574 (w), 1494 (s), 1467 (m), 1386 (w), 1375 (m), 1361 (m), 1270 (m), 1254 (s), 1221 (m), 1192 (m), 1173 (m), 1088 (w), 1039 (s), 1007 (w), 992 (w), 968 (w), 879 (m), 806 (s), 770 (m), 755 (m), 745 (m), 736 (m), 712 (m), 638 (w), 581 (w), 471 (m).

LRMS: (EI, 70 eV)

55.1 (15), 69.1 (33), 83.1 (10), 91.1 (11), 115.1 (12), 121.1 (13), 128.1 (10), 147.1 (21), 151.1 (16), 159.1 (17), 161.1 (59), 173.1 (38), 174.1 (12), 175.1 (12), 187.1 (29), 201.1 (12), 241.2 (25), 256.2 (29), 257.2 (100), 258.2 (21), 450.3 (53), 451.3 (18).

Analysis: $C_{30}H_{42}OS$ (450.73)

Calcd: C, 79.94%; H, 9.39%

Found: C, 79.75%; H, 9.45%

TLC: R_f 0.11 (silica gel, hexanes/CH_2Cl_2, 90:10, UV/CAM or PMA)

HPLC: t_R 8.9 min (50%); t_R 9.6 min (50%) (Supelco Astec, hexanes/*i*-PrOH, 90:10, 0.5 mL/min, 220 nm, 24 °C)

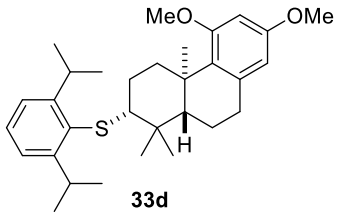
Data for (–)-**33c**:

HPLC: t_R 8.8 min (8%); t_R 9.5 min (92%) (Supelco Astec, hexanes/*i*-PrOH, 90:10, 0.5 mL/min, 220 nm, 24 °C)

after recrystallization: t_R 8.8 min (9%); t_R 9.7 min (91%)

Opt. Rot: $[\alpha]_D^{25}$ –29.5 (*c* = 1.05 in $CHCl_3$)

Compound 33d



33d

Data for (±)-**33d**:

HPLC: t_R 7.7 min (50%); t_R 8.9 min (50%) (Supelco Astec, hexanes/*i*-PrOH, 98:2, 0.5 mL/min, 220 nm, 24 °C)

Data for (–)-**33d**:

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

7.31 – 7.27 (m, 1H, HC(20)), 7.15 (d, J = 7.7 Hz, 2H, HC(19)), 6.25 (d, J = 2.6 Hz, 1H, HC(12)), 6.19 (d, J = 2.6 Hz, 1H, HC(10)), 4.02 (hept, J = 6.8 Hz, 2H, HC(21)), 3.74 (s, 3H, H_3C(23)), 3.69 (s, 3H, H_3C(24)), 3.02 (dt, J = 13.6, 3.5 Hz, 1H, H_2C(2)), 2.88 – 2.83 (m, 2H, H_2C(8)), 2.64 (dd, J = 12.6, 4.0 Hz, 1H, HC(4)), 1.92 – 1.76 (m, 2H, H_2C(7) and H_2C(3)), 1.68 – 1.58 (m, 1H, H_2C(7)), 1.44 (dq, J = 14.0, 3.7 Hz, 1H, H_2C(3)), 1.38 (s, 3H, H_3C(16)), 1.31 – 1.24 (m, 10H, H_3C(15), H_3C(22), and HC(6)), 1.18 (d, J = 6.9 Hz, 6H, H_3C(22)), 1.10 (s, 3H, H_3C(16)), 1.00 (td, J = 13.6, 3.2 Hz, 1H, H_2C(2)).

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

159.5 (C(13)), 157.9 (C(11)), 154.0 (C(18)), 138.5 (C(9)), 131.0 (C(17)), 129.5 (C(14)), 128.6 (HC(20)), 123.5 (HC(19)), 104.7 (HC(10)), 97.6 (HC(12)), 61.8 (HC(4)), 55.4 (HC(6)), 55.1 (H_3C(23)), 54.9 (H_3C(24)), 39.2 (C(5)), 39.1 (C(1)), 37.2 (H_2C(2)), 33.6 (H_2C(8)), 31.3 (HC(21)), 30.1 (H_3C(16)), 26.3 (H_2C(3)), 24.9 (H_3C(22)), 24.0 (H_3C(22)), 19.8 (H_3C(15)), 19.5 (H_2C(7)), 18.1 (H_3C(16)).

IR: (neat)

2960 (w), 2866 (w), 2836 (w), 1604 (w), 1581 (w), 1461 (w), 1420 (w), 1390 (w), 1361 (w), 1350 (w), 1328 (w), 1307 (w), 1268 (w), 1246 (w), 1215 (w), 1201 (w), 1158 (m), 1095 (w), 1081 (w), 1053 (w), 1032 (w), 1020 (w), 998 (w), 974 (w),

939 (w), 909 (w), 883 (w), 826 (w), 802 (w), 767 (w), 753 (w), 732 (m), 649 (w), 632 (w), 568 (w), 463 (w).

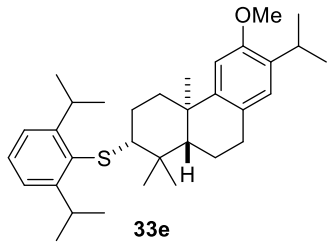
LRMS: (EI, 70 eV)
57.1 (19), 69.1 (17), 83.1 (11), 191.1 (23), 203.1 (21), 271.2 (16), 287.2 (100), 446.2 (59), 480.3 (26).

HRMS: Calcd for $C_{31}H_{44}O_2S$ ($[M]^+$): 480.3062, Found: 480.3061

TLC: R_f 0.29 (silica gel, hexanes/CH_2Cl_2, 67:33, PMA)

HPLC: t_R 7.7 min (90%); t_R 8.9 min (10%) (Supelco Astec, hexanes/*i*-PrOH, 98:2, 0.5 mL/min, 220 nm, 24 °C)
After recrystallization: t_R 7.6 min (95%); t_R 8.6 min (5%)

Compound 33e



33e

Data for (±)-**33e**:

m.p.: 143–145 °C (hexanes)

^{1}H NMR: (500 MHz, $CDCl_3$)
7.30 (t, *J* = 7.7 Hz, 1H, HC(24)), 7.15 (d, 7.7 Hz, 2H, HC(23)), 6.84 (s, 1H, HC(17)), 6.61 (s, 1H, HC(14)), 4.01 (hept, *J* = 6.9 Hz, 2H, HC(25)), 3.72 (s, 3H, $H_3C(18)$), 3.19 (hept, *J* = 6.9 Hz, 1H, HC(19)), 2.93-2.85 (m, 1H, $H_2C(11^{eq})$), 2.84-2.74 (m, 1H, $H_2C(11^{ax})$), 2.61 (dd, *J* = 12.5, 3.8 Hz, 1H, HC(4)), 2.20 (dt, *J* = 13.1, 3.4 Hz, 1H, $H_2C(6^{eq})$), 1.98-1.92 (m, 1H, $H_2C(10^{eq})$), 1.92-1.83 (m, 1H, $H_2C(5^{ax})$), 1.82-1.72 (m, 1H, $H_2C(10^{ax})$), 1.57 (dq, *J* = 10.2, 3.6 Hz, 1H, $H_2C(5^{eq})$), 1.39 (s, 3H, $H_3C(2)$), 1.38 (dd, *J* = 12.0, 2.0 Hz, 1H, HC(9)), 1.30 (dd, *J* = 13.4, 3.5 Hz, 1H, $H_2C(6^{ax})$), 1.26 (d, *J* = 7.0 Hz, 6H, $H_3C(26)$), 1.23 (s, 3H, $H_3C(8)$), 1.18 (d, *J* = 7.0 Hz, 3H, $H_3C(20)$), 1.17 (d, *J* = 7.0 Hz, 6H, $H_3C(26')$), 1.16 (d, *J* = 7.0 Hz, 3H, $H_3C(20')$), 1.11 (s, 3H, $H_3C(1)$).

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

155.21 (C(15)), 154.16 (C(22)), 147.41 (C(13)), 134.59 (C(16)), 130.98 (C(21)), 128.89 (HC(24)), 126.68 (C(12)), 126.49 (HC(17)), 123.69 (HC(23)), 106.50 (HC(14)), 61.96 (HC(4)), 55.60 (H_3C(18)), 52.59 (HC(9)), 39.41 (H_2C(6)), 39.03 (C(3)), 37.96 (C(7)), 31.48 (HC(25)), 30.24 (H_2C(11)), 29.78 (H_3C(2)), 26.58 (HC(19)), 26.23 (H_2C(5)), 25.05 (H_3C(26')), 24.91 (H_3C(8)), 24.12 (H_3C(26)), 23.00 (H_3C(20') or H_3C(20)), 22.81 (H_3C(20) or H_3C(20')), 19.89 (H_2C(10)), 17.75 (H_3C(1)).

IR: (neat)

2965 (s), 2934 (s), 2868 (m), 1614 (w), 1574 (w), 1498 (s), 1463 (s), 1405 (m), 1383 (m), 1361 (m), 1303 (m), 1252 (s), 1235 (s), 1196 (s), 1166 (m), 1102 (m), 1074 (m), 1055 (s), 997 (m), 968 (m), 892 (m), 878 (m), 843 (s), 798 (s), 778 (s), 746 (s), 732 (m), 713 (w), 573 (w), 481 (m).

LRMS: (EI, 70 eV)

55.1 (13), 69.1 (23), 149.0 (11), 151.1 (16), 163.1 (16), 179.1 (10), 189.1 (17), 201.1 (14), 203.1 (39), 215.1 (30), 229.2 (18), 257.2 (16), 283.2 (20), 298.2 (27), 299.2 (100), 300.2 (29), 492.3 (62), 493.3 (23).

Analysis: $C_{33}H_{48}OS$ (492.81)

Calcd: C, 80.43%; H, 9.82%

Found: C, 80.76%; H, 9.99%

TLC: R_f 0.19 (silica gel, hexanes/CH_2Cl_2, 90:10, UV/CAM or PMA)

HPLC: HPLC analysis is performed on derivative (±)-**46** (major sulfoxide diastereomer).

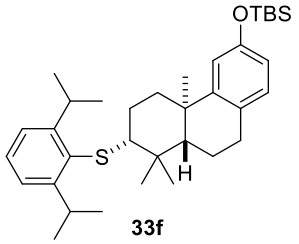
Data for (–)-**4e**:

HPLC: Conditions were not identified for separation of enantiomers of **33e**. After oxidation to sulfoxide (–)-**46**, the e.r. was determined to be 92:8.

After recrystallization: 91:1 (measured on derivative (–)-**46**).

Opt. Rot.: $[\alpha]_D^{24}$ –29.8 (*c* = 1.10 in $CHCl_3$) (82% ee)

Compound 33f



33f

Data for (±)-**33f**:

m.p.: 93–98 °C (ethanol)

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

7.31 (t, *J* = 7.7 Hz, 1H, HC(24)), 7.16 (d, *J* = 7.7 Hz, 2H, HC(23)), 6.87 (d, *J* = 8.2 Hz, 1H, HC(17)), 6.61 (d, *J* = 2.5 Hz, 1H, HC(14)), 6.55 (dd, *J* = 8.2, 2.5 Hz, 1H, HC(16)), 4.01 (hept, *J* = 6.8 Hz, 2H, HC(25)), 2.93-2.84 (m, 1H, $H_2C(11^{eq})$), 2.83-2.74 (m, 1H, $H_2C(11^{ax})$), 2.60 (dd, *J* = 12.5, 3.8 Hz, 1H, HC(4)), 2.13 (dt, *J* = 13.3, 3.3 Hz, 1H, $H_2C(6^{eq})$), 1.97-1.91 (m, 1H, $H_2C(10^{eq})$), 1.91-1.82 (m, 1H, $H_2C(5^{ax})$), 1.80-1.70 (m, 1H, $H_2C(10^{ax})$), 1.56 (dq, *J* = 13.5, 3.6 Hz, 1H, $H_2C(5^{eq})$), 1.39 (s, 3H, $H_3C(2)$), 1.36-1.33 (m, 1H, HC(9)), 1.26 (d, *J* = 6.9 Hz, 6H, $H_3C(26)$), 1.24-1.21 (m, 1H, $H_2C(6^{ax})$), 1.20 (s, 3H, $H_3C(8)$), 1.18 (d, *J* = 6.9 Hz, 6H, $H_3C(26')$), 1.10 (s, 3H, $H_3C(1)$), 0.94 (s, 9H, $H_3C(20)$), 0.13 (s, 3H, $H_3C(18)$), 0.12 (s, 3H, $H_3C(18')$).

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

154.21 (C(22)), 153.66 (C(15)), 150.53 (C(13)), 130.98 (C(21)), 129.72 (HC(17)), 128.93 (HC(24)), 127.66 (C(12)), 123.69 (HC(23)), 117.61 (HC(16)), 115.91 (HC(14)), 61.96 (HC(4)), 52.43 (HC(9)), 39.30 ($H_2C(6)$), 39.03 (C(3)), 37.94 (C(7)), 31.48 (HC(25)), 30.17 ($H_2C(11)$), 29.77 ($H_3C(2)$), 26.27 ($H_2C(5)$), 25.88 ($H_3C(20)$), 25.05 ($H_3C(26')$), 24.86 ($H_3C(8)$), 24.13 ($H_3C(26)$), 19.83 ($H_2C(10)$), 18.35 (C(19)), 17.78 ($H_3C(1)$), -4.24 ($H_3C(18)$ or $H_3C(18')$), -4.28 ($H_3C(18)$ or $H_3C(18')$).

IR: (neat)

2961 (m), 2858 (w), 1606 (w), 1573 (w), 1490 (m), 1470 (w), 1391 (w), 1376 (w), 1361 (w), 1288 (w), 1266 (m), 1252 (m), 1222 (w), 1188 (w), 1162 (w), 1054 (w), 1006 (w), 967 (m), 927 (w), 905 (m), 882 (w), 872 (w), 836 (s), 797 (m), 779 (s), 746 (m), 734 (w), 692 (w), 628 (w), 570 (w), 481 (w).

LRMS: (EI, 70 eV)

163.1 (21), 183.1 (10), 221.1 (50), 222.1 (11), 231.1 (11), 247.1 (33), 261.2 (55), 262.2 (12), 273.2 (17), 287.2 (12), 315.2 (14), 341.2 (21), 356.2 (27), 357.3 (100), 358.3 (31), 446.1 (41), 447.2 (14), 550.4 (26), 551.4 (12).

Analysis: $C_{35}H_{54}OSSi$ (550.96)

Calcd: C, 76.30% H, 9.88%

Found: C, 76.05% H, 9.95%

TLC: R_f 0.20 (silica gel, hexanes/CH_2Cl_2, 90:10, UV/CAM or PMA)

HPLC: Analysis performed on de-silylated compound (±)-**33g**.

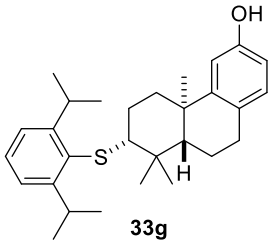
Data for (–)-**33f**:

HPLC: Conditions were not identified for separation of enantiomers of **33f**. After TBAF-mediated de-silylation to derivative (–)-**33g**, the e.r. was determined to be 93:7 using the same HPLC conditions developed to measure the e.r. of **33g** resulting from direct cyclization of **17g** (*vida infra*).

After recrystallization: 95:5 (measured on derivative (–)-**33g**).

Opt. Rot.: $[\alpha]_D^{25}$ –40.4 (*c* = 1.06 in $CHCl_3$) (90% ee)

Compound 33g



33g

Data for (±)-**33g**:

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

7.31 (t, *J* = 7.7 Hz, 1H, HC(21)), 7.16 (d, *J* = 7.7 Hz, 2H, HC(20)), 6.90 (d, *J* = 8.2 Hz, 1H, HC(17)), 6.61 (d, *J* = 2.6 Hz, 1H, HC(14)), 6.56 (dd, *J* = 8.2, 2.6 Hz, 1H, HC(16)), 4.38 (s, 1H, OH), 4.00 (hept, *J* = 6.9 Hz, 2H, HC(22)), 2.94-2.83 (m, 1H, $H_2C(11^{eq})$), 2.82-2.74 (m, 1H, $H_2C(11^{ax})$), 2.61 (dd, *J* = 12.5, 3.8 Hz, 1H, HC(4)), 2.13 (dt, *J* = 13.3, 3.4 Hz, 1H, $H_2C(6^{eq})$), 1.98-1.91 (m, 1H, $H_2C(10^{eq})$), 1.90-1.81 (m, 1H, $H_2C(5^{ax})$), 1.81-1.70 (m, 1H, $H_2C(10^{ax})$), 1.55 (dq, *J* = 13.5, 3.5 Hz, 1H, $H_2C(5^{eq})$), 1.38 (s, 3H, $H_3C(2)$), 1.35 (dd, *J* = 12.2, 2.0 Hz, 1H, HC(9)), 1.26 (d, *J* = 6.8 Hz, 6H, $H_3C(23)$), 1.26-1.22 (m, 1H, $H_2C(6^{ax})$), 1.20 (s, 3H, $H_3C(8)$), 1.18 (d, *J* = 6.9 Hz, 6H, $H_3C(23')$), 1.10 (s, 3H, $H_3C(1)$).

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

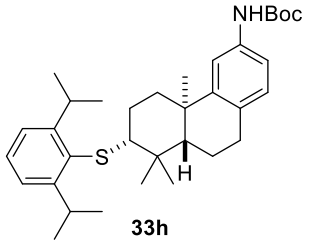
154.18 (C(19)), 153.59 (C(15)), 150.99 (C(13)), 130.92 (C(18)), 130.12 (HC(17)), 128.92 (HC(21)), 127.33 (C(12)), 123.71 (HC(20)), 112.97 (HC(16)), 111.06 (HC(14)), 61.80 (HC(4)), 52.40 (HC(9)), 39.25 ($H_2C(6)$), 39.05 (C(3)), 38.04 (C(7)), 31.50 (HC(22)), 30.05 ($H_2C(11)$), 29.78 ($H_3C(2)$), 26.19 ($H_2C(5)$), 25.04 ($H_3C(23')$), 24.86 ($H_3C(8)$), 24.13 ($H_3C(23)$), 19.79 ($H_2C(10)$), 17.77 ($H_3C(1)$).

HPLC: t_R 8.4 min (50%); t_R 15.8 min (50%) (Chiralpak IB-3, hexanes/*i*-PrOH, 95:5, 0.75 mL/min, 220 nm, 24 °C)

Data for (*enr*)-**33g**:

HPLC: t_R 8.3 min (9%); t_R 15.6 min (91%) (Chiralpak IB-3, hexanes/*i*-PrOH, 95:5, 0.75 mL/min, 220 nm, 24 °C)

Compound 33h



33h

Data for (±)-**33h**:

m.p.: 156-157 °C (methanol)

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

7.30 (t, *J* = 7.7 Hz, 1H, HC(24)), 7.21 (bs, 1H, HC(14)), 7.16 (d, *J* = 7.7 Hz, 2H, HC(23)), 7.01-6.96 (m, 1H, HC(16)), 6.94 (d, *J* = 8.2 Hz, 1H, HC(17)), 6.30 (bs, 1H, NH), 4.00 (hept, *J* = 6.8 Hz, 2H, HC(25)), 2.95-2.87 (m, 1H, $H_2C(11^{eq})$), 2.85-2.75 (m, 1H, $H_2C(11^{ax})$), 2.59 (dd, *J* = 12.5, 3.8 Hz, 1H, HC(4)), 2.26-2.16 (m, 1H, $H_2C(6^{eq})$), 1.99-1.91 (m, 1H, $H_2C(10^{eq})$), 1.86 (qd, *J* = 13.8, 3.3 Hz, 1H, $H_2C(5^{ax})$), 1.81-1.72 (m, 1H, $H_2C(10^{ax})$), 1.56 (dq, *J* = 13.5, 3.5 Hz, 1H, $H_2C(5^{eq})$), 1.48 (s, 9H, $H_3C(20)$), 1.38 (s, 3H, $H_3C(2)$), 1.34 (dd, *J* = 12.1, 2.0 Hz, 1H, HC(9)), 1.26 (d, *J* = 6.9 Hz, 6H, $H_3C(26)$), 1.26-1.23 (m, 1H, $H_2C(6^{ax})$), 1.21 (s, 3H, $H_3C(8)$), 1.18 (d, *J* = 6.9 Hz, 6H, $H_3C(26')$), 1.10 (s, 3H, $H_3C(1)$).

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

154.13 (C(22)), 152.93 (C(18)), 150.13 (C(13)), 136.16 (C(15)), 130.92 (C(21)), 129.86 (C(12)), 129.45 (HC(17)), 128.92 (HC(24)), 123.69 (HC(23)), 116.44 (HC(16)), 114.87 (HC(14)), 80.31 (C(19)), 61.93 (HC(4)), 52.43 (HC(9)), 39.26 ($H_2C(6)$), 39.05 (C(3)), 38.05 (C(7)), 31.48 (HC(25)), 30.18 ($H_2C(11)$), 29.78 ($H_3C(2)$), 28.51 ($H_3C(20)$), 26.12 ($H_2C(5)$), 25.04 ($H_3C(26')$), 24.85 ($H_3C(8)$), 24.13 ($H_3C(26)$), 19.69 ($H_2C(10)$), 17.77 ($H_3C(1)$).

IR: (neat)

3455 (w), 2965 (m), 1729 (m), 1705 (m), 1616 (w), 1586 (w), 1512 (m), 1461 (m), 1392 (m), 1366 (s), 1299 (w), 1222 (m), 1157 (s), 1054 (m), 1029 (w), 956 (w), 874 (w), 854 (w), 840 (w), 803 (m), 768 (w), 745 (w), 734 (w), 526 (m), 469 (w).

LRMS: (EI, 70 eV)

91.1 (14), 115.1 (16), 137.0 (31), 144.1 (16), 146.1 (21), 149.0 (18), 151.1 (20), 158.1 (19), 159.1 (15), 172.1 (14), 176.1 (13), 179.1 (63), 190.1 (39), 194.1 (82), 195.1 (14), 203.1 (27), 204.1 (15), 226.2 (13), 241.2 (30), 242.2 (40), 243.2 (38), 270.1 (22), 272.2 (14), 285.2 (52), 286.2 (40), 287.2 (100), 288.2 (25), 341.2 (21), 343.2 (28), 435.3 (39), 436.3 (14), 446.1 (28), 535.3 (19).

Analysis: $C_{34}H_{49}NO_2S$ (535.83)

Calcd: C, 76.21% H, 9.22% N, 2.61%

Found: C, 76.01% H, 9.23% N, 2.78%

TLC: R_f 0.56 (silica gel, hexanes/EtOAc, 80:20, UV/CAM or PMA)

HPLC: t_R 4.3 min (50%); t_R 12.4 min (50%) (Chiralpak IB-3, hexanes/*i*-PrOH, 90:10, 1.0 mL/min, 220 nm, 24 °C)

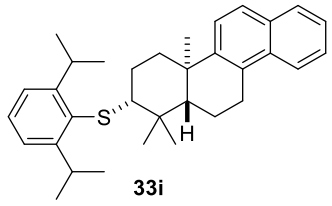
Data for (–)-**33h**:

HPLC: t_R 4.3 min (92%); t_R 12.6 min (8%) (Chiralpak IB-3, hexanes/*i*-PrOH, 90:10, 1.0 mL/min, 220 nm, 24 °C)

After recrystallization: t_R 4.3 min (93%); t_R 12.1 min (7%)

Opt. Rot.: $[\alpha]_D^{23}$ –61.8 (*c* = 1.30 in $CHCl_3$) (86% ee)

Compound 33i



33i

Data for (±)-**33i**:

m.p.: 199–201 °C (hexanes)

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

7.96 (d, *J* = 8.5 Hz, 1H, HC(20)), 7.77-7.73 (m, 1H, HC(17)), 7.63 (d, *J* = 8.8 Hz, 1H, HC(15)), 7.48 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H, HC(19)), 7.42 (ddd, *J* = 7.9, 6.9,

1.1 Hz, 1H, HC(18)), 7.36 (d, *J* = 8.8 Hz, 1H, HC(14)), 7.31 (t, *J* = 7.7 Hz, 1H, HC(25)), 7.17 (d, *J* = 7.7 Hz, 2H, HC(24)), 4.03 (hept, *J* = 6.8 Hz, 2H, HC(26)), 3.39 (dd, *J* = 17.3, 6.0 Hz, 1H, $H_2C(11^{eq})$), 3.15 (ddd, *J* = 17.7, 11.8, 7.5 Hz, 1H, $H_2C(11^{ax})$), 2.65 (dd, *J* = 12.6, 3.9 Hz, 1H, HC(4)), 2.34 (dt, *J* = 13.1, 3.4 Hz, 1H, $H_2C(6^{eq})$), 2.19 (dd, *J* = 13.2, 7.5 Hz, 1H, $H_2C(10^{eq})$), 2.01-1.93 (m, 1H, $H_2C(5^{ax})$), 1.92-1.85 (m, 1H, $H_2C(10^{ax})$), 1.61 (dq, *J* = 13.7, 3.6 Hz, 1H, $H_2C(5^{eq})$), 1.49 (dd, *J* = 12.3, 1.6 Hz, 1H, HC(9)), 1.45 (s, 3H, $H_3C(2)$), 1.33 (s, 3H, $H_3C(8)$), 1.27 (d, *J* = 6.9 Hz, 6H, $H_3C(27)$), 1.24 (dd, *J* = 13.5, 3.4 Hz, 1H, $H_2C(6^{ax})$), 1.18 (d, *J* = 6.9 Hz, 6H, $H_3C(27')$),1.16 (s, 3H, $H_3C(1)$).

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

154.17 (C(23)), 146.14 (C(13)), 132.30 (C(21)), 131.67 (C(16)), 130.95 (C(22)), 129.63 (C(12)), 128.92 (HC(25)), 128.27 (HC(17)), 126.50 (HC(15)), 126.06 (HC(19)), 125.14 (HC(18)), 123.71 (HC(24)), 123.38 (HC(14)), 123.31 (HC(20)), 61.83 (HC(4)), 52.64 (HC(9)), 39.50 ($H_2C(6)$), 39.00 (C(3)), 38.33 (C(7)), 31.50 (HC(26)), 29.79 ($H_3C(2)$), 28.17 ($H_2C(11)$), 26.33 ($H_2C(5)$), 25.03 ($H_3C(27')$), 24.43 ($H_3C(8)$), 24.15 ($H_3C(27)$), 19.57 ($H_2C(10)$), 17.77 ($H_3C(1)$).

IR: (neat)

3051 (w), 2944 (w), 2863 (w), 1572 (w), 1508 (w), 1458 (m), 1436 (w), 1382 (w), 1362 (w), 1302 (w), 1201 (w), 1173 (w), 1158 (w), 1048 (w), 1037 (w), 991 (w), 974 (w), 956 (w), 923 (w), 883 (w), 858 (w), 806 (s), 778 (w), 744 (s), 688 (w), 668 (w), 618 (w), 544 (w), 529 (w).

LRMS: (EI, 70 eV)

69.1 (13), 141.1 (16), 149.0 (10), 151.1 (14), 165.1 (16), 167.1 (35), 178.1 (20), 179.1 (33), 181.1 (60), 191.1 (12), 192.1 (12), 193.1 (49), 194.1 (24), 195.1 (14), 207.1 (29), 221.1 (11), 261.2 (27), 276.2 (25), 277.2 (100), 278.2 (25), 470.3 (68), 471.3 (26).

Analysis: $C_{33}H_{42}S$ (470.76)

Calcd: C, 84.20% H, 8.99%

Found: C, 84.37% H, 9.18%

TLC: R_f 0.26 (silica gel, hexanes/CH_2Cl_2, 90:10, UV/CAM or PMA)

HPLC: t_R 3.5 min (50%); t_R 4.4 min (50%) (Supelco Astec, hexanes/*i*-PrOH, 95:5, 1.0 mL/min, 254 nm, 24 °C)

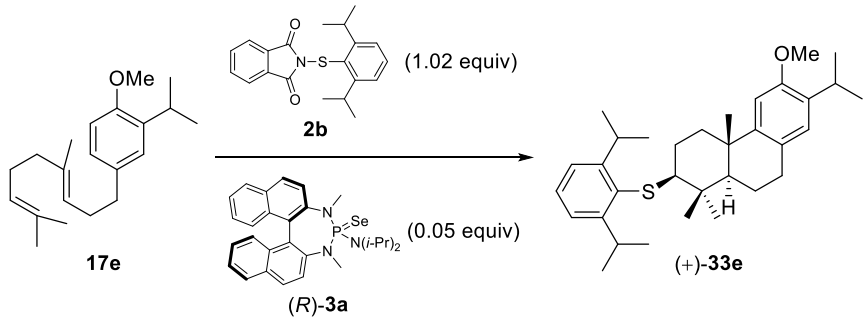
Data for (+)-**33i**:

HPLC: t_R 3.5 min (92%); t_R 4.5 min (8%) (Supelco Astec, hexanes/*i*-PrOH, 95:5, 1.0 mL/min, 254 nm, 24 °C)

After trituration: t_R 3.5 min (92%); t_R 4.5 min (8%)

Opt. Rot.: $[\alpha]_D^{25}$ +69.8 (*c* = 1.29 in $CHCl_3$) (84% ee)

Large Scale Preparation of (+)-33e



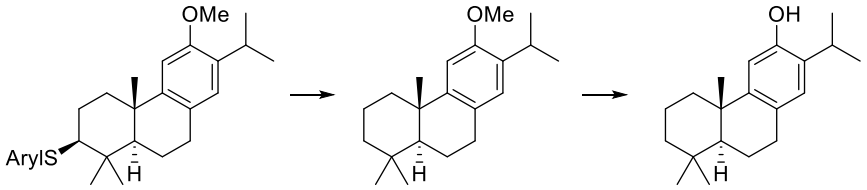
A 250-mL, round-bottomed flask equipped with a stir bar and argon inlet adapter was charged with *N*-(2,6-diisopropylphenylthio)phthalimide **2b** (1.0416 g, 3.07 mmol, 1.02 equiv), hexafluoroisopropyl alcohol (30 mL, 0.1 M), and (*E*)-4-(4,8-dimethylnona-3,7-dien-1-yl)-2-isopropyl-1-methoxybenzene **17e** (901.9 mg, 3.00 mmol). A homogeneous, yellow solution resulted. Catalyst (*R*)-**3a** (78.0 mg, 0.15 mmol, 0.05 equiv, e.r. = 97:3) was added in one portion and the mixture was stirred at 25 °C for 12 h. Full conversion was observed by TLC (hexanes/CH_2Cl_2, 90:10). The reaction mixture was diluted with CH_2Cl_2 (30 mL), and the volatiles were removed by rotary evaporation (30 °C, 15 mmHg) to afford crude (+)-**33e**. The crude product was purified by column chromatography (silica gel, 5 x 20 cm, dry load on Celite, 50-mL fractions, hexanes/CH_2Cl_2 gradient elution, 95:5 (500 mL) to 90:10 (500 mL) to 85:15 (500 mL) to 80:20 (500 mL) to 75:15 (500 mL)) to afford (+)-**33e** (1.2321 g, 83%) as a white foam solid. The solid contained trace impurities which cannot be removed by chromatography. The compound was

dissolved in a minimal amount of boiling abs. ethanol (9 mL) and the solution was allowed to cool slowly to 25 °C, followed by cooling in a –20 °C freezer for 12 h. The product was collected by vacuum filtration and rinsed with ice-cold hexanes (2 mL) to afford 820.8 (55%) of (+)-**33e** as white crystals. Spectroscopic data matched those reported for (–)-**33e**. Enantiomeric ratio was determined on derivative (+)-**46**. A second crop was obtained in the following manner. The mother liquor was concentrated (30 °C, 15 mmHg) and subjected to column chromatography (silica gel, 3 x 25 cm, dry load on Celite, 25-mL fractions, hexanes/CH_2Cl_2 gradient elution, 95:5 (300 mL) to 90:10 (300 mL) to 85:15 (300 mL) to 80:20 (300 mL)) to afford 257.4 mg of (+)-**33e**. The solid was recrystallized from ethanol (1 mL) as described previously to afford 108.9 mg (8%) of (+)-**33e**.

Data for (+)-**33e**:

HPLC: Conditions were not identified for separation of enantiomers of **33e**. After oxidation to sulfoxide (+)-**46**, the e.r. was determined to be 91:9.
After recrystallization: 90:10 (measured on derivative (+)-**46**).

Total Synthesis of (+)-**Ferruginol (**(+)-**43)**



Preparation of (+)-**45**

A flame-dried, 25-mL, Schlenk flask equipped with a glass-coated stir bar was charged with lithium granules (21 mg, 3.0 mmol, 5.7 equiv) inside a glove box. The flask was removed from the glove box, placed under argon, and charged with THF (7.5 mL). The flask was fitted with a temperature probe and the mixture was cooled to an internal temperature of -50 °C (using a Cryo-Cool) and stirred for 1 h. *N*,*N*-Dimethyl-1-aminonaphthalene (495 μL, 3.0 mmol, 5.7 equiv) was added dropwise over 10 min. [**Notes:** This viscous amine should be added directly into the solution rather than dripped down the side of the flask, as it tends to adhere to the chilled walls of the flask.

Also, if added too quickly, the amine may gel at the bottom of the flask and cause the stir bar to stick. If either of these problems are encountered, gently swirl the flask (while still submerged in the cold bath) until the amine is solubilized.] The resulting solution was allowed to stir for 12 h at -50 °C. Generally within 1 h, a dark-green color is observed, but it takes several hours for the reagent to fully form. The temperature must be maintained at -50 °C or lower to prevent decomposition of the reagent (signaled by the solution turning brown). To the dark-green solution, sulfide (+)-**33e** (260.4 mg, 0.53 mmol) was added portionwise as a solid over 5-10 min. No change in solution color was observed. After addition, the walls of the flask were rinsed down (slowly, over 5 min) with THF (1.5 mL). The solution was stirred at -50 °C for 1 h, at which point full conversion was observed by TLC (hexanes/CH_2Cl_2, 90:10). The reaction was quenched by the addition of methanol (1 mL) which caused the dark green color to immediately discharge. The cold bath was removed, and the clear, pale-yellow solution was allowed to warm to 25 °C. The mixture was partitioned between aq. 1 N HCl (25 mL) and diethyl ether (25 mL) in a 125-mL separatory funnel and the layers were separated. The aqueous phase was extracted with diethyl ether (2 x 25 mL) and the combined organic extracts were washed with brine (25 mL), dried over sodium sulfate, filtered, and concentrated (30 °C, 15 mmHg) to afford crude (+)-**45** (304.1 mg) as a yellow oil. [**Note:** It is not necessary in this case to oxidize the thiol to remove it from the crude mixture. The thiol is easily separated from the desired product by chromatography.] The product was purified by chromatography (silica gel, 3 x 20 cm, dry load on Celite, 25-mL fractions, hexanes/CH_2Cl_2 gradient elution: 100:0 (300 mL) to 97.5:2.5 (300 mL) to 95:5 (300 mL) to 92.5:7.5 (300 mL)) which was then dried under high vacuum for 12 h (45 °C, 0.1 mmHg) to afford 145.3 mg (92%) of (+)-**45** as a clear, colorless, highly viscous oil. The spectroscopic data for (+)-**45** matched those reported previously.[229]

Data for (+)-**45**:

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

6.84 (s, 1H, HC(17)), 6.72 (s, 1H, HC(14)), 3.79 (s, 3H, $H_3C(18)$), 3.22 (hept, J = 6.9 Hz, 1H, HC(19)), 2.91-2.83 (m, 1H, $H_2C(11^{eq})$), 2.82-2.73 (m, 1H, $H_2C(11^{ax})$), 2.30-2.20 (m, 1H, $H_2C(6^{eq})$), 1.86 (ddt, J = 10.9, 7.2, 1.8 Hz, 1H, $H_2C(10^{eq})$), 1.82-1.71 (m, 1H, $H_2C(5^{ax})$), 1.71-1.63 (m, 1H, $H_2C(10^{ax})$), 1.60 (dq, J = 14.0, 3.6 Hz, 1H, $H_2C(5^{eq})$), 1.51-1.46 (m, 1H, $H_2C(4^{eq})$), 1.46-1.39 (m, 1H, $H_2C(6^{ax})$), 1.34 (dd, J = 12.4, 2.2 Hz, 1H, HC(9)), 1.23 (dd, J = 13.6, 4.1 Hz, 1H,

$H_2C(4^{ax})$), 1.20 (s, 3H, $H_3C(8)$), 1.19 (d, J = 7.0 Hz, 3H, $H_3C(20)$), 1.18 (d, J = 7.0 Hz, 3H, $H_3C(20')$), 0.94 (s, 3H, $H_3C(2)$), 0.93 (s, 3H, $H_3C(1)$).

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

155.14 (C(15)), 148.23 (C(13)), 134.27 (C(16)), 127.03 (C(12)), 126.52 (HC(17)), 106.71 (HC(14)), 55.74 ($H_3C(18)$), 50.64 (HC(9)), 41.86 ($H_2C(4)$), 39.08 ($H_2C(6)$), 38.00 (C(7)), 33.62 (C(3)), 33.49 ($H_3C(2)$), 29.98 ($H_2C(11)$), 26.59 (HC(19)), 24.97 ($H_3C(8)$), 23.06 ($H_3C(20')$), 22.85 ($H_3C(20)$), 21.78 ($H_3C(1)$), 19.51 ($H_2C(5)$), 19.39 ($H_2C(10)$).

Opt. Rot.: $[\alpha]_D^{25}$ +49.1 (c = 1.38 in $CHCl_3$) (80% ee)

Synthesis of (+)-**Ferruginol (**(+)-**43)**

A solution of boron tribromide in CH_2Cl_2 (1 M) was prepared as follows. A flame-dried, 10-mL, Schlenk flask equipped with a stir bar was charged with CH_2Cl_2 (5 mL) and cooled to –78 °C using a dry ice/acetone bath. Boron tribromide (482 μL, 5 mmol) was injected quickly in one portion at –78 °C. The cold bath was removed and the solution was allowed to warm to 25 °C and then used immediately.

A flame-dried, 25-mL, Schlenk flask equipped with a stir bar was charged with a solution of (+)-**45** (102.1 mg, 0.34 mmol, 90:10 e.r.) in CH_2Cl_2 (8 mL). The pale, yellow solution was cooled to –10 °C using an ice/salt bath. Freshly prepared BBr_3 solution (3.4 mL, 1.0 M, 3.4 mmol, 10 equiv) was added dropwise over 10 min. The resulting darker, yellow solution was stirred for 3 h and allowed to warm slowly to 0 °C. Incomplete conversion was observed by TLC (hexanes/EtOAc, 90:10). An additional portion of BBr_3 solution (1.6 mL, 1.0 M, 1.6 mmol, 5 equiv) was added dropwise at 0 °C and the reaction was stirred for an additional 3 h at 0 °C. An orange solution was observed. Full conversion was observed by TLC. The reaction was quenched by the addition of water (10 mL). The resulting grey suspension was poured into a 125-mL separatory funnel. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (25 mL), and then dried over sodium sulfate, filtered, and concentrated (30 °C, 15 mmHg) to afford crude (+)-**43** (119.1 mg). The product was purified by column chromatography (silica gel, 2 x 15 cm, dry load on Celite, 10-mL fractions, hexanes/EtOAc gradient elution, 98:2 (200 mL) to 96:4 (200 mL) to 94:6 (200 mL)

to 92:8 (200 mL)) and dried under vacuum (60 °C, 0.1 mmHg, 12 h) to afford 88.6 mg (91%) of (+)-**43** as a beige solid. Spectroscopic data for (+)-**43** matched those previously reported.[229]

Data for (+)-**43**:

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

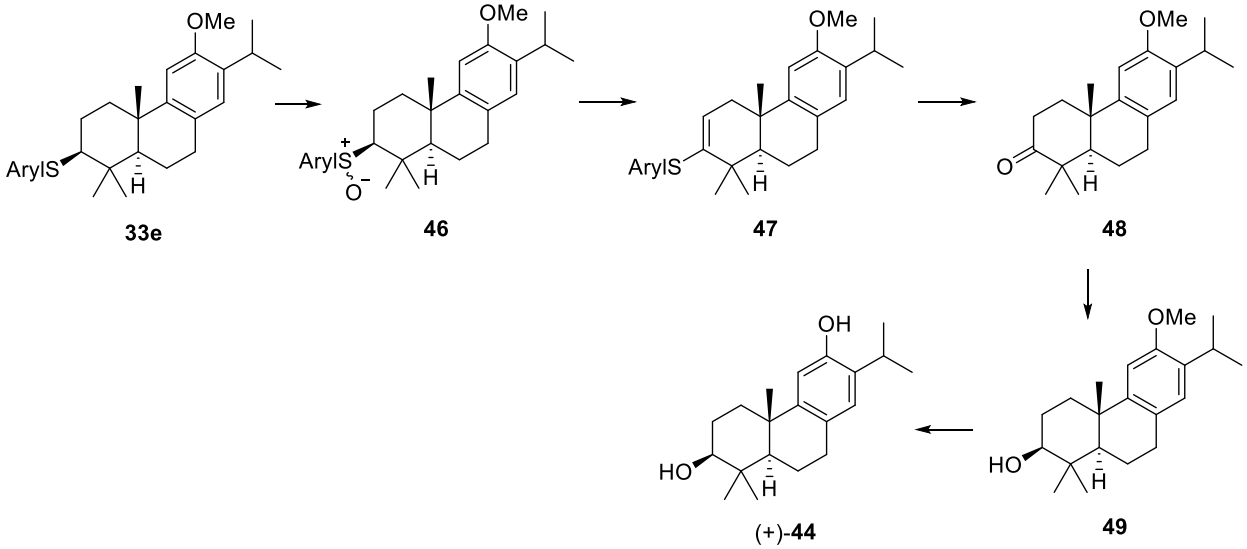
6.83 (s, 1H, HC(17)), 6.63 (s, 1H, HC(14)), 4.42 (s, 1H, OH), 3.11 (hept, *J* = 6.9 Hz, 1H, HC(18)), 2.91-2.82 (m, 1H, $H_2C(11^{eq})$), 2.81-2.72 (m, 1H, $H_2C(11^{ax})$), 2.17 (dtd, *J* = 12.6, 3.3, 1.3 Hz, 1H, $H_2C(6^{eq})$), 1.86 (ddt, *J* = 12.7, 7.3, 1.8 Hz, 1H, $H_2C(10^{eq})$), 1.78-1.70 (m, 1H, $H_2C(5^{ax})$), 1.69-1.62 (m, 1H, $H_2C(10^{ax})$), 1.62-1.55 (m, 1H, $H_2C(5^{eq})$), 1.47 (dtd, *J* = 13.2, 3.2, 1.6 Hz, 1H, $H_2C(4^{eq})$), 1.38 (td, *J* = 13.0, 3.6 Hz, 1H, $H_2C(6^{ax})$), 1.32 (dd, *J* = 12.4, 2.3 Hz, 1H, HC(9)), 1.24 (d, *J* = 6.9 Hz, 3H, $H_3C(19)$), 1.23 (d, *J* = 6.9 Hz, 3H, $H_3C(19')$), 1.23-1.19 (m, 1H, $H_2C(4^{ax})$), 1.17 (s, 3H, $H_3C(8)$), 0.94 (s, 3H, $H_3C(2)$), 0.92 (s, 3H, $H_3C(1)$).

^{13}C NMR: (126 MHz, CDCl3)

150.78 (C(15)), 148.83 (C(13)), 131.48 (C(16)), 127.47 (C(12)), 126.77 (HC(17)), 111.11 (HC(14)), 50.50 (HC(9)), 41.84 ($H_2C(4)$), 39.02 ($H_2C(6)$), 37.66 (C(7)), 33.59 (C(3)), 33.47 ($H_3C(2)$), 29.91 ($H_2C(11)$), 26.97 (HC(18)), 24.95 ($H_3C(8)$), 22.89 ($H_3C(19')$), 22.71 ($H_3C(19)$), 21.78 ($H_3C(1)$), 19.47 ($H_2C(5)$), 19.38 ($H_2C(10)$).

Opt. Rot.: $[\alpha]_D^{25}$ +41.5 (*c* = 0.98 in $CHCl_3$) (80% ee)

Total Synthesis of (+)-**Hinokiol (**(+)-**44)**



Preparation of (+)-**46**

A 200-mL, round-bottomed flask equipped with a stir bar and argon inlet was charged with sulfide (+)-**33e** (502.2 mg, 1.02 mmol) and hexafluoroisopropanol (20 mL). The mixture was sonicated for 2 min until a fine, white suspension was observed. Hydrogen peroxide (aq., 30% w/w, 0.19 mL, 0.21 g, 1.8 equiv) was added dropwise at 23 °C. The white suspension was stirred at 25 °C for 2.5 h, over which time the suspension cleared to a nearly colorless solution. Full conversion was observed by TLC (hexanes/EtOAc, 9:1). The reaction was quenched by the addition of sat. aq. sodium thiosulfate (5 mL) and was stirred vigorously for 5 min. The majority of the HFIP was removed by rotary evaporation (30 °C, 15 mmHg). The residue was diluted with water (30 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate, filtered, and concentrated (30 °C, 15 mmHg) to afford crude (*enr*)-**46** as a white foam solid. The product was purified by chromatography (silica gel, 3 cm x 15 cm, dry load on Celite, 25 mL fractions, hexanes/EtOAc gradient elution: 19:1 (500 mL) to 9:1 (500 mL) to 5.67:1 (500 mL) to 4:1 (500 mL)). Since both diastereomers of (*enr*)-**46** are competent in the Pummerer rearrangement, the fractions were combined, but prior to pooling the chromatography fractions, a small sample was removed from an early fraction (containing only major diastereomer) for HPLC analysis. After solvent removal, the combined yield of both diastereomers was 545.0 mg (>100%). The product was again chromatographed (silica gel, 3 cm

x 15 cm, dry load on Celite, 25 mL fractions, hexanes/Et_2O gradient elution: 9:1 (300 mL) to 4:1 (300 mL) to 2.33:1 (300 mL) to 1.5:1 (300 mL)) to afford 494.3 mg (95%) of (*enr*)-**46** as a fluffy white foam solid. The d.r. of the isolated solid was 65:35 (measured by ^{1}H NMR integration). A racemic sample of **46** was obtained by a similar procedure, beginning with (±)-**33e**. Analytically pure samples of (±)-**46** were obtained by chromatography and recrystallization.

Data for (±)-**46** (major diastereomer):

m.p.: 188–190 °C

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

7.40 (t, *J* = 7.8 Hz, 1H, HC(24)), 7.30 (dd, *J* = 7.8, 1.2 Hz, 1H, HC(23a)), 7.17 (dd, *J* = 7.8, 1.2 Hz, HC(23b)), 6.86 (s, 1H, HC(17)), 6.58 (s, 1H, HC(14)), 4.40 (hept, *J* = 6.7 Hz, 1H, HC(25a)), 3.71 (s, 3H, H_3C(18)), 3.64 (hept, *J* = 6.9 Hz, 1H, HC(25b)), 3.27 (dd, *J* = 13.2, 3.6 Hz, 1H, HC(4)), 3.20 (hept, *J* = 6.9 Hz, 1H, HC(19)), 2.96-2.87 (m, 1H, $H_2C(11^{eq})$), 2.85-2.76 (m, 1H, $H_2C(11^{ax})$), 2.25 (dt, *J* = 12.9, 3.4 Hz, 1H, $H_2C(6^{eq})$), 2.08-2.00 (m, 1H, $H_2C(10^{eq})$), 1.72 (qd, *J* = 12.1, 6.4 Hz, 1H, $H_2C(10^{ax})$), 1.59 (qd, *J* = 13.3, 3.3 Hz, 1H, $H_2C(5^{ax})$), 1.56 (s, 3H, H_3C(2)), 1.47 (dd, *J* = 12.0, 1.5 Hz, 1H, HC(9)), 1.42 (td, *J* = 13.3, 3.3 Hz, 1H, $H_2C(6^{ax})$), 1.36 (s, 3H, H_3C(1)), 1.30 (d, *J* = 6.5 Hz, 3H, H_3C(26b)), 1.29 (d, *J* = 6.5 Hz, 3H, H_3C(26a)), 1.27 (d, *J* = 6.5 Hz, 3H, H_3C(26b')), 1.23 (d, *J* = 6.5 Hz, 3H, H_3C(26a')), 1.22 (s, 3H, H_3C(8)), 1.18 (d, *J* = 7.0 Hz, 3H, H_3C(20)), 1.19-1.14 (m, 1H, $H_2C(5^{eq})$), 1.16 (d, *J* = 7.0 Hz, 3H, H_3C(20')).

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

155.27 (C(15)), 151.85 (C(22a)), 149.69 (C(22b)), 146.63 (C(13)), 136.89 (C(21)), 134.90 (C(16)), 131.67 (HC(24)), 126.92 (HC(23a)), 126.77 (C(12)), 126.65 (HC(17)), 123.40 (HC(23b)), 106.37 (HC(14)), 70.92 (HC(4)), 55.60 (H_3C(18)), 53.12 (HC(9)), 39.16 (C(3)), 38.51 (H_2C(6)), 37.59 (C(7)), 30.31 (H_2C(11)), 30.18 (H_3C(2)), 29.61 (HC(25b)), 27.76 (HC(25a)), 26.60 (HC(19)), 25.66 (H_3C(26b)), 25.24 (H_3C(26a)), 24.74 (H_3C(26a')), 24.20 (H_3C(8)), 22.99 (H_3C(20')), 22.89 (H_3C(26b')), 22.79 (H_3C(20)), 21.12 (H_2C(5)), 18.66 (H_2C(10)), 17.75 (H_3C(1)).

IR: (neat)

2949 (m), 1614 (w), 1579 (w), 1500 (m), 1459 (m), 1382 (w), 1361 (w), 1328 (w), 1309 (w), 1254 (m), 1234 (m), 1200 (w), 1164 (w), 1119 (w), 1043 (m), 1027 (s),

974 (w), 883 (w), 840 (w), 801 (m), 733 (w), 716 (w), 681 (w), 620 (w), 504 (w), 476 (w).

LRMS: (ESI, $[M+H]^+$)

299.1 (16), 300.1 (3), 509.2 (100), 510.2 (36), 511.3 (11), 609.2 (2), 610.3 (5), 611.3 (2), 611.5 (2), 638.3 (12), 639.3 (5), 790.4 (3), 791.4 (2).

Analysis: $C_{33}H_{48}O_2S$ (508.81)

Calcd: C, 77.90% H, 9.51%

Found: C, 77.80% H, 9.55%

TLC: R_f 0.40 (silica gel, hexanes/diethyl ether, 50:50, UV/CAM)

HPLC: t_R 11.0 min (50%); t_R 13.2 min (50%) (Whelk, hexanes/*i*-PrOH, 95:5, 0.8 mL/min, 220 nm, 24 °C)

Data for (±)-**46** (minor diastereomer):

Note: Some NMR signals are not well resolved at 23 °C, so ^{1}H and ^{13}C spectra were also collected at -50 °C. Both data sets are reported below.

m.p.: 163–165 °C

^{1}H NMR: (500 MHz, $CDCl_3$, 23 °C)

7.37 (t, *J* = 7.7 Hz, 1H, HC(24)), 7.22 (bs, 2H, HC(23a) and HC(23b)), 6.84 (s, 1H, HC(17)), 6.68 (s, 1H, HC(14)), 4.61 (bs, 1H, HC(25a)), 3.76 (s, 3H, H_3C(18)), 3.38 (bs, 1H, HC(25b)), 3.21 (hept, *J* = 6.9 Hz, 1H, HC(19)), 2.91 (dd, *J* = 16.7, 5.6 Hz, 1H, $H_2C(11^{eq})$), 2.82-2.73 (m, 1H, $H_2C(11^{ax})$), 2.55-2.48 (m, 2H, HC(4) and $H_2C(6^{eq})$), 2.42 (qd, *J* = 13.3, 3.4 Hz, 1H, $H_2C(5^{ax})$), 2.12 (dq, *J* = 13.5, 3.3 Hz, 1H, $H_2C(5^{eq})$), 1.97-1.89 (m, 1H, $H_2C(10^{eq})$), 1.77 (qd, *J* = 12.2, 6.4 Hz, 1H, $H_2C(10^{ax})$), 1.51 (td, *J* = 13.1, 3.5 Hz, 1H, $H_2C(6^{ax})$), 1.40 (dd, *J* = 12.0, 1.7 Hz, 1H, HC(9)), 1.30 (bd, 6H, H_3C(26a) and H_3C(26a')), 1.29 (s, 3H, H_3C(8)), 1.27 (s, 6H, H_3C(1) and H_3C(2)), 1.22 (bd, *J* = 5.0 Hz, 6H, H_3C(26b) and H_3C(26b')), 1.18 (d, *J* = 7.0 Hz, 3H, H_3C(20)), 1.16 (d, *J* = 7.0 Hz, 3H, H_3C(20')).

(600 MHz, $CDCl_3$, -50 °C)

7.40 (t, *J* = 7.7 Hz, 1H, HC(24)), 7.32 (d, *J* = 7.2 Hz, 1H, HC(23a)), 7.15 (d, *J* = 7.2 Hz, 1H, HC(23b)), 6.89 (s, 1H, HC(17)), 6.68 (s, 1H, HC(14)), 4.55 (hept, *J* = 6.5 Hz, 1H, HC(25a)), 3.76 (s, 3H, H_3C(18)), 3.24 (hept, *J* = 6.5 Hz, 1H, HC(25b)),

3.17 (hept, J = 6.9 Hz, 1H, HC(19)), 2.91 (dd, J = 16.7, 5.6 Hz, 1H, $H_2C(11^{eq})$), 2.81-2.71 (m, 1H, $H_2C(11^{ax})$), 2.56-2.49 (m, 1H, $H_2C(6^{eq})$), 2.48-2.37 (m, 2H, HC(4) and $H_2C(5^{ax})$), 2.11-2.02 (m, 1H, $H_2C(5^{eq})$), 1.94-1.90 (m, 1H, $H_2C(10^{eq})$), 1.74 (qd, J = 12.3, 5.7 Hz, 1H, $H_2C(10^{ax})$), 1.55-1.44 (m, 1H, $H_2C(6^{ax})$), 1.41 (d, J = 11.6 Hz, 1H, HC(9)), 1.30 (d, 3H, H_3C(26a)), 1.30 (s, 3H, H_3C(2)), 1.28 (s, 3H, H_3C(8)), 1.23 (s, 3H, H_3C(1)), 1.25-1.19 (m, 6H, H_3C(26a') and H_3C(26b)), 1.17 (d, J = 6.9 Hz, 3H, H_3C(20)), 1.13 (d, J = 7.0 Hz, 3H, H_3C(20')), 1.11 (d, J = 7.0 Hz, 3H, H_3C(26b')).

^{13}C NMR: (126 MHz, $CDCl_3$, 23 °C)

155.33 (C(15)), 146.94 (C(13)), 136.07 (C(21)), 134.79 (C(16)), 131.02 (HC(24)), 126.49 (C(12) and HC(17)), 106.54 (HC(14)), 73.26 (HC(4)), 55.68 (H_3C(18)), 52.86 (HC(9)), 38.82 (H_2C(6) or C(3)), 38.80 (H_2C(6) or C(3)), 37.90 (C(7)), 30.48 (H_3C(2)), 30.21 (H_2C(11)), 26.58 (HC(19)), 24.81 (H_3C(8)), 22.97 (H_3C(20')), 22.80 (H_3C(20)), 19.21 (H_2C(10)), 18.91 (H_3C(1)), 16.81 (H_2C(5)).

(151 MHz, $CDCl_3$, -50 °C)

154.65 (C(15)), 152.15 (C(22a)), 146.57 (C(22b) and C(13)), 134.76 (C(21)), 134.19 (C(16)), 130.94 (HC(24)), 126.47 (HC(23a)), 126.11 (HC(17) and C(12)), 124.05 (HC(23b)), 105.68 (HC(14)), 72.47 (HC(4)), 55.29 (H_3C(18)), 52.13 (HC(9)), 38.56 (C(3)), 38.14 (H_2C(6)), 37.58 (C(7)), 30.40 (H_3C(2)), 30.08 (H_2C(11)), 28.17 (HC(25b)), 26.65 (HC(25a)), 26.42 (H_3C(26a')), 26.03 (HC(19)), 25.05 (H_3C(26b)), 24.74 (H_3C(8)), 22.96 (H_3C(20')), 22.93 (H_3C(26a)), 22.84 (H_3C(26b')), 22.54 (H_3C(20)), 18.86 (H_2C(10) or H_3C(1)), 18.83 (H_2C(10) or H_3C(1)), 16.07 (H_2C(5)).

IR: (neat)

2964 (m), 1613 (w), 1577 (w), 1498 (s), 1463 (s), 1395 (w), 1373 (m), 1360 (m), 1328 (m), 1254 (m), 1235 (s), 1196 (m), 1166 (w), 1120 (w), 1101 (w), 1078 (s), 1067 (s), 1044 (s), 1000 (w), 969 (m), 892 (m), 880 (w), 844 (m), 800 (s), 768 (w), 745 (s), 618 (w), 573 (w), 540 (m), 477 (m).

LRMS: (ESI, $[M+H]^+$)
163.1 (2), 189.1 (2), 203.1 (12), 204.2 (2), 215.1 (4), 229.2 (2), 243.2 (2), 257.2 (8), 258.2 (2), 297.2 (4), 298.2 (3), 299.2 (100), 300.2 (48), 301.2 (8), 313.2 (7), 314.2 (2), 355.2 (4), 491.3 (2), 509.3 (88), 510.4 (41), 511.4 (14), 512.4 (3), 531.3 (3).

Analysis: $C_{33}H_{48}O_2S$ (508.81)
Calcd: C, 77.90% H, 9.51%
Found: C, 78.03% H, 9.69%

TLC: R_f 0.35 (silica gel, hexanes/diethyl ether, 50:50, UV/CAM)

Data for (*enr*)-**46**:

d.r.: 65:35

HPLC: (measured on major diastereomer)
From chromatographed (+)-**33e**: t_R 11.3 min (9%); t_R 13.5 min (91%) (Regis (*R*,*R*)-Whelk O1, hexanes/*i*-PrOH, 95:5, 0.8 mL/min, 220 nm, 24 °C)
From recrystallized (+)-**33e**: t_R 11.3 min (10%); t_R 13.4 min (90%)

Preparation of (+)-**47**

A flame-dried, 10-mL, Schlenk flask equipped with a stir bar was charged with sulfoxide (+)-**46** (460.3 mg, 0.90 mmol, mixture of diastereomers). Acetonitrile (4.0 mL) was added, resulting in a thin, white suspension. [**Note:** If needed, the suspension may be sonicated for 1 min to achieve a fine consistency.] To the flask was added 2,6-lutidine (0.32 mL, 291 mg, 2.71 mmol, 3.0 equiv) in one portion at 25 °C resulting in a pale-yellow suspension. Trifluoroacetic anhydride (0.38 mL, 570 mg, 2.71 mmol, 3.0 equiv) was added dropwise over 30 sec at 25 °C resulting in a bright-yellow suspension. Some thick, white vapor was observed in the headspace of the flask. The mixture was heated to 45 °C (pre-warmed oil bath) and was maintained at this temperature for 10 min. Within 1 min, a yellow solution was observed, which reverted to a thin, yellow suspension over time. Full conversion was observed by TLC (hexanes/EtOAc, 90:10). The mixture was cooled to 25 °C and transferred to a 100-mL recovery flask with CH_2Cl_2 (10 mL). The volatiles were removed by rotary evaporation (30 °C, 15 mmHg). The crude residue was directly subjected to chromatography (silica gel, 3 x 20 cm, dry load on Celite, 25-mL fractions, hexanes/CH_2Cl_2

gradient elution: 95:5 (300 mL) to 90:10 (300 mL) to 85:15 (300 mL) to 80:20 (300 mL)) to afford 415.6 mg (94%) of (+)-**47** as a white solid. A racemic sample of **47** was obtained by a similar procedure, beginning with (±)-**46** (as a mixture of diastereomers). An analytically pure sample of (±)-**47** was obtained by precipitation from ethanol.

Data for (±)-**47**:

m.p.: 114–116 °C (ethanol)

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

7.37 (t, *J* = 7.7 Hz, 1H, HC(24)), 7.22 (d, *J* = 7.7 Hz, 2H, HC(23)), 6.84 (s, 1H, HC(17)), 6.60 (s, 1H, HC(14)), 4.54 (dd, *J* = 6.7, 2.1 Hz, 1H, HC(5)), 3.72 (hept, *J* = 6.8 Hz, 2H, HC(25)), 3.72 (s, 3H, $H_3C(18)$), 3.20 (hept, *J* = 6.9 Hz, 1H, HC(19)), 2.91-2.82 (m, 1H, $H_2C(11^{eq})$), 2.81-2.69 (m, 1H, $H_2C(11^{ax})$), 2.39 (dd, *J* = 16.7, 6.7 Hz, 1H, $H_2C(6^{eq})$), 2.11-2.00 (m, 1H, $H_2C(6^{ax})$), 1.95-1.83 (m, 1H, $H_2C(10^{eq})$), 1.76-1.65 (m, 2H, $H_2C(10^{ax})$ and HC(9)), 1.39 (s, 3H, $H_3C(2)$), 1.32 (s, 3H, $H_3C(1)$), 1.23 (s, 3H, $H_3C(8)$), 1.22 (d, *J* = 7.0 Hz, 6H, $H_3C(26)$), 1.20 (d, *J* = 6.5 Hz, 6H, $H_3C(26')$), 1.19 (d, *J* = 7.0 Hz, 3H, $H_3C(20)$), 1.16 (d, *J* = 6.9 Hz, 3H, $H_3C(20')$).

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

155.41 (C(15)), 154.31 (C(22)), 145.47 (C(13)), 144.73 (C(4)), 134.71 (C(16)), 129.74 (HC(24)), 128.79 (C(21)), 127.19 (C(12)), 126.28 (HC(17)), 123.91 (HC(23)), 115.01 (HC(5)), 107.71 (HC(14)), 55.60 ($H_3C(18)$), 50.45 (HC(9)), 41.40 ($H_2C(6)$), 39.73 (C(3)), 36.94 (C(7)), 31.71 (HC(25)), 30.91 ($H_2C(11)$), 30.85 ($H_3C(2)$), 26.62 (HC(19)), 24.88 ($H_3C(8)$), 24.51 ($H_3C(26)$ or $H_3C(26')$), 24.42 ($H_3C(26)$ or $H_3C(26')$), 23.00 ($H_3C(20)$ or $H_3C(20')$), 22.80 ($H_3C(20)$ or $H_3C(20')$), 21.24 ($H_3C(1)$), 20.89 ($H_2C(10)$).

IR: (neat)

2958 (s), 2863 (m), 1615 (w), 1576 (w), 1501 (s), 1464 (s), 1406 (w), 1373 (m), 1357 (m), 1323 (m), 1247 (s), 1205 (m), 1166 (m), 1122 (w), 1102 (m), 1073 (m), 1053 (s), 954 (m), 922 (m), 881 (m), 850 (m), 795 (s), 743 (s), 686 (w), 559 (w), 480 (w).

LRMS: (EI, 70 eV)

149.0 (18), 189.1 (54), 201.1 (31), 203.1 (25), 216.2 (49), 217.2 (17), 231.1 (49), 232.1 (10), 259.2 (100), 260.2 (33), 446.1 (26), 490.3 (43), 491.3 (16).

Analysis: $C_{33}H_{46}OS$ (490.79)

Calcd: C, 80.76% H, 9.45%

Found: C, 80.51% H, 9.63%

TLC: R_f 0.19 (silica gel, hexanes/CH_2Cl_2, 90:10, UV/CAM)

Data for (+)-**47**:

Opt. Rot.: $[\alpha]_D$ +81.0 (c = 1.04 in $CHCl_3$) (80% ee)

Preparation of (+)-**48**

A 50-mL, round-bottomed flask equipped with a stir bar was charged with vinyl sulfide (+)-**47** (380.3 mg, 0.77 mmol) and CH_2Cl_2 (3.75 mL). Water (1.5 mL) and trifluoroacetic acid (6.0 mL) were added to the flask. The resulting, yellow-pink, biphasic mixture was stirred vigorously at 25 °C for 2 h. Within 30 min, a pink-red homogeneous solution was observed. After 2 h, full conversion was observed by TLC (hexanes/EtOAc, 80:20). [**Note:** Careful inspection of the TLC plate is required, as the 2,6-diisopropylthiophenol byproduct has nearly the same R_f value as (+)-**47**.] The reaction was quenched by adding the mixture dropwise into a 250-mL Erlenmeyer flask containing sat. aq. $NaHCO_3$ (150 mL) cooled in an ice bath. Gas evolution was observed, and the pink color disappeared. Additional CH_2Cl_2 (50 mL) was added to the flask, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL), and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated (30 °C, 15 mmHg) to afford crude (+)-**48**. The product was purified by chromatography (silica gel, 3 x 20 cm, dry load on Celite, 25-mL fractions, hexanes/EtOAc gradient elution: 95:5 (300 mL) to 90:10 (300 mL) to 85:15 (300 mL) to 80:20 (300 mL)) to afford 225.4 mg (93%) of (+)-**48** as a white solid. A racemic sample of **48** was obtained by a similar procedure, beginning with (±)-**47**. Analytically pure (±)-**48** was obtained by recrystallization from hexanes.

Data for (±)-**48**:

m.p.: 132–133 °C (hexanes)

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

6.87 (s, 1H, HC(17)), 6.69 (s, 1H, HC(14)), 3.80 (s, 3H, $H_3C(18)$), 3.23 (hept, J = 6.9 Hz, 1H, HC(19)), 2.90 (ddd, J = 16.5, 5.7, 1.9 Hz, 1H, $H_2C(11^{eq})$), 2.85-2.75 (m, 1H, $H_2C(11^{ax})$), 2.69 (ddd, J = 15.8, 9.8, 7.6 Hz, 1H, $H_2C(5^{ax})$), 2.60 (ddd, J = 15.8, 7.8, 4.2 Hz, 1H, $H_2C(5^{eq})$), 2.46 (ddd, J = 12.9, 7.6, 4.2 Hz, 1H, $H_2C(6^{eq})$), 2.05-1.95 (m, 1H, $H_2C(6^{ax})$), 1.92 (dd, J = 12.0, 2.5 Hz, 1H, HC(9)), 1.86-1.80 (m, 1H, $H_2C(10^{eq})$), 1.79-1.69 (m, 1H, $H_2C(10^{ax})$), 1.31 (s, 3H, $H_3C(8)$), 1.20 (d, J = 6.9 Hz, 3H, $H_3C(20)$), 1.18 (d, J = 6.9 Hz, 3H, $H_3C(20')$), 1.17 (s, 3H, $H_3C(2)$), 1.14 (s, 3H, $H_3C(1)$).

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

217.55 (C(4)), 155.44 (C(15)), 145.33 (C(13)), 135.17 (C(16)), 126.73 (C(12)), 126.57 (HC(17)), 107.38 (HC(14)), 55.72 ($H_3C(18)$), 50.78 (HC(9)), 47.49 (C(3)), 37.75 ($H_2C(6)$), 37.54 (C(7)), 34.79 ($H_2C(5)$), 30.36 ($H_2C(11)$), 27.14 ($H_3C(2)$), 26.63 (HC(19)), 24.78 ($H_3C(8)$), 22.97 ($H_3C(20)$ or $H_3C(20')$), 22.80 ($H_3C(20)$ or $H_3C(20')$), 21.20 ($H_3C(1)$), 20.57 ($H_2C(10)$).

IR: (neat)

2932 (m), 2848 (w), 1699 (s), 1613 (w), 1502 (s), 1458 (m), 1442 (m), 1407 (m), 1384 (m), 1362 (m), 1322 (m), 1310 (m), 1247 (s), 1233 (m), 1206 (m), 1193 (m), 1163 (m), 1122 (m), 1099 (m), 1076 (w), 1058 (m), 1046 (s), 1013 (w), 969 (w), 926 (w), 888 (m), 866 (m), 763 (m), 706 (w), 580 (w).

LRMS: (EI, 70 eV)

125.1 (9), 201.1 (9), 213.1 (18), 215.1 (9), 257.2 (25), 299.2 (70), 300.2 (15), 314.2 (100), 315.2 (24).

Analysis: $C_{21}H_{30}O_2$ (314.47)

Calcd: C, 80.21% H, 9.62%

Found: C, 80.13% H, 9.74%

TLC: R_f 0.38 (silica gel, hexanes/EtOAc, 80:20, UV/CAM)

Data for (+)-**48**:

Opt. Rot.: $[\alpha]_D$ +97.1 (c = 1.23 in $CHCl_3$) (80% ee)

Preparation of (+)-**49**

A flame-dried, 50-mL, round-bottomed flask equipped with a stir bar and argon inlet adapter was charged with ketone (+)-**48** (190.1 mg, 0.60 mmol) and absolute ethanol (10 mL). The resulting white suspension was cooled to -10 °C using an ice/salt bath. Sodium borohydride (94.1 mg, 2.49 mmol, 4.1 equiv) was added in three portions within 1 min at -10 °C. The reaction was stirred for 3.5 h at -10 °C under argon, over which time a clear, colorless solution resulted. Full conversion was observed by TLC (hexanes/EtOAc, 80:20). The reaction was quenched by the *cautious*, dropwise addition of sat. aq. NH_4Cl (10 mL). Ethanol was removed by rotary evaporation (35 °C, 15 mmHg), and the remaining aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were washed with brine (25 mL) and then dried over sodium sulfate, filtered, and concentrated (30 °C, 15 mmHg) to afford crude (+)-**49** (0.19 g) as a white foam solid (d.r. = 93:7, determined from analysis of the crude ^{1}H NMR spectrum). The product was purified by column chromatography (silica gel, 2 x 22 cm, dry load on Celite, 10-mL fractions, hexanes/EtOAc gradient elution: 95:5 (200 mL) to 90:10 (200 mL) to 85:15 (200 mL) to 80:20 (200 mL) to 75:25 (200 mL)) to afford 168.3 mg (88%) of (+)-**49** as a white solid (single diastereomer). A racemic sample of **49** was obtained by a similar procedure, beginning with (±)-**48**. Analytically pure (±)-**49** was obtained by chromatography.

Data for (±)-**49**:

m.p.: 118–119 °C (ethyl acetate:hexanes)

^{1}H NMR: (500 MHz, $CDCl_3$)
6.85 (s, 1H, HC(17)), 6.70 (s, 1H, HC(14)), 3.79 (s, 3H, H_3C(18)), 3.34-3.27 (m, 1H, HC(4)), 3.22 (hept, *J* = 6.9 Hz, 1H, HC(19)), 2.95-2.85 (m, 1H, $H_2C(11^{eq})$), 2.84-2.73 (m, 1H, $H_2C(11^{ax})$), 2.29 (dt, *J* = 13.0, 3.5 Hz, 1H, $H_2C(6^{eq})$), 1.92-1.86 (m, 1H, $H_2C(10^{eq})$), 1.86-1.81 (m, 1H, $H_2C(5^{ax})$), 1.81-1.76 (m, 1H, $H_2C(5^{eq})$), 1.76-1.67 (m, 1H, $H_2C(10^{ax})$), 1.58 (td, *J* = 13.0, 4.5 Hz, 1H, $H_2C(6^{ax})$), 1.37 (d, *J* = 5.9 Hz, 1H, OH), 1.33 (dd, *J* = 12.3, 2.1 Hz, 1H, HC(9)), 1.21 (s, 3H, H_3C(8)), 1.19 (d, *J* = 6.9 Hz, 3H, H_3C(20)), 1.17 (d *J* = 6.9 Hz, 3H, H_3C(20')), 1.07 (s, 3H, H_3C(2)), 0.90 (s, 3H, H_3C(1)).

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

155.23 (C(15)), 147.37 (C(13)), 134.63 (C(16)), 126.82 (C(12)), 126.52 (HC(17)), 106.68 (HC(14)), 78.91 (HC(4)), 55.72 (H_3C(18)), 50.06 (HC(9)), 39.15 (C(3)), 37.80 (C(7)), 37.19 (H_2C(6)), 30.24 (H_2C(11)), 28.33 (H_3C(2)), 28.19 (H_2C(5)), 26.60 (HC(19)), 24.99 (H_3C(8)), 23.03 (H_3C(20) or H_3C(20')), 22.82 (H_3C(20) or H_3C(20')), 19.17 (H_2C(10)), 15.54 (H_3C(1)).

IR: (neat)

3500 (wb), 2944 (m), 2868 (m), 2834 (w), 1613 (w), 1571 (w), 1498 (m), 1464 (m), 1403 (m), 1370 (m), 1359 (m), 1339 (w), 1323 (w), 1305 (w), 1250 (m), 1192 (m), 1164 (m), 1118 (w), 1076 (m), 1054 (w), 1028 (s), 1005 (m), 968 (m), 936 (m), 888 (m), 848 (m), 810 (w), 761 (m), 716 (w), 686 (w), 611 (w), 559 (w), 499 (w), 479 (m).

LRMS: (EI, 70 eV)

161.1 (13), 163.1 (13), 173.1 (11), 189.1 (15), 201.1 (14), 213.1 (17), 215.1 (17), 229.2 (15), 241.2 (19), 283.2 (64), 284.2 (14), 301.2 (42), 302.2 (10), 316.2 (100), 317.2 (37).

Analysis: $C_{21}H_{32}O_2$ (316.48)

Calcd: C, 79.70% H, 10.19%

Found: C, 79.35% H, 10.11%

TLC: R_f 0.14 (silica gel, hexanes/EtOAc, 80:20, UV/CAM)

Data for (+)-**49**:

Opt. Rot.: $[\alpha]_D$ +47.5 (*c* = 1.00 in $CHCl_3$) (80% ee)

Synthesis of (+)-**hinokiol** ((+)-**44**)

A solution of methylmagnesium iodide in diethyl ether was prepared in the following manner.[230] A flame-dried, three-necked, 250-mL round-bottomed flask equipped with a stir bar, addition funnel, argon inlet adapter, temperature probe, and septum was charged with magnesium turnings (0.86 g, 35.3 mmol) and diethyl ether (50 mL). The turnings were mechanically activated immediately before use by grinding with a mortar and pestle for 10 min. The addition funnel was charged with a solution of methyl iodide (2.20 mL) in diethyl ether (15 mL). A portion of this

solution (2 mL) was added quickly to the reaction flask, with rapid stirring. The mixture was brought just to the boiling point (40 °C) using a heat gun. The remaining methyl iodide solution was added dropwise over 15 min (the mixture maintained a gentle reflux without external heating, indicating that initiation had occurred). The resulting turbid, grey mixture was stirred for 1 h (without external heat input). The reagent was titrated (0.48 M; expected 0.54 M) as previously described for **35b**. [**Note:** In this case, the Grignard-phenanthroline complex turns only a light purple color even after stirring for several minutes (as opposed to the typical dark purple). For this reason, the yellow endpoint is more difficult to discern, but the cessation of methane gas generation also indicates that the endpoint has been reached.] The reagent may be stored in a Schlenk bottle for several weeks at 25 °C with no appreciable decrease in concentration.

A flame-dried, 20-mL, Schlenk flask equipped with a stir bar was attached via a three-way valve to both the Schlenk manifold and a diaphragm pump with programmable pressure control. The flask was charged with compound (+)-**49** (84.5 mg, 0.27 mmol), evacuated, and placed under argon. Methylmagnesium iodide (0.48 M solution in diethyl ether, 33 mL, 16.0 mmol, 60 equiv) was added portionwise to the flask in the following manner. Approx. 10 mL of the reagent was added to the flask through the septum. Mild bubbling was observed upon contact with (+)-**49**. The three-way valve was opened to the diaphragm pump, and the solution was concentrated to remove most of the diethyl ether. The pressure should be decreased slowly (760 mmHg to 150 mmHg over 15 min) and a rapid stir rate should be maintained in order to avoid excessive bumping of the solution. The flask was placed under argon, an additional portion of Grignard reagent (approx. 10 mL) was added, and this process was repeated until a total of 33 mL of (concentrated) reagent had been dispensed into the reaction flask. The resulting viscous, yellow mixture was heated under vacuum (160 °C, 150 mmHg) for 2 h. The mixture was allowed to cool to 25 °C and the pale, yellow solid was transferred to a 250-mL Erlenmeyer flask. This was accomplished by adding diethyl ether (10 mL) to the flask, sonicating for 5 min, transferring the resulting milky, white suspension to the Erlenmeyer flask, and repeating this process until all of the reaction mixture had been transferred. The suspension was cooled to 0 °C and quenched by the cautious addition of water (50 mL). The resulting biphasic mixture was acidified with 1 M HCl and transferred to a 250-mL separatory funnel. The layers were separated, and the aqueous phase was extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with brine (50 mL), and then dried over sodium sulfate, filtered, and concentrated to afford 280.4 mg of crude (+)-**44** as a white,

oily solid. The product was purified by column chromatography (silica gel, 2 x 20 cm, dry load on Celite, 10-mL fractions, hexanes/EtOAc gradient elution, 90:10 (200 mL) to 80:20 (200 mL) to 70:30 (200 mL) to 60:40 (200 mL) to 50:50 (200 mL)) to afford 70.5 mg (85%) of (+)-**44** as a white solid. The compound contains 3% EtOAc by mass which cannot be purged even after extended drying times (90 °C, 0.1 mmHg, 24 h). Spectroscopic data for (+)-**44** matched those previously reported.[231] The compound is only sparingly soluble in $CDCl_3$, so the spectral data in DMSO-d_6 are also provided.

Data for (+)-**44**:

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

6.84 (s, 1H, HC(17)), 6.61 (s, 1H, HC(14)), 4.48 (s, 1H, phenolic OH), 3.29 (dd, *J* = 11.4, 4.8 Hz, 1H, HC(4)), 3.10 (hept, *J* = 6.9 Hz, 1H, HC(18)), 2.94-2.84 (m, 1H, $H_2C(11^{eq})$), 2.83-2.71 (m, 1H, $H_2C(11^{ax})$), 2.20 (dt, *J* = 13.0, 3.5 Hz, 1H, $H_2C(6^{eq})$), 1.88 (ddt, *J* = 13.1, 7.3, 1.8 Hz, 1H, $H_2C(10^{eq})$), 1.84-1.79 (m, 1H, $H_2C(5^{ax})$), 1.79-1.74 (m, 1H, $H_2C(5^{eq})$), 1.74-1.67 (m, 1H, $H_2C(10^{ax})$), 1.54 (td, *J* = 12.9, 4.3 Hz, 1H, $H_2C(6^{ax})$), 1.36 (bs, 1H, 2° OH), 1.31 (dd, *J* = 12.3, 2.2 Hz, 1H, HC(9)), 1.24 (d, *J* = 6.9 Hz, 3H, $H_3C(19)$), 1.22 (d, *J* = 6.9 Hz, 3H, $H_3C(19')$), 1.18 (s, 3H, $H_3C(8)$), 1.06 (s, 3H, $H_3C(2)$), 0.89 (s, 3H, $H_3C(1)$).

(500 MHz, DMSO-d_6)

8.75 (s, 1H, phenolic OH), 6.69 (s, 1H, HC(17)), 6.61 (s, 1H, HC(14)), 4.40 (d, J = 5.1 Hz, 1H, 2° OH), 3.15-3.00 (m, 2H, HC(18) and HC(4)), 2.76 (dd, J = 16.5, 5.8 Hz, 1H, $H_2C(11^{eq})$), 2.70-2.58 (m, 1H, $H_2C(11^{ax})$), 2.07 (dt, J = 12.8, 3.1 Hz, 1H, $H_2C(6^{eq})$), 1.82-1.72 (m, 1H, $H_2C(10^{eq})$), 1.69-1.54 (m, 3H, $H_2C(5)$ and $H_2C(10^{ax})$), 1.41-1.30 (m, 1H, $H_2C(6^{ax})$), 1.15 (dd, J = 12.1, 2.0 Hz, 1H, HC(9)), 1.11 (d, J = 7.0 Hz, 3H, $H_3C(19)$), 1.09 (d, J = 7.0 Hz, 3H, $H_3C(19')$), 1.07 (s, 3H, $H_3C(8)$), 0.96 (s, 3H, $H_3C(2)$), 0.76 (s, 3H, $H_3C(1)$).

^{13}C NMR: (126 MHz, CDCl3)

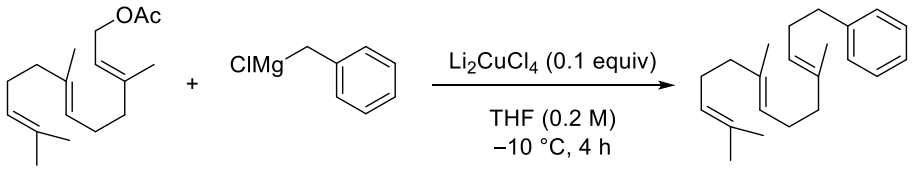
150.90 (C(15)), 147.96 (C(13)), 131.84 (C(16)), 127.25 (C(12)), 126.76 (HC(17)), 111.16 (HC(14)), 78.90 (HC(4)), 49.92 (HC(9)), 39.13 (C(3)), 37.47 (C(7)), 37.13 ($H_2C(6)$), 30.16 ($H_2C(11)$), 28.31 ($H_3C(2)$), 28.16 ($H_2C(5)$), 26.97 (HC(18)), 24.98 ($H_3C(8)$), 22.88 ($H_3C(19')$), 22.69 ($H_3C(19)$), 19.17 ($H_2C(10)$), 15.53 ($H_3C(1)$).

(126 MHz, DMSO-d_6)

152.12 (C(15)), 147.15 (C(13)), 131.46 (C(16)), 125.76 (HC(17)), 124.50 (C(12)), 110.38 (HC(14)), 76.60 (HC(4)), 49.59 (HC(9)), 38.60 (C(3)), 36.81 (H_2C(6)), 29.63 (H_2C(11)), 28.25 (H_3C(2)), 27.83 (H_2C(5)), 26.06 (HC(18)), 24.78 (H_3C(8)), 22.65 (H_3C(19')), 22.50 (H_3C(19)), 18.74 (H_2C(10)), 15.78 (H_3C(1)).

Opt. Rot.: $[\alpha]_D^{25}$ +47.9 (*c* = 0.92 in 95% EtOH) (80% ee)

((3*E*,7*E*)-4,8,12-Trimethyltrideca-3,7,11-trien-1-yl)benzene (**55a**)



54 **35a** **55a**

An oven-dried, 25-mL, Schlenk flask was charged with anhydrous lithium chloride (183 mg, 4.3 mmol, 0.2 equiv) and anhydrous copper(II) chloride (290 mg, 2.2 mmol, 0.1 equiv) inside of the glovebox. The flask was sealed, removed from the glovebox, and placed under argon. THF (8 mL) was added to the flask, and the mixture was sonicated under argon for 5 min until an orange solution was obtained. A separate, flame-dried, 300-mL, round bottomed flask equipped with a stir bar and addition funnel was charged with (*E*,*E*)-farnesyl acetate **54** (5.70 g, 21.6 mmol) and THF (42 mL), and the resulting colorless solution was cooled to 0 °C. The freshly prepared solution of Li_2CuCl_4 complex in THF was added to the flask containing farnesyl acetate **54**. The flask was maintained at 0 °C for 10 min and subsequently cooled to –10 °C using a Cryo-Cool. Benzylmagnesium chloride **35a** (Alfa-Aesar, 0.53 M, 45 mL, 23.7 mmol, 1.1 equiv) was added dropwise to the reaction flask over 30 min through the addition funnel, at such a rate that the internal reaction temperature did not exceed –5 °C at any point during the addition. The orange solution turned colorless, then yellow, and ultimately brown over the course of the addition. The reaction was stirred at –10 °C for 4 h. Full conversion was observed by TLC (hexanes/CH_2Cl_2, 90:10). The reaction was quenched by the addition of sat. aq. NH_4Cl (100 mL). The mixture was poured into a 500-mL separatory funnel, and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 100 mL). The combined organic layers were washed with 1 M HCl (1 x 100 mL), sat. aq. $NaHCO_3$ (1 x 100 mL), and brine (1 x 100 mL), and then dried over Na_2SO_4,

filtered, and concentrated to afford 6.96 g of crude **55a**. The product was purified by chromatography (silica gel) using a hexanes/CH_2Cl_2 gradient elution (97.5:2.5 to 95:5 to 92.5:7.5 to 90:10) to afford 6.39 g (95%) of **55a** as a clear, colorless oil. The product co-eluted with less than 5% of the 1,2-bis(aryl)ethane by-product **39a**.

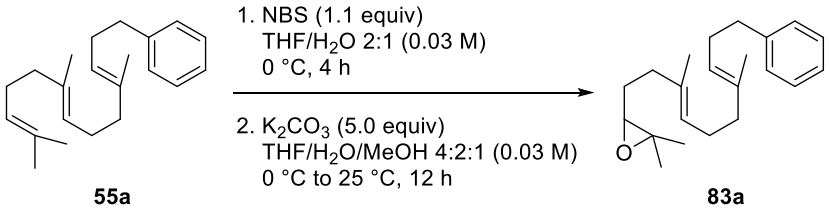
Data for **55a**:

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

7.29 – 7.26 (m, 2H), 7.21 – 7.17 (m, 3H), 5.22 – 5.17 (m, 1H), 5.13 – 5.08 (m, 2H), 2.67 – 2.61 (m, 2H), 2.30 (q, J = 7.4 Hz, 2H), 2.11 – 2.03 (m, 4H), 2.02 – 1.95 (m, 4H), 1.70 – 1.67 (m, 3H), 1.62 – 1.59 (m, 6H), 1.56 (s, 3H).

TLC: R_f 0.53 (hexanes/CH_2Cl_2, 90:10, CAM)

3-((3*E*,7*E*)-3,7-Dimethyl-10-phenyldeca-3,7-dien-1-yl)-2,2-dimethyloxirane (**83a**)



A 1-L, round bottomed flask equipped with a stir bar and addition funnel was charged with triene **55a** (6.39 g, 20 mmol), THF (400 mL), and H_2O (200 mL). The mixture was cooled to 0 °C, resulting in a thin, colorless suspension. A solution of *N*-bromosuccinimide (4.0 g, 23 mmol, 1.1 equiv) in THF (40 mL) and H_2O (20 mL) was added portionwise over 1 h at 0 °C using the addition funnel. Residual solids were rinsed into the reaction flask with a minimal amount of THF. The resulting colorless, turbid solution was stirred at 0 °C for 4 h. Sat. aq. $Na_2S_2O_3$ (20 mL) was added at 0 °C, followed by MeOH (100 mL) and potassium carbonate (14 g, 100 mmol, 5.0 equiv). The reaction mixture was warmed to 25 °C and the resulting solution was stirred at this temperature for 12 h. Most of the organic solvent was removed by rotary evaporation, and the remaining aqueous phase was extracted with Et_2O (3 x 200 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford 8.32 g of crude **83a**. The product was purified by chromatography (silica gel) using hexanes/Et_2O/Et_3N (95:5:1 isocratic) to afford 3.63 g (55%) of **83a** as an oil.

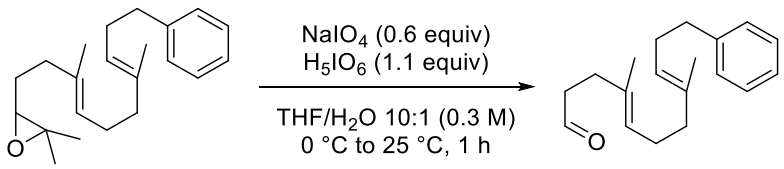
Data for **83a**:

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

7.30 – 7.26 (m, 2H), 7.21 – 7.15 (m, 3H), 5.21 – 5.12 (m, 2H), 2.70 (t, *J* = 6.2 Hz, 1H), 2.66 – 2.60 (m, 2H), 2.30 (q, *J* = 7.4 Hz, 2H), 2.19 – 2.04 (m, 4H), 2.01 – 1.96 (m, 2H), 1.69 – 1.57 (m, 5H), 1.56 (s, 3H), 1.30 (s, 3H), 1.26 (s, 3H).

TLC: R_f 0.27 (hexanes/Et_2O/Et_3N, 95:5:1, UV/CAM)

(4*E*,8*E*)-4,8-Dimethyl-11-phenylundeca-4,8-dienal (**84a**)



83a **84a**

A 100-mL, round bottomed flask equipped with a stir bar was charged with epoxide **83a** (3.63 g, 11 mmol), THF (36 mL), and H_2O (4 mL). The resulting solution was cooled to 0 °C. Sodium periodate (1.4 g, 6.8 mmol, 0.6 equiv) and periodic acid (2.8 g, 12 mmol, 1.1 equiv) were added sequentially. The mixture was warmed to 25 °C and stirring was continued for 1 h. Within 15 min, a colorless, turbid solution was observed. Full conversion was observed by TLC (hexanes/Et_2O, 90:10). The reaction was quenched by the cautious addition of sat. aq. $NaHCO_3$ (50 mL). The white suspension was extracted with EtOAc (3 x 50 mL), and the combined organic extracts were washed with brine (1 x 50 mL), dried over Na_2SO_4, filtered, and concentrated to afford 3.15 g of crude **84a**. The product was purified by chromatography (silica gel) using a hexanes/EtOAc gradient elution (95:5 to 90:10 to 85:15) to afford 2.66 g (85%) of **xx** as an oil.

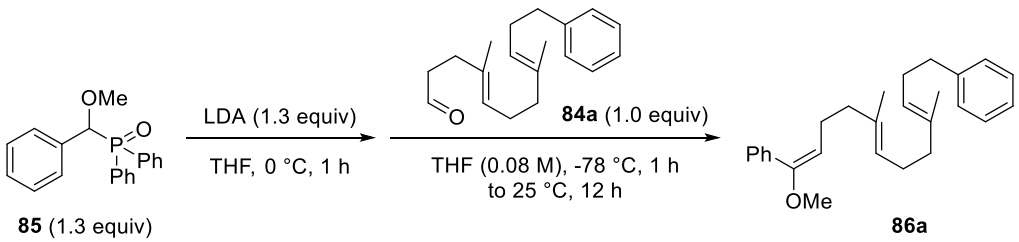
Data for **84a**:

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

9.74 (t, *J* = 1.9 Hz, 1H), 7.29 – 7.26 (m, 2H), 7.21 – 7.15 (m, 3H), 5.19 – 5.10 (m, 2H), 2.66 – 2.61 (m, 2H), 2.50 (td, *J* = 7.4, 1.7 Hz, 2H), 2.33 – 2.27 (m, 4H), 2.10 – 2.04 (m, 2H), 2.00 – 1.95 (m, 2H), 1.61 (s, 3H), 1.55 (s, 3H).

TLC: R_f 0.44 (hexanes/EtOAc, 90:10, UV/CAM)

((5*E*,9*E*)-1-Methoxy-5,9-dimethyldodeca-1,5,9-triene-1,12-diyl)dibenzene (**86a**)



85 (1.3 equiv) **86a**

Preparation of LDA: An oven-dried, 50-mL, Schlenk flask equipped with a stir bar was charged with THF (13.3 mL) and DIPA (1.90 mL, 13.1 mmol). The colorless solution was cooled to –20 °C, and n-butyllithium (2.3 M in hexanes, 5.7 mL, 13.1 mmol) was added dropwise. The resulting solution was stirred for 2 h at –20 °C to afford 19 mL of 0.69 M LDA solution. The solution was used immediately, and was not allowed to warm above 0 °C.

Preparation of 86a: An oven-dried, 200-mL, Schlenk flask equipped with a stir bar was charged with phosphine oxide **85** (4.22 g, 13.1 mmol, 1.33 equiv) and THF (93.5 mL). The white suspension was cooled to 0 °C, and freshly-prepared LDA solution (19 mL, 0.69 M, 13.1 mmol, 1.33 equiv) was added dropwise. The resulting dark, red solution was stirred at 0 °C for 1 h and then cooled to –78 °C. A solution of aldehyde **84a** (2.66 g, 9.8 mmol) in THF (9.3 mL) was added dropwise at –78 °C. An orange-red solution resulted. The reaction was maintained at this temperature for 1 h and then allowed to slowly warm to 25 °C over 12 h. A pale yellow suspension was observed. Full conversion was observed by TLC (hexanes/EtOAc, 90:10). The reaction was quenched by the addition of sat. aq. NH_4Cl (100 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with brine (1 x 100 mL), dried over Na_2SO_4, filtered, and concentrated to afford crude **86a**. The product was purified by chromatography (silica gel) using a hexanes/EtOAc/Et_3N gradient elution (99:1:0.5 to 97:3:0.5 to 95:5:0.5) to afford 3.16 g (86%) of **86a** as a mixture of geometric isomers (75:25 ≥ *E*/*Z* ≥ 70:30).

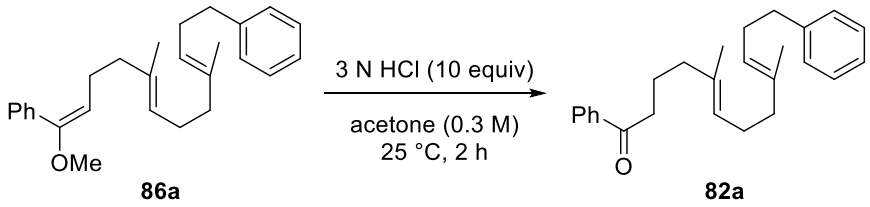
Data for **86a**:

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

7.45 – 7.24 (m, 7H), 7.20 – 7.15 (m, 3H), 5.29 (t, *J* = 7.2 Hz, 0.3H, (*Z*)-**86a**), 5.21 – 5.07 (m, 2H), 4.69 (t, *J* = 7.4 Hz, 0.7H, (*E*)-**86a**), 3.63 (s, 2.2H, (*E*)-**86a**), 3.52 (s, 0.8H, (*Z*)-**86a**), 2.65 – 2.60 (m, 2H), 2.40 – 1.95 (m, 10H), 1.65 (s, 0.8H, (*Z*)-**86a**), 1.55 (s, 0.8H, (*Z*)-**86a**), 1.55 (s, 2.2H, (*E*)-**86a**), 1.52 (s, 2.2H, (*E*)-**86a**).

TLC: R_f 0.60 (hexanes/EtOAc, 90:10, UV/CAM)

(5*E*,9*E*)-5,9-Dimethyl-1,12-diphenyldodeca-5,9-dien-1-one (**82a**)



A 200-mL, round bottomed flask equipped with a stir bar was charged with enol ether **86a** (3.16 g, 8.4 mmol), acetone (28 mL), and 3 N HCl (28 mL). The cloudy mixture was stirred rapidly at 25 °C for 2 h. A colorless solution resulted, containing suspended droplets of colorless oil. Full conversion was observed by TLC (hexanes/EtOAc, 90:10). The mixture was partitioned between water (100 mL) and CH_2Cl_2 (100 mL), and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (1 x 50 mL) and brine (1 x 50 mL), and then dried over Na_2SO_4, filtered, and concentrated to afford crude **82a**. The product was purified by chromatography (silica gel) using a hexanes/EtOAc gradient elution (97.5:2.5 to 95:5 to 92.5:7.5) to afford 2.82 g (93%) of **82a** as a colorless oil.

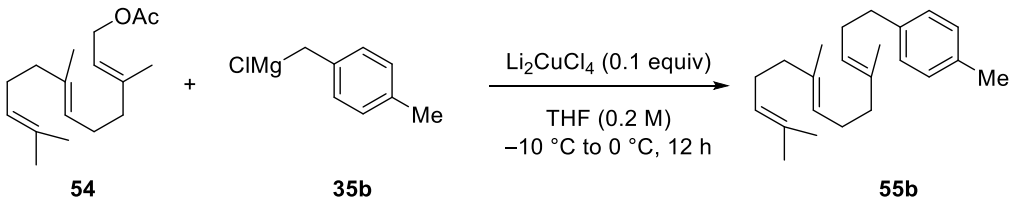
Data for **82a**:

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

7.97 – 7.92 (m, 2H), 7.57 – 7.52 (m, 1H), 7.47 – 7.43 (m, 2H), 7.29 – 7.24 (m, 2H), 7.19 – 7.15 (m, 3H), 5.19 – 5.10 (m, 2H), 2.92 (t, *J* = 7.4 Hz, 2H), 2.65 – 2.59 (m, 2H), 2.28 (q, *J* = 7.5 Hz, 2H), 2.10 – 2.04 (m, 4H), 1.99 – 1.94 (m, 2H), 1.85 (p, *J* = 7.4 Hz, 2H), 1.61 (s, 3H), 1.54 (s, 3H).

TLC: R_f 0.50 (hexanes/EtOAc, 90:10, UV)

1-Methyl-4-((3E,7E)-4,8,12-trimethyltrideca-3,7,11-trien-1-yl)benzene (**55b**)



54 **35b** **55b**

4-Methylbenzylmagnesium chloride **35b** (0.37 M in THF) was freshly prepared from 4-methylbenzyl chloride **38b** (0.66 mL, 5.0 mmol), magnesium turnings (0.15 g, 6.3 mmol), and THF (12.5 mL total) using the procedure described in the preparation of **17b** (*vida supra*).

An oven-dried, 5-mL, Schlenk flask was charged with anhydrous lithium chloride (33 mg, 0.8 mmol, 0.2 equiv) and anhydrous copper(II) chloride (53 mg, 0.4 mmol, 0.1 equiv) inside of the glovebox. The flask was sealed, removed from the glovebox, and placed under argon. THF (1.5 mL) was added to the flask, and the mixture was sonicated under argon for 5 min until an orange solution was obtained. A separate, oven-dried, 100-mL Schlenk flask equipped with a stir bar was charged with (*E*,*E*)-farnesyl acetate **54** (1.04 g, 3.9 mmol) and THF (8 mL), and the resulting colorless solution was cooled to 0 °C. The freshly prepared solution of Li_2CuCl_4 complex in THF was added to the flask containing farnesyl acetate **54**. The flask was maintained at 0 °C for 10 min and subsequently cooled to –10 °C using a Cryo-Cool. 4-Methylbenzylmagnesium chloride **35b** (0.37 M in THF, 11.8 mL, 4.3 mmol, 1.1 equiv) was added dropwise to the reaction flask over 20 min using a syringe, at such a rate that the internal reaction temperature did not exceed –5 °C at any point during the addition. The orange solution turned colorless, then yellow, and ultimately brown over the course of the addition. The reaction was stirred at –10 °C for 12 h. Conversion was assessed by TLC (hexanes/CH_2Cl_2, 90:10). The reaction was quenched by the addition of sat. aq. NH_4Cl (25 mL). The mixture was poured into a 250-mL separatory funnel, and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 50 mL). The combined organic layers were washed with 1 M HCl (1 x 25 mL), sat. aq. $NaHCO_3$ (1 x 25 mL), and brine (1 x 25 mL), and then dried over Na_2SO_4, filtered, and concentrated to afford 1.44 g of crude **55b**. The product was purified by chromatography (silica gel) using a hexanes/CH_2Cl_2 gradient elution (97.5:2.5 to 95:5

to 92.5:7.5 to 90:10) to afford 1.01 g (79%) of **55b** as a clear, colorless oil. The product co-eluted with less than 5% of the 1,2-bis(aryl)ethane by-product **39b**.

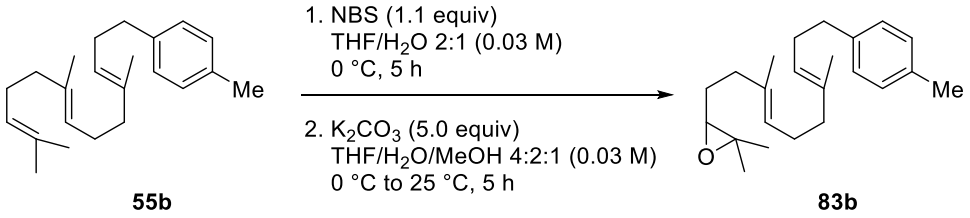
Data for **55b**:

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

7.08 (s, 4H), 5.22 – 5.16 (m, 1H), 5.14 – 5.07 (m, 2H), 2.62 – 2.57 (m, 2H), 2.32 (s, 3H), 2.28 (q, J = 7.4 Hz, 2H), 2.11 – 2.03 (m, 4H), 2.01 – 1.95 (m, 4H), 1.68 (s, 3H), 1.61 – 1.59 (m, 6H), 1.57 (s, 3H).

TLC: R_f 0.50 (hexanes/CH_2Cl_2, 90:10, UV/CAM)

3-((3*E*,7*E*)-3,7-Dimethyl-10-(*p*-tolyl)deca-3,7-dien-1-yl)-2,2-dimethyloxirane (**83b**)



55b **83b**

A 250-mL, three-necked, round bottomed flask equipped with a stir bar was charged with triene **55b** (0.964 g, 3.1 mmol), THF (62 mL), and H_2O (31 mL). The mixture was cooled to 0 °C, resulting in a thin, colorless suspension. A solution of *N*-bromosuccinimide (0.60 g, 3.4 mmol, 1.1 equiv) in THF (6.2 mL) and H_2O (3.1 mL) was added portionwise over 1 h at 0 °C. Residual solids were rinsed into the reaction flask with a minimal amount of THF/H_2O mixture. The resulting colorless solution was stirred at 0 °C for 5 h. ^{1}H NMR analysis of a reaction aliquot indicated complete consumption of triene **55b**. Sat. aq. $Na_2S_2O_3$ (3.1 mL) was added at 0 °C, followed by MeOH (15.5 mL) and potassium carbonate (2.15 g, 15.5 mmol, 5.0 equiv). The reaction mixture was warmed to 25 °C and the resulting solution was stirred at this temperature for 5 h. 1H NMR analysis of a reaction aliquot indicated complete consumption of the earlier intermediate. Most of the organic solvent was removed by rotary evaporation, and the remaining aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford crude **83b**. The product was purified by chromatography (silica gel) using a hexanes/Et_2O/Et_3N gradient elution (98:2:1 to 95:5:1 to 90:10:1) to afford 497 mg (49%) of **83b** as an oil.

Data for **83b**:

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

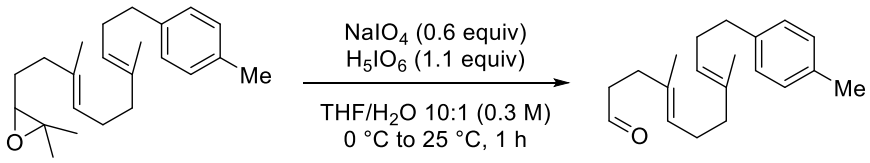
7.08 (s, 4H), 5.21 – 5.13 (m, 2H), 2.70 (t, *J* = 6.2 Hz, 1H), 2.62 – 2.56 (m, 2H), 2.32 (s, 3H), 2.28 (q, *J* = 7.4 Hz, 2H), 2.19 – 2.12 (m, 1H), 2.11 – 2.04 (m, 3H), 2.02 – 1.96 (m, 2H), 1.70 – 1.57 (m, 3H), 1.62 (s, 3H), 1.56 (s, 3H), 1.30 (s, 3H), 1.26 (s, 3H).

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

139.47, 135.66, 135.21, 134.20, 129.05, 128.45, 125.03, 123.98, 64.36, 58.46, 39.78, 36.47, 35.85, 30.25, 27.65, 26.78, 25.07, 21.16, 18.92, 16.16, 16.15.

TLC: R_f 0.42 (hexanes/Et_2O/Et_3N, 98:2:1, CAM)

(4*E*,8*E*)-4,8-Dimethyl-11-(*p*-tolyl)undeca-4,8-dienal (**84b**)



83b **84b**

A 25-mL, round bottomed flask equipped with a stir bar was charged with epoxide **83b** (497 mg, 1.5 mmol), THF (4.5 mL), and H_2O (0.5 mL). The resulting solution was cooled to 0 °C. Sodium periodate (197 mg, 0.9 mmol, 0.6 equiv) and periodic acid (385 mg, 1.7 mmol, 1.1 equiv) were added sequentially. The mixture was warmed to 25 °C and stirring was continued for 1 h. Initially, a thin white suspension was observed, but within minutes most of the solid coalesced into large globules, which mostly dissolved as the reaction progressed. Full conversion was observed by TLC (hexanes/Et_2O, 90:10). The reaction was quenched by the cautious addition of sat. aq. $NaHCO_3$. The white suspension was extracted with EtOAc (3 x 50 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to afford crude **84b**. The product was purified by chromatography (silica gel) using a hexanes/Et_2O gradient elution (90:10 to 85:15 to 80:20) to afford 367 mg (85%) of **84b** as an oil.

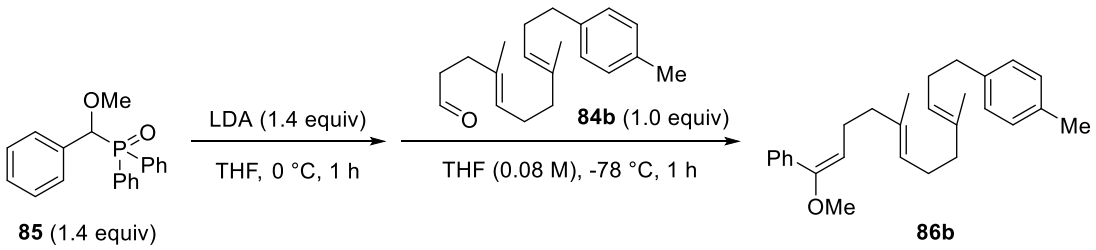
Data for **84b**:

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

9.74 (t, *J* = 1.9 Hz, 1H), 7.08 (s, 4H), 5.20 – 5.10 (m, 2H), 2.62 – 2.57 (m, 2H), 2.50 (td, *J* = 7.5, 1.9 Hz, 2H), 2.34 – 2.25 (m, 7H), 2.07 (q, *J* = 7.1 Hz, 2H), 2.00 – 1.95 (m, 2H), 1.61 (s, 3H), 1.56 (s, 3H).

TLC: R_f 0.32 (hexanes/Et_2O, 90:10, CAM)

1-((3*E*,7*E*)-12-Methoxy-4,8-dimethyl-12-phenyldodeca-3,7,11-trien-1-yl)-4-methylbenzene (**86b**)



Preparation of LDA: An oven-dried, 10-mL, Schlenk flask equipped with a stir bar was charged with THF (2.65 mL) and DIPA (350 μL, 2.45 mmol). The colorless solution was cooled to –20 °C, and n-butyllithium (2.3 M in hexanes, 1.05 mL, 2.45 mmol) was added dropwise. The resulting solution was stirred for 2 h at –20 °C to afford 3.70 mL of 0.66 M LDA solution. The solution was used immediately, and was not allowed to warm above 0 °C.

Preparation of 86b: An oven-dried, 10-mL, Schlenk flask equipped with a stir bar was charged with phosphine oxide **85** (159.8 mg, 0.50 mmol, 1.4 equiv) and THF (3.5 mL). The white suspension was cooled to 0 °C, and freshly-prepared LDA solution (0.74 mL, 0.66 M, 0.49 mmol, 1.4 equiv) was added dropwise. The resulting dark, red solution was stirred at 0 °C for 1 h and then cooled to –78 °C. A solution of aldehyde **84b** (100.9 mg, 0.35 mmol) in THF (0.35 mL) was added dropwise at –78 °C. An orange-red solution resulted. The reaction was maintained at this temperature for 1 h and then allowed to slowly warm to 25 °C over 12 h. A pale yellow suspension was observed. Full conversion was observed by TLC (hexanes/EtOAc, 90:10). The reaction was quenched by the addition of sat. aq. NH_4Cl (10 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (1 x 20 mL), dried over Na_2SO_4, filtered, and concentrated to afford 185.4 mg of crude **86b**. The

product was purified by chromatography (silica gel) using a hexanes/EtOAc/Et_3N gradient elution (99:1:0.5 to 97:3:0.5 to 95:5:0.5) to afford 121.1 mg (88%) of **86b** as a mixture of geometric isomers (75:25 ≥ *E*/*Z* ≥ 70:30).

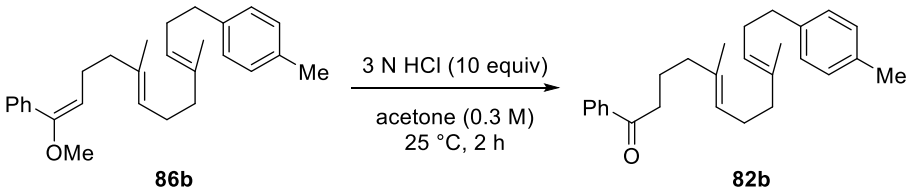
Data for **86b**:

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

7.47 – 7.26 (m, 5H), 7.08 (app. s, 4H), 5.29 (t, *J* = 7.2 Hz, 0.3H, (*Z*)-**86b**), 5.21 – 5.07 (m, 2H), 4.69 (t, *J* = 7.3 Hz, 0.7H, (*E*)-**86b**), 3.63 (s, 2.2H, (*E*)-**86b**), 3.52 (s, 0.8H, (*Z*)-**86b**), 2.61 – 2.56 (m, 2H), 2.40 – 1.94 (m, 13H), 1.65 (s, 0.8H, (*Z*)-**86b**), 1.56 (s, 0.8H, (*Z*)-**86b**), 1.56 (s, 2.2H, (*E*)-**86b**), 1.52 (s, 2.2H, (*E*)-**86b**).

TLC: R_f 0.66 (hexanes/EtOAc, 90:10, UV/CAM)

(5*E*,9*E*)-5,9-Dimethyl-1-phenyl-12-(*p*-tolyl)dodeca-5,9-dien-1-one (**82b**)



86b **82b**

A 20-mL vial equipped with a stir bar was charged with enol ether **86b** (120 mg, 0.31 mmol), acetone (1 mL), and 3 N HCl (1 mL). The cloudy mixture was stirred rapidly at 25 °C for 2 h. A colorless solution resulted, containing suspended droplets of colorless oil. The mixture was partitioned between water (10 mL) and CH_2Cl_2 (10 mL), and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (1 x 10 mL) and brine (1 x 10 mL), and then dried over Na_2SO_4, filtered, and concentrated to afford 131.4 mg of crude **82b**. The product was purified by chromatography (silica gel) using a hexanes/EtOAc gradient elution (97.5:2.5 to 95:5 to 92.5:7.5) to afford 109.7 mg (95%) of **82b** as a colorless oil.

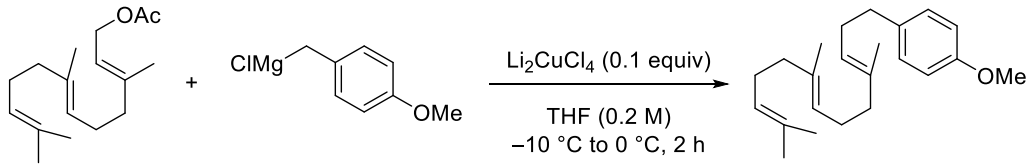
Data for **82b**:

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

7.97 – 7.93 (m, 2H), 7.57 – 7.52 (m, 1H), 7.47 – 7.43 (m, 2H), 7.09 – 7.05 (m, 4H), 5.19 – 5.10 (m, 2H), 2.92 (t, *J* = 7.4 Hz, 2H), 2.60 – 2.55 (m, 2H), 2.31 (s, 3H), 2.26 (q, *J* = 7.5 Hz, 2H), 2.09 – 2.04 (m, 4H), 1.99 – 1.94 (m, 2H), 1.85 (p, *J* = 7.4 Hz, 2H), 1.61 (s, 3H), 1.55 (s, 3H).

TLC: R_f 0.47 (hexanes/EtOAc, 90:10, UV/CAM)

1-Methoxy-4-((3*E*,7*E*)-4,8,12-trimethyltrideca-3,7,11-trien-1-yl)benzene (**55c**)



54 **35c** **55c**

4-Methoxybenzylmagnesium chloride **35c** (0.40 M in THF) was freshly prepared from 4-methoxybenzyl chloride **38c** (0.98 mL, 7.25 mmol), magnesium turnings (0.22 g, 9.1 mmol), and THF (18.5 mL total) using the procedure described in the preparation of **17c** (*vida supra*).

An oven-dried, 5-mL, Schlenk flask was charged with anhydrous lithium chloride (42 mg, 1.0 mmol, 0.2 equiv) and anhydrous copper(II) chloride (67 mg, 0.5 mmol, 0.1 equiv) inside of the glovebox. The flask was sealed, removed from the glovebox, and placed under argon. THF (1.5 mL) was added to the flask, and the mixture was sonicated under argon for 5 min until an orange solution was obtained. A separate, oven-dried, 100-mL Schlenk flask equipped with a stir bar was charged with (*E*,*E*)-farnesyl acetate **54** (1.32 g, 5.0 mmol) and THF (10.5 mL), and the resulting colorless solution was cooled to 0 °C. The freshly prepared solution of Li_2CuCl_4 complex in THF was added to the flask containing farnesyl acetate **54**. The flask was maintained at 0 °C for 10 min and subsequently cooled to –10 °C using an ice/salt bath. 4-Methoxybenzylmagnesium chloride **35c** (0.40 M in THF, 14 mL, 5.5 mmol, 1.1 equiv) was added dropwise to the reaction flask over 20 min using a syringe, at such a rate that the internal reaction temperature did not exceed –5 °C at any point during the addition. The orange solution turned colorless, then yellow, and ultimately brown over the course of the addition. The reaction was stirred at 0 °C for 2 h.

Conversion was assessed by TLC (hexanes/Et_2O, 90:10). The reaction was quenched by the addition of sat. aq. NH_4Cl (25 mL). The mixture was poured into a 250-mL separatory funnel, and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 50 mL). The combined organic layers were washed with 1 M HCl (1 x 25 mL), sat. aq. $NaHCO_3$ (1 x 25 mL), and brine (1 x 25 mL), and then dried over Na_2SO_4, filtered, and concentrated to afford crude **xx**. The product was purified by chromatography (silica gel) using a hexanes/Et_2O gradient elution (98:2 to 96:4 to 94:6 to 92:8) to afford 1.07 g (66%) of **55c** as a slightly turbid, pale, yellow oil. Additionally, approx. 0.30 g of unreacted (*E*,*E*)-farnesyl acetate were isolated, so the yield of **55c** was 85% based on recovered starting material.

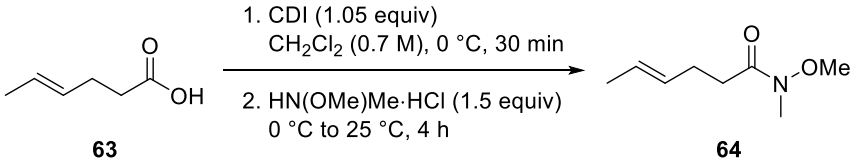
Data for **55c**:

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

7.10 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 5.21 – 5.14 (m, 1H), 5.14 – 5.07 (m, 2H), 3.79 (s, 3H), 2.61 – 2.55 (m, 2H), 2.27 (q, *J* = 7.4 Hz, 2H), 2.10 – 2.03 (m, 4H), 2.01 – 1.95 (dt, *J* = 10.7, 5.6 Hz, 4H), 1.68 (s, 3H), 1.60 (s, 6H), 1.56 (s, 3H).

TLC: R_f 0.78 (hexanes/Et_2O, 90:10, $KMnO_4$)

(*E*)-*N*-Methoxy-*N*-methylhex-4-enamide (64)



63 **64**

A flame-dried, 250-mL, round bottomed flask equipped with a stir bar was charged with carboxylic acid **63** (3.01 g, 26.4 mmol) and CH_2Cl_2 (38 mL). The resulting colorless solution was cooled to 0 °C, and recrystallized carbonyldiimidazole (CDI, 4.47 g, 27.6 mmol, 1.05 equiv) was added portionwise as a solid. Vigorous bubbling was observed. The resulting light brown solution was stirred for 30 min at 0 °C. Then, *N*,*O*-dimethylhydroxylamine hydrochloride (3.85 g, 39.5 mmol, 1.50 equiv) was added in one portion as a solid at 0 °C. Some bubbling was observed. The resulting light brown suspension was allowed to warm to 25 °C, and stirring was continued for 4 h. Full conversion was observed by TLC (hexanes/EtOAc, 80:20). The reaction was quenched by the addition of 3 M HCl (38 mL). The layers were separated, and the aqueous layer was extracted

with CH2Cl2 (1 x 30 mL). The combined organic phases were washed with 1 M HCl (1 x 30 mL), sat. aq. NaHCO3 (1 x 30 mL), and brine (1 x 30 mL), and then dried over MgSO4, filtered, and concentrated to afford 4.00 g (97%) of **64** as a clear, colorless oil requiring no further purification.

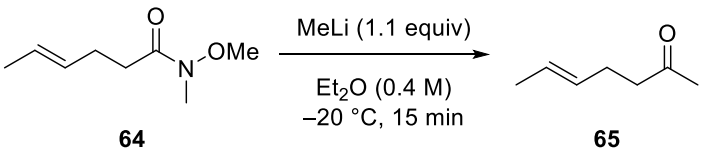
Data for **64**:

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

5.54 – 5.42 (m, 2H), 3.68 (s, 3H), 3.18 (s, 3H), 2.51 – 2.44 (m, 2H), 2.34 – 2.28 (m, 2H), 1.66 – 1.63 (m, 3H).

TLC: R_f 0.25 (hexanes/EtOAc, 80:20, $KMnO_4$)

(*E*)-hept-5-en-2-one (65)



64 **65**

A flame-dried, 250-mL, round bottomed flask equipped with a stir bar was charged with Weinreb amide **64** (4.00 g, 25.4 mmol) and Et_2O (50 mL). The resulting colorless solution was cooled to –20 °C, and methyllithium (1.68 M in Et_2O, 16.7 mL, 28.0 mmol, 1.1 equiv) was added dropwise. The resulting pale, yellow solution was stirred at –20 °C for 15 min. Full conversion was observed by TLC (hexanes/EtOAc, 90:10). The reaction was quenched by the addition of 1 M HCl until pH < 7 was obtained. The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 30 mL). The combined organic layers were washed with 1 M HCl (1 x 30 mL), sat. aq. $NaHCO_3$ (1 x 30 mL), and brine (1 x 30 mL), and then dried over Na_2SO_4, filtered, and concentrated to afford 2.70 g (88%) of **65** as a pale, yellow oil requiring no further purification. [**Note:** Due to the volatile nature of **65**, it should not be exposed to vacuum below 100 mmHg at 25 °C.]

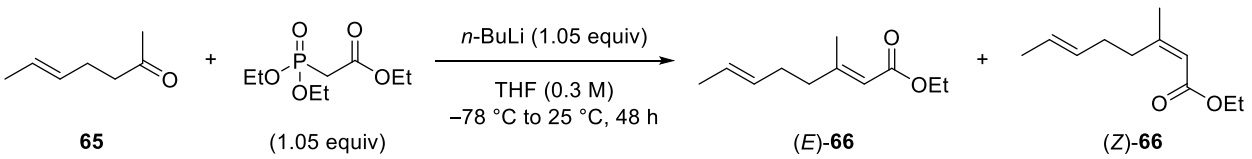
Data for **65**:

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

5.51 – 5.35 (m, 2H), 2.48 (t, J = 7.4 Hz, 2H), 2.29 – 2.21 (m, 2H), 2.13 (s, 3H), 1.65 – 1.61 (m, 3H).

TLC: R_f 0.38 (hexanes/EtOAc, 90:10, $KMnO_4$)

Ethyl (*E*,*E*)-3-Methylocta-2,6-dienoate (66)



An oven-dried, 200-mL, Schlenk flask equipped with a stir bar was charged with triethyl phosphonoacetate (4.7 mL, 23.5 mmol, 1.05 equiv) and THF (50 mL). The resulting clear, colorless solution was cooled to –78 °C, and *n*-butyllithium (2.33 M in hexanes, 10.1 mL, 23.5 mmol, 1.05 equiv) was added dropwise. The (still colorless) solution was stirred at –78 °C for 30 min. A solution of 5-hepten-2-one **65** (2.70 g, 22.4 mmol) was added dropwise. The reaction mixture was allowed to warm gradually to 25 °C, and stirring was continued for 48 h. A turbid, orange solution resulted. Nearly full conversion was observed by TLC (hexanes/EtOAc, 90:10). The reaction was quenched by the addition of sat. aq. NH_4Cl. The biphasic mixture was diluted with water and Et_2O, and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 30 mL). The combined organic layers were washed with brine, dried over Na_2SO4, filtered, and concentrated to afford 4.29 g of crude **66** as a 4:1 mixture of (*E*:*Z*) isomers. The mixture was purified by chromatography (silica gel) using pentane/Et_2O (98:2, isocratic) to afford 2.51 g (61%) of (*E*)-**66** and 0.64 g (16%) of (*Z*)-**66**, both in >98:2 geometric purity.

Data for (*E*)-**66**:

^{1}H NMR: (500 MHz, $CDCl_3$)
5.67 – 5.64 (m, 1H), 5.52 – 5.33 (m, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.21 – 2.12 (m, 4H), 2.15 (d, *J* = 1.2 Hz, 3H), 1.66 – 1.62 (m, 3H), 1.28 (t, *J* = 7.1 Hz, 3H).

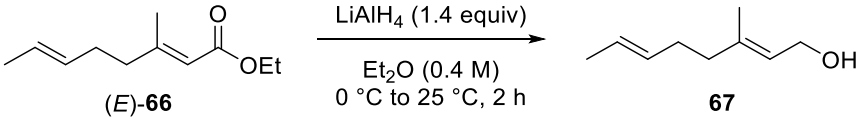
TLC: R_f 0.33 (pentane/Et_2O, 98:2, $KMnO_4$)

Data for (*Z*)-**66**:

^{1}H NMR: (500 MHz, $CDCl_3$)
5.67 – 5.63 (m, 1H), 5.51 – 5.40 (m, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.70 – 2.63 (m, 2H), 2.19 – 2.11 (m, 2H), 1.87 (d, *J* = 1.3 Hz, 3H), 1.66 – 1.61 (m, 3H), 1.27 (t, *J* = 7.1 Hz, 3H).

TLC: R_f 0.39 (pentane/Et_2O, 98:2, $KMnO_4$)

(2*E*,6*E*)-3-Methylocta-2,6-dien-1-ol (67)



(*E*)-**66** **67**

An oven-dried, 200-mL, Schlenk flask equipped with a stir bar was charged with lithium aluminum hydride (0.71 g, 19 mmol, 1.4 equiv) and Et_2O (28 mL). The resulting gray suspension was cooled to 0 °C. A solution of ethyl ester (*E*)-**66** (2.51 g, 13.8 mmol) in Et_2O (9 mL) was added dropwise over 15 min. Some mild gas evolution was observed. The reaction mixture was allowed to warm to 25 °C and stirring was continued for 2 h. Full conversion was observed by TLC (hexanes/EtOAc, 80:20). The reaction mixture was again cooled to 0 °C and quenched by the ***cautious*** dropwise addition of EtOAc (4.4 mL) with vigorous stirring. This step is highly exothermic and must be done slowly. The mixture was stirred for 10 min. A classic Fieser workup was performed in the following manner. Water (0.75 mL), 2 M NaOH (1.5 mL), and additional water (2.5 mL) were added to the mixture in succession, cautiously, at 0 °C. This caused the aluminum salts to clump together, and the organic phase was simply decanted from the flask into a separatory funnel. The residual salts were rinsed with Et_2O and likewise decanted (2 x 20 mL). The combined organic phases were washed with water (2 x 20 mL) and dried over Na_2SO_4, filtered, and concentrated to afford 1.85 g of crude **67** as a pale oil. The product was purified by chromatography (silica gel) using a hexanes/EtOAc gradient elution (95:5 to 90:10 to 85:15 to 80:20 to 75:25) to afford 1.58 g (82%) of **67** as a pale, yellow oil.

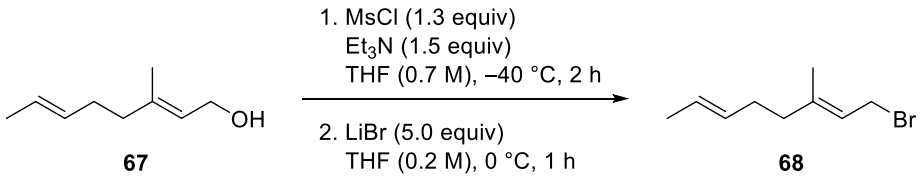
Data for **67**:

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

5.50 – 5.35 (m, 3H), 4.15 (d, J = 6.9 Hz, 2H), 2.15 – 2.02 (m, 4H), 1.68 – 1.66 (m, 3H), 1.66 – 1.62 (m, 3H), 1.11 (bs, 1H).

TLC: R_f 0.28 (hexanes/EtOAc, 80:20, UV/$KMnO_4$)

(2*E*,6*E*)-1-Bromo-3-methylocta-2,6-diene (68)



A flame-dried, three-necked, 100-mL, round bottomed flask equipped with a stir bar, addition funnel, septum, digital thermometer, and argon inlet adapter was charged with alcohol **67** (1.58 g, 11.3 mmol), THF (16 mL), and Et_3N (2.36 mL, 14.6 mmol, 1.3 equiv). The resulting clear, colorless solution was cooled to –40 °C, and mesyl chloride (1.13 mL, 16.9 mmol, 1.5 equiv) was added dropwise. The resulting white suspension was stirred at –40 °C for 2 h and then warmed to 0 °C. The suspension developed a pale yellow-cream color upon warming. The addition funnel was charged with a (cloudy) solution of anhydrous lithium bromide (4.84 g, 55.8 mmol, 5.0 equiv) in THF (34 mL). [**Note**: The dissolution of anhydrous LiBr in THF is substantially exothermic.] The solution was added dropwise to the reaction mixture at 0 °C over 30 min. Stirring was continued at 0 °C for 1 h. Full conversion was observed by TLC (hexanes/EtOAc, 90:10). The reaction was quenched by the addition of cold water (30 mL) and diluted with Et_2O. The layers were separated, and the aqueous phase was extracted with Et_2O (2 x 30 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated to afford 2.19 g (96%) of **68** as a yellow oil requiring no further purification.

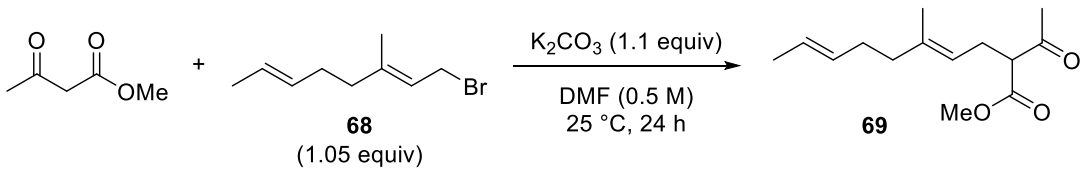
Data for **68**:

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

5.56 – 5.49 (m, 1H), 5.49 – 5.33 (m, 2H), 4.02 (d, J = 8.4 Hz, 2H), 2.11 – 2.07 (m, 4H), 1.73 – 1.70 (m, 3H), 1.64 (d, J = 5.1 Hz, 3H).

TLC: R_f 0.88 (hexanes/EtOAc, 90:10, UV/$KMnO_4$)

Methyl (4*E*,8*E*)-2-Acetyl-5-methyldeca-4,8-dienoate (69)



A flame-dried, 100-mL, round bottomed flask equipped with a stir bar was charged with bromide **68** (2.19 g, 10.9 mmol, 1.05 equiv) and DMF (20 mL). Anhydrous K_2CO_3 (1.57 g, 11.4 mmol, 1.1 equiv) was added in one portion (insoluble). Methyl acetoacetate (1.12 mL, 10.3 mmol) was added in one portion. The reaction mixture was stirred rapidly at 25 °C for 24 h. Over time, a yellow suspension resulted. Full conversion was observed by TLC (hexanes/EtOAc, 90:10). The reaction was quenched by the ***cautious*** addition of 1 M HCl until pH = 3 was obtained. The mixture was diluted with water and extracted with Et_2O (4 x 20 mL). The combined organic layers were washed with water (2 x 100 mL) and brine (100 mL), and then dried over $MgSO_4$, filtered, and concentrated to afford 2.27 g of crude **69**. The product was purified by chromatography (silica gel) using a hexanes/EtOAc gradient elution (95:5 to 92.7:7.5 to 90:10 to 87.5:12.5) to afford 1.76 g (72%) of **69** as an oil. Additionally, 0.20 g of the bis-alkylation product was isolated (R_f 0.45).

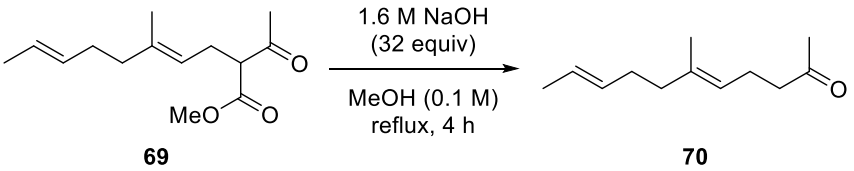
Data for **69**:

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

5.46 – 5.31 (m, 2H), 5.06 – 4.99 (m, 1H), 3.72 (s, 3H), 3.45 (t, J = 7.5 Hz, 1H), 2.55 (t, J = 7.4 Hz, 2H), 2.22 (s, 3H), 2.07 – 1.97 (m, 4H), 1.64 – 1.60 (m, 6H).

TLC: R_f 0.35 (hexanes/EtOAc, 90:10, UV/CAM)

(5*E*,9*E*)-6-Methylundeca-5,9-dien-2-one (70)



A 500-mL, round bottomed flask equipped with a stir bar and reflux condenser was charged with ketoester **69** (1.76 g, 7.38 mmol), MeOH (70 mL) and aq. NaOH (1.6 M, 150 mL, 236 mmol, 32 equiv). The resulting white suspension was heated to reflux for 4 h. Full conversion was observed by TLC (hexanes/EtOAc, 90:10). The reaction mixture was cooled to 0 °C and quenched by the addition of 6 M HCl until pH < 7 was obtained. The mixture was partitioned between water and Et_2O, and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to afford 1.29 g (97%) of **70** as a yellow oil requiring no further purification.

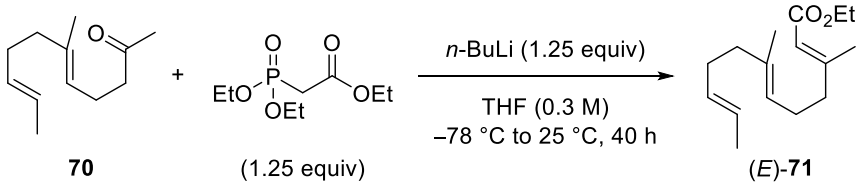
Data for **70**:

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

5.46 – 5.33 (m, 2H), 5.10 – 5.03 (m, 1H), 2.45 (t, *J* = 7.4 Hz, 2H), 2.26 (q, *J* = 7.2 Hz, 2H), 2.13 (s, 3H), 2.09 – 1.96 (m, 4H), 1.65 – 1.61 (m, 3H), 1.61 – 1.58 (m, 3H).

TLC: R_f 0.48 (hexanes/EtOAc, 90:10, UV/CAM)

Ethyl (2*E*,6*E*,10*E*)-3,7-Dimethyldodeca-2,6,10-trienoate (71)



An oven-dried, 100-mL, Schlenk flask equipped with a stir bar was charged with triethyl phosphonoacetate (1.60 mL, 8.0 mmol, 1.25 equiv) and THF (25 mL). The resulting clear, colorless solution was cooled to –78 °C, and *n*-butyllithium (2.33 M in hexanes, 3.44 mL, 8.0

mmol, 1.25 equiv) was added dropwise. The (still colorless) solution was stirred at –78 °C for 2 h. A solution of ketone **70** (1.16 g, 6.4 mmol) in THF (2 mL) was added dropwise at –78 °C. The reaction mixture was allowed to warm gradually to 25 °C, and stirring was continued for 36 h. A yellow solution resulted. Nearly full conversion was observed by TLC (hexanes/EtOAc, 90:10). The reaction was quenched by the addition of sat. aq. NH_4Cl. The biphasic mixture was diluted with water and Et_2O, and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 30 mL). The combined organic layers were washed with brine, dried over Na_2SO4, filtered, and concentrated to afford 1.86 g of crude **71** as a 4:1 mixture of (*E*:*Z*) isomers. The mixture was purified by chromatography (silica gel) using pentane/Et_2O (98:2, isocratic) to afford 1.00 g (62%) of (*E*)-**71** in >99:1 geometric purity.

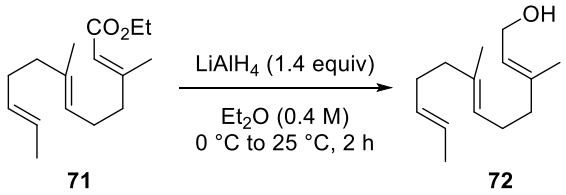
Data for (*E*)-**71**:

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

5.66 (s, 1H), 5.47 – 5.35 (m, 2H), 5.11 – 5.06 (m, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 2.18 – 2.14 (m, 7H), 2.09 – 2.04 (m, 2H), 2.03 – 1.98 (m, 2H), 1.65 – 1.62 (m, 3H), 1.59 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H).

TLC: R_f 0.25 (pentane/Et_2O, 98:2, UV/CAM)

(2*E*,6*E*,10*E*)-3,7-Dimethyldodeca-2,6,10-trien-1-ol (72)



An oven-dried, 50-mL, Schlenk flask equipped with a stir bar was charged with lithium aluminum hydride (0.21 g, 5.6 mmol, 1.4 equiv) and Et_2O (7 mL). The resulting gray suspension was cooled to 0 °C. A solution of ethyl ester (*E*)-**71** (1.00 g, 4.0 mmol) in Et_2O (3 mL) was added dropwise over 15 min. Some mild gas evolution was observed. The reaction mixture was allowed to warm to 25 °C and stirring was continued for 2 h. Full conversion was observed by TLC (hexanes/EtOAc, 90:10). The reaction mixture was again cooled to 0 °C and quenched by the ***cautious*** dropwise addition of EtOAc (1.5 mL) with vigorous stirring. This step is highly

exothermic and must be done slowly. The mixture was stirred for 10 min. A classic Fieser workup was performed in the following manner. Water (0.25 mL), 2 M NaOH (0.5 mL), and additional water (0.8 mL) were added to the mixture in succession, cautiously, at 0 °C. This caused the aluminum salts to clump together, and the organic phase was decanted from the flask into a separatory funnel. The residual salts were rinsed with Et_2O and likewise decanted (2 x 10 mL). The combined organic phases were washed with water (2 x 10 mL) and dried over Na_2SO_4, filtered, and concentrated to afford 0.84 g of crude **72** as a pale oil. The product was purified by chromatography (silica gel) using a hexanes/EtOAc gradient elution (90:10 to 80:20 to 70:30 to 60:40) to afford 0.65 g (78%) of **72** as a pale, yellow oil.

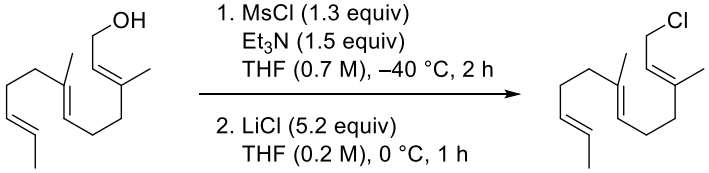
Data for **72**:

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

5.47 – 5.36 (m, 3H), 5.13 – 5.08 (m, 1H), 4.16 (app. t, J = 6.1 Hz, 2H), 2.14 – 1.98 (m, 8H), 1.68 (s, 3H), 1.64 (d, J = 4.3 Hz, 3H), 1.59 (s, 3H), 1.09 (t, J = 5.5 Hz, 1H).

TLC: R_f 0.17 (hexanes/EtOAc, 90:10, UV/$KMnO_4$)

(2*E*,6*E*,10*E*)-1-Chloro-3,7-dimethyldodeca-2,6,10-triene (73)



72 **73**

A flame-dried, 10-mL, Schlenk flask equipped with a stir bar was charged with alcohol **72** (203.3 mg, 0.98 mmol), THF (1.5 mL), and Et_3N (0.20 mL, 1.5 mmol, 1.5 equiv). The resulting clear, colorless solution was cooled to –40 °C, and mesyl chloride (0.10 mL, 1.3 mmol, 1.3 equiv) was added dropwise. The resulting white suspension was stirred at –40 °C for 2 h and then warmed to 0 °C. A turbid solution of anhydrous lithium chloride (214 mg, 5.0 mmol, 5.2 equiv) in THF (3.5 mL) was added dropwise to the suspension at 0 °C. [**Note**: The dissolution of anhydrous LiCl in THF is substantially exothermic.] Stirring was continued at 0 °C for 1 h. Full conversion was observed by TLC (hexanes/EtOAc, 90:10). The reaction was quenched by the addition of cold

water (5 mL) and diluted with Et_2O. The layers were separated, and the aqueous phase was extracted with Et_2O (2 x 10 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated to afford 222.3 mg (90%) of **73** as a yellow oil requiring no further purification. Yield shown has been adjusted for approx. 90% purity.

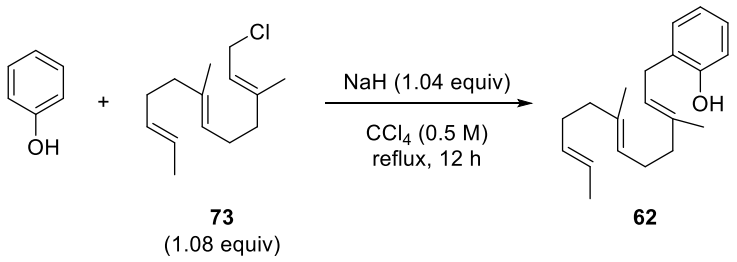
Data for **73**:

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

5.48 – 5.36 (m, 3H), 5.11 – 5.06 (m, 1H), 4.10 (d, J = 8.0 Hz, 2H), 2.15 – 2.04 (m, 6H), 2.03 – 1.98 (m, 2H), 1.75 – 1.71 (m, 3H), 1.64 (d, J = 4.4 Hz, 3H), 1.59 (s, 3H).

TLC: R_f 0.88 (hexanes/EtOAc, 90:10, UV/CAM)

2-((2*E*,6*E*,10*E*)-3,7-Dimethyldodeca-2,6,10-trien-1-yl)phenol (62)



An oven-dried, 5-mL, round bottomed flask equipped with a stir bar was charged with 100% sodium hydride (20.4 mg, 0.85 mmol, 1.04 equiv) inside of the glovebox. The flask was removed from the glovebox, placed under argon, and charged with CCl_4 (1.0 mL). The resulting white suspension was cooled to 0 °C, and phenol (76.8 mg, 0.82 mmol) was added as a solid. Gas evolution was observed. The pinkish suspension was allowed to warm to 25 °C, and stirring was continued for 30 min. Neat **73** (222 mg, 0.88 mmol, 1.08 equiv) was added dropwise to the suspension. An additional portion of CCl_4 (0.5 mL) was used to rinse the syringe and ensure complete transfer of **73** to the reaction flask. The flask was fitted with a reflux condenser, and the suspension was heated to reflux for 12 h. A turbid, yellow solution resulted. Full conversion was observed by TLC (hexanes/EtOAc, 90:10). The reaction mixture was cooled to 25 °C and quenched with water. The mixture was transferred to a separatory funnel and diluted with water, 3 M HCl, and Et_2O. The layers were separated, and the aqueous phase was extracted with Et_2O (2

x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford 0.29 g of crude **62**. The product was purified by chromatography (silica gel) using a hexanes/EtOAc gradient elution (97.5:2.5 to 95:5 to 92.5:7.5 to 90:10) to afford 126.8 mg (55%) of **62** as an oil.

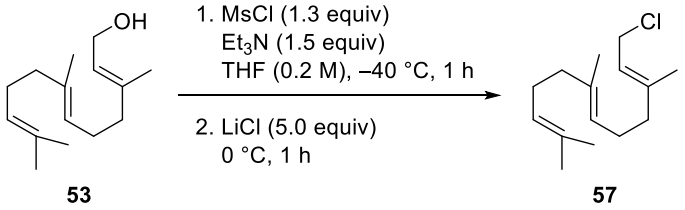
Data for **62**:

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

7.14 – 7.09 (m, 2H), 6.86 (app. t, *J* = 7.4 Hz, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 5.46 – 5.36 (m, 2H), 5.33 (app. t, *J* = 7.2 Hz, 1H), 5.09 (app. t, *J* = 6.7 Hz, 1H), 5.05 (s, 1H), 3.37 (d, *J* = 7.2 Hz, 2H), 2.16 – 2.03 (m, 6H), 2.02 – 1.97 (m, 2H), 1.77 (s, 3H), 1.63 (d, *J* = 3.8 Hz, 3H), 1.58 (s, 3H).

TLC: R_f 0.36 (hexanes/EtOAc, 90:10, UV/CAM)

Preparation of Farnesyl Chloride (**57**)



A flame-dried, 50-mL, Schlenk flask equipped with a stir bar was charged with *trans*,*trans*-farnesol **53** (445.5 mg, 2.0 mmol), THF (10 mL), and Et_3N (0.42 mL, 3.0 mmol, 1.5 equiv). The resulting clear, colorless solution was cooled to –40 °C, and mesyl chloride (0.20 mL, 2.6 mmol, 1.3 equiv) was added dropwise. The resulting white suspension was stirred at –40 °C for 1 h and then warmed to 0 °C. Solid, anhydrous lithium chloride (422 mg, 10.0 mmol, 5.0 equiv) was added in one portion to the suspension at 0 °C. [**Note**: The dissolution of anhydrous LiCl in THF is substantially exothermic.] Stirring was continued at 0 °C for 1 h. Full conversion was observed by TLC (hexanes/EtOAc, 90:10). The reaction was quenched by the addition of cold water (10 mL) and diluted with Et_2O. The layers were separated, and the aqueous phase was extracted with Et_2O (2 x 25 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated to afford 503.7 mg (94%) of **57** as a yellow oil requiring no further purification. Yield shown has been adjusted for approx. 90% purity.

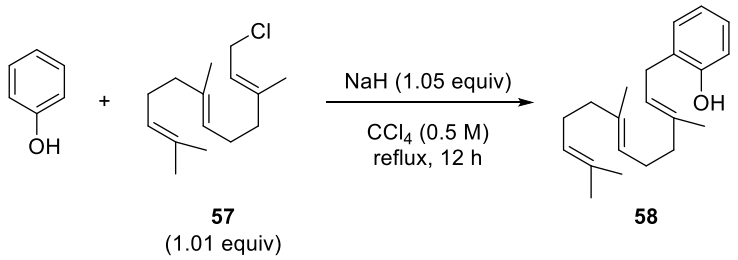
Data for **57**:

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

5.48 – 5.41 (m, 1H), 5.11 – 5.05 (m, 2H), 4.10 (d, *J* = 8.0 Hz, 2H), 2.15 – 2.10 (m, 2H), 2.09 – 2.03 (m, 4H), 2.01 – 1.95 (m, 2H), 1.73 (m, 3H), 1.68 (m, 3H), 1.60 (s, 6H).

TLC: R_f 0.87 (hexanes/EtOAc, 90:10, UV/CAM)

2-((2*E*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trien-1-yl)phenol (**58**)



57
(1.01 equiv)

58

An oven-dried, 5-mL, round bottomed flask equipped with a stir bar was charged with 100% sodium hydride (46.8 mg, 1.95 mmol, 1.05 equiv) inside of the glovebox. The flask was removed from the glovebox, placed under argon, and charged with CCl_4 (3.0 mL). The resulting white suspension was cooled to 0 °C, and phenol (175 mg, 1.86 mmol) was added as a solid. Gas evolution was observed. The pinkish suspension was allowed to warm to 25 °C, and stirring was continued for 30 min. Neat **57** (504 mg, 1.88 mmol, 1.01 equiv) was added dropwise to the suspension. An additional portion of CCl_4 (0.5 mL) was used to rinse the syringe and ensure complete transfer of **57** to the reaction flask. The flask was fitted with a reflux condenser, and the suspension was heated to reflux for 12 h. A turbid, yellow solution resulted. Full conversion was observed by TLC (hexanes/EtOAc, 90:10). The reaction mixture was cooled to 25 °C and quenched with water. The mixture was transferred to a separatory funnel and diluted with water, 3 M HCl, and Et_2O. The layers were separated, and the aqueous phase was extracted with Et_2O (2 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford 0.62 g of crude **58**. The product was purified by chromatography (silica gel) using a hexanes/EtOAc gradient elution (98:2 to 96:4 to 94:6 to 92:8) to afford 247.9 mg (45%) of **58** as an oil.

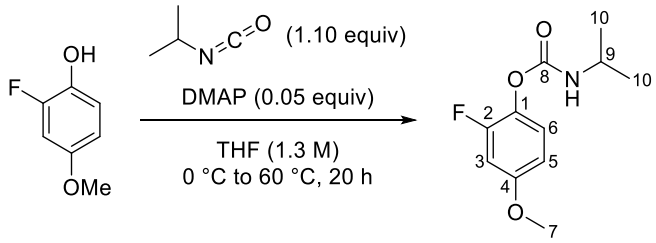
Data for **58**:

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

7.14 – 7.09 (m, 2H), 6.86 (td, *J* = 7.5, 1.1 Hz, 1H), 6.80 (app. d, *J* = 7.6 Hz, 1H), 5.36 – 5.31 (m, 1H), 5.12 – 5.07 (m, 2H), 5.06 (s, 1H), 3.37 (d, *J* = 7.2 Hz, 2H), 2.16 – 2.02 (m, 6H), 2.01 – 1.95 (m, 2H), 1.77 (app. s, 3H), 1.67 (app. s, 3H), 1.60 (app. s, 3H).

TLC: R_f 0.39 (hexanes/EtOAc, 90:10, UV/CAM)

Preparation of 2-Fluoro-4-methoxyphenyl Isopropylcarbamate (**94a**)



The following procedure is analogous to the one described by Hoppe et al. for the preparation of carbamate **94b**.[90] A flame-dried, 5-mL, round-bottomed flask equipped with a stir bar was charged with DMAP (8.0 mg, 0.065 mmol, 0.05 equiv) and THF (1.0 mL). A thin, white suspension resulted. 2-Fluoro-4-methoxyphenol **93a** (182.3 mg, 1.28 mmol) was added in one portion. The resulting clear, colorless solution was cooled to 0 °C using an ice bath. Isopropyl isocyanate (139 μL, 120 mg, 1.40 mmol, 1.10 equiv) was added dropwise to the solution over 1 min. The ice bath was removed and replaced with an oil bath. The flask was equipped with a reflux condenser and the reaction was heated to 60 °C for 20 h. Over time, a very pale, yellow solution resulted. Conversion was assessed by TLC (hexanes/Et_2O, 50:50). The reaction was cooled to 25 °C and quenched by the addition of 3 M HCl (1 mL). The biphasic mixture was stirred rapidly for 2 min and then partitioned between Et_2O (5 mL) and water (5 mL) in a separatory funnel. The layers were separated, and the aqueous phase was extracted with Et_2O (2 x 5 mL). The combined organic layers were washed with 1 M HCl (1 x 5 mL), sat. aq. $NaHCO_3$ (1 x 5 mL), and brine (1 x 5 mL), and then dried over $MgSO_4$, filtered, and concentrated (30 °C, 15 mmHg) to afford 258.3 mg (89%) of **94a** as a white solid. At this point, the level of purity is sufficient for most applications. To obtain analytically pure material, the solid was dissolved in a minimal amount of

boiling Et_2O (2 mL, 40 °C) and the resulting colorless solution was cooled to 0 °C for 30 min. The resulting crystals were collected by vacuum filtration and rinsed with ice-cold Et_2O (1 mL) to afford 144.8 mg (50%) of **94a** as small, white needles.

Data for **94a**:

m.p.: 85–87 °C (diethyl ether)

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

7.08 (t, J = 8.9 Hz, 1H, HC(6)), 6.70 (dd, J = 11.9, 2.6 Hz, 1H, HC(3)), 6.67 – 6.60 (m, 1H, HC(5)), 4.88 (bs, 1H, NH), 3.88 (oct, J = 6.4 Hz, 1H, HC(9)), 3.78 (s, 3H, H_3C(7)), 1.24 (d, J = 6.5 Hz, 6H, H_3C(10)). Minor rotameric signals observed: 4.54 (bs, NH) and 3.97 (bs, HC(9)).

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

157.9 (d, $J_{C–F}$ = 9.7 Hz, C(4)), 155.0 (d, $J_{C–F}$ = 248.2 Hz, C(2)), 153.3 (C(8)), 132.1 (d, $J_{C–F}$ = 12.7 Hz, C(1)), 124.4 (d, $J_{C–F}$ = 1.9 Hz, HC(6)), 109.5 (d, $J_{C–F}$ = 2.9 Hz, HC(5)), 102.9 (d, $J_{C–F}$ = 22.1 Hz, HC(3)), 55.9 (H_3C(7)), 43.8 (HC(9)), 23.0 (H_3C(10)).

^{19}F NMR: (471 MHz, $CDCl_3$)

–127.20 (t, J = 10.1 Hz). Minor rotameric signal observed: –127.11 (bs).

IR: 3342 (m), 3085 (w), 2980 (w), 2937 (w), 2837 (w), 1707 (s), 1623 (m), 1601 (m), 1506 (s), 1456 (m), 1432 (m), 1388 (w), 1372 (m), 1351 (w), 1324 (m), 1285 (w), 1268 (m), 1244 (s), 1204 (s), 1193 (s), 1173 (s), 1154 (s), 1134 (m), 1120 (s), 1040 (s), 1024 (s), 955 (m), 947 (m), 933 (m), 853 (s), 823 (s), 787 (m), 769 (m), 722 (m), 620 (s), 591 (m), 563 (s), 525 (m), 469 (m).

LRMS: (ESI, $[M+H]^+$)

86.0 (43), 127.0 (17), 129.0 (12), 142.0 (82), 143.1 (76), 228.1 (100), 229.1 (14).

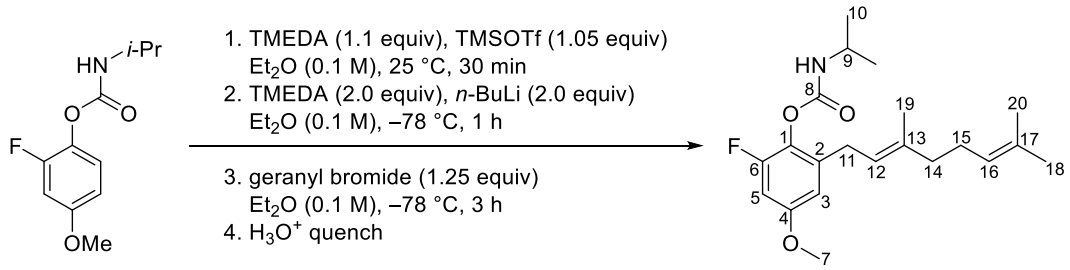
Analysis: $C_{11}H_{14}FNO_3$ (227.24)

Calcd: C, 58.14%; H, 6.21%; N, 6.16%

Found: C, 58.19%; H, 6.35%; N, 6.11%

TLC: R_f 0.31 (hexanes/Et_2O, 50:50, CAM)

Preparation of (*E*)**-2-(3,7-Dimethylocta-2,6-dien-1-yl)-6-fluoro-4-methoxyphenyl Isopropyl Carbamate** (**95a**)



The following procedure is adapted from the one published by Hoppe et al.[91] An oven-dried, 25-mL Schlenk flask equipped with a stir bar was charged with carbamate **94a** (229.1 mg, 1.01 mmol), diethyl ether (10 mL), and TMEDA (165 μL, 1.09 mmol, 1.1 equiv). A clear, colorless solution resulted. Neat TMSOTf (190 μL, 1.06 mmol, 1.05 equiv) was added dropwise at 25 °C. The resulting white suspension was stirred for 30 min at 25 °C. The suspension cleared to afford a colorless, slightly turbid solution. An additional bolus of TMEDA (303 μL, 2.01 mmol, 2.0 equiv) was added at 25 °C. With *vigorous stirring*, the solution was cooled to –78 °C using a dry ice/isopropanol bath. A solution of *n*-butyllithium in hexanes (2.25 M, 0.89 mL, 2.0 mmol, 2.0 equiv) was added dropwise at –78 °C, and the mixture was stirred for 1 h at –78 °C. Neat geranyl bromide (271.3 mg, 1.25 mmol, 1.24 equiv) was added dropwise at –78 °C and the reaction was stirred for 3 h at –78 °C. After 3 h, the reaction was quenched with methanol (0.1 mL) followed by aq. 2 M HCl (6 mL). The cold bath was removed and the mixture was warmed to 25 °C. The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 25 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ and brine, and then dried over magnesium sulfate, filtered, and concentrated (25 °C, 20 mmHg) to afford 0.44 g of crude **95a**. The product was purified by column chromatography (silica gel, 3 x 29 cm, dry load on Celite, 25-mL fractions, hexanes/EtOAc gradient elution: 97.5:2.5 (400 mL) to 95:5 (300 mL) to 92.5:7.5 (300 mL) to 90:10 (300 mL) to 87.5:12.5 (300 mL)) to afford 166.6 mg (45%) of mostly pure **95a**. The product was purified again by column chromatography (silica gel, 2 x 28 cm, dry load on Celite, 10-mL fractions, hexanes/EtOAc gradient elution: 97.5:2.5 (300 mL) to 95:5 (200 mL) to 92.5:7.5 (200 mL) to 90:10 (200 mL) to 87.5:12.5 (200 mL)) to afford 142.4 mg (39%) of analytically pure **95a** as a clear, colorless oil. The oil solidified after standing at –20 °C for 6 days to afford white crystals.

Data for **95a**:

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

6.60 – 6.47 (m, 2H, HC(5) and HC(3)), 5.24 (t, J = 7.0 Hz, 1H, HC(12)), 5.14 – 5.06 (m, 1H, HC(16)), 4.88 (bd, J = 6.9 Hz, 1H, NH), 3.89 (oct, J = 6.4 Hz, 1H, HC(9)), 3.75 (s, 3H, H_3C(7)), 3.25 (d, J = 7.0 Hz, 2H, H_2C(11)), 2.15 – 2.07 (m, 2H, H_2C(15)), 2.07 – 2.00 (m, 2H, H_2C(14)), 1.68 (s, 6H, H_3C(19) and H_3C(18)), 1.60 (s, 3H, H_3C(20)), 1.24 (d, J = 6.4 Hz, 6H, H_3C(10)). Minor rotameric signals observed: 4.54 (bs, NH) and 3.99 (bs, HC(9)).

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

157.4 (d, $J_{C–F}$ = 10.7 Hz, C(4)), 155.4 (d, $J_{C–F}$ = 247.5 Hz, C(6)), 153.1 (C(8)), 137.5 (C(13) or C(2)), 137.4 (C(13) or C(2)), 131.7 (C(17)), 130.5 (d, $J_{C–F}$ = 13.1 Hz, C(1)), 124.3 (HC(16)), 121.1 (HC(12)), 110.2 (d, $J_{C–F}$ = 2.4 Hz, HC(3)), 100.0 (d, $J_{C–F}$ = 22.7 Hz, HC(5)), 55.8 (H_3C(7)), 43.8 (HC(9)), 39.8 (H_2C(14)), 28.6 (d, $J_{C–F}$ = 2.6 Hz, H_2C(11)), 26.8 (H_2C(15)), 25.8 (H_3C(18)), 23.0 (H_3C(10)), 17.9 (H_3C(20)), 16.3 (H_3C(19)).

^{19}F NMR: (471 MHz, CDCl3)

–127.63 (d, J = 11.3 Hz)

IR: 3322 (m), 2973 (m), 2919 (w), 1710 (s), 1633 (m), 1597 (m), 1537 (m), 1492 (s), 1468 (m), 1447 (s), 1365 (m), 1344 (s), 1261 (m), 1233 (s), 1211 (s), 1170 (s), 1142 (s), 1108 (w), 1079 (m), 1055 (s), 1035 (s), 1021 (s), 949 (m), 928 (m), 872 (m), 858 (m), 809 (m), 800 (m), 764 (w), 652 (m), 629 (m), 609 (w), 548 (m).

LRMS: (ESI, $[M+H]^+$)

169.1 (20), 183.1 (9), 197.1 (16), 279.2 (100), 280.2 (32), 364.2 (31), 386.2 (63).

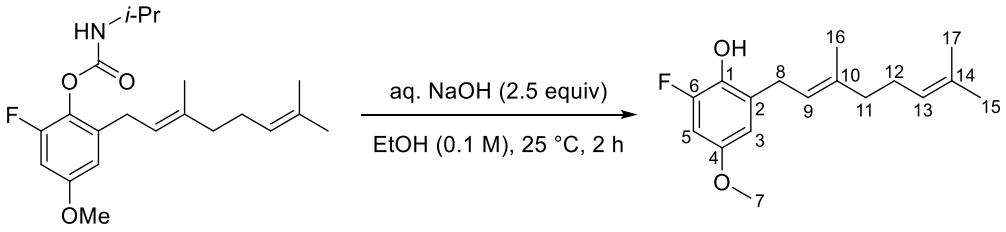
Analysis: $C_{21}H_{30}FNO_3$ (363.47)

Calcd: C, 69.39%; H, 8.32%; N, 3.85%

Found: C, 69.02%; H, 8.25%; N, 3.96%

TLC: R_f 0.15 (hexanes/EtOAc, 90:10, CAM)

Preparation of (*E*)**-2-(3,7-Dimethylocta-2,6-dien-1-yl)-6-fluoro-4-methoxyphenol** (**89a**)



The following procedure is adapted from the one published by Hoppe et al.[91] A 50-mL round-bottomed flask equipped with a stir bar was charged with carbamate **95a** (365.9 mg, 1.01 mmol) and ethanol (9 mL). To this clear, colorless solution was added aq. 2 M NaOH (1.25 mL). The resulting yellow solution was stirred at 25 °C for 2 h and became turbid over time. Full conversion was observed by TLC (hexanes/EtOAc, 90:10). The reaction was acidified to pH = 1 by the addition of aq. 2 M HCl, resulting in a clear, colorless solution. The mixture was partitioned between water (25 mL) and Et_2O (25 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (2 x 25 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated (25 °C, 20 mmHg) to afford 0.32 g of crude **89a**. The product was purified by column chromatography (silica gel, 3 x 25 cm, dry load on Celite, 25-mL fractions, hexanes/EtOAc gradient elution: 97.5:2.5 (300 mL) to 95:5 (300 mL) to 92.5:7.5 (300 mL) to 90:10 (300 mL)) to afford 250.5 mg (89%) of **89a**. The product was purified to an analytical standard by diffusion pump Kugelrohr distillation (ABT 70 °C, 3.4 x 10^{-5} mmHg) to afford 243.3 mg (87%) of **89a** as a clear, colorless oil.

Data for **89a**:

b.p.: 70 °C (ABT, 3.4 x 10^{-5} mmHg)

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

6.56 – 6.51 (m, 1H, HC(5)), 6.50 – 6.46 (m, 1H, HC(3)), 5.33 – 5.27 (m, 1H, HC(9)), 5.12 – 5.06 (m, 1H, HC(13)), 4.74 (d, *J* = 4.0 Hz, 1H, OH), 3.73 (s, 3H, H_3C(7)), 3.35 (d, *J* = 7.3 Hz, 2H, H_2C(8)), 2.15 – 2.08 (m, 2H, H_2C(12)), 2.08 – 2.02 (m, 2H, H_2C(11)), 1.72 (s, 3H, H_3C(16)), 1.68 (s, 3H, H_3C(15)), 1.60 (s, 3H, H_3C(17)).

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

153.0 (d, $J_{C–F}$ = 10.1 Hz, C(4)), 151.3 (d, $J_{C–F}$ = 236.9 Hz, C(6)), 137.8 (C(10)), 135.6 (d, $J_{C–F}$ = 13.9 Hz, C(1)), 131.8 (C(14)), 130.7 (d, $J_{C–F}$ = 2.4 Hz, C(2)), 124.2 (HC(13)), 121.4 (HC(9)), 110.6 (d, $J_{C–F}$ = 2.6 Hz, HC(3)), 99.5 (d, $J_{C–F}$ = 22.3 Hz, HC(5)), 55.9 (H_3C(7)), 39.9 (H_2C(11)), 28.7 (d, $J_{C–F}$ = 2.5 Hz, H_2C(8)), 26.7 (H_2C(12)), 25.8 (H_3C(15)), 17.9 (H_3C(17)), 16.3 (H_3C(16)).

^{19}F NMR: (471 MHz, $CDCl_3$)

–138.38 (d, J = 10.8 Hz).

IR: 3434 (bw), 2917 (w), 2847 (w), 1601 (m), 1498 (s), 1467 (m), 1445 (s), 1376 (w), 1341 (m), 1220 (s), 1191 (m), 1135 (s), 1045 (s), 977 (m), 948 (w), 839 (m), 816 (m), 786 (m), 726 (w), 618 (w), 562 (w), 527 (w).

LRMS: (ESI, $[M]^+$)

109.1 (29), 123.1 (93), 124.1 (10), 139.1 (10), 141.0 (12), 154.0 (40), 155.1 (90), 156.1 (55), 157.1 (10), 161.1 (14), 167.1 (12), 169.1 (13), 179.1 (13), 181.1 (14), 189.1 (25), 193.1 (42), 194.1 (13), 195.1 (49), 196.1 (13), 207.1 (12), 209.1 (42), 210.1 (37), 222.1 (11), 235.1 (14), 278.2 (100), 279.2 (49).

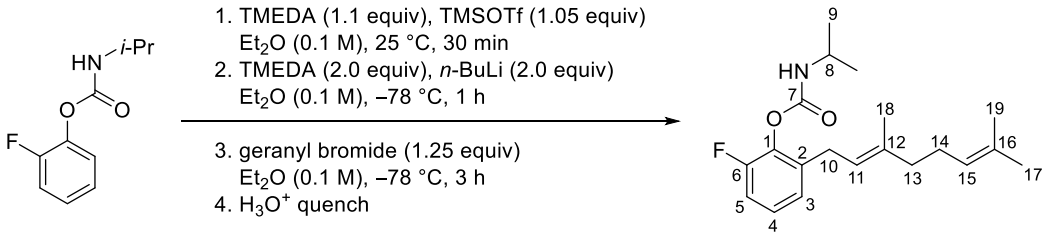
Analysis: $C_{17}H_{23}FO_2$ (278.37)

Calcd: C, 73.35%; H, 8.33%

Found: C, 73.08%; H, 8.25%

TLC: R_f 0.28 (hexanes/EtOAc, 90:10, CAM)

Preparation of (*E*)**-2-(3,7-Dimethylocta-2,6-dien-1-yl)-6-fluorophenyl Isopropyl Carbamate** (**95b**)



The following procedure is adapted from the one published by Hoppe et al. An oven-dried, 25-mL Schlenk flask equipped with a stir bar was charged with carbamate **94b** (201.0 mg, 1.02

mmol), diethyl ether (10 mL), and TMEDA (165 μL, 1.09 mmol, 1.1 equiv). A clear, colorless solution resulted. Neat TMSOTf (190 μL, 1.05 mmol, 1.03 equiv) was added dropwise at 25 °C. The resulting white suspension was stirred for 30 min at 25 °C. The suspension cleared to afford a colorless, slightly turbid solution. An additional bolus of TMEDA (303 μL, 2.01 mmol, 2.0 equiv) was added at 25 °C. With *vigorous stirring*, the solution was cooled to –78 °C using a dry ice/isopropanol bath. A solution of *n*-butyllithium in hexanes (2.25 M, 0.89 mL, 2.0 mmol, 2.0 equiv) was added dropwise at –78 °C, and the mixture was stirred for 1 h at –78 °C. Neat geranyl bromide (271.3 mg, 1.25 mmol, 1.23 equiv) was added dropwise at –78 °C and the reaction was stirred for 3 h at –78 °C. After 3 h, the reaction was quenched with methanol (0.1 mL) followed by aq. 2 M HCl (6 mL). The cold bath was removed and the mixture was warmed to 25 °C. The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 25 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ and brine, and then dried over magnesium sulfate, filtered, and concentrated (25 °C, 20 mmHg) to afford 0.42 g of crude **95b**. The product was purified by column chromatography (silica gel, 3 x 28 cm, dry load on Celite, 25-mL fractions, hexanes/EtOAc gradient elution: 97.5:2.5 (400 mL) to 95:5 (300 mL) to 92.5:7.5 (300 mL) to 90:10 (300 mL) to 87.5:12.5 (300 mL)) to afford 145.5 mg (43%) of mostly pure **95b**. The product was purified again by column chromatography (silica gel, 2 x 30 cm, dry load on Celite, 10-mL fractions, hexanes/acetone gradient elution: 95:5 (200 mL) to 90:10 (200 mL) to 85:15 (200 mL)) to afford 135.0 mg (40%) of analytically pure **95b** as a clear, colorless oil.

Data for **95b**:

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

7.11 – 7.04 (m, 1H, HC(4)), 7.02 – 6.92 (m, 2H, HC(5) and HC(3)), 5.31 – 5.21 (m, 1H, HC(11)), 5.14 – 5.05 (m, 1H, HC(15)), 4.91 (d, J = 6.7 Hz, 1H, NH), 3.90 (oct, J = 6.5 Hz, 1H, HC(8)), 3.30 (d, J = 7.1 Hz, 2H, H_2C(10)), 2.15 – 2.07 (m, 2H, H_2C(14)), 2.07 – 2.00 (m, 2H, H_2C(13)), 1.68 (s, 6H, H_3C(18) and H_3C(17)), 1.60 (s, 3H, H_3C(19)), 1.25 (d, J = 6.5 Hz, 6H, H_3C(9)). Minor rotameric signals observed: 4.56 (bs, NH) and 4.00 (bs, HC(8)).

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

155.3 (d, $J_{C–F}$ = 248.1 Hz, C(6)), 152.7 (C(7)), 137.2 (C(12) or C(2)), 137.1 (C(12) or C(2)), 136.9 (d, $J_{C–F}$ = 12.7 Hz, C(1)), 131.7 (C(16)), 126.1 (d, $J_{C–F}$ = 7.8 Hz, HC(4)), 124.7 (d, $J_{C–F}$ = 3.0 Hz, HC(3)), 124.3 (HC(15)), 121.3 (HC(11)), 114.0 (d,

$J_{C–F}$ = 18.9 Hz, HC(5)), 43.8 (HC(8)), 39.8 (H_2C(13)), 28.4 (d, $J_{C–F}$ = 2.3 Hz, H_2C(10)), 26.7 (H_2C(14)), 25.8 (H_3C(17)), 23.0 (H_3C(9)), 17.8 (H_3C(19)), 16.3 (H_3C(18)).

^{19}F NMR: (471 MHz, CDCl3)

–129.86 (dd, *J* = 9.6, 5.1 Hz).

IR: (neat)

3326 (w), 2972 (w), 2921 (w), 1719 (s), 1617 (w), 1594 (w), 1528 (m), 1474 (s), 1457 (m), 1387 (w), 1369 (m), 1352 (w), 1323 (w), 1273 (s), 1244 (s), 1194 (s), 1171 (s), 1132 (w), 1108 (w), 1067 (m), 1024 (m), 934 (m), 823 (w), 770 (s), 714 (w), 692 (w), 628 (w), 553 (w).

LRMS: (ESI, $[M+H]^+$)

125.0 (46), 139.1 (55), 153.1 (12), 167.1 (15), 249.2 (100), 250.2 (18), 303.1 (13), 334.2 (38), 340.2 (14), 351.2 (10), 356.2 (31).

HRMS: calcd for $C_{20}H_{28}FNO_2Na$ ($[M+Na]^+$): 356.2002, found: 356.2018

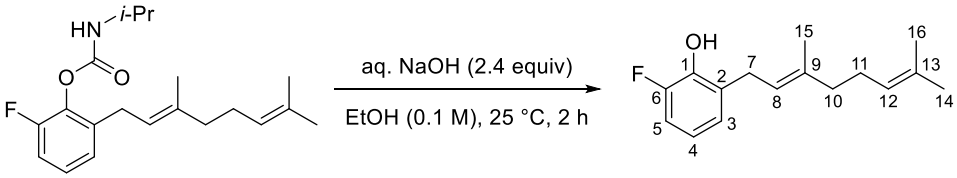
Analysis: $C_{20}H_{28}FNO_2$ (333.45)

Calcd: C, 72.04%; H, 8.46%; N, 4.20%

Found: C, 71.95%; H, 8.38%; N, 4.25%

TLC: R_f 0.25 (hexanes/EtOAc, 90:10, UV/CAM)

Preparation of (*E*)**-2-(3,7-Dimethylocta-2,6-dien-1-yl)-6-fluorophenol** (**89b**)



The following procedure is adapted from the one published by Hoppe et al. A 50-mL round-bottomed flask equipped with a stir bar was charged with carbamate **95b** (342.3 mg, 1.03 mmol) and ethanol (9 mL). To this clear, colorless solution was added aq. 2 M NaOH (1.25 mL). The resulting yellow solution was stirred at 25 °C for 2 h and became turbid over time. Full conversion was observed by TLC (hexanes/EtOAc, 90:10). The reaction was acidified to pH = 1 by the addition of aq. 2 M HCl, resulting in a clear, colorless solution. The mixture was partitioned

between water (25 mL) and Et_2O (25 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (2 x 25 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated (25 °C, 20 mmHg) to afford 0.35 g of crude **xx**. The product was purified by column chromatography (silica gel, 3 x 25 cm, dry load on Celite, 25-mL fractions, hexanes/EtOAc gradient elution: 97.5:2.5 (300 mL) to 95:5 (300 mL) to 92.5:7.5 (300 mL)) to afford 233.4 mg (92%) of **89b**. The product was purified to an analytical standard by diffusion pump Kugelrohr distillation (ABT 70 °C, 3.6 x 10^{-5} mmHg) to afford 225.1 mg (88%) of **89b** as a clear, colorless oil.

Data for **89b**:

b.p.: 70 °C (ABT, 3.6 x 10^{-5} mmHg)

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

6.96 – 6.87 (m, 2H, HC(3) and HC(5)), 6.77 (td, J = 7.9, 5.5 Hz, 1H, HC(4)), 5.36 – 5.28 (m, 1H, HC(8)), 5.13 (d, J = 4.5 Hz, 1H, OH), 5.12 – 5.06 (m, 1H, HC(12)), 3.38 (d, J = 7.3 Hz, 2H, H_2C(7)), 2.16 – 2.09 (m, 2H, H_2C(11)), 2.08 – 2.02 (m, 2H, H_2C(10)), 1.73 (s, 3H, H_3C(15)), 1.68 (s, 3H, H_3C(14)), 1.60 (s, 3H, H_3C(16)).

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

151.3 (d, $J_{C–F}$ = 237.0 Hz, C(6)), 141.8 (d, $J_{C–F}$ = 13.7 Hz, C(1)), 137.5 (C(9)), 131.8 (C(13)), 130.3 (d, $J_{C–F}$ = 1.0 Hz, C(2)), 125.0 (d, $J_{C–F}$ = 3.0 Hz, HC(3)), 124.3 (HC(12)), 121.6 (HC(8)), 120.0 (d, $J_{C–F}$ = 7.4 Hz, HC(4)), 113.1 (d, $J_{C–F}$ = 18.4 Hz, HC(5)), 39.9 (H_2C(10)), 28.4 (d, $J_{C–F}$ = 2.8 Hz, H_2C(7)), 26.7 (H_2C(11)), 25.8 (H_3C(14)), 17.9 (H_3C(16)), 16.3 (H_3C(15)).

^{19}F NMR: (471 MHz, $CDCl_3$)

–141.47 (dt, J = 10.0, 5.0 Hz).

IR: (neat)

3584 (w), 3467 (w), 2967 (w), 2915 (w), 2855 (w), 1667 (w), 1619 (w), 1596 (w), 1489 (m), 1474 (s), 1449 (m), 1377 (w), 1343 (w), 1299 (w), 1258 (s), 1207 (m), 1154 (w), 1108 (w), 1083 (w), 1064 (w), 963 (m), 949 (w), 918 (w), 885 (w), 830 (m), 768 (m), 744 (w), 727 (m), 695 (w), 560 (w).

LRMS: (ESI, $[M]^+$)

67.1 (10), 69.1 (70), 81.1 (13), 109.1 (12), 115.1 (11), 122.1 (13), 123.1 (100), 124.1 (11), 125.0 (59), 126.0 (10), 139.1 (11), 149.0 (10), 151.1 (19), 159.1 (15),

163.1 (39), 164.1 (16), 165.1 (23), 177.1 (15), 178.1 (15), 179.1 (89), 180.1 (17), 205.1 (24), 248.1 (26).

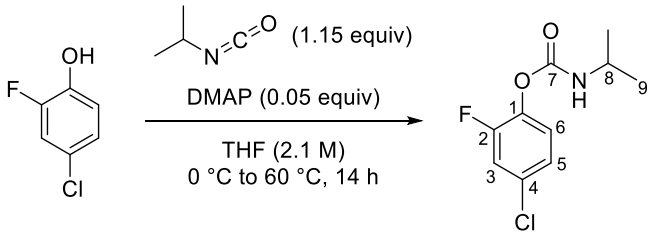
Analysis: $C_{16}H_{21}FO$ (248.34)

Calcd: C, 77.38%; H, 8.52%

Found: C, 77.19%; H, 8.38%

TLC: R_f 0.41 (hexanes/EtOAc, 90:10, UV/CAM)

Preparation of 4-Chloro-2-fluorophenyl Isopropyl Carbamate (94c)



The following procedure is analogous to the one described by Hoppe et al. for the preparation of carbamate **94b**. A flame-dried, 5-mL, round-bottomed flask equipped with a stir bar was charged with DMAP (9.5 mg, 78 μmol, 0.05 equiv) and THF (0.75 mL). Next, 4-chloro-2-fluorophenol **93c** (227.6 mg, 1.55 mmol) was added in one portion. The resulting clear, colorless solution was cooled to 0 °C using an ice bath. Isopropyl isocyanate (160 μL, 138 mg, 1.62 mmol, 1.05 equiv) was added dropwise to the solution over 1 min. The ice bath was removed and replaced with an oil bath. The flask was equipped with a reflux condenser and the reaction was heated to 60 °C for 12 h. Over time, a yellow solution resulted. Conversion was assessed by TLC (hexanes/EtOAc, 80:20, UV) which indicated incomplete consumption of phenol. The reaction mixture was again cooled to 0 °C and an additional portion of isopropyl isocyanate (15 μL, 13 mg, 0.15 mmol, 0.10 equiv). The mixture was again heated to 60 °C for 2 h. Upon reaching full conversion, the reaction was cooled to 25 °C and quenched by the addition of 3 M HCl (1 mL). The biphasic mixture was stirred rapidly for 2 min and then partitioned between Et_2O (5 mL) and water (5 mL) in a separatory funnel. The layers were separated, and the aqueous phase was extracted with Et_2O (2 x 5 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (1 x 5 mL) and then dried over $MgSO_4$, filtered, and concentrated (30 °C, 15 mmHg) to afford

314.3 mg (87%) of **94c** as a white solid. At this point, the level of purity is sufficient for most applications. To obtain analytically pure material, the solid was dissolved in a minimal amount of boiling Et_2O (2 mL, 40 °C) and the resulting colorless solution was cooled to 0 °C for 30 min. The resulting crystals were collected by vacuum filtration and rinsed with ice-cold Et_2O (1 mL) to afford 142.9 mg (40%) of **94c** as small, white needles.

Data for **94c**:

m.p.: 136–137 °C (Et_2O)

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

7.21 – 7.05 (m, 3H, HC(3), HC(6), HC(5)), 4.94 (bs, 1H, NH), 3.89 (oct, J = 6.6 Hz, 1H, HC(8)), 1.24 (d, J = 6.6 Hz, 6H, H_3C(9)). Minor rotameric signals observed: 4.59 (bs, NH) and 3.97 (bs, HC(8)).

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

154.5 (d, $J_{C–F}$ = 252.6 Hz, C(2)), 152.4 (C(7)), 137.5 (d, $J_{C–F}$ = 12.2 Hz, C(1)), 131.2 (d, $J_{C–F}$ = 9.1 Hz, C(4)), 125.1 (d, $J_{C–F}$ = 1.3 Hz, HC(6)), 124.6 (d, $J_{C–F}$ = 3.8 Hz, HC(5)), 117.5 (d, $J_{C–F}$ = 22.1 Hz, HC(3)), 44.0 (HC(8)), 22.9 (H_3C(9)).

^{19}F NMR: (471 MHz, $CDCl_3$)

–126.23 (t, J = 8.9 Hz). Minor rotameric signal observed: –126.13 (bs).

IR: (neat)

3319 (m), 2980 (m), 2935 (w), 2878 (w), 2055 (w), 1704 (s), 1600 (m), 1535 (m), 1493 (s), 1455 (m), 1409 (m), 1364 (m), 1341 (m), 1272 (m), 1251 (s), 1217 (m), 1201 (s), 1162 (s), 1110 (s), 1070 (m), 1037 (s), 951 (m), 939 (m), 903 (s), 861 (s), 830 (s), 786 (m), 765 (m), 697 (m), 581 (s), 572 (s), 511 (m), 461 (m).

LRMS: (ESI, $[M+H]^+$)

86.1 (26), 145.1 (21), 147.0 (89), 149.0 (26), 186.0 (10), 232.1 (100), 233.1 (11), 234.1 (35), 241.9 (38), 243.9 (14), 245.9 (18), 251.0 (12), 332.0 (47), 334.0 (17), 366.6 (11), 367.5 (11), 432.0 (14).

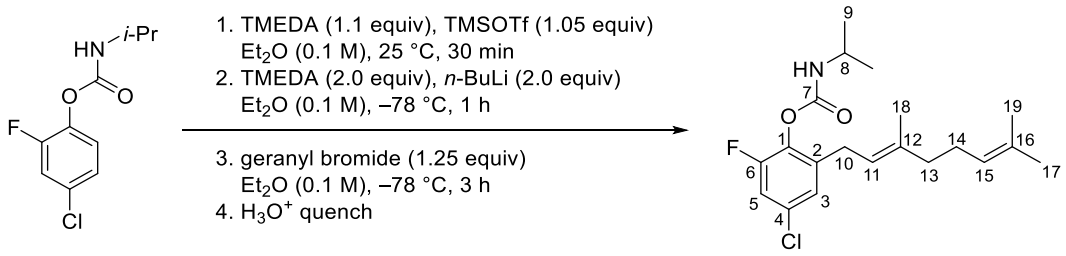
Analysis: $C_{10}H_{11}ClFNO_2$ (231.65)

Calcd: C, 51.85%; H, 4.79%; N, 6.05%

Found: C, 51.46%; H, 4.69%; N, 6.03%

TLC: R_f 0.31 (hexanes/EtOAc, 80:20, UV)

(*E*)-4-Chloro-2-(3,7-dimethylocta-2,6-dien-1-yl)-6-fluorophenyl Isopropyl Carbamate (95c)



An oven-dried, 25-mL Schlenk flask equipped with a stir bar was charged with carbamate **94c** (236.5 mg, 1.02 mmol), diethyl ether (10 mL), and TMEDA (165 μL, 1.09 mmol, 1.1 equiv). A clear, colorless solution resulted. Neat TMSOTf (190 μL, 1.06 mmol, 1.04 equiv) was added dropwise at 25 °C. The resulting white suspension was stirred for 30 min at 25 °C. The suspension cleared to afford a colorless, slightly turbid solution. An additional bolus of TMEDA (303 μL, 2.01 mmol, 2.0 equiv) was added at 25 °C. With *vigorous stirring*, the solution was cooled to –78 °C using a dry ice/isopropanol bath. A solution of *n*-butyllithium in hexanes (2.25 M, 0.89 mL, 2.0 mmol, 2.0 equiv) was added dropwise at –78 °C, and the mixture was stirred for 1 h at –78 °C. Neat geranyl bromide (269.6 mg, 1.24 mmol, 1.2 equiv) was added dropwise at –78 °C and the reaction was stirred for 3 h at –78 °C. After 3 h, the reaction was quenched with methanol (0.1 mL) followed by aq. 2 M HCl (6 mL). The cold bath was removed and the mixture was warmed to 25 °C. The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 25 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ and brine, and then dried over magnesium sulfate, filtered, and concentrated (25 °C, 20 mmHg) to afford 0.32 g of crude **95c**. The product was purified by column chromatography (silica gel, 3 x 30 cm, dry load on Celite, 25-mL fractions, hexanes/EtOAc gradient elution: 97.5:2.5 (300 mL) to 95:5 (300 mL) to 92.5:7.5 (300 mL) to 90:10 (300 mL)) to afford 81.5 mg (22%) of mostly pure **95c**. The product was purified again by column chromatography (silica gel, 2 x 30 cm, dry load on Celite, 10-mL fractions, hexanes/CH_2Cl_2 gradient elution: 90:10 (200 mL) to 80:20 (200 mL) to 70:30 (200 mL) to 60:40 (200 mL) to 50:50 (200 mL) to 40:60 (200 mL)) to afford 66.8 mg (18%) of **95c** as a clear, colorless oil. The oil was dried in an Abderhalden (TBME, 55 °C, 0.01 torr, 8 h) to remove residual CH_2Cl_2, and upon cooling the oil solidified to afford 62.2 mg (17%) of analytically pure **95c** as a white,

crystalline solid. A trace impurity is still visible by 1H-NMR in the aryl region, but this is easily removed after the next step (carbamate deprotection).

Data for **95c**:

m.p.: 51–53 °C (hexanes/CH_2Cl_2)

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

7.04 – 6.98 (m, 1H, HC(5)), 6.96 (bs, 1H, HC(3)), 5.21 (bt, J = 6.9 Hz, 1H, HC(11)), 5.14 – 5.05 (m, 1H, HC(15)), 4.93 (bd, J = 7.3 Hz, 1H, NH), 3.88 (oct, J = 6.6 Hz, 1H, HC(8)), 3.26 (d, J = 7.2 Hz, 2H, H_2C(10)), 2.16 – 2.08 (m, 2H, H_2C(14)), 2.08 – 1.99 (m, 2H, H_2C(13)), 1.69 (s, 3H, H_3C(17)), 1.67 (s, 3H, H_3C(18)), 1.60 (s, 3H, H_3C(19)), 1.24 (d, J = 6.5 Hz, 6H, H_3C(9)). Minor rotameric signals observed: 4.59 (bs, NH) and 3.98 (bs, HC(8)).

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

155.0 (d, $J_{C–F}$ = 251.4 Hz, C(6)), 152.3 (C(7)), 138.4 (C(2)), 138.2 (C(12)), 135.7 (d, $J_{C–F}$ = 12.7 Hz, C(1)), 131.8 (C(16)), 130.9 (d, $J_{C–F}$ = 10.0 Hz, C(4)), 124.8 (d, $J_{C–F}$ = 3.0 Hz, HC(3)), 124.1 (HC(15)), 120.3 (HC(11)), 114.8 (d, $J_{C–F}$ = 22.4 Hz, HC(5)), 43.9 (HC(8)), 39.8 (H_2C(13)), 28.3 (d, $J_{C–F}$ = 2.3 Hz, H_2C(10)), 26.6 (H_2C(14)), 25.9 (H_3C(17)), 23.0 (H_3C(9)), 17.9 (H_3C(19)), 16.3 (H_3C(18)).

^{19}F NMR: (471 MHz, $CDCl_3$)

–126.58 (d, J = 9.3 Hz)

IR: (neat)

3324 (m), 2974 (w), 2925 (w), 1705 (s), 1591 (m), 1535 (s), 1480 (s), 1453 (m), 1427 (m), 1365 (m), 1344 (m), 1301 (m), 1282 (w), 1260 (s), 1227 (s), 1206 (s), 1168 (s), 1133 (m), 1076 (w), 1039 (s), 1016 (m), 945 (m), 896 (m), 855 (s), 803 (w), 786 (w), 765 (w), 655 (m), 576 (m), 481 (w).

LRMS: (ESI, $[M+Na]^+$)

159.0 (13), 173.0 (65), 175.0 (25), 187.0 (21), 201.0 (16), 283.1 (62), 284.1 (11), 285.1 (21), 368.2 (14), 390.2 (100), 391.2 (23), 392.2 (36).

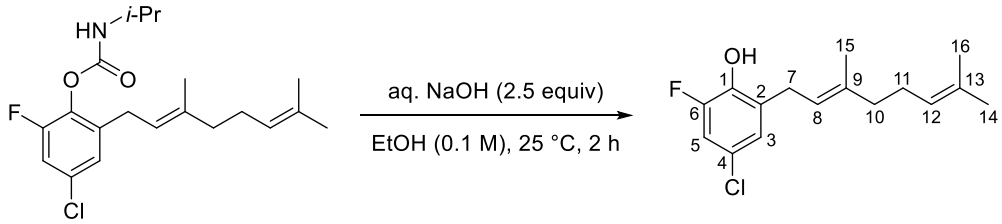
Analysis: $C_{20}H_{27}ClFNO_2$ (367.89)

Calcd: C, 65.30%; H, 7.40%; N, 3.81%

Found: C, 64.96%; H, 7.41%; N, 3.97%

TLC: R_f 0.27 (hexanes/EtOAc, 90:10, UV/CAM)

Preparation of (*E*)**-4-Chloro-2-(3,7-dimethylocta-2,6-dien-1-yl)-6-fluorophenol** (**89c**)



A 50-mL round-bottomed flask equipped with a stir bar was charged with carbamate **95c** (439 mg, 1.19 mmol) and ethanol (10.8 mL). To this clear, colorless solution was added aq. 2 M NaOH (1.5 mL). The resulting yellow solution was stirred at 25 °C for 2 h and became turbid over time. Full conversion was observed by TLC (hexanes/EtOAc, 90:10). The reaction was acidified to pH = 1 by the addition of aq. 2 M HCl. The mixture was partitioned between water (25 mL) and Et_2O (25 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (2 x 25 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated (25 °C, 20 mmHg) to afford crude **89c**. The product was purified by column chromatography (silica gel, 3 x 28 cm, dry load on Celite, 25-mL fractions, hexanes/EtOAc gradient elution: 97.5:2.5 (300 mL) to 95:5 (300 mL) to 92.5:7.5 (300 mL) to 90:10 (300 mL)) to afford 316.2 mg (94%) of **89c** containing some trace impurities visible in the aryl region of the ^{1}H NMR. The product was again chromatographed (silica gel, 3 x 29 cm, dry load on Celite, 25-mL fractions, hexanes/CH_2Cl_2 gradient elution: 90:10 (300 mL) to 80:20 (300 mL) to 70:30 (300 mL) to 60:40 (300 mL)) to afford 291.6 mg (86%) of **89c** containing no visible impurities by ^{1}H NMR. The product was purified to an analytical standard by diffusion pump Kugelrohr distillation (ABT 75 °C, 3.4 x 10^{-5} mmHg) to afford 283.1 mg (84%) of **89c** as a clear, colorless oil.

Data for **89c**:

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

6.96 (dd, *J* = 9.8, 2.4 Hz, 1H, HC(5)), 6.90 – 6.87 (m, 1H, HC(3)), 5.30 – 5.24 (m, 1H, HC(8)), 5.10 (d, *J* = 4.5 Hz, 1H, OH), 5.11 – 5.06 (m, 1H, HC(12)), 3.34 (d, *J* = 7.3 Hz, 2H, H_2C(7)), 2.16 – 2.09 (m, 2H, H_2C(11)), 2.09 – 2.03 (m, 2H, H_2C(10)), 1.71 (s, 3H, H_3C(15)), 1.69 (s, 3H, H_3C(14)), 1.60 (s, 3H, H_3C(16)).

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

150.8 (d, $J_{C–F}$ = 240.4 Hz, C(6)), 140.6 (d, $J_{C–F}$ = 13.9 Hz, C(1)), 138.4 (C(9)), 131.9 (C(13)), 131.5 (d, $J_{C–F}$ = 1.8 Hz, C(2)), 125.0 (d, $J_{C–F}$ = 3.0 Hz, HC(3)), 124.4 (d, $J_{C–F}$ = 10.1 Hz, C(4)), 124.1 (HC(12)), 120.6 (HC(8)), 113.8 (d, $J_{C–F}$ = 22.1 Hz, HC(5)), 39.8 (H_2C(10)), 28.2 (d, $J_{C–F}$ = 2.9 Hz, H_2C(7)), 26.6 (H_2C(11)), 25.9 (H_3C(14)), 17.9 (H_3C(16)), 16.3 (H_3C(15)).

^{19}F NMR: (471 MHz, CDCl3)

–138.36 (ddd, J = 9.6, 4.3, 1.3 Hz)

IR: (neat)

3581 (bw), 3455 (bw), 2968 (w), 2916 (w), 2855 (w), 1668 (w), 1615 (w), 1600 (w), 1484 (s), 1431 (m), 1377 (w), 1338 (m), 1299 (w), 1281 (w), 1217 (s), 1108 (w), 1082 (w), 967 (m), 929 (w), 895 (m), 843 (m), 771 (m), 760 (m), 731 (w), 627 (w), 580 (m), 547 (w), 504 (w).

LRMS: (ESI, $[M]^+$)

69.1 (100), 109.1 (10), 123.1 (58), 159.0 (16), 178.1 (12), 282.1 (9), 284.1 (3).

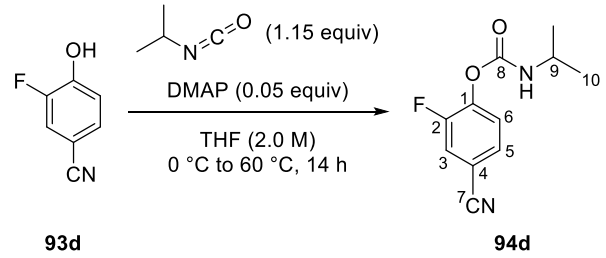
Analysis: $C_{16}H_{20}ClFO$ (282.78)

Calcd: C, 67.96%; H, 7.13%

Found: C, 67.75%; H, 7.15%

TLC: R_f 0.38 (hexanes/EtOAc, 90:10, UV/CAM)

Preparation of 4-Cyano-2-fluorophenyl isopropylcarbamate (94d)



93d **94d**

The following procedure is analogous to the one described by Hoppe et al. A flame-dried, 5-mL, round-bottomed flask equipped with a stir bar was charged with DMAP (9.3 mg, 76 μmol, 0.05 equiv) and THF (0.75 mL). Next, 3-fluoro-4-hydroxybenzonitrile **93d** (208.4 mg, 1.52 mmol)

was added in one portion. The resulting pale, yellow solution was cooled to 0 °C using an ice bath. Isopropyl isocyanate (160 μL, 138 mg, 1.62 mmol, 1.05 equiv) was added dropwise to the solution over 1 min. The ice bath was removed and replaced with an oil bath. The flask was equipped with a reflux condenser and the reaction was heated to 60 °C for 12 h. Conversion was assessed by TLC (hexanes/EtOAc, 80:20, UV) which indicated incomplete consumption of phenol. The reaction mixture was again cooled to 0 °C and an additional portion of isopropyl isocyanate (15 μL, 13 mg, 0.15 mmol, 0.10 equiv). The mixture was again heated to 60 °C for 2 h. Upon reaching full conversion, the reaction was cooled to 25 °C and quenched by the addition of 3 M HCl (1 mL). The biphasic mixture was stirred rapidly for 2 min and then partitioned between Et_2O (5 mL) and water (5 mL) in a separatory funnel. The layers were separated, and the aqueous phase was extracted with Et_2O (2 x 5 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (1 x 5 mL) and then dried over $MgSO_4$, filtered, and concentrated (30 °C, 15 mmHg) to afford 316.8 mg (89% adj.) of **94d** as a white solid which was contaminated with ~5% phenol **93d**. At this point, the level of purity is sufficient for most applications. To obtain analytically pure material, the solid was dissolved in a minimal amount of boiling Et_2O (2 mL, 40 °C) and the resulting colorless solution was cooled to 0 °C for 30 min. The resulting crystals were collected by vacuum filtration and rinsed with ice-cold Et_2O (1 mL) to afford 129.8 mg (38%) of **94d** as small, white needles. The percent recovery was improved when the reaction was performed on a larger scale. On a 10 mmol scale, a 71% isolated yield of **94d** was observed after recrystallization.

Data for **94d**:

m.p.: 129–130 °C (Et_2O)

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

7.49 – 7.41 (m, 2H, HC(3), HC(5)), 7.40 – 7.33 (m, 1H, HC(6)), 5.03 (bd, 1H, NH), 3.89 (oct, J = 6.6 Hz, 1H, HC(9)), 1.25 (d, J = 6.6 Hz, 6H, H_3C(10)). Minor rotameric signals observed: 4.66 (bs, NH) and 3.97 (bs, HC(9)).

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

154.3 (d, $J_{C–F}$ = 253.4 Hz, C(2)), 151.5 (C(8)), 142.9 (d, $J_{C–F}$ = 12.0 Hz, C(1)), 129.0 (d, $J_{C–F}$ = 4.0 Hz, HC(5)), 125.4 (bs, HC(6)), 120.6 (d, $J_{C–F}$ = 22.1 Hz, HC(3)), 117.4 (d, $J_{C–F}$ = 2.4 Hz, C(7)), 110.0 (d, $J_{C–F}$ = 8.3 Hz, C(4)), 44.1 (HC(9)), 22.9 (H_3C(10)).

^{19}F NMR: (471 MHz, $CDCl_3$)

–125.39 (t, J = 8.2 Hz). Minor rotameric signal observed: –125.20 (bs).

IR: (neat)

3322 (m), 2984 (w), 2935 (w), 2233 (w), 1708 (s), 1589 (m), 1532 (m), 1505 (s), 1453 (m), 1419 (s), 1367 (m), 1339 (m), 1281 (s), 1265 (m), 1245 (s), 1207 (s), 1154 (m), 1110 (s), 1025 (s), 935 (s), 878 (s), 869 (m), 841 (s), 788 (m), 759 (m), 668 (s), 614 (s), 535 (m), 508 (m), 474 (m).

LRMS: (ESI, $[M+H]^+$)

97.0 (11), 98.0 (14), 99.0 (13), 100.0 (10), 101.0 (10), 114.0 (11), 117.0 (15), 119.1 (15), 123.1 (14), 126.0 (24), 128.0 (10), 135.0 (56), 137.0 (61), 137.5 (25), 138.0 (59), 140.0 (21), 142.0 (26), 145.1 (100), 146.5 (37), 169.1 (10), 185.5 (26), 194.5 (21), 196.0 (10), 210.0 (13), 223.1 (57), 233.5 (15), 245.1 (11), 254.0 (27), 255.0 (11), 269.0 (17), 302.0 (11), 367.2 (10), 415.2 (53), 416.2 (14), 437.2 (18).

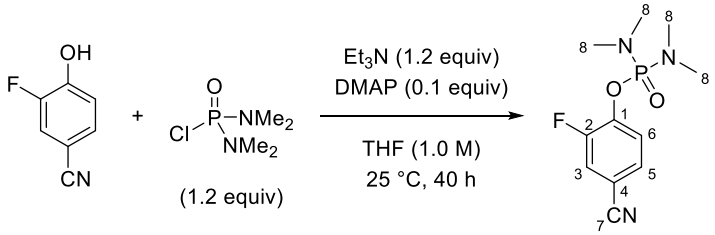
Analysis: $C_{11}H_{11}FN_2O_2$ (222.22)

Calcd: C, 59.45%; H, 4.99%; N, 12.61%

Found: C, 59.31%; H, 4.99%; N, 12.46%

TLC: R_f 0.17 (hexanes/EtOAc, 80:20, UV)

Preparation of 4-Cyano-2-fluorophenyl *N,N,N',N'*-Tetramethylphosphorodiamidate (96)



The following procedures are adapted from those reported by Knochel et al. for the preparation of a similar compound.[92] An oven-dried, 25-mL, Schlenk flask equipped with a stir bar was charged with 3-fluoro-4-hydroxybenzonitrile **93d** (687.1 mg, 5.01 mmol), THF (5 mL), and DMAP (65.3 mg, 0.535 mmol, 0.1 equiv). A pale, yellow solution resulted. Bis(dimethylamino)phosphoryl chloride (0.89 mL, 1.0 g, 6.0 mmol, 1.2 equiv) was added dropwise, followed by triethylamine (0.83 mL, 0.61 g, 6.0 mmol, 1.2 equiv). The resulting white suspension was stirred at 25 °C for 40 h. Conversion was assessed by TLC (EtOAc/hexanes, 50:50). Upon completion, the reaction was quenched by the addition of sat. aq. NH_4Cl (3 mL) and

water (3 mL). The mixture was diluted with EtOAc (10 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic phases were washed with brine (1 x 10 mL), dried over MgSO4, filtered, and concentrated (30 °C, 30 mmHg) to afford a viscous oil (1.37 g) which solidified upon standing. The product was recrystallized from 10 mL of boiling Et_2O/hexanes (approx. 1:1 ratio) to afford 1.14 g (84%) of analytically pure **96** as white needles.

Data for **96**:

m.p.: 59–60 °C (Et_2O/hexanes)

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

7.59 – 7.51 (m, 1H, HC(6)), 7.47 – 7.37 (m, 2H, HC(3), HC(5)), 2.74 (d, $J_{H–P}$ = 10.3 Hz, 12H, H_3C(8)).

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

153.5 (dd, J = 253.4 Hz, 6.3 Hz, C(2)), 143.8 (dd, J = 11.6 Hz, 5.4 Hz, C(1)), 129.4 (dd, HC(5)), 123.7 (dd, HC(6)), 120.6 (d, J = 21.9 Hz, HC(3)), 117.6 (d, C(7)), 108.4 (dd, C(4)), 36.7 (d, J = 4.2 Hz, H_3C(8)).

^{19}F NMR: (471 MHz, $CDCl_3$)

–128.42 (t, J = 8.4 Hz).

^{31}P NMR: (162 MHz, $CDCl_3$)

17.47 (^{1}H decoupled).

IR: (neat)

3063 (w), 3035 (w), 2901 (w), 2858 (w), 2820 (w), 2231 (w), 1611 (w), 1585 (w), 1505 (s), 1457 (w), 1420 (m), 1313 (m), 1296 (m), 1277 (s), 1265 (m), 1229 (s), 1216 (s), 1184 (m), 1119 (s), 1077 (w), 990 (s), 945 (m), 924 (m), 888 (m), 867 (s), 839 (s), 828 (s), 763 (s), 737 (m), 721 (s), 683 (s), 616 (s), 539 (m), 520 (s), 471 (s).

LRMS: (ESI, $[M+H]^+$)

272.1 (100), 273.1 (13).

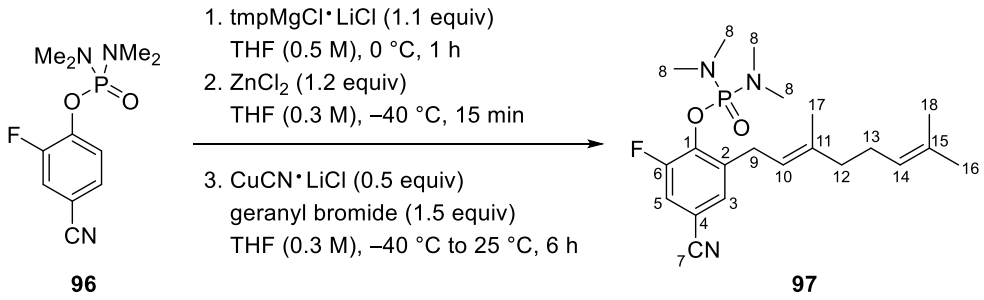
Analysis: $C_{11}H_{15}FN_3O_2P$ (271.23)

Calcd: C, 48.71%; H, 5.57%; N, 15.49%

Found: C, 48.76%; H, 5.57%; N, 15.21%

TLC: R_f 0.12 (EtOAc, UV)

Preparation of (*E*)**-4-Cyano-2-(3,7-dimethylocta-2,6-dien-1-yl)-6-fluorophenyl *N,N,N',N'*-Tetramethylphosphorodiamidate** (**97**)



An oven-dried, 10-mL, Schlenk flask equipped with a stir bar was charged with phosphorodiamidate **96** (273.8 mg, 1.01 mmol) and THF (1.2 mL). The resulting colorless solution was cooled to 0 °C using either a CryoCool or an ice bath. A solution of tmpMgCl·LiCl complex (1.12 M in THF, 1.0 mL, 1.12 mmol, 1.1 equiv) was added dropwise at 0 °C. The resulting orange solution was stirred for 1 h at 0 °C. Next, the flask was cooled to –40 °C using either a CryoCool or a dry ice/acetonitrile slush bath. A solution of $ZnCl_2$ (1.0 M in THF, 1.2 mL, 1.2 mmol, 1.2 equiv) was added dropwise at –40 °C and the solution was maintained for 15 min at this temperature. [The $ZnCl_2$ solution was prepared by dissolving 272 mg of anhydrous zinc chloride in 2 mL of THF and stirring for 2 h under argon, which afforded a turbid, colorless solution.] Next, a solution of CuCN·2LiCl complex (1.0 M in THF, 0.50 mL, 0.5 mmol, 0.5 equiv) was added dropwise at –40 °C, followed by the dropwise addition of neat geranyl bromide (336 mg, 1.5 mmol, 1.5 equiv) at –40 °C. [The CuCN·2LiCl solution was prepared by dissolving 89 mg of anhydrous copper(I) cyanide and 85 mg of anhydrous lithium chloride in 1 mL of THF and stirring for 2 h under argon, which afford a turbid, brown-gray solution.] The reaction mixture was allowed to warm slowly to 25 °C over a period of 6 h. Over time, the mixture became turbid. Full conversion was observed by TLC (EtOAc). The reaction was quenched by the addition of sat. aq. NH_4Cl (10 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated (30 °C, 30 mmHg) to afford 0.52 g of crude **97**. [**Note:** Following the workup, the reaction flask and separatory funnels were caked with various metal salt deposits, which were expediently removed by treatment with aqua regia.] The product was purified by column

chromatography (silica gel, 3 x 30 cm, wet load, 25-mL fractions, hexanes/EtOAc gradient elution: 50:50 (300 mL) to 40:60 (300 mL) to 30:70 (300 mL) to 20:80 (300 mL) to 10:90 (300 mL)) to afford 223.8 mg of **97** as a yellow oil. The oil was dried in an Abderhalden (EtOH, 80 °C, 0.01 torr, 3 h) to remove residual EtOAc. Upon cooling the sample to –20 °C for several days and subsequent warming to 25 °C, the oil spontaneously crystallized to afford 216.3 mg (53%) of analytically pure **97** as a white, crystalline solid.

Data for **97**:

m.p.: 68–70 °C (EtOAc/hexanes)

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

7.29 – 7.26 (m, 2H, HC(3), HC(5)), 5.29 – 5.23 (m, 1H, HC(10)), 5.12 – 5.06 (m, 1H, HC(14)), 3.51 (d, J = 7.3 Hz, 2H, $H_2C(9)$), 2.77 (d, $J_{H–P}$ = 10.2 Hz, 12H, $H_3C(8)$), 2.16 – 2.06 (m, 4H, $H_2C(12)$, $H_2C(13)$), 1.70 (s, 3H, $H_3C(16)$), 1.67 (s, 3H, $H_3C(17)$), 1.61 (s, 3H, $H_3C(18)$).

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

154.4 (dd, J = 250.3 Hz, 3.0 Hz, C(6)), 141.6 (dd, J = 12.2 Hz, 6.9 Hz, C(1)), 139.5 (C(11)), 139.0 (d, J = 3.4 Hz, C(2)), 132.0 (C(15)), 129.4 (dd, HC(3)), 124.0 (HC(14)), 119.6 (HC(10)), 118.2 (dd, HC(5)), 117.9 (d, C(7)), 108.6 (dd, J = 9.6 Hz, 1.8 Hz, C(4)), 39.7 ($H_2C(12)$), 36.9 (dd, J = 4.4 Hz, 1.6 Hz, $H_3C(8)$), 28.2 (d, J = 1.9 Hz, $H_2C(9)$), 26.6 ($H_2C(13)$), 25.9 ($H_3C(16)$), 17.9 ($H_3C(18)$), 16.4 ($H_3C(17)$).

^{19}F NMR: (471 MHz, $CDCl_3$)

–126.49 (d, J = 9.7 Hz).

^{31}P NMR: (162 MHz, $CDCl_3$)

16.93 (^{1}H decoupled).

IR: (neat)

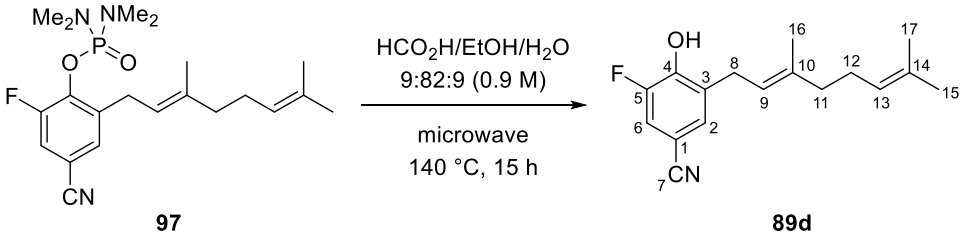
3037 (w), 2911 (w), 2853 (w), 2819 (w), 2232 (w), 1608 (w), 1584 (w), 1477 (m), 1441 (m), 1423 (w), 1378 (w), 1350 (w), 1314 (m), 1276 (w), 1228 (s), 1206 (m), 1175 (m), 1128 (m), 1085 (w), 1068 (w), 1001 (s), 986 (s), 957 (w), 918 (m), 875 (s), 843 (m), 765 (m), 751 (s), 713 (s), 663 (w), 624 (m), 566 (w), 535 (m), 516 (m), 487 (m), 468 (m), 454 (s).

LRMS: (EI, 70 eV)

69.0 (20), 135.1 (98), 338.2 (100), 339.2 (23), 407.2 (46), 408.2 (15).

Analysis:	$C_{21}H_{31}FN_3O_2P$	(407.47)	
	Calcd: C, 61.90%;	H, 7.67%;	N, 10.31%
	Found: C, 61.88%;	H, 7.75%;	N, 10.24%
TLC:	R_f 0.34 (EtOAc, UV/CAM)		

(*E*)-**3-(3,7-dimethylocta-2,6-dien-1-yl)-5-fluoro-4-hydroxybenzonitrile** (**89d**)



A 2-mL, glass microwave reaction vessel equipped with a magnetic spin vane was charged with phosphorodiamidate **97** (411.2 mg, 1.01 mmol), EtOH (0.90 mL), formic acid (0.10 mL), and water (0.10 mL). The substrate **97** is only sparingly soluble in the reaction mixture, so the vessel was gently heated with a heat gun until **97** melted, resulting in a liquid biphasic mixture. The vessel was sealed with a Teflon-coated septum and irradiated for 15 h at 140 °C (100 W maximum) with stirring (600 rpm). The internal pressure of the system was observed to rise over time, reaching a maximum of approx. 8-9 bar. The reaction was cooled to room temperature, and the now homogeneous solution was partitioned between water (10 mL) and EtOAc (10 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). [**Note:** Any emulsions formed during the workup are best cleared by adding solid NaCl directly to the separatory funnel. Do not perform any brine washes.] The combined organic layers were dried over MgSO4, filtered, and concentrated (30 °C, 25 mmHg) to afford 0.33 g of crude **89d**. Approx. 75% conversion was observed by ^{1}H NMR, based on the relative integrations of the benzylic methylene signals for **97** (d, 3.51) and **89d** (d, 3.38). The product was purified by column chromatography (silica gel, 3 x 20 cm, dry load on Celite, 25-mL fractions, hexanes/EtOAc gradient elution: 95:5 (200 mL) to 90:10 (300 mL) to 85:15 (300 mL) to 40:60 (300 mL) to 0:100 (500 mL)) to afford 172.6 mg (63%) of **89d** as a colorless oil, which spontaneously crystallized upon drying (25 °C, 0.01 mmHg, 72 h) to afford analytically pure, white crystals of **89d**.

Data for **89d**:

m.p.: 52–55 °C (EtOAc/hexanes)

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

7.27 – 7.22 (m, 2H, HC(6), HC(2)), 5.71 – 5.66 (m, 1H, OH), 5.29 – 5.24 (m, 1H, HC(9)), 5.11 – 5.05 (m, 1H, HC(13)), 3.38 (d, J = 7.4 Hz, 2H, H_2C(8)), 2.16 – 2.04 (m, 4H, H_2C(11), H_2C(12)), 1.71 (s, 3H, H_3C(16)), 1.69 (s, 3H, H_3C(15)), 1.61 (s, 3H, H_3C(17)).

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

150.3 (d, $J_{C–F}$ = 240.2 Hz, C(5)), 146.2 (d, $J_{C–F}$ = 13.6 Hz, C(4)), 139.3 (C(10)), 132.1 (C(14)), 132.0 (d, $J_{C–F}$ = 1.9 Hz, C(3)), 129.7 (d, $J_{C–F}$ = 2.8 Hz, HC(2)), 124.0 (HC(13)), 119.7 (HC(9)), 118.5 (d, $J_{C–F}$ = 3.0 Hz, C(7)), 117.2 (d, $J_{C–F}$ = 21.8 Hz, HC(6)), 103.5 (d, $J_{C–F}$ = 9.2 Hz, C(1)), 39.8 (H_2C(11), 28.0 (d, $J_{C–F}$ = 2.7 Hz, H_2C(8)), 26.5 (H_2C(12)), 25.9 (H_3C(15)), 17.9 (H_3C(17)), 16.3 (H_3C(16)).

^{19}F NMR: (471 MHz, $CDCl_3$)

–138.40 (dd, J = 9.4, 4.5 Hz)

IR: (neat)

3241 (m, br), 2972 (w), 2929 (w), 2236 (m), 1671 (w), 1609 (m), 1594 (m), 1494 (s), 1439 (s), 1422 (m), 1376 (m), 1352 (w), 1328 (m), 1304 (s), 1243 (s), 1202 (s), 1159 (m), 1122 (m), 1107 (m), 1094 (w), 1009 (w), 980 (s), 938 (w), 912 (w), 887 (m), 870 (s), 806 (m), 783 (m), 751 (w), 678 (s), 659 (s), 617 (s), 562 (m), 546 (m), 538 (m), 496 (w), 479 (m), 456 (m).

LRMS: (EI, 70 eV)

69.1 (100), 82.9 (32), 84.9 (21), 109.1 (13), 123.1 (75), 150.0 (23), 162.0 (10), 188.1 (19), 190.1 (10), 202.1 (13), 205.1 (12), 230.1 (12), 258.1 (14), 273.2 (23), 274.2 (4).

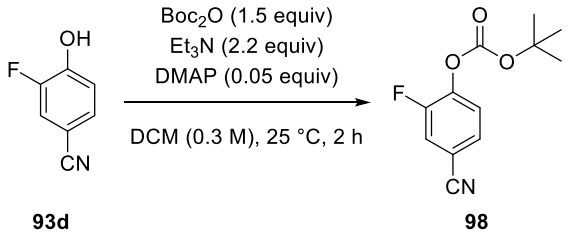
Analysis: $C_{17}H_{20}FNO$ (273.35)

Calcd: C, 74.70%; H, 7.37%; N, 5.12%

Found: C, 74.52%; H, 7.39%; N, 5.21%

TLC: R_f 0.34 (hexanes/EtOAc, 80:20, UV/CAM/$KMnO_4$)

***tert*-Butyl (4-Cyano-2-fluorophenyl) Carbonate (98)**



93d **98**

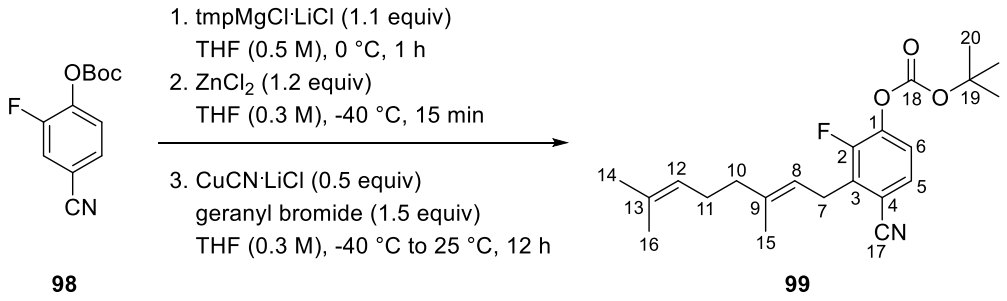
A flame-dried, 50-mL, round-bottomed flask equipped with a stir bar was charged with 3-fluoro-4-hydroxybenzonitrile **93d** (414.3 mg, 3.02 mmol), CH_2Cl_2 (9 mL), Et_3N (0.92 mL, 0.67 g, 6.6 mmol, 2.2 equiv), and 4-(dimethylamino)pyridine (18 mg, 0.15 mmol, 0.05 equiv). An off-white suspension resulted. Di-*tert*-butyl dicarbonate (1.1 mL, 0.99 g, 4.5 mmol, 1.5 equiv) was added in one portion at 25 °C. Mild gas evolution was observed, and within minutes the off-white suspension had cleared to a nearly colorless solution. Stirring was continued at 25 °C for 2 h. Full conversion was observed by TLC (hexanes/EtOAc, 90:10). The solution was transferred to a separatory funnel and washed with 1 N HCl (1 x 15 mL), sat. aq. $NaHCO_3$ (1 x 15 mL), and brine (1 x 15 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated (30 °C, 25 mmHg) to afford 0.77 g of crude **98** as an off-white solid. The product was purified by column chromatography (silica gel, 3 x 23 cm, dry load on Celite, 25-mL fractions, hexanes/EtOAc gradient elution: 90:10 (250 mL) to 80:20 (250 mL) to 70:30 (250 mL)) to afford 675.3 mg (94%) of **98** as a white solid.

Data for **98**:

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

7.50 – 7.46 (m (app. d), 2H), 7.36 (app. t, J = 7.7 Hz, 1H), 1.56 (s, 9H).

(*E*)-*tert*-Butyl (4-Cyano-3-(3,7-dimethylocta-2,6-dien-1-yl)-2-fluorophenyl) Carbonate (**99**)



An oven-dried, 10-mL, Schlenk flask equipped with a stir bar was charged with carbamate **98** (120.9 mg, 0.51 mmol) and THF (0.6 mL). The resulting colorless solution was cooled to 0 °C using either a CryoCool. A solution of tmpMgCl·LiCl complex (1.12 M in THF, 0.5 mL, 0.56 mmol, 1.1 equiv) was added dropwise at 0 °C. The resulting red-brown solution was stirred for 1 h at 0 °C. Next, the flask was cooled to –40 °C using either a CryoCool or a dry ice/acetonitrile slush bath. A solution of $ZnCl_2$ (1.0 M in THF, 0.61 mL, 0.61 mmol, 1.2 equiv) was added dropwise at –40 °C and the solution was maintained for 15 min at this temperature. [The $ZnCl_2$ solution was prepared by dissolving 272 mg of anhydrous zinc chloride in 2 mL of THF and stirring for 2 h under argon, which afforded a turbid, colorless solution.] Next, a solution of CuCN·2LiCl complex (1.0 M in THF, 0.25 mL, 0.25 mmol, 0.5 equiv) was added dropwise at –40 °C, followed by the dropwise addition of neat geranyl bromide (166 mg, 0.76 mmol, 1.5 equiv) at –40 °C. [The CuCN·2LiCl solution was prepared by dissolving 89 mg of anhydrous copper(I) cyanide and 85 mg of anhydrous lithium chloride in 1 mL of THF and stirring for 2 h under argon, which afford a turbid, brown-gray solution.] The reaction mixture was allowed to warm slowly to 25 °C over a period of 6 h. Over time, the mixture became turbid. Full conversion was observed by TLC (hexanes/EtOAc, 90:10). The reaction was quenched by the addition of sat. aq. NH_4Cl (5 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated (30 °C, 30 mmHg) to afford 0.25 g of crude **99**. [**Note:** Following the workup, the reaction flask and separatory funnels were caked with various metal salt deposits, which were expediently removed by treatment with aqua regia.] The product was purified by column chromatography (silica gel, 2 x 20 cm, dry load on Celite, 10-mL fractions, hexanes/EtOAc

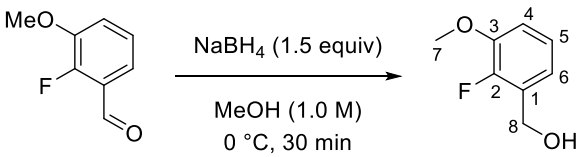
gradient elution: 95:5 (200 mL) to 90:10 (200 mL) to 85:15 (200 mL)) to afford 51.4 mg (27%) of **99**. The site of alkylation was unambiguously confirmed by 2D HMBC correlations.

Data for **99**:

^{1}H NMR: (500 MHz, $CDCl_3$)
7.42 (dd, *J* = 8.5, 1.5 Hz, 1H, HC(5)), 7.17 (dd, *J* = 8.4, 7.3 Hz, 1H, HC(6)), 5.19 (app. t, *J* = 7.1 Hz, 1H, HC(8)), 5.08 – 5.01 (m, 1H, HC(12)), 3.60 (d, *J* = 7.1 Hz, 2H, H_2C(7)), 2.09 – 2.04 (m, 2H, H_2C(11)), 2.02 – 1.97 (m, 2H, H_2C(10)), 1.79 (s, 3H, H_3C(15)), 1.64 (s, 3H, H_3C(14)), 1.57 (s, 3H, H_3C(16)), 1.56 (s, 9H, H_3C(20)).

^{13}C NMR: 152.7 (d, *J* = 251.2 Hz, C(2)), 150.0 (C(18)), 142.5 (d, *J* = 13.1 Hz, C(1)), 138.6 (C(9)), 135.3 (d, *J* = 17.3 Hz, C(3)), 131.8 (C(13)), 129.1 (d, *J* = 4.5 Hz, HC(5)), 124.1 (HC(12)), 122.0 (HC(6)), 119.1 (HC(8)), 116.9 (d, *J* = 3.5 Hz, C(17)), 111.4 (d, *J* = 5.6 Hz, C(4)), 85.3 (C(19)), 39.8 (H_2C(10)), 27.7 (H_3C(20)), 27.4 (d, *J* = 2.1 Hz, H_2C(7)), 26.6 (H_2C(11)), 25.8 (H_3C(14)), 17.8 (H_3C(16)), 16.5 (H_3C(15)).

(2-Fluoro-3-methoxyphenyl)methanol (**101n**)



A flame-dried, 50-mL, round bottomed flask equipped with a stir bar was charged with 2-fluoro-3-methoxybenzaldehyde **100n** (1.0 g, 6.5 mmol) and MeOH (6.5 mL). The resulting pale, orange solution was cooled to 0 °C. [**Note:** Some of the aldehyde precipitated out at this temperature, which does not affect the performance of the reaction.] Sodium borohydride (0.37 g, 9.7 mmol, 1.5 equiv) was added to the suspension in one portion. Gas evolution was observed, and the orange color disappeared. The reaction was stirred under argon for 30 min at 0 °C. A pale, yellow solution was ultimately observed. Full conversion was observed by TLC (hexanes/EtOAc, 80:20). The reaction was quenched by careful addition of sat. aq. NH_4Cl (6.5 mL). The mixture was partitioned between water (50 mL) and CH_2Cl_2 (50 mL), and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were washed

with brine (1 x 25 mL), dried over Na_2SO_4, filtered, and concentrated (30 °C, 25 mmHg) to afford 1.01 g (quant.) of **101n** as an off-white solid requiring no further purification.

Data for **101n**:

m.p.: 59–61 °C (CH_2Cl_2)

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

7.08 (td, J = 8.0, 1.2 Hz, 1H, HC(5)), 7.02 – 6.97 (m, app. t, 1H, HC(6)), 6.92 (td, J = 8.1, 1.3 Hz, 1H, HC(4)), 4.77 (d, J = 6.3 Hz, 2H, H_2C(8)), 3.89 (s, 3H, H_3C(7)), 1.73 (t, J = 6.3 Hz, 1H, OH).

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

150.4 (d, $J_{C–F}$ = 245.6 Hz, C(2)), 147.7 (d, $J_{C–F}$ = 10.5 Hz, C(3)), 128.9 (d, $J_{C–F}$ = 12.1 Hz, C(1)), 124.2 (d, $J_{C–F}$ = 4.7 Hz, HC(5)), 120.6 (d, $J_{C–F}$ = 3.4 Hz, HC(6)), 113.0 (d, $J_{C–F}$ = 1.8 Hz, HC(4)), 59.5 (d, $J_{C–F}$ = 5.4 Hz, H_2C(8)), 56.5 (H_3C(7)).

^{19}F NMR: (471 MHz, $CDCl_3$)

–142.43 (t, J = 7.0 Hz).

IR: (neat)

3320 (m, br), 3035 (w), 2925 (w), 2842 (w), 1621 (w), 1587 (m), 1479 (s), 1454 (s), 1440 (m), 1374 (m), 1313 (m), 1284 (s), 1249 (m), 1194 (s), 1179 (s), 1083 (m), 1042 (s), 959 (m), 903 (m), 872 (m), 816 (s), 766 (s), 727 (m), 714 (s), 622 (m), 560 (w), 535 (m), 500 (w).

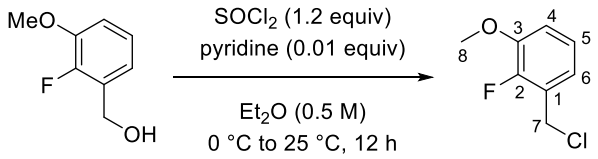
HRMS: calcd for $C_8H_9O_2F$ ($[M]^+$): 156.0587, found: 156.0590

LRMS: (EI, 70 eV)

97.1 (13), 112.0 (12), 127.1 (28), 135.0 (28), 136.1 (11), 140.1 (11), 141.0 (10), 153.0 (14), 154.0 (24), 155.1 (23), 156.1 (100).

TLC: R_f 0.13 (hexanes/EtOAc, 80:20, UV/CAM)

1-(Chloromethyl)-2-fluoro-3-methoxybenzene (**38n**)



An oven-dried, 50-mL, Schlenk flask equipped with a stir bar was charged with alcohol **101n** (0.99 g, 6.3 mmol), Et_2O (13 mL), and pyridine (5 μL, 0.063 mmol, 0.01 equiv). The resulting clear, colorless solution was cooled to –5 °C with an ice/salt bath. Neat thionyl chloride (0.56 mL, 7.6 mmol, 1.2 equiv) was added dropwise over 15 min. A white suspension initially formed, but a pale, yellow solution ultimately resulted. The reaction mixture was warmed slowly to 25 °C and stirred for an additional 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 80:20). The reaction was quenched by the addition of water (13 mL), and the biphasic mixture was stirred vigorously for 2 min. The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 15 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (2 x 30 mL) and brine (1 x 30 mL), and then dried over Na_2SO_4, filtered, and concentrated (30 °C, 25 mmHg) to afford 1.07 (97%) of **38n** as a pale, yellow oil requiring no further purification.

Data for **38n**:

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

7.07 (td, J = 8.0, 1.4 Hz, 1H, HC(5)), 7.01 – 6.97 (m, 1H, HC(6)), 6.94 (td, J = 8.1, 1.4 Hz, 1H, HC(4)), 4.65 – 4.63 (m, 2H, H_2C(7)), 3.90 (s, 3H, H_3C(8)).

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

150.6 (d, $J_{C–F}$ = 249.2 Hz, C(2)), 147.9 (d, $J_{C–F}$ = 10.4 Hz, C(3)), 125.8 (d, $J_{C–F}$ = 11.9 Hz, C(1)), 124.3 (d, $J_{C–F}$ = 4.9 Hz, HC(5)), 122.0 (d, $J_{C–F}$ = 2.1 Hz, HC(6)), 113.8 (d, $J_{C–F}$ = 2.0 Hz, HC(4)), 56.5 (H_3C(8)), 39.3 (d, $J_{C–F}$ = 5.8 Hz, H_2C(7)).

^{19}F NMR: (471 MHz, $CDCl_3$)

–139.97 (t, J = 7.1 Hz).

IR: (neat)

3010 (w), 2969 (w), 2943 (w), 2842 (w), 1622 (w), 1588 (m), 1489 (s), 1463 (m), 1440 (m), 1319 (m), 1274 (s), 1211 (s), 1190 (w), 1172 (w), 1153 (w), 1075 (s), 947 (m), 896 (w), 877 (w), 820 (m), 784 (m), 730 (s), 707 (s), 687 (s), 585 (m), 555 (w), 544 (w), 517 (w), 485 (w).

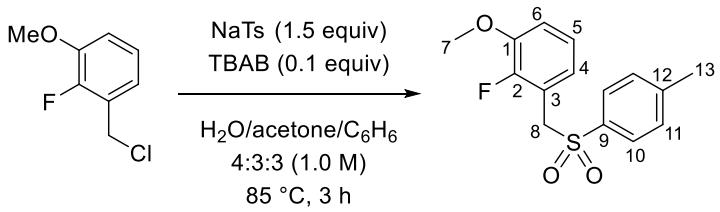
HRMS: calcd for C_8H_8OClF ($[M]^+$): 174.0248, found: 174.0249

LRMS: (EI, 70 eV)

96.0 (19), 109.1 (16), 139.1 (100), 140.1 (10), 174.0 (35), 176.0 (12).

TLC: R_f 0.45 (hexanes/EtOAc, 80:20, UV/CAM)

2-Fluoro-1-methoxy-3-(tosylmethyl)benzene (**41n**)



A 50-mL, round-bottomed flask equipped with a stir bar and reflux condenser was charged with benzyl chloride **38n** (1.71 g, 9.8 mmol), sodium p-toluenesulfinate (2.62 g, 14.7 mmol, 1.5 equiv), tetra-*n*-butylammonium bromide (0.32 g, 0.98 mmol, 0.1 equiv), water (4 mL), acetone (3 mL), and benzene (3 mL). The biphasic mixture was heated to 85 °C for 3 h with vigorous stirring. The reaction was cooled to 25 °C. Full conversion was observed by TLC (hexanes/EtOAc, 80:20). The reaction mixture was partitioned between water (20 mL) and Et_2O (20 mL), at which point the product **xx** began to spontaneously crystallize from the organic phase. The aqueous layer was drained and extracted with $E_{t2}O$ (2 x 20 mL). The combined organic layers were washed with brine (1 x 20 mL) and water (1 x 20 mL). The combined organic layers (crystalline slurry) were transferred to a 250-mL, round-bottomed flask and concentrated (30 °C, 25 mmHg) to a volume of approx. 20 mL Et_2O. The flask was gently heated to dissolve most of the solid. The solution was cooled to 25 °C and then cooled further to –20 °C for 2 h. The resulting crystals were collected by vacuum filtration and rinsed with a minimal amount of ice-cold Et_2O to afford 2.22 g (77%) of **41n** as white needles. A second crop afforded an additional 0.22 g (8%) of **41n** as white needles.

Data for **41n**:

m.p.: 108–109 °C (Et_2O)

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

7.57 (d, J = 8.2 Hz, 2H, HC(10)), 7.25 (d, J = 8.2 Hz, 2H, HC(11)), 7.04 (td, J = 8.1, 1.3 Hz, 1H, HC(5)), 6.95 – 6.87 (m, 2H, HC(6), HC(4)), 4.39 (s, 2H, H_2C(8)), 3.81 (s, 3H, H_3C(7)), 2.42 (s, 3H, H_3C(13)).

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

151.3 (d, $J_{C–F}$ = 249.6 Hz, C(2)), 147.8 (d, $J_{C–F}$ = 10.8 Hz, C(1)), 145.0 (C(12)), 135.3 (C(9)), 129.7 (HC(11)), 128.6 (HC(10)), 124.1 (d, $J_{C–F}$ = 4.9 Hz, HC(5)), 123.7 (d, $J_{C–F}$ = 1.6 Hz, HC(4)), 117.0 (d, $J_{C–F}$ = 12.0 Hz, C(3)), 114.3 (d, $J_{C–F}$ = 2.1 Hz, HC(6)), 56.5 (H_3C(7)), 55.8 (d, $J_{C–F}$ = 3.3 Hz, H_2C(8)), 21.8 (H_3C(13)).

^{19}F NMR: (471 MHz, $CDCl_3$)

–138.94 (t, J = 7.0 Hz).

IR: (neat)

2986 (w), 2945 (w), 2844 (w), 1618 (w), 1586 (w), 1490 (m), 1443 (m), 1408 (w), 1310 (m), 1302 (m), 1279 (s), 1250 (m), 1206 (m), 1171 (w), 1133 (s), 1082 (m), 1070 (s), 1017 (w), 939 (w), 879 (w), 817 (m), 802 (m), 791 (s), 752 (w), 730 (s), 706 (m), 669 (m), 629 (m), 614 (m), 601 (m), 555 (m), 539 (s), 509 (s), 484 (m), 467 (m), 455 (m).

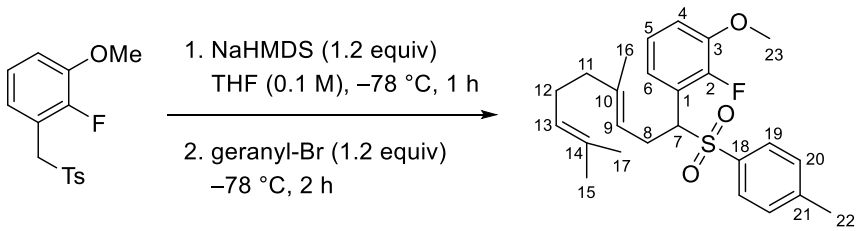
HRMS: calcd for $C_{15}H_{15}O_3FS$ ($[M]^+$): 294.07260; found: 294.07206

LRMS: (EI, 70 eV)

91.1 (10), 96.0 (12), 109.1 (13), 139.1 (100), 140.1 (18), 294.1 (25), 295.1 (5).

TLC: R_f 0.13 (hexanes/EtOAc, 80:20, UV)

(*E*)-1-(4,8-dimethyl-1-tosylnona-3,7-dien-1-yl)-2-fluoro-3-methoxybenzene (42n)



41n **42n**

A flame-dried, 200-mL, three-necked, round-bottomed flask equipped with a stir bar was charged with sulfone **41n** (2.32 g, 7.88 mmol) and THF (60 mL). The resulting colorless solution was cooled to –78 °C with a dry ice/isopropanol bath. A solution of sodium bis(trimethylsilyl)amide (1.0 M in THF, 9.5 mL, 9.5 mmol, 1.2 equiv) was added dropwise at –78 °C over 10 min. A yellow solution resulted. Stirring was continued for 1 h at –78 °C. A solution of geranyl bromide (2.05 g, 9.5 mmol, 1.2 equiv) in THF (10 mL) was added dropwise at –78 °C over 20 min, such that the internal temperature did not exceed –70 °C. Stirring was continued for 4 h at –78 °C. A turbid, light orange solution was observed. Conversion was monitored by TLC (hexanes/EtOAc, 80:20). The reaction was quenched (cold) with sat. aq. NH_4Cl (100 mL), and the mixture was warmed to room temperature with stirring. The mixture was partitioned between water (50 mL) and EtOAc (100 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (1 x 50 mL), dried over Na_2SO_4, filtered, and concentrated (30 °C, 25 mmHg) to afford 3.86 g of crude **42n**. The product was purified by column chromatography (silica gel, 4 x 20 cm, dry load on Celite, 50-mL fractions, hexanes/EtOAc gradient elution: 90:10 (500 mL) to 85:15 (500 mL) to 80:20 (500 mL) to 70:30 (500 mL)) to afford 2.64 g (73%) of **42n** as a pale, yellow, viscous oil.

Data for **42n**:

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

7.50 (d, *J* = 8.3 Hz, 2H, HC(19)), 7.19 (d, *J* = 8.4 Hz, 2H, HC(20)), 7.15 – 7.11 (m, 1H, HC(6)), 7.07 (td, *J* = 8.1, 1.1 Hz, 1H, HC(5)), 6.87 (td, *J* = 8.1, 1.3 Hz, 1H, HC(4)), 4.90 – 4.86 (m, 1H, HC(13)), 4.84 – 4.80 (m, 1H, HC(9)), 4.56 (dd, *J* = 11.5, 3.9 Hz, 1H, HC(7)), 3.77 (s, 3H, H_3C(23)), 3.09 (ddd, *J* = 14.4, 6.3, 4.3 Hz, 1H, H_2C(8)), 2.82 (ddd, *J* = 14.2, 12.0, 7.5 Hz, 1H, H_2C(8)), 2.38 (s, 3H, H_3C(22)),

1.94 – 1.81 (m, 4H, $H_2C(12)$, $H_2C(11)$), 1.59 (s, 3H, $H_3C(15)$), 1.54 (s, 3H, $H_3C(16)$), 1.50 (s, 3H, $H_3C(17)$).

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

151.5 (d, *J* = 247.7 Hz, C(2)), 147.4 (d, *J* = 11.5 Hz, C(3)), 144.6 (C(21)), 139.3 (C(10)), 134.9 (C(18)), 131.6 (C(14)), 129.4 (HC(20)), 129.0 (HC(19)), 124.0 (d, *J* = 4.7 Hz, HC(5)), 123.9 (HC(13)), 121.2 (d, *J* = 11.2 Hz, C(1)), 120.9 (bs, HC(6)), 118.3 (HC(9)), 113.6 (d, *J* = 1.9 Hz, HC(4)), 62.3 (bs, HC(7)), 56.4 ($H_3C(23)$), 39.7 ($H_2C(11)$), 26.5 ($H_2C(12)$), 26.3 ($H_2C(8)$), 25.7 ($H_3C(15)$), 21.8 ($H_3C(22)$), 17.7 ($H_3C(17)$), 16.4 ($H_3C(16)$).

^{19}F NMR: (471 MHz, $CDCl_3$)

–139.32 (bs).

IR: (neat)

2966 (w), 2917 (w), 2855 (w), 1667 (w), 1618 (w), 1597 (w), 1587 (w), 1487 (s), 1441 (m), 1402 (w), 1378 (w), 1319 (m), 1302 (m), 1278 (s), 1203 (m), 1178 (w), 1144 (s), 1084 (s), 1037 (w), 1019 (w), 885 (w), 816 (m), 801 (m), 725 (s), 709 (m), 664 (s), 635 (w), 601 (m), 565 (s), 551 (m), 516 (s), 473 (w).

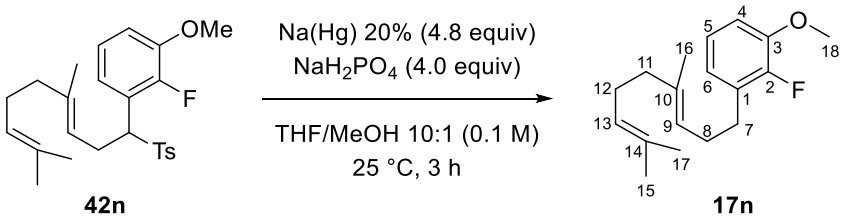
HRMS: calcd for $C_{25}H_{31}O_3FS$ ($[M]^+$): 430.19780; found: 430.19856.

LRMS: (EI, 70 eV)

91.0 (13), 109.1 (10), 122.1 (51), 123.1 (27), 135.1 (14), 139.0 (47), 165.0 (14), 176.0 (14), 177.0 (16), 179.1 (13), 191.1 (43), 193.1 (19), 205.1 (100), 206.1 (34), 207.1 (19), 219.1 (36), 231.1 (17), 274.1 (70), 275.1 (68), 276.1 (12), 430.1 (3).

TLC: R_f 0.24 (hexanes/EtOAc, 80:20, UV/CAM)

(*E*)-1-(4,8-dimethylnona-3,7-dien-1-yl)-2-fluoro-3-methoxybenzene (17n)



A flame-dried, 200-mL, three-necked, round-bottomed flask equipped with a glass-coated stir bar, argon inlet adapter, and two septa was charged with sulfone **42n** (2.48 g, 5.76 mmol), THF (50 mL), and sodium dihydrogen phosphate monohydrate (2.76 g, 20.0 mmol, 3.5 equiv). The mixture was cooled to 0 °C. Sodium amalgam (20% Na (w/w), 0.53 g, 4.6 mmol, 0.8 equiv Na) was added in one portion, followed immediately by the dropwise addition of MeOH (5 mL) over 5 min. Some gas evolution was observed. The cloudy mixture was warmed to 25 °C and stirred for 3 h. Incomplete conversion was observed by TLC (hexanes/EtOAc, 90:10). An additional portion of sodium amalgam (20% Na (w/w), 0.53 g, 4.6 mmol, 0.8 equiv Na) was added at 25 °C. Some gas evolution was observed. The mixture was stirred at 25 °C for 9 h. Incomplete conversion was observed by TLC (hexanes/EtOAc, 90:10). An additional portion of sodium amalgam (20% Na (w/w), 2.12 g, 18.4 mmol, 3.2 equiv Na) was added at 25 °C. Some gas evolution was observed. The mixture was stirred at 25 °C for 3 h. Full conversion was observed by TLC (hexanes/EtOAc, 90:10). **Note:** In total, the amount of sodium amalgam added was 3.18 g (20% Na (w/w), 27.6 mmol, 4.8 equiv Na). Upon completion, the reaction mixture was filtered through a pad of Celite to remove elemental mercury. The pad was rinsed with water (25 mL) and EtOAc (25 mL). The filtrate was transferred to an addition funnel, and the layers were separated. The aqueous phase was extracted with EtOAc (2 x 25 mL). The combined organic layers were dried over Na2SO4, filtered, and concentrated (30 °C, 25 mmHg) to afford 1.48 g (93%) of **17n** in sufficient purity for kinetics experiments. A portion of the product was purified to an analytical standard by Kugelrohr distillation (175 °C ABT, 0.01 mmHg) to afford 1.27 g (80%) of **17n** as a colorless oil.

Data for **17n**:

b.p.: 175 °C (ABT, 0.01 mmHg)

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

6.97 (td, *J* = 8.0, 1.5 Hz, 1H, HC(5)), 6.83 – 6.74 (m, 2H, HC(4), HC(6)), 5.21 – 5.15 (m, 1H, HC(9)), 5.12 – 5.05 (m, 1H, HC(13)), 3.87 (s, 3H, H_3C(18)), 2.69 – 2.64 (m, 2H, H_2C(7)), 2.29 (q, *J* = 7.4 Hz, 2H, H_2C(8)), 2.09 – 2.01 (m, 2H, H_2C(12)), 2.00 – 1.94 (m, 2H, H_2C(11)), 1.68 (s, 3H, H_3C(15)), 1.60 (s, 3H, H_3C(17)), 1.55 (s, 3H, H_3C(16)).

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

151.0 (d, *J* = 243.6 Hz, C(2)), 147.7 (d, *J* = 11.2 Hz, C(3)), 136.3 (C(10)), 131.5 (C(14)), 130.3 (d, *J* = 13.7 Hz, C(1)), 124.5 (HC(13)), 123.5 (d, *J* = 4.7 Hz, HC(5)), 123.4 (HC(9)), 122.2 (d, *J* = 4.1 Hz, HC(6)), 111.0 (d, *J* = 1.4 Hz, HC(4)), 56.4 (H_3C(18)), 39.9 (H_2C(11)), 29.3 (d, *J* = 2.6 Hz, H_2C(7)), 28.7 (m, H_2C(8)), 26.9 (H_2C(12)), 25.8 (H_3C(15)), 17.8 (H_3C(17)), 16.1 (H_3C(16)).

^{19}F NMR: (471 MHz, $CDCl_3$)

–141.70 (t, *J* = 7.1 Hz).

IR: (neat)

2965 (w), 2917 (m), 2857 (w), 1668 (w), 1619 (w), 1585 (w), 1487 (s), 1454 (m), 1440 (m), 1376 (w), 1318 (m), 1274 (s), 1203 (m), 1185 (m), 1150 (w), 1079 (s), 985 (w), 930 (w), 819 (m), 773 (m), 726 (s), 704 (w), 687 (w), 614 (w), 587 (w), 558 (w).

HRMS: calcd for $C_{18}H_{25}OF$ ($[M]^+$): 276.1889; found: 276.1898.

LRMS: (EI, 70 eV)

109.0 (20), 109.1 (16), 123.1 (20), 137.1 (19), 139.1 (100), 140.1 (25), 152.1 (50), 165.1 (21), 177.1 (11), 179.1 (27), 191.1 (27), 192.1 (12), 193.1 (36), 205.1 (24), 206.1 (11), 233.1 (67), 234.1 (11), 256.2 (13), 261.2 (63), 262.2 (12), 276.2 (50), 277.2 (10).

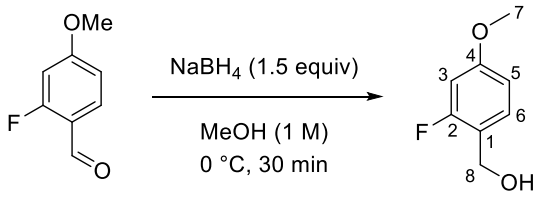
Analysis: $C_{18}H_{25}FO$ (276.40)

Calcd: C, 78.22%; H, 9.12%

Found: C, 78.02%; H, 8.92%

TLC: R_f 0.60 (hexanes/EtOAc, 80:20, UV/CAM)

(2-Fluoro-4-methoxyphenyl)methanol (**101m**)



A flame-dried, 25-mL, round bottomed flask equipped with a stir bar and argon inlet adapter was charged with 2-fluoro-4-methoxybenzaldehyde **100m** (0.77 g, 5.0 mmol) and methanol (5 mL). The resulting yellow solution was cooled to 0 °C. Sodium borohydride (0.28 g, 7.5 mmol, 1.5 equiv) was added in three portions over 1 min. Gas evolution was observed, and the yellow color disappeared almost immediately. The reaction mixture was stirred for 30 min at 0 °C under argon. Full conversion was observed by TLC (hexanes/EtOAc, 80:20). The reaction was quenched by the careful addition of sat. aq. NH_4Cl (5 mL). The mixture was partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL), and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with brine (1 x 20 mL) and then dried over Na_2SO_4, filtered, and concentrated (30 °C, 25 mmHg) to afford 0.73 g (93%) of **101m** as a pale, yellow oil requiring no further purification. Spectroscopic data matched those previously reported.

Data for **101m**:

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

7.29 (t, J = 8.6 Hz, 1H, HC(6)), 6.71 – 6.67 (m, 1H, HC(5)), 6.63 (dd, J = 11.9, 2.4 Hz, 1H, HC(3)), 4.68 (d, J = 6.1 Hz, 2H, H_2C(8)), 3.80 (s, 3H, H_3C(7)), 1.67 – 1.62 (m, 1H, OH).

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

161.6 (d, $J_{C–F}$ = 246.6 Hz, C(2)), 160.8 (d, $J_{C–F}$ = 11.0 Hz, C(4)), 130.5 (d, $J_{C–F}$ = 6.4 Hz, HC(6)), 120.0 (d, $J_{C–F}$ = 15.4 Hz, C(1)), 109.9 (d, $J_{C–F}$ = 3.1 Hz, HC(5)), 101.8 (d, $J_{C–F}$ = 25.1 Hz, HC(3)), 59.4 (d, $J_{C–F}$ = 3.6 Hz, H_2C(8)), 55.7 (H_3C(7)).

^{19}F NMR: (471 MHz, $CDCl_3$)

–117.55 (dd, J = 11.6, 8.9 Hz).

IR: (neat)

3334 (w, br), 3007 (w), 2940 (w), 2839 (w), 1625 (s), 1587 (m), 1508 (s), 1466 (m), 1444 (m), 1320 (m), 1282 (s), 1267 (s), 1191 (m), 1152 (s), 1113 (s), 1099 (s), 1029 (s), 1003 (s), 968 (m), 944 (s), 834 (s), 815 (m), 780 (m), 731 (m), 707 (m), 629 (m), 564 (m), 553 (m), 540 (m), 522 (m), 508 (m), 455 (m).

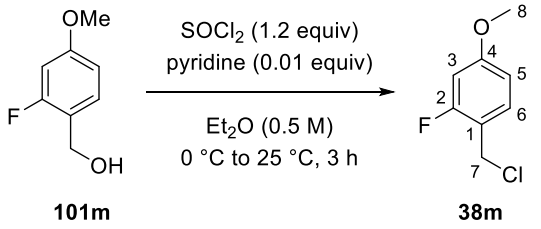
HRMS: calcd for $C_8H_9O_2F$ ($[M]^+$): 156.0587; found: 156.0589

LRMS: (EI, 70 eV)

83.0 (18), 96.0 (33), 97.0 (18), 109.0 (18), 112.0 (29), 125.0 (30), 126.0 (13), 127.1 (47), 135.0 (16), 139.1 (98), 140.1 (14), 153.0 (21), 155.1 (77), 156.1 (100), 157.1 (8).

TLC: R_f 0.12 (hexanes/EtOAc, 80:20, UV/CAM)

1-(Chloromethyl)-2-fluoro-4-methoxybenzene (**38m**)



101m **38m**

An oven-dried, 50-mL, Schlenk flask equipped with a stir bar was charged with alcohol **101m** (0.73 g, 4.7 mmol), Et_2O (9.4 mL), and a drop of pyridine (4 μL, 47 μmol, 0.01 equiv). The resulting clear, colorless solution was cooled to –5 °C using an ice/salt bath. Neat thionyl chloride (0.41 mL, 5.6 mmol, 1.2 equiv) was added dropwise, taking care to maintain the internal temperature below 0 °C. A white suspension initially resulted, but this soon cleared to form a turbid, colorless suspension once the addition was complete. The reaction mixture was allowed to warm slowly to 25 °C and stirring was continued for 6 h. Full conversion was observed by TLC (hexanes/EtOAc, 80:20). The reaction was quenched by the addition of water (10 mL), and the resulting biphasic mixture was stirred vigorously for 2 min. The mixture was transferred to a separatory funnel, and the layers were separated. The aqueous phase was extracted with Et_2O (2 x 10 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (1 x 25 mL) and brine

(1 x 25 mL), and then dried over Na_2SO_4, filtered, and concentrated (30 °C, 25 mmHg) to afford crude **38m** as a pale, yellow oil. The product was purified to an analytical standard by Kugelrohr distillation (ABT 105 °C, 0.01 mmHg) to afford 734.8 mg (90%) of **38m** as a clear, colorless oil.

Data for **38m**:

b.p.: 105 °C (ABT, 0.01 mmHg)

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

7.30 (t, J = 8.6 Hz, 1H, HC(6)), 6.69 (dd, J = 8.5, 2.4 Hz, 1H, HC(5)), 6.63 (dd, J = 11.7, 2.5 Hz, 1H, HC(3)), 4.61 (s, 2H, H_2C(7)), 3.80 (s, 3H, H_3C(8)).

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

161.6 (d, $J_{C–F}$ = 249.6 Hz, C(2)), 161.5 (d, $J_{C–F}$ = 11.0 Hz, C(4)), 131.7 (d, $J_{C–F}$ = 5.2 Hz, HC(6)), 116.9 (d, $J_{C–F}$ = 15.1 Hz, C(1)), 110.4 (d, $J_{C–F}$ = 3.2 Hz, HC(5)), 101.9 (d, $J_{C–F}$ = 24.9 Hz, HC(3)), 55.8 (H_3C(8)), 39.7 (d, $J_{C–F}$ = 4.0 Hz, H_2C(7)).

^{19}F NMR: (471 MHz, $CDCl_3$)

–115.26 (dd, J = 11.3, 9.1 Hz).

IR: (neat)

3009 (w), 2968 (w), 2940 (w), 2840 (w), 1625 (s), 1587 (m), 1509 (s), 1466 (m), 1443 (m), 1327 (m), 1288 (m), 1262 (s), 1191 (m), 1151 (s), 1106 (s), 1092 (s), 1029 (s), 954 (m), 900 (w), 836 (s), 811 (m), 787 (w), 734 (m), 664 (s), 623 (m), 564 (w), 551 (m), 523 (m), 478 (m).

LRMS: (EI, 70 eV)

95.0 (10), 96.0 (17), 109.0 (11), 112.0 (14), 125.0 (13), 127.1 (23), 139.1 (100), 140.1 (13), 155.1 (37), 156.1 (47), 174.0 (7), 176.0 (4).

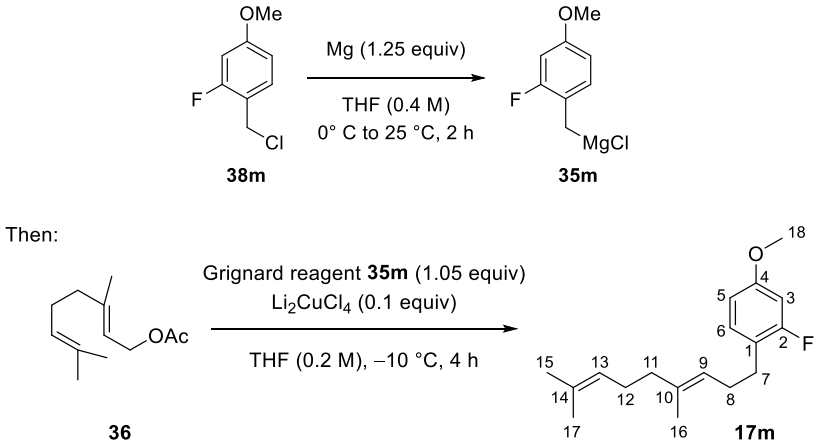
Analysis: C_8H_8ClFO (174.60)

Calcd: C, 55.03%; H, 4.62%

Found: C, 55.13%; H, 4.45%

TLC: R_f 0.48 (hexanes/EtOAc, 80:20, UV/CAM)

(*E*)-1-(4,8-dimethylnona-3,7-dien-1-yl)-2-fluoro-4-methoxybenzene (17m)



A flame-dried, 50-mL, three-necked, round-bottomed flask equipped with a stir bar, argon inlet, two septa, and temperature probe was charged with magnesium turnings (115.2 mg, 4.74 mmol, 1.30 equiv). The turnings were mechanically activated immediately before use by grinding with a mortar and pestle for 15 min. The flask was again evacuated, flame-dried, and placed under argon. Once cool, the flask was charged with THF (6.2 mL) and a single drop (1 μL) of 1,2-dibromoethane. The mixture was stirred at 25 °C for 15 min and then cooled to 0 °C using an ice bath. A solution of benzyl chloride **38m** (637.8 mg, 3.65 mmol) in THF (2.9 mL) was taken up in a 5-mL plastic Leur-Lock syringe and added dropwise to the reaction flask at 0 °C over 30 min using a syringe pump. The external ice bath was maintained throughout the addition, but a slight exotherm (approx. 3 °C) was observed over the course of addition, along with a slight color change to pale yellow. Once the addition was complete, the ice bath was removed and the mixture was allowed to warm to 25 °C. Stirring was continued for 1 h at 25 °C, and then the Grignard reagent **35m** was titrated in the usual manner. The concentration of **35m** was determined to be 0.30 M (average of two runs; expected 0.40 M). The reagent was used immediately.

A flame-dried, 5-mL, Schlenk flask was charged with anhydrous lithium chloride (21 mg, 0.50 mmol, 0.2 equiv) and anhydrous copper(II) chloride (34 mg, 0.25 mmol, 0.1 equiv) inside of the glovebox. The flask was sealed, removed from the glovebox, charged with THF (1 mL), and sonicated at 25 °C under argon for 5 min. An orange solution resulted, indicating formation of the desired Li_2CuCl_4 complex. A separate, flame-dried, 50-mL, three-necked, round-bottomed flask equipped with a stir bar, temperature probe, two septa, and argon inlet was charged with geranyl

acetate **36** (0.53 mL, 0.49 g, 2.50 mmol) and THF (5.5 mL). The resulting clear, colorless solution was cooled to 0 °C using an ice bath. The orange solution of the Li_2CuCl_4 complex was added dropwise to the solution of geranyl acetate **36**. The homogenous mixture was stirred at 0 °C for 10 min and then cooled to an internal temperature of -10 °C using an ice/salt bath. The freshly-prepared Grignard reagent **35m** (8.7 mL, 0.30 M, 2.6 mmol, 1.05 equiv) was added dropwise to the reaction flask over 30 min using a syringe pump. The rate of addition was adjusted as needed such that the internal temperature did not exceed –5 °C. During the course of addition, the initially orange reaction mixture turned colorless, then yellow and eventually brown. Stirring was continued (below 0 °C) for 3 h. Conversion was monitored by TLC (hexanes/CH_2Cl_2, 50:50). The cold bath was removed, and the reaction was quenched by the addition of sat. aq. NH_4Cl (25 mL). The resulting biphasic mixture was stirred vigorously for 5 min and then partitioned between diethyl ether (50 mL) and water (50 mL). The layers were separated, and the aqueous phase was extracted with diethyl ether (2 x 25 mL). The combined organic layers were washed with 1 M HCl (1 x 25 mL), sat. aq. $NaHCO_3$ (1 x 25 mL), and brine (1 x 25 mL), and then dried over Na_2SO_4, filtered, and concentrated (30 °C, 15 mmHg) to afford 0.90 g of crude **17m**. The product was purified by chromatography (silica gel, 3 cm x 22 cm, dry load on Celite, 25 mL fractions, hexanes/CH_2Cl_2 gradient elution: 95:5 (300 mL) to 90:10 (300 mL) to 80:20 (300 mL) to 70:30 (300 mL)) to afford 557.3 mg of **17m** as a clear, colorless oil in approx. 95% purity. The product co-eluted with 3-fluoro-4-methylanisole (by-product of quenching excess **35m**). The more volatile impurity was removed by Kugelrohr distillation (100 °C ABT, 0.01 mmHg, 20 min). ^{1}H NMR analysis of desired **17m** remaining in the distillation pot indicated >99.8% purity. The product was purified to an analytical standard by Kugelrohr distillation (160 °C ABT, 0.01 mmHg) to afford 516.8 mg (75%) of **17m** as a colorless oil.

Data for **17m**:

b.p.: 160 °C (ABT, 0.01 mmHg)

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

7.06 (t, J = 8.5 Hz, 1H, HC(6)), 6.63 – 6.55 (m, 2H, HC(5), HC(3)), 5.19 – 5.14 (m, 1H, HC(9)), 5.11 – 5.06 (m, 1H, HC(13)), 3.77 (s, 3H, H_3C(18)), 2.59 (app. t, J = 7.7 Hz, 2H, H_2C(7)), 2.25 (q, J = 7.4 Hz, 2H, H_2C(8)), 2.08 – 2.01 (m, 2H, H_2C(12)), 2.00 – 1.94 (m, 2H, H_2C(11)), 1.68 (s, 3H, H_3C(15)), 1.60 (s, 3H, H_3C(17)), 1.54 (s, 3H, H_3C(16)).

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

161.7 (d, $J_{C–F}$ = 244.3 Hz, C(2)), 159.1 (d, $J_{C–F}$ = 10.7 Hz, C(4)), 136.2 (C(10)), 131.5 (C(14)), 131.0 (d, $J_{C–F}$ = 7.3 Hz, HC(6)), 124.5 (HC(13)), 123.5 (HC(9)), 121.1 (d, $J_{C–F}$ = 16.7 Hz, C(1)), 109.5 (d, $J_{C–F}$ = 3.0 Hz, HC(5)), 101.5 (d, $J_{C–F}$ = 26.1 Hz, HC(3)), 55.7 (H_3C(18)), 39.9 (H_2C(11)), 28.9 (H_2C(8)), 28.7 (d, H_2C(7)), 26.9 (H_2C(12)), 25.9 (H_3C(15)), 17.8 (H_3C(17)), 16.1 (H_3C(16)).

^{19}F NMR: (471 MHz, $CDCl_3$)

–116.65 (dd, J = 11.1, 9.7 Hz).

IR: (neat)

2964 (w), 2915 (m), 2857 (w), 1626 (m), 1585 (m), 1507 (s), 1466 (m), 1443 (m), 1376 (w), 1322 (w), 1283 (m), 1267 (m), 1189 (m), 1144 (s), 1109 (m), 1035 (m), 985 (w), 949 (m), 935 (w), 847 (m), 831 (s), 801 (w), 740 (w), 706 (w), 626 (w), 555 (w), 527 (w), 459 (w).

LRMS: (EI, 70 eV)

67.1 (22), 68.1 (11), 69.1 (68), 77.0 (10), 79.1 (11), 81.1 (31), 91.1 (26), 93.1 (12), 95.0 (10), 95.1 (12), 96.0 (36), 109.0 (33), 109.1 (10), 123.1 (24), 137.1 (15), 139.0 (100), 139.8 (23), 140.1 (45), 152.0 (98), 153.1 (21), 233.1 (19), 276.2 (23), 277.2 (4).

Analysis: $C_{18}H_{25}FO$ (276.40)

Calcd: C, 78.22%; H, 9.12%

Found: C, 78.05%; H, 8.98%

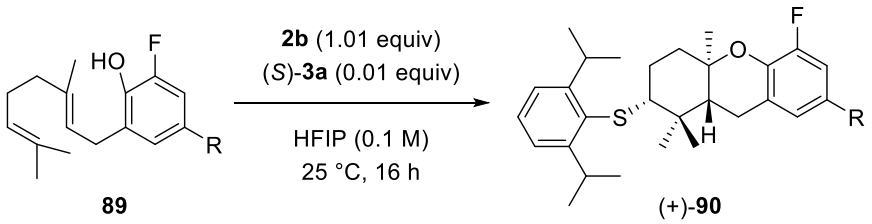
TLC: R_f 0.28 (hexanes/CH_2Cl_2, 80:20, UV/CAM)

Preparation of Racemic Standards ((±)-90)

A 20-mL scintillation vial equipped with a stir bar was charged with sulfenylating agent **2b** (93 mg, 0.27 mmol, 1.1 equiv), phenol substrate **89** (0.25 mmol), and hexafluoroisopropanol (2.5 mL). A yellow solution resulted. Tetrahydrothiophene (0.2 μL, 0.0025 mmol, 0.01 equiv) was added to the solution. The vial was capped and the reaction mixture was stirred for 1.5 h at 25 °C. Conversion was assessed by TLC (hexanes/CH_2Cl_2, 80:20). Upon completion, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and volatile components were removed by rotary evaporation (25

°C, 30 mmHg). The crude product was purified by column chromatography, and further purified by recrystallization if necessary.

General Procedure for Synthesis of Enantiomerically Enriched (+)-90 (1.0 mmol scale)

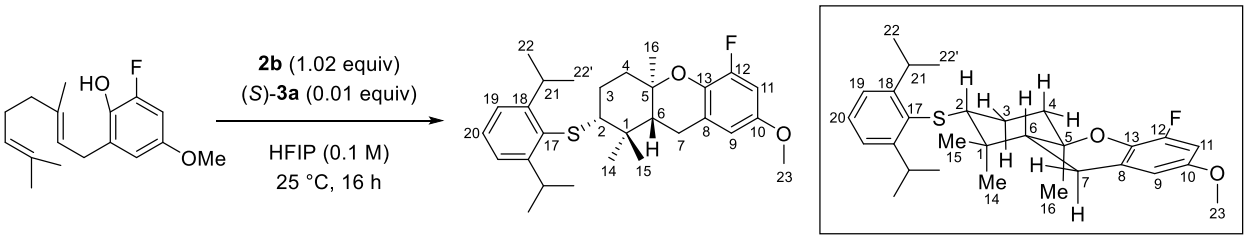


A 50-mL, round-bottomed flask equipped with a stir bar was charged with *N*-(2,6-diisopropylphenylthio)phthalimide **2b** (1.01 mmol, 1.01 equiv), hexafluoroisopropyl alcohol (10 mL), and phenol **89** (1.0 mmol). Lewis base catalyst (*S*)-**3a** (0.01 mmol, 0.01 equiv) was added. The mixture was stirred at 25 °C for 12 h. Some white precipitates and/or a color change were often observed at longer reaction times. Full conversion was observed by TLC (hexanes/CH_2Cl_2, 80:20). The reaction mixture was diluted with CH_2Cl_2 (5 mL), and volatile components were removed by rotary evaporation (30 °C, 15 mmHg). The crude product was purified by chromatography (hexanes/CH_2Cl_2 gradient elution) to afford **90** as a white, foamy solid. [**Note**: Generally, other solvents systems like hexanes/EtOAc or hexanes/Et_2O were less effective for separating **90** from impurities.] The product was triturated in boiling MeOH or EtOH (approx. 1.5 mL) and the mother liquor was decanted to afford **90** in >99% purity by quantitative ^{1}H NMR. The protocol for assessing purity is as follows. A sample of tricycle **90** (approx. 10–15 mg) was dissolved in $CDCl_3$ (approx. 1 mL). To this solution was added 1,1,1,2-tetrachloroethane (3.0 μL, D = 1.598 g/mL, 4.79 mg, 0.02856 mmol) using a Hamilton gastight syringe. The solution was transferred to an NMR tube and a ^{1}H spectrum was acquired (nt = 16, d1 = 15 sec, S/N >300). The integral of the signal arising from the internal standard (4.3 ppm, s, 2H) was normalized to 1.00. Then, the integral of a signal arising from the product (4.0 ppm, hept, 2H) was measured, and the purity of the sample was given by the following equation:

$$\%\ \text{purity} = \frac{(0.02856\ \text{mmol} \times \text{integral of } \mathbf{90} \times \text{molar mass } \mathbf{90})}{(\text{mass of } \mathbf{90})} \times 100$$

Other product signals can be used instead, and similar results are obtained. It is important to use at least 3 μL of internal standard (exactly measured using a gastight syringe). Smaller quantities lead to irreproducible measurements.

Preparation of (2*R*,5*R*,6*R*)-2-((2,6-Diisopropylphenyl)thio)-12-fluoro-10-methoxy-1,1,5-trimethyl-1,2,3,4,5,6-hexahydro-7*H*-xanthene ((+)-90a)



A 50-mL, round-bottomed flask equipped with a stir bar was charged with *N*-(2,6-diisopropylphenylthio)phthalimide **2b** (345.5 mg, 1.02 mmol, 1.02 equiv), hexafluoroisopropyl alcohol (10 mL), and phenol **89a** (278.7 mg, 1.0 mmol). Lewis base catalyst (*S*)-**3a** (6.3 mg, 0.012 mmol, 0.01 equiv) was added. The yellow solution was stirred at 25 °C for 16 h. Full conversion was observed by TLC (hexanes/CH_2Cl_2, 50:50). The reaction mixture was diluted with CH_2Cl_2 (5 mL), and volatile components were removed by rotary evaporation (30 °C, 15 mmHg). The crude product was purified by chromatography (silica gel, 3 cm x 25 cm, dry load on Celite, 25 mL fractions, hexanes/CH_2Cl_2 gradient elution: 90:10 (300 mL) to 80:20 (300 mL) to 70:30 (300 mL) to 60:40 (300 mL) to 50:50 (300 mL) to 40:60 (300 mL)) to afford 419.5 mg (89%) of **90a** as a white, foam solid in >95% purity. The product was triturated in boiling methanol (1.5 mL) for 30 min. The suspension was cooled to –20 °C, and the mother liquor was decanted. This process was repeated once, and the white solid was dried in an Abderhalden (TBME, 55 °C, 0.01 mmHg, 12 h) to afford 355.5 mg (75%) of **90a** in >99% purity by quantitative ^{1}H NMR.

Data for (+)-**90a**:

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

7.33 (t, *J* = 7.7 Hz, 1H, HC(20)), 7.18 (d, *J* = 7.7 Hz, 2H, HC(19)), 6.52 (dd, *J* = 12.3, 2.7 Hz, 1H, HC(11)), 6.41 (bs, 1H, HC(9)), 3.96 (hept, *J* = 6.7 Hz, 2H,

HC(21)), 3.73 (s, 3H, $H_3C(23)$), 2.77 (dd, J = 16.7, 5.3 Hz, 1H, $H_2C(7^{eq})$), 2.75 – 2.70 (m, 1H, $H_2C(7^{ax})$), 2.69 (dd, J = 12.1, 3.9 Hz, 1H, HC(2)), 1.97 (dt, J = 12.7, 2.9 Hz, 1H, $H_2C(4^{eq})$), 1.76 (dd, J = 12.6, 5.3 Hz, 1H, HC(6)), 1.74 – 1.64 (m, 1H, $H_2C(3^{ax})$), 1.61 (dq, J = 14.0, 3.7 Hz, 1H, $H_2C(3^{eq})$), 1.48 (td, J = 13.3, 3.6 Hz, 1H, $H_2C(4^{ax})$), 1.41 (s, 3H, $H_3C(15)$), 1.26 (d, J = 6.8 Hz, 6H, $H_3C(22)$), 1.23 (s, 3H, $H_3C(16)$), 1.20 (d, J = 6.9 Hz, 6H, $H_3C(22')$), 1.08 (s, 3H, $H_3C(14)$).

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

154.1 (C(18)), 152.5 (d, $J_{C–F}$ = 10.0 Hz, C(10)), 152.0 (d, $J_{C–F}$ = 244.4 Hz, C(12)), 135.3 (d, $J_{C–F}$ = 11.4 Hz, C(13)), 130.3 (C(17)), 129.2 (HC(20)), 124.9 (d, $J_{C–F}$ = 3.2 Hz, C(8)), 123.9 (HC(19)), 109.0 (d, $J_{C–F}$ = 3.0 Hz, HC(9)), 101.3 (d, $J_{C–F}$ = 21.8 Hz, HC(11)), 77.0 (C(5)), 60.9 (HC(2)), 55.9 ($H_3C(23)$), 49.6 (HC(6)), 39.9 ($H_2C(4)$), 38.7 (C(1)), 31.5 (HC(21)), 28.9 ($H_3C(15)$), 26.7 ($H_2C(3)$), 25.0 (bs, $H_3C(22')$), 24.1 (bs, $H_3C(22)$), 23.9 (d, $J_{C–F}$ = 2.7 Hz, $H_2C(7)$), 19.7 ($H_3C(16)$), 16.6 ($H_3C(14)$).

^{19}F NMR: (471 MHz, $CDCl_3$)

–134.63 (d, J = 12.4 Hz).

IR: (neat)

2960 (m), 2867 (w), 1594 (w), 1496 (s), 1463 (m), 1391 (w), 1380 (m), 1361 (m), 1337 (w), 1302 (w), 1289 (w), 1237 (s), 1216 (m), 1190 (m), 1143 (s), 1127 (m), 1070 (w), 1043 (s), 972 (w), 950 (m), 929 (m), 912 (m), 865 (w), 835 (m), 798 (m), 755 (m), 746 (w), 737 (m), 706 (w), 611 (w).

HRMS: calcd for $C_{29}H_{39}O_2FS$ ($[M]^+$): 470.2655; found: 470.2671.

LRMS: (EI, 70 eV)

116.9 (15), 117.9 (30), 118.9 (16), 119.9 (30), 123.1 (90), 154.0 (27), 155.1 (68), 156.1 (37), 193.1 (28), 195.1 (21), 207.1 (14), 277.2 (12), 278.2 (100), 279.2 (19), 470.3 (7).

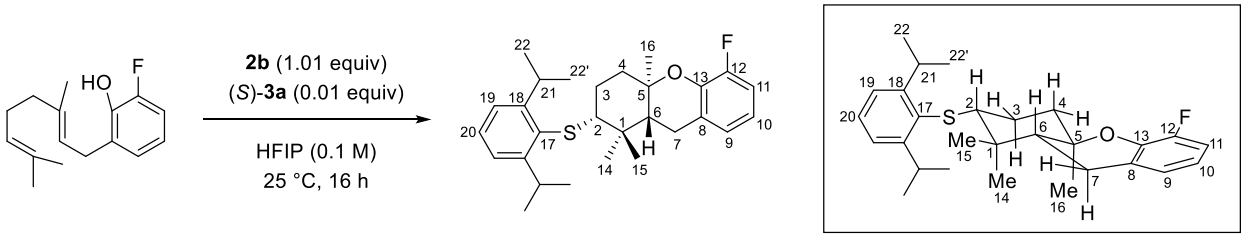
TLC: R_f 0.42 (hexanes/CH_2Cl_2, 50:50, UV/CAM)

Opt. Rot.: $[\alpha]_D^{24}$ = +69.6 (c = 0.99 in $CHCl_3$) (72% ee)

HPLC: t_R 3.7 min (91%); 5.2 min (9%) (Supelco Astec, hexanes/i-PrOH, 95:5, 1.0 mL/min, 220 nm, 24 °C)

After trituration: t_R 3.7 min (86%); 5.2 min (14%)

Preparation of (2*R*,5*R*,6*R*)-2-((2,6-Diisopropylphenyl)thio)-12-fluoro-1,1,5-trimethyl-1,2,3,4,5,6-hexahydro-7*H*-xanthene ((+)-90b)



A 50-mL, round-bottomed flask equipped with a stir bar was charged with *N*-(2,6-diisopropylphenylthio)phthalimide **2b** (344.3 mg, 1.01 mmol, 1.01 equiv), hexafluoroisopropyl alcohol (10 mL), and phenol **89b** (249.8 mg, 1.0 mmol). Lewis base catalyst (*S*)-**3a** (5.7 mg, 0.011 mmol, 0.01 equiv) was added. The yellow solution was stirred at 25 °C for 12 h. Some white precipitates were observed at longer reaction times. Full conversion was observed by TLC (hexanes/CH_2Cl_2, 80:20). The reaction mixture was diluted with CH_2Cl_2 (5 mL), and volatile components were removed by rotary evaporation (30 °C, 15 mmHg). The crude product was purified by chromatography (high resolution silica gel, 3 cm x 27 cm, dry load on Celite, 25 mL fractions, hexanes/CH_2Cl_2 gradient elution: 90:10 (600 mL) to 80:20 (600 mL) to 70:30 (300 mL)) to afford 220.0 mg of **90b** as a white, foam solid in approx. 99% purity, plus 117.9 mg of **90b** as a white, foam solid in approx. 90% purity. The less pure material was re-purified by chromatography using similar conditions to afford 75.0 mg of **90b** in approx. 99% purity. After combining the samples and drying on an Abderhalden (pentane, 35 °C, 0.01 mmHg, 3 h), a total of 286.7 mg (65%) of **90b** was obtained from chromatographic purification. The product was triturated in boiling methanol (1.5 mL) for 30 min. The suspension was cooled to –20 °C, and the mother liquor was decanted to afford (after two crops) 246.4 mg (56%) of **90b** in >99% purity by quantitative ^{1}H NMR.

Data for (+)-**90b**:

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

7.33 (t, *J* = 7.7 Hz, 1H, HC(20)), 7.18 (d, *J* = 7.7 Hz, 2H, HC(19)), 6.90 – 6.85 (m, 1H, HC(11)), 6.84 (app. d, *J* = 8.1 Hz, 1H, HC(9)), 6.74 (td, *J* = 7.9, 4.9 Hz, 1H, HC(10)), 3.96 (hept, *J* = 6.9 Hz, 2H, HC(21)), 2.81 (dd, *J* = 16.5, 5.1 Hz, 1H,

$H_2C(7^{eq})$), 2.77 – 2.70 (m, 1H, $H_2C(7^{ax})$), 2.69 (dd, J = 12.0, 4.0 Hz, 1H, HC(2)), 2.00 (dt, J = 12.8, 3.2 Hz, 1H, $H_2C(4^{eq})$), 1.76 (dd, J = 12.8, 5.1 Hz, 1H, HC(6)), 1.74 – 1.65 (m, 1H, $H_2C(3^{ax})$), 1.62 (dq, J = 13.9, 3.9 Hz, 1H, $H_2C(3^{eq})$), 1.50 (td, J = 13.3, 3.9 Hz, 1H, $H_2C(4^{ax})$), 1.42 (s, 3H, H_3C(15)), 1.26 (d, J = 6.9 Hz, 6H, H_3C(22)), 1.26 (s, 3H, H_3C(16)), 1.20 (d, J = 6.9 Hz, 6H, H_3C(22')), 1.09 (s, 3H, H_3C(14)).

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

154.1 (C(18)), 152.1 (d, $J_{C–F}$ = 244.1 Hz, C(12)), 141.4 (d, $J_{C–F}$ = 10.9 Hz, C(13)), 130.3 (C(17)), 129.2 (HC(20)), 124.9 (d, $J_{C–F}$ = 1.8 Hz, C(8)), 124.6 (d, $J_{C–F}$ = 3.3 Hz, HC(9)), 123.9 (HC(19)), 119.3 (d, $J_{C–F}$ = 7.3 Hz, HC(10)), 113.8 (d, $J_{C–F}$ = 18.2 Hz, HC(11)), 77.4 (C(5)), 60.9 (HC(2)), 49.4 (HC(6)), 39.9 (H_2C(4)), 38.7 (C(1)), 31.5 (HC(21)), 29.0 (H_3C(15)), 26.7 (H_2C(3)), 25.0 (bs, H_3C(22')), 24.1 (bs, H_3C(22)), 23.5 (d, $J_{C–F}$ = 2.3 Hz, H_2C(7)), 19.9 (H_3C(16)), 16.7 (H_3C(14)).

^{19}F NMR: (471 MHz, $CDCl_3$)

–137.08 (dd, J = 11.0, 4.9 Hz).

IR: (neat)

2962 (m), 2866 (w), 1589 (w), 1483 (s), 1462 (s), 1391 (m), 1381 (m), 1361 (m), 1310 (m), 1262 (s), 1236 (m), 1147 (m), 1125 (m), 1042 (s), 1015 (s), 967 (w), 950 (m), 929 (m), 914 (m), 862 (w), 799 (m), 768 (s), 756 (m), 740 (m), 722 (s), 700 (m), 640 (w), 572 (w), 525 (w), 476 (w).

HRMS: calcd for $C_{28}H_{37}FOS$ ($[M]^+$): 440.2549; found: 440.2568.

LRMS: (EI, 70 eV)

121.1 (14), 125.0 (50), 149.0 (16), 151.1 (33), 163.1 (28), 177.1 (12), 179.1 (14), 191.1 (12), 194.1 (41), 203.1 (24), 246.1 (26), 247.2 (100), 248.2 (19), 440.3 (61), 441.3 (20).

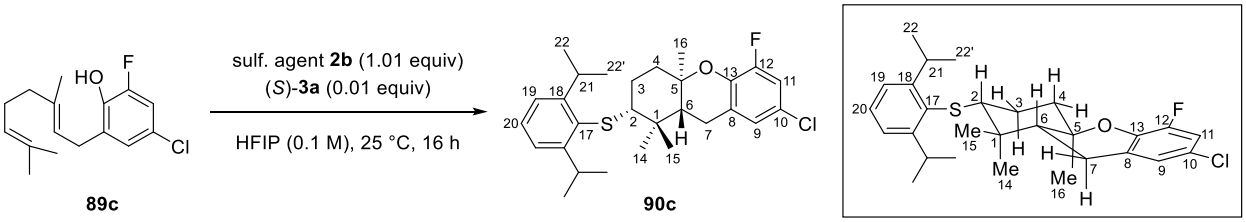
TLC: R_f 0.59 (hexanes/CH_2Cl_2, 50:50, UV/CAM)

Opt. Rot.: $[\alpha]_D^{24}$ = +56.6 (c = 1.04 in $CHCl_3$) (76% ee)

HPLC: t_R 3.3 min (90%); 4.4 min (10%) (Supelco Astec, hexanes/i-PrOH, 95:5, 1.0 mL/min, 220 nm, 24 °C)

After trituration: t_R 3.3 min (88%); 4.4 min (12%)

Preparation of (2*R*,5*R*,6*R*)-10-Chloro-2-((2,6-diisopropylphenyl)thio)-12-fluoro-1,1,5-trimethyl-1,2,3,4,5,6-hexahydro-7*H*-xanthene ((+)-**90c)**



A 50-mL, round-bottomed flask equipped with a stir bar was charged with *N*-(2,6-diisopropylphenylthio)phthalimide **2b** (344.4 mg, 1.01 mmol, 1.01 equiv), hexafluoroisopropyl alcohol (10 mL), and phenol **89c** (283.1 mg, 1.0 mmol). Lewis base catalyst (*S*)-**3a** (6.0 mg, 0.012 mmol, 0.01 equiv) was added. The mixture was stirred at 25 °C for 16 h. Over time, a yellow suspension resulted. Full conversion was observed by TLC (hexanes/CH_2Cl_2, 80:20). The reaction mixture was diluted with CH_2Cl_2 (5 mL), and volatile components were removed by rotary evaporation (30 °C, 15 mmHg). The crude product was purified by chromatography (silica gel, 3 cm x 30 cm, dry load on Celite, 25 mL fractions, hexanes/CH_2Cl_2 gradient elution: 95:5 (300 mL) to 90:10 (300 mL) to 85:15 (300 mL) to 80:20 (300 mL) to 70:30 (300 mL)) to afford 357.6 mg (75%) of **90c** as a white, foam solid in >95% purity. The product was triturated in boiling methanol (1.5 mL) for 30 min. The suspension was cooled to –20 °C, and the mother liquor was decanted. The white solid was dried in an Abderhalden (TBME, 55 °C, 0.01 mmHg, 24 h) to afford 302.0 mg (63%) of **90c** in >99% purity by quantitative ^{1}H NMR.

Data for (+)-**90c**:

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

7.33 (t, *J* = 7.7 Hz, 1H, HC(20)), 7.18 (d, *J* = 7.7 Hz, 2H, HC(19)), 6.90 (dd, *J* = 10.4, 2.4 Hz, 1H, HC(11)), 6.87 – 6.84 (bm, 1H, HC(9)), 3.95 (hept, *J* = 6.8 Hz, 2H, HC(21)), 2.77 (dd, *J* = 16.7, 5.2 Hz, 1H, $H_2C(7^{eq})$), 2.70 (dd, *J* = 16.5, 13.0 Hz, 1H, $H_2C(7^{ax})$), 2.67 (dd, *J* = 11.8, 4.3 Hz, 1H, HC(2)), 1.99 (dt, *J* = 12.9, 3.3 Hz, 1H, $H_2C(4^{eq})$), 1.74 (dd, *J* = 12.7, 5.2 Hz, 1H, HC(6)), 1.73 – 1.63 (m, 1H, $H_2C(3^{ax})$), 1.62 (dq, *J* = 14.0, 4.0 Hz, 1H, $H_2C(3^{eq})$), 1.48 (td, *J* = 13.3, 4.1 Hz, 1H, $H_2C(4^{ax})$), 1.41 (s, 3H, H_3C(15)), 1.26 (d, *J* = 6.9 Hz, 6H, H_3C(22)), 1.24 (s, 3H, H_3C(16)), 1.20 (d, *J* = 6.9 Hz, 6H, H_3C(22')), 1.08 (s, 3H, H_3C(14)).

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

154.1 (C(18)), 151.8 (d, $J_{C–F}$ = 248.1 Hz, C(12)), 140.3 (d, $J_{C–F}$ = 10.9 Hz, C(13)), 130.2 (C(17)), 129.3 (HC(20)), 125.8 (d, $J_{C–F}$ = 2.5 Hz, C(8)), 124.4 (d, $J_{C–F}$ = 3.5 Hz, HC(9)), 123.9 (HC(19)), 123.7 (d, $J_{C–F}$ = 9.7 Hz, C(10)), 114.6 (d, $J_{C–F}$ = 21.7 Hz, HC(11)), 77.8 (C(5)), 60.8 (HC(2)), 49.2 (HC(6)), 39.8 (H_2C(4)), 38.7 (C(1)), 31.5 (HC(21)), 28.9 (H_3C(15)), 26.6 (H_2C(3)), 25.0 (bs, H_3C(22')), 24.1 (bs, H_3C(22)), 23.5 (d, $J_{C–F}$ = 2.4 Hz, H_2C(7)), 19.8 (H_3C(16)), 16.6 (H_3C(14)).

^{19}F NMR: (471 MHz, $CDCl_3$)

–133.92 (d, J = 10.4 Hz).

IR: (neat)

2961 (m), 2869 (w), 1590 (w), 1483 (s), 1391 (m), 1381 (m), 1360 (w), 1312 (w), 1281 (w), 1262 (w), 1236 (s), 1215 (w), 1178 (w), 1144 (m), 1126 (m), 1048 (s), 1030 (m), 971 (w), 951 (w), 931 (w), 915 (w), 893 (m), 859 (m), 845 (m), 838 (m), 799 (s), 774 (m), 755 (m), 745 (m), 720 (w), 705 (m), 597 (w), 575 (w), 524 (w), 480 (w).

HRMS: calcd for $C_{28}H_{36}ClFOS$ ($[M]^+$): 474.21594; found: 474.21625.

LRMS: (EI, 70 eV)

55.1 (12), 69.1 (25), 91.0 (10), 95.0 (10), 109.1 (16), 121.1 (26), 123.1 (13), 149.0 (21), 151.0 (18), 159.0 (30), 185.0 (12), 194.1 (56), 197.0 (14), 219.1 (15), 237.1 (11), 280.1 (18), 281.1 (100), 282.1 (22), 283.1 (34), 474.2 (42), 475.2 (14), 476.2 (18), 477.2 (6).

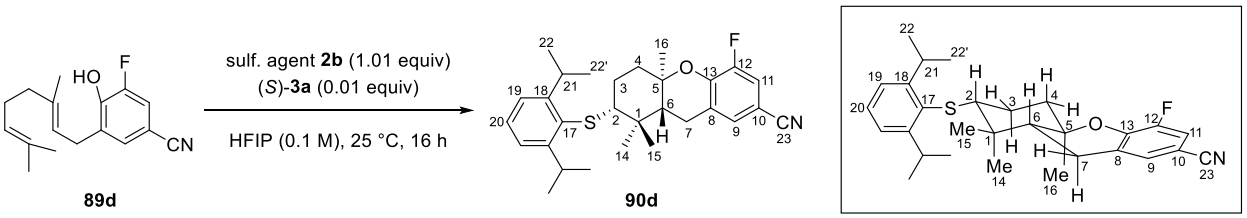
TLC: R_f 0.31 (hexanes/CH_2Cl_2, 80:20, UV/CAM)

Opt. Rot.: $[\alpha]_D^{24}$ = +90.1 (c = 1.01 in $CHCl_3$) (84% ee)

HPLC: t_R 7.3 min (91%); 10.7 min (9%) (Supelco Astec, hexanes/i-PrOH, 98:2, 0.5 mL/min, 220 nm, 24 °C)

After trituration: t_R 7.3 min (92%); 10.6 min (8%)

Preparation of (2*R*,5*R*,6*R*)-2-((2,6-Diisopropylphenyl)thio)-12-fluoro-1,1,5-trimethyl-1,2,3,4,5,6-hexahydro-7*H*-xanthene-10-carbonitrile ((+)-**90d**)



A 50-mL, round-bottomed flask equipped with a stir bar was charged with *N*-(2,6-diisopropylphenylthio)phthalimide **2b** (343.9 mg, 1.01 mmol, 1.01 equiv), hexafluoroisopropyl alcohol (10 mL), and phenol **89d** (274.0 mg, 1.0 mmol). Lewis base catalyst (*S*)-**3a** (5.9 mg, 0.011 mmol, 0.01 equiv) was added. The mixture was stirred at 25 °C for 16 h. Full conversion was observed by TLC (hexanes/CH_2Cl_2, 50:50) and confirmed by ^{1}H NMR analysis of a reaction aliquot. The reaction mixture was diluted with CH_2Cl_2 (5 mL), and volatile components were removed by rotary evaporation (30 °C, 15 mmHg). The crude product was purified by chromatography (silica gel, 3 cm x 30 cm, dry load on Celite, 25 mL fractions, hexanes/CH_2Cl_2 gradient elution: 80:20 (300 mL) to 60:40 (300 mL) to 40:60 (300 mL) to 20:80 (300 mL)) to afford 327.8 mg (70%) of **90d** as a white, foam solid which was contaminated with (*S*)-**3a**. The product was again purified by chromatography (silica gel, 3 x 30 cm, dry load on Celite, 25 mL fractions, hexanes/EtOAc gradient elution: 95:5 (300 mL) to 92.5:7.5 (300 mL) to 90:10 (300 mL) to 85:15 (300 mL)) to afford one pure fraction containing only **90d**, plus several mixed fractions containing **90d** and (*S*)-**3a**. Concentration of the pure fraction afforded **90d** as a wet-looking, dense white solid. Abs. ethanol (approx. 4 mL) was added, and the suspension was briefly sonicated. Solvent removal afforded 120.2 mg (26%) of **90d** as a free-flowing, white powder in >99% purity by quantitative ^{1}H NMR.

Data for (+)-**90d**:

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

7.34 (t, *J* = 7.7 Hz, 1H, HC(20)), 7.22 – 7.19 (bm, 1H, HC(9)), 7.18 (d, *J* = 7.7 Hz, 2H, HC(19)), 7.18 – 7.14 (m, 1H, HC(11)), 3.94 (hept, *J* = 6.8 Hz, 2H, HC(21)), 2.82 (dd, *J* = 16.8, 4.9 Hz, 1H, $H_2C(7^{eq})$), 2.74 (dd, *J* = 16.6, 13.0 Hz, 1H, $H_2C(7^{ax})$), 2.66 (dd, *J* = 11.5, 4.5 Hz, 1H, HC(2)), 2.02 (dt, *J* = 12.9, 3.2 Hz, 1H, $H_2C(4^{eq})$), 1.73 (dd, *J* = 12.9, 5.0 Hz, 1H, HC(6)), 1.75 – 1.61 (m, 2H, H_2C(3)), 1.50 (td, *J* =

13.2, 4.4 Hz, 1H, $H_2C(4^{ax})$), 1.43 (s, 3H, $H_3C(15)$), 1.27 (s, 3H, $H_3C(16)$), 1.26 (d, J = 6.9 Hz, 6H, $H_3C(22)$), 1.19 (d, J = 6.9 Hz, 6H, $H_3C(22')$), 1.09 (s, 3H, $H_3C(14)$).

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

154.1 (C(18)), 151.5 (d, $J_{C–F}$ = 248.8 Hz, C(12)), 146.2 (d, $J_{C–F}$ = 10.7 Hz, C(13)), 130.0 (C(17)), 129.6 (d, $J_{C–F}$ = 3.2 Hz, HC(9)), 129.4 (HC(20)), 126.0 (d, $J_{C–F}$ = 2.6 Hz, C(8)), 123.9 (HC(19)), 118.6 (d, $J_{C–F}$ = 2.7 Hz, C(23)), 117.5 (d, $J_{C–F}$ = 21.4 Hz, HC(11)), 102.4 (d, $J_{C–F}$ = 8.9 Hz, C(10)), 79.3 (C(5)), 60.5 (HC(2)), 48.9 (HC(6)), 39.6 ($H_2C(4)$), 38.8 (C(1)), 31.6 (HC(21)), 28.9 ($H_3C(15)$), 26.6 ($H_2C(3)$), 25.0 (bs, $H_3C(22')$), 24.1 (bs, $H_3C(22)$), 23.3 (d, $J_{C–F}$ = 2.1 Hz, $H_2C(7)$), 20.1 ($H_3C(16)$), 16.7 ($H_3C(14)$).

^{19}F NMR: (471 MHz, $CDCl_3$)

–133.34 (d, J = 10.1 Hz).

IR: (neat)

2962 (m), 2867 (w), 2224 (w), 1614 (w), 1585 (w), 1491 (s), 1462 (m), 1434 (m), 1393 (m), 1383 (m), 1361 (m), 1332 (m), 1256 (s), 1224 (w), 1148 (w), 1124 (s), 1049 (s), 975 (w), 949 (w), 933 (m), 908 (m), 864 (s), 799 (s), 783 (m), 756 (m), 738 (m), 730 (m), 705 (w), 619 (m), 585 (w), 527 (w), 487 (w).

HRMS: calcd for $C_{29}H_{36}FNOS$ ($[M]^+$): 465.2502; found: 465.2496.

LRMS: (EI, 70 eV)

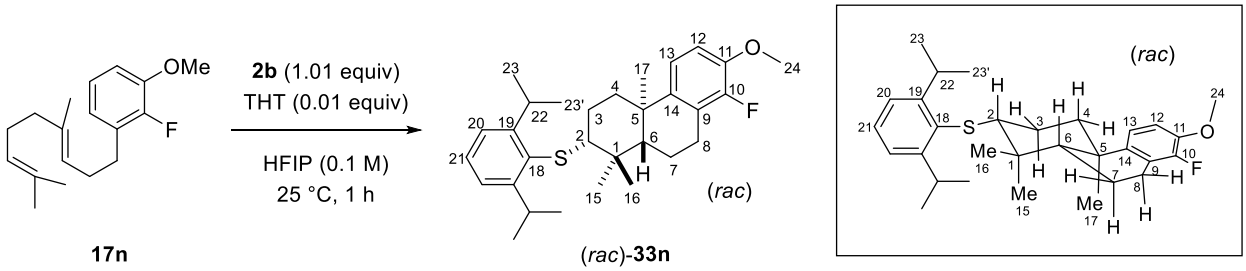
69.1 (20), 91.0 (13), 109.1 (11), 121.1 (17), 123.0 (14), 134.0 (12), 135.0 (17), 137.0 (20), 149.0 (32), 150.0 (35), 151.1 (28), 174.0 (12), 175.1 (13), 176.1 (17), 179.1 (45), 188.1 (18), 194.1 (100), 195.1 (15), 202.1 (11), 272.1 (55), 273.1 (11), 465.2 (72), 466.3 (20).

TLC: R_f 0.36 (hexanes/EtOAc, 90:10, UV/CAM)

Opt. Rot.: $[\alpha]_D^{24}$ = +141.2 (c = 1.03 in $CHCl_3$) (88% ee)

HPLC: t_R 5.6 min (94%); 6.4 min (6%) (Supelco Astec, hexanes/i-PrOH, 80:20, 1.0 mL/min, 220 nm, 24 °C)

Preparation of (±)-(*rel*)-**(2,6-Diisopropylphenyl) ((2*R*,5*R*,6*S*)-10-Fluoro-11-methoxy-1,1,5-trimethyl 1,2,3,4,5,6,7,8-octahydrophenanthren-2-yl) Sulfane** ((±)-**33n**)



A 100-mL, round-bottomed flask equipped with a stir bar was charged with *N*-(2,6-diisopropylphenylthio)phthalimide **2b** (344.6 mg, 1.02 mmol, 1.02 equiv), hexafluoroisopropyl alcohol (10 mL), and diene **17n** (275.2 mg, 1.00 mmol). Tetrahydrothiophene (0.9 μL, 0.9 mg, 0.01 mmol, 0.01 equiv) was added. The yellow solution was stirred at 25 °C for 1 h. Over time, a dark red/purple suspension resulted. Full conversion was observed by TLC (hexanes/CH_2Cl_2, 80:20). The reaction mixture was diluted with CH_2Cl_2 (5 mL), and volatile components were removed by rotary evaporation (30 °C, 15 mmHg). The crude product was purified by chromatography (silica gel, 3 cm x 30 cm, dry load on Celite, 25 mL fractions, hexanes/CH_2Cl_2 gradient elution: 90:10 (300 mL) to 80:20 (300 mL) to 70:30 (300 mL) to 60:40 (300 mL)) to afford 305.0 mg (65%) of **33n** as a white, foam solid which still contained trace impurities. The product was further purified by recrystallization from a minimal amount of boiling hexanes (approx. 4 mL). The solution was cooled in a –20 °C freezer for 4 h, and the resulting white crystals were collected by vacuum filtration and rinsed with cold hexanes to afford 187.8 mg (40%) of **33n** in >99% purity by quantitative ^{1}H NMR.

Data for (±)-**33n**:

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

7.31 (t, *J* = 7.7 Hz, 1H, HC(21)), 7.16 (d, *J* = 7.7 Hz, 2H, HC(20)), 6.84 (dd, *J* = 9.0, 1.0 Hz, 1H, HC(13)), 6.73 (t, *J* = 8.7 Hz, 1H, HC(12)), 4.00 (hept, *J* = 6.8 Hz, 2H, HC(22)), 3.82 (s, 3H, $H_3C(24)$), 3.05 – 2.97 (m, 1H, $H_2C(8^{ax})$), 2.70 (ddd, *J* = 18.5, 11.7, 7.7 Hz, 1H, $H_2C(8^{eq})$), 2.60 (dd, *J* = 12.5, 3.8 Hz, 1H, HC(2)), 2.18 (dt, *J* = 13.3, 3.3 Hz, 1H, $H_2C(4^{eq})$), 2.04 – 1.96 (m, 1H, $H_2C(7^{eq})$), 1.85 (qd, *J* = 13.6, 3.2 Hz, 1H, $H_2C(3^{ax})$), 1.73 (app. tq, *J* = 12.3, 6.6 Hz, 1H, $H_2C(7^{ax})$), 1.55 (dq, *J* =

3.5, 1H, $H_2C(3^{eq})$), 1.39 (s, 3H, $H_3C(16)$), 1.31 (dd, J = 12.2, 1.7 Hz, 1H, HC(6)), 1.26 (d, J = 6.9 Hz, 6H, $H_3C(23)$, 1.24 – 1.18 (m, 1H, $H_2C(4^{ax})$), 1.19 (s, 3H, $H_3C(17)$), 1.18 (d, J = 6.9 Hz, 6H, $H_3C(23')$), 1.10 (s, 3H, $H_3C(15)$).

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

154.2 (C(19)), 150.0 (d, $J_{C–F}$ = 242.5 Hz, C(10)), 144.8 (d, $J_{C–F}$ = 11.1 Hz, C(11)), 143.6 (d, $J_{C–F}$ = 2.4 Hz, C(14)), 130.9 (C(18)), 128.9 (HC(21)), 124.0 (d, $J_{C–F}$ = 14.2 Hz, C(9)), 123.7 (HC(20)), 119.2 (d, $J_{C–F}$ = 4.1 Hz, HC(13)), 111.0 (d, $J_{C–F}$ = 1.9 Hz, HC(12)), 61.8 (HC(2)), 56.4 ($H_3C(24)$), 52.1 (HC(6)), 39.5 ($H_2C(4)$), 38.9 (C(1)), 37.4 (d, $J_{C–F}$ = 1.5 Hz, C(5)), 31.5 (HC(22)), 29.8 ($H_3C(16)$), 26.1 ($H_2C(3)$), 25.1 ($H_3C(17)$), 25.0 (bs, $H_3C(23')$), 24.1 (bs, $H_3C(23)$), 23.7 (d, $J_{C–F}$ = 5.0 Hz, $H_2C(8)$), 18.6 ($H_2C(7)$), 17.7 ($H_3C(15)$).

^{19}F NMR: (471 MHz, $CDCl_3$)

–139.85 (d, J = 7.9 Hz)

IR: (neat)

2963 (m), 2928 (m), 1623 (w), 1575 (w), 1497 (m), 1440 (m), 1376 (w), 1360 (w), 1340 (w), 1304 (m), 1279 (m), 1243 (w), 1213 (w), 1193 (w), 1171 (w), 1149 (w), 1093 (m), 1077 (m), 1068 (w), 1014 (w), 999 (w), 978 (m), 894 (w), 864 (m), 795 (s), 768 (w), 743 (m), 724 (m), 683 (w), 642 (w), 628 (w), 532 (w), 464 (w).

HRMS: calcd for $C_{30}H_{41}FOS$ ($[M]^+$): 468.2862; found: 468.2865.

LRMS: (EI, 70 eV)

69.1 (27), 82.9 (100), 84.9 (88), 86.9 (15), 149.0 (12), 151.1 (12), 165.1 (20), 177.1 (15), 179.1 (50), 191.1 (34), 192.1 (12), 193.1 (12), 205.1 (28), 259.1 (50), 274.2 (22), 275.2 (77), 276.2 (14), 468.3 (32), 469.3 (10).

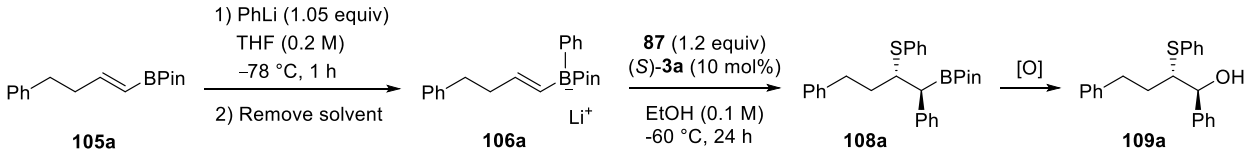
TLC: R_f 0.23 (hexanes/CH_2Cl_2, 80:20, UV/CAM)

Experimental for Chapter 3

Literature Preparation

The following compounds from Chapter 3 were prepared by literature methods and the characterization data matched those previously reported: (*E*)-4-phenylbut-1-en-1-yl pinacolborane **105a**,[232] isopropenyl pinacolborane **105g**,[233-234] (*Z*)-5-phenylpent-2-en-2-yl pinacolborane **105h**,[128] vinyl pinacolborane **105i**,[235] and *N*-(phenylthio)saccharin **87**.[83] (*E*)-4-(*tert*-Butyldimethylsilyl)oxybut-1-en-1-yl pinacolborane **105b** was prepared from (but-3-yn-1-yloxy)(*tert*-butyl)dimethylsilane using a procedure described for an analogous transformation[232] and the characterization data matched those previously reported.[236] (*Z*)-4-Phenylbut-1-en-1-yl pinacolborane **105f** was prepared from 4-phenyl-1-butyne using a procedure described for an analogous transformation[237] and the characterization data matched those previously reported.[238] (*E*)-2-Methylhex-1-en-1-yl pinacolborane **105j** was prepared from (*Z*)-(2-bromohex-1-en-1-yl)pinacolborane[239] using a procedure described for an analogous transformation[240] and the characterization data matched those previously reported.[241]

Preparation of (1*S*,2*S*)-(–)-**1,4-Diphenyl-2-(phenylthio)butan-1-ol (**(1*S*,2*S*)-(–)-**109a)**



An oven-dried, 25-mL, Schlenk flask (**A**) equipped with a stir bar, septum, and digital thermocouple probe was charged with THF (5 mL) and (*E*)-4-phenylbut-1-en-1-yl pinacolborane **105a** (259.1 mg, 1.00 mmol). The resulting colorless solution was cooled to –78 °C using a dry ice/isopropanol bath, and then stirred for 15 min to allow the temperature to equilibrate. A solution of phenyllithium in diethyl ether (1.77 M, 595 μL, 1.05 mmol, 1.05 equiv) was added dropwise over 10 min, such that the internal temperature did not exceed –68 °C. The resulting pale, yellow solution was stirred at –78 °C for 1 h. A separate, oven-dried, 25-mL, Schlenk flask (**B**) equipped with a stir bar was charged with (*S*)-**3a** (51.6 mg, 0.10 mmol, 0.10 equiv) and brought into the glovebox. To the flask was added *N*-(phenylthio)saccharin **87** (350.9 mg, 1.20 mmol, 1.20 equiv). The flask was sealed with a septum and removed from the glovebox. Absolute ethanol (5 mL) was

added to flask **B**, and the resulting yellow suspension was sonicated under argon for 10 min. Flask **B** was equipped with a digital thermocouple probe and cooled to an internal temperature of –60 °C using a Cryo-Cool. Flask **A**, having been stirred for 1 h at –78 °C, was placed under vacuum (0.01 mmHg) and the cold bath was removed. The solution was stirred rapidly under vacuum for 30 min until all of the THF was removed. The resulting beige-colored, foam solid boronate complex **106a** in flask **A** was taken up in ethanol (2.5 mL) at 25 °C, and the resulting solution was added dropwise via syringe to flask **B** over 10 min. A white suspension resulted. An additional portion of ethanol (2.5 mL) was added to flask **A** and then transferred to flask **B** as just described, to ensure complete transfer of the boronate. Flask **B** was stirred at –60 °C for 36 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (2.5 mL). The flask was removed from the cold bath and the biphasic mixture was allowed to warm to 25 °C. The mixture was diluted with Et_2O (5 mL) and water (5 mL) and stirred rapidly to dissolve all solids. The biphasic mixture was transferred to a 60-mL separatory funnel and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 10 mL), and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated (30 °C, 15 torr) to afford 551.6 mg of crude alkylborane **108a** as a red oil. The yield of **108a** was determined to be 97% by quantitative ^{1}H-NMR (using 1,1,1,2-tetrachloroethane as an internal standard) in the following manner. A Hamilton gastight syringe was used to transfer 1,1,1,2-tetrachloroethane (55 μL, 2.00 mmol) to the flask containing crude **108a**, and the mixture was dissolved in CDCl3 (approx. 3 mL). An aliquot of this solution (approx. 0.25 mL) was passed through a pipet filter (to remove any insoluble components) into an NMR tube, and the filtrate was diluted with enough CDCl3 to reach a typical NMR sample volume. The ^{1}H signal of the internal standard (singlet, 4.31 ppm, 2H) was integrated and normalized to 1.00. Then, the integration value of any non-overlapping (1H) signal of **108a** (typically in the 4.00-1.00 ppm region) is equal to the yield of **108a**.

A 100-mL, round-bottomed flask equipped with a stir bar was charged with crude **108a** (551.6 mg), THF (10 mL) and water (10 mL). Sodium perborate tetrahydrate (600.3 mg, 3.9 mmol) and tetra-*n*-butylammonium chloride (28.0 mg, 0.10 mmol) were added sequentially to the rapidly stirred biphasic mixture at 25 °C. The beige-colored mixture was stirred rapidly for 3 h. Full conversion was observed by TLC (hexanes/EtOAc, 90:10, CAM). The oxidation was quenched by the addition of solid sodium bisulfite, $NaHSO_3$ (1.20 g) and the resulting cream-colored mixture was stirred for 15 min. Then, aq. NaOH was added (1 M, 20 mL) and the mixture was stirred for

30 min. The mixture was transferred to a separatory funnel and diluted with Et_2O (30 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 15 mL). The combined organic phases were washed with brine (25 mL) and then dried over magnesium sulfate, filtered, and concentrated (30 °C, 15 torr) to afford 444.4 mg of crude **109a** as a red oil. The product was purified by chromatography (silica gel, 3 x 20 cm, dry load on Celite, 25-mL fractions, hexanes/EtOAc gradient elution: 95:5 (600 mL) to 90:10 (600 mL)) to afford 299.3 mg of **109a** as a pink oil. The product was purified to an analytical standard by diffusion pump Kugelrohr distillation (135 °C ABT, 4.0 x 10^{-5} mmHg) to afford 283.0 mg (85% yield) of **109a** as a viscous, pale, yellow oil.

Data for (1*S*,2*S*)-(–)-**109a**:

b.p.: 135 °C (ABT, 4.0 x 10^{-5} mmHg)

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

7.50–7.44 (m, 2H, HC(10)), 7.35–7.26 (m, 8H, HC(6), HC(8), HC(7), HC(11), HC(12)), 7.22–7.17 (m, 2H, HC(15)), 7.16–7.11 (m, 1H, HC(16)), 6.96 (d, *J* = 7.1 Hz, 2H, HC(14)), 4.47 (dd, *J* = 8.4, 2.0 Hz, 1H, HC(1)), 3.39 (d, *J* = 2.0 Hz, 1H, OH), 3.15 (ddd, *J* = 10.0, 8.7, 3.5 Hz, 1H, HC(2)), 2.95 (ddd, *J* = 14.1, 9.4, 4.8 Hz, 1H, H_2C(4)), 2.65 (ddd, *J* = 13.9, 9.2, 7.5 Hz, 1H, H_2C(4)), 1.79–1.69 (m, 1H, H_2C(3)), 1.61 (dtd, *J* = 14.4, 9.7, 4.8 Hz, 1H, H_2C(3)).

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

141.25 (C(13)), 141.01 (C(5)), 133.50 (HC(10)), 132.97 (C(9)), 129.22 (HC(11) or HC(14) or HC(15) or HC(7)), 128.53 (two overlapping signals: HC(14) or HC(15) or HC(11) or HC(7)), 128.46 (HC(7) or HC(11) or HC(14) or HC(15)), 128.23 (HC(8)), 127.94 (HC(12)), 127.29 (HC(6)), 126.04 (HC(16)), 75.82 (HC(1)), 58.68 (HC(2)), 33.16 (H_2C(4)), 32.40 (H_2C(3)).

IR: (neat)

3436 (w), 3060 (w), 3026 (w), 2924 (w), 2858 (w), 1948 (w), 1879 (w), 1807 (w), 1602 (w), 1583 (w), 1495 (w), 1479 (w), 1453 (m), 1438 (w), 1383 (w), 1332 (w), 1319 (w), 1298 (w), 1239 (w), 1188 (w), 1156 (w), 1088 (w), 1061 (w), 1025 (m), 1001 (w), 985 (w), 912 (w), 843 (w), 824 (w), 782 (w), 743 (s), 695 (s), 636 (w), 603 (w), 561 (w), 512 (m), 488 (m).

LRMS: (EI, 70 eV)

51.0 (11), 65.1 (14), 77.0 (27), 79.0 (21), 91.0 (100), 92.1 (10), 107.0 (11), 110.0 (12), 115.0 (10), 117.1 (79), 118.1 (21), 123.0 (11), 135.0 (10), 228.1 (49), 334.1 (4), 335.1 (1).

Analysis: $C_{22}H_{22}OS$ (334.48)

Calcd: C, 79.00%; H, 6.63%

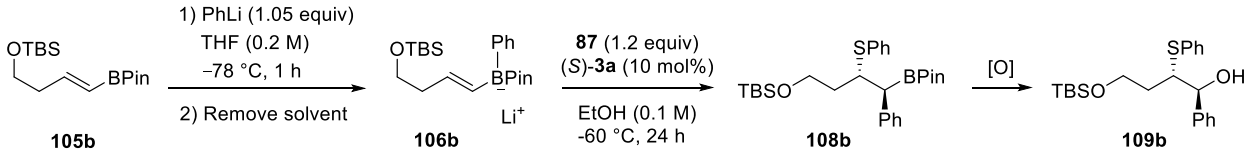
Found: C, 79.14%; H, 6.45%

TLC: R_f 0.14 (hexanes/EtOAc, 90:10, CAM)

HPLC: (1*R*,2*R*)-**109a** t_R 13.9 min (2%); (1*S*,2*S*)-**109a** t_R 14.9 min (98%) (Supelco Astec, hexanes/*i*-PrOH, 80:20, 0.5 mL/min, 220 nm, 24 °C)

Opt. Rot.: $[\alpha]_D^{24}$ –58.6 (*c* = 1.41 in 95% EtOH) (96% ee)

Preparation of (1*S*,2*S*)-(–)-**4-((*tert*-Butyldimethylsilyl)oxy)-1-phenyl-2-(phenylthio)butan-1-ol (**(1*S*,2*S*)-(–)-**109b)**



An oven-dried, 25-mL, Schlenk flask (**A**) equipped with a stir bar, septum, and digital thermocouple probe was charged with THF (5 mL) and (*E*)-4-(*tert*-butyldimethylsilyl)oxybut-1-en-1-yl pinacolborane **105b** (312.3 mg, 1.00 mmol). The resulting colorless solution was cooled to –78 °C using a dry ice/isopropanol bath. A solution of phenyllithium in diethyl ether (1.77 M, 595 μL, 1.05 mmol, 1.05 equiv) was added dropwise over 10 min, such that the internal temperature did not exceed –68 °C. The dark red color of the phenyllithium solution immediately disappeared upon addition to the reaction mixture. The resulting pale, beige solution was stirred at –78 °C for 1 h. A separate, oven-dried, 25-mL, Schlenk flask (**B**) equipped with a stir bar was charged with (*S*)-**3a** (52.3 mg, 0.10 mmol, 0.10 equiv) and brought into the glovebox. To the flask was added *N*-(phenylthio)saccharin **87** (352.2 mg, 1.20 mmol, 1.20 equiv). The flask was sealed with a septum and removed from the glovebox. Absolute ethanol (5 mL) was added to flask **B**, and the resulting yellow suspension was sonicated under argon for 10 min. Flask **B** was equipped with a digital thermocouple probe and cooled to an internal temperature of –60 °C using a Cryo-Cool.

Flask **A**, having been stirred for 1 h at –78 °C, was placed under vacuum (0.01 mmHg) and the cold bath was removed. The solution was stirred rapidly under vacuum for 30 min until all of the THF was removed. The resulting beige-colored, foam solid boronate complex **106b** in flask **A** was taken up in ethanol (2.5 mL) at 25 °C, and the resulting solution was added dropwise via syringe to flask **B** over 10 min. A white suspension resulted. An additional portion of ethanol (2.5 mL) was added to flask **A** and then transferred to flask **B** as just described, to ensure complete transfer of the boronate complex. Flask **B** was stirred at –60 °C for 24 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (2.5 mL). The flask was removed from the cold bath and the biphasic mixture was allowed to warm to 25 °C. The mixture was diluted with diethyl ether (5 mL) and water (5 mL) and stirred rapidly to dissolve all solids. The biphasic mixture was transferred to a 60-mL separatory funnel and the layers were separated. The aqueous layer was washed with diethyl ether (2 x 10 mL), and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated (30 °C, 15 torr) to afford 671.7 mg of crude borane **108b** as a yellow oil. The yield of **108b** was determined to be 75% by quantitative ^{1}H-NMR as described previously for **108a**.

A 100-mL, round-bottomed flask equipped with a stir bar was charged with crude **108b** (671.7 mg), THF (10 mL) and water (10 mL). Sodium perborate tetrahydrate (0.60 g, 3.9 mmol) and tetra-*n*-butylammonium chloride (28.0 mg, 0.10 mmol) were added sequentially to the rapidly stirred biphasic mixture at 25 °C. The mixture was stirred rapidly for 2.5 h. Full conversion was observed by TLC (hexanes/EtOAc, 90:10, CAM). The oxidation was quenched by the addition of solid sodium bisulfite, $NaHSO_3$ (1.20 g) and the resulting mixture was stirred for 15 min. Then, aq. NaOH was added (1 M, 20 mL) and the mixture was stirred for 30 min. The mixture was transferred to a separatory funnel and diluted with diethyl ether (30 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (2 x 15 mL). The combined organic phases were washed with brine (25 mL) and then dried over magnesium sulfate, filtered, and concentrated (30 °C, 15 torr) to afford 442.0 mg of crude **109b** as a yellow oil. The product was purified by chromatography (silica gel, 3 x 25 cm, dry load on Celite, 25-mL fractions, hexanes/EtOAc gradient elution: 95:5 (600 mL) to 92.5:7.5 (300 mL) to 90:10 (300 mL)) to afford 262.9 mg of **109b** as a yellow oil. The product was purified to an analytical standard by diffusion pump Kugelrohr distillation (120 °C ABT, 3.4 x 10^{-5} mmHg) to afford 253.9 mg (65% yield) of **109b** as a viscous, pale, yellow oil.

Data for (1*S*,2*S*)-(–)-**109b**:

b.p.: 120 °C (ABT, 3.4 x 10^{-5} mmHg)

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

7.42–7.38 (m, 2H, HC(13)), 7.38–7.34 (m, 2H, HC(9)), 7.33–7.29 (m, 2H, HC(10)), 7.28–7.21 (m, 4H, HC(11), HC(14), HC(15)), 4.60 (dd, *J* = 7.2, 2.7 Hz, 1H, HC(1)), 3.86–3.76 (m, 2H, H_2C(4)), 3.71 (d, *J* = 2.3 Hz, 1H, OH), 3.52 (ddd, *J* = 8.9, 7.4, 4.2 Hz, 1H, HC(2)), 1.78–1.68 (m, 1H, H_2C(3)), 1.63–1.55 (m, 1H, H_2C(3)), 0.84 (s, 9H, H_3C(7)), –0.02 (s, 3H, H_3C(5)), –0.04 (s, 3H, H_3C(5')).

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

141.40 (C(8)), 134.08 (C(12)), 132.76 (HC(13)), 129.07 (HC(14)), 128.39 (HC(10)), 127.97 (HC(11)), 127.42 (HC(15)), 127.21 (HC(9)), 75.89 (HC(1)), 60.13 (H_2C(4)), 56.13 (HC(2)), 34.66 (H_2C(3)), 26.01 (H_3C(7)), 18.32 (C(6)), –5.29 (H_3C(5 or 5')), –5.33 (H_3C(5 or 5')).

IR: (neat)

3435 (w), 3061 (w), 3031 (w), 2953 (w), 2928 (w), 2883 (w), 2856 (w), 1947 (w), 1805 (w), 1584 (w), 1494 (w), 1471 (m), 1463 (w), 1439 (w), 1386 (w), 1361 (w), 1332 (w), 1318 (w), 1296 (w), 1253 (m), 1188 (w), 1156 (w), 1089 (s), 1041 (m), 1025 (m), 1005 (m), 938 (m), 913 (w), 832 (s), 809 (m), 774 (s), 742 (s), 697 (s), 662 (m), 608 (w), 573 (w), 530 (w), 512 (w), 483 (w).

LRMS: (CI, 70 eV)

89.0 (27), 111.0 (19), 129.0 (14), 131.0 (16), 147.0 (18), 213.0 (21), 225.0 (75), 226.0 (13), 239.0 (100), 240.0 (19), 371.1 (29), 388.1 (1), 389.1 (2).

Analysis: $C_{22}H_{32}O_2SSi$ (388.64)

Calcd: C, 67.99%; H, 8.30%

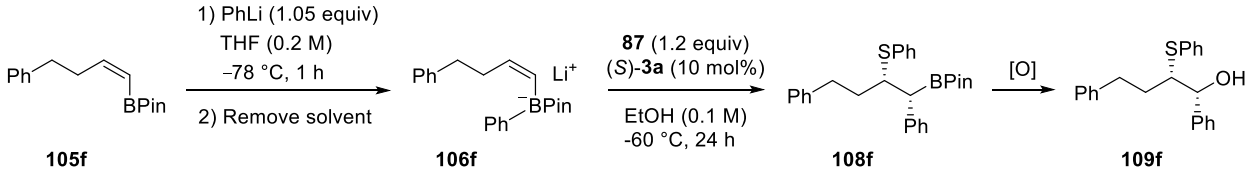
Found: C, 67.87%; H, 8.39%

TLC: R_f 0.23 (hexanes/EtOAc, 90:10, CAM)

HPLC: (1*S*,2*S*)-**109b** t_R 22.0 min (96%); (1*R*,2*R*)-**109b** t_R 26.0 min (4%) (Regis (*R*,*R*)-Whelk O1, hexanes/*i*-PrOH, 98:2, 0.5 mL/min, 220 nm, 24 °C)

Opt. Rot.: $[\alpha]_D^{24}$ –70.8 (*c* = 1.03 in 95% EtOH) (92% ee)

Preparation of (1*R*,2*S*)-(+)-**1,4-Diphenyl-2-(phenylthio)butan-1-ol (**(1*R*,2*S*)-(+)-**109f)**



An oven-dried, 25-mL, Schlenk flask (**A**) equipped with a stir bar, septum, and digital thermocouple probe was charged with THF (5 mL) and (*Z*)-4-phenylbut-1-en-1-yl pinacolborane **105f** (259.5 mg, 1.01 mmol). The resulting clear, colorless solution was cooled to –78 °C using a dry ice/isopropanol bath, and then stirred for 15 min to allow the temperature to equilibrate. A solution of phenyllithium in diethyl ether (1.77 M, 596 μL, 1.06 mmol, 1.05 equiv) was added dropwise over 10 min, such that the internal temperature did not exceed –68 °C. The dark red color of the phenyllithium solution immediately disappeared upon addition to the reaction mixture. After the addition, the resulting pale, yellow solution was stirred at –78 °C for 1 h. A separate, oven-dried, 25-mL, Schlenk flask (**B**) equipped with a stir bar was charged with (*S*)-**3a** (52.8 mg, 0.10 mmol, 0.10 equiv) and brought into the glovebox. To the flask was added *N*-(phenylthio)saccharin **87** (352.3 mg, 1.21 mmol, 1.20 equiv). The flask was sealed with a septum and removed from the glovebox. Ethanol (5 mL) was added to flask **B**, and the resulting yellow suspension was sonicated under argon for 10 min. Flask **B** was equipped with a digital thermocouple probe and cooled to an internal temperature of –60 °C using a Cryo-Cool. At this point, flask **A**, having been stirred for 1 h at –78 °C, was placed under vacuum (0.01 mmHg) and the cold bath was removed. The solution was stirred rapidly under vacuum until all of the THF was removed (30 min). The resulting white, solid boronate complex **106f** in flask **A** was taken up in ethanol (2.5 mL) at 25 °C, and the resulting solution was added dropwise via syringe to flask **B** over 10 min. A white suspension resulted. An additional portion of ethanol (2.5 mL) was added to flask **A** and then transferred to flask **B** as just described, to ensure complete transfer of the boronate. Flask **B** was stirred at –60 °C for 48 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (2.5 mL). The flask was removed from the cold bath and the biphasic mixture was allowed to warm to 25 °C. The mixture was diluted with diethyl ether (5 mL) and water (5 mL) and stirred rapidly to dissolve all solids. The biphasic

mixture was transferred to a 60-mL separatory funnel and the layers were separated. The aqueous layer was washed with diethyl ether (2 x 10 mL), and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated (30 °C, 15 torr) to afford the crude borane **108f** as a red oil. The yield of **108f** was determined to be 62% by quantitative ^{1}H-NMR as described previously for **108a**.

A 100-mL, round-bottomed flask equipped with a stir bar was charged with crude **108f** (0.65 g), THF (10 mL) and water (10 mL). Sodium perborate tetrahydrate (600 mg, 4.42 mmol) and tetra-*n*-butylammonium chloride (30 mg, 0.11 mmol) were added sequentially to the rapidly stirred biphasic mixture at 25 °C. The mixture was stirred rapidly for 2 h. Full conversion was observed by TLC (hexanes/EtOAc, 90:10, CAM). The oxidation was quenched by the addition of solid sodium bisulfite, $NaHSO_3$ (1.20 g) and the resulting mixture was stirred for 15 min. Then, aq. NaOH was added (1 M, 20 mL) and the mixture was stirred for 30 min. The mixture was transferred to a separatory funnel and diluted with diethyl ether (30 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (2 x 15 mL). The combined organic phases were washed with brine (25 mL) and then dried over magnesium sulfate, filtered, and concentrated (30 °C, 15 torr) to afford 0.47 g of crude **109f**. The product was purified by chromatography (silica gel, 3 x 20 cm, dry load on Celite, 25-mL fractions, hexanes/EtOAc gradient elution: 95:5 (600 mL) to 92.5:7.5 (300 mL) to 90:10 (600 mL)) to afford 222.4 mg of **109f** as an oil. The product was purified to an analytical standard by diffusion pump Kugelrohr distillation (125 °C ABT, 3.4 x 10^{-5} mmHg) to afford 205.1 mg (61% yield) of **109f** as a viscous, clear, colorless oil.

Data for (1*R*,2*S*)-(+)-**109f**:

b.p.: 125 °C (ABT, 3.4 x 10^{-5} mmHg)

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

7.46–7.40 (m, 2H, HC(10)), 7.34–7.26 (m, 5H, HC(11), HC(12), HC(7)), 7.25–7.23 (m, 1H, HC(8)), 7.23–7.19 (m, 4H, HC(6), HC(15)), 7.18–7.13 (m, 1H, HC(16)), 7.03–6.98 (m, 2H, HC(14)), 4.78 (t, *J* = 3.1 Hz, 1H, HC(1)), 3.34 (dt, *J* = 10.1, 3.2 Hz, 1H, HC(2)), 2.90 (ddd, *J* = 13.8, 9.1, 4.7 Hz, 1H, H_2C(4)), 2.79–2.75 (m, 1H, OH), 2.61 (dt, *J* = 14.0, 8.4 Hz, 1H, H_2C(4)), 1.97–1.86 (m, 1H, H_2C(3)), 1.80–1.69 (m, 1H, H_2C(3)).

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

141.36 (C(13)), 140.76 (C(5)), 134.55 (C(9)), 132.46 (HC(10)), 129.35 (HC(11)), 128.57 (HC(14) or HC(15)), 128.44 (HC(14) or HC(15)), 128.32 (HC(7)), 127.60 (HC(8) or HC(12)), 127.49 (HC(8) or HC(12)), 126.08 (HC(6)), 126.03 (HC(16)), 73.59 (HC(1)), 57.16 (HC(2)), 33.47 (H_2C(4)), 28.97 (H_2C(3)).

IR: (neat)

3448 (w), 3060 (w), 3026 (w), 2928 (w), 1602 (w), 1583 (w), 1496 (w), 1480 (w), 1452 (m), 1438 (w), 1388 (w), 1327 (w), 1221 (w), 1186 (w), 1091 (w), 1049 (m), 1025 (m), 918 (w), 845 (w), 742 (s), 695 (s), 604 (w), 561 (w), 544 (w), 492 (m).

LRMS: (EI, 70 eV)

65.0 (13), 77.0 (15), 91.1 (89), 104.1 (15), 109.0 (12), 110.0 (26), 115.1 (41), 116.1 (10), 117.1 (100), 118.1 (14), 128.1 (14), 129.1 (19), 165.1 (11), 169.1 (12), 170.1 (17), 178.1 (15), 179.1 (14), 191.1 (10), 205.1 (10), 206.1 (36), 207.1 (29), 208.1 (24), 228.1 (17), 316.1 (28), 334.1 (2).

Analysis: $C_{22}H_{22}OS$ (334.48)

Calcd: C, 79.00%; H, 6.63%

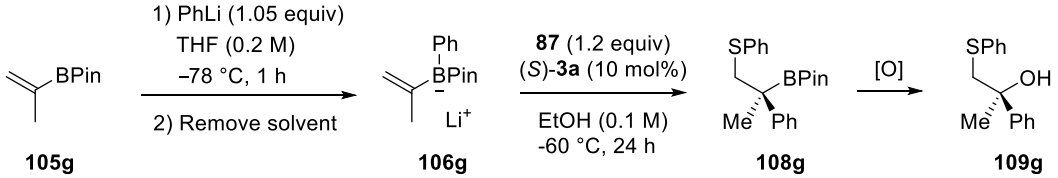
Found: C, 78.77%; H, 6.57%

TLC: R_f 0.23 (hexanes/EtOAc, 90:10, CAM)

HPLC: (1*S*,2*R*)-**109f** t_R 20.2 min (31%); (1*R*,2*S*)-**109f** t_R 22.6 min (69%) (Regis (*R*,*R*)-Whelk O1, hexanes/*i*-PrOH, 98:2, 0.5 mL/min, 220 nm, 24 °C)

Opt. Rot.: $[\alpha]_D^{24}$ +7.6 (*c* = 1.18 in 95% EtOH) (38% ee)

Preparation of (*S*)-(–)-**2-Phenyl-1-(phenylthio)propan-2-ol (**(*S*)-(–)-**109g)**



An oven-dried, 25-mL, Schlenk flask (**A**) equipped with a stir bar, septum, and digital thermocouple probe was charged with THF (5 mL) and isopropenyl pinacolborane **105g** (167.9

mg, 1.00 mmol). The resulting colorless solution was cooled to –78 °C using a dry ice/isopropanol bath, and then stirred for 15 min to allow the temperature to equilibrate. A solution of phenyllithium in diethyl ether (1.77 M, 595 μL, 1.05 mmol, 1.05 equiv) was added dropwise over 10 min, such that the internal temperature did not exceed –68 °C. The dark red color of the phenyllithium solution immediately disappeared upon addition to the reaction mixture. The resulting *white suspension* was stirred at –78 °C for 10 min, then warmed to 0 °C, resulting in a pale, yellow solution. The solution was maintained at 0 °C for 50 min and then returned to –78 °C, again resulting in a white suspension. A separate, oven-dried, 25-mL, Schlenk flask (**B**) equipped with a stir bar was charged with (*S*)-**3a** (52.1 mg, 0.10 mmol, 0.10 equiv) and brought into the glovebox. To the flask was added *N*-(phenylthio)saccharin **87** (350.0 mg, 1.20 mmol, 1.20 equiv). The flask was sealed with a septum and removed from the glovebox. Absolute ethanol (5 mL) was added to flask **B**, and the resulting yellow suspension was sonicated under argon for 10 min. Flask **B** was equipped with a digital thermocouple probe and cooled to an internal temperature of –60 °C using a Cryo-Cool. Flask **A**, having been stirred for 1 h at –78 °C, was placed under vacuum (0.01 mmHg) and the cold bath was removed. The white suspension was stirred rapidly under vacuum for 30 min until all of the THF was removed. The resulting white, flaky solid boronate complex **106g** in flask **A** was taken up in ethanol (2.5 mL) at 25 °C, and the resulting solution was added dropwise via syringe to flask **B** over 10 min. A white suspension resulted. An additional portion of ethanol (2.5 mL) was added to flask **A** and then transferred to flask **B** as just described, to ensure complete transfer of the boronate. Flask **B** was stirred at –60 °C for 36 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (2.5 mL). The flask was removed from the cold bath and the biphasic mixture was allowed to warm to 25 °C. The mixture was diluted with diethyl ether (5 mL) and water (5 mL) and stirred rapidly to dissolve all solids. The biphasic mixture was transferred to a 60-mL separatory funnel and the layers were separated. The aqueous layer was washed with diethyl ether (2 x 10 mL), and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated (30 °C, 15 torr) to afford 466.3 mg of crude borane **108g** as a red oil. The yield of **108g** was determined to be 89% by quantitative ^{1}H-NMR as described previously for **108a**.

A 100-mL, round-bottomed flask equipped with a stir bar was charged with crude **108g** and THF (10 mL). The turbid, red-colored solution was cooled to 0 °C with an ice bath. To this solution was added a mixture of 30% aq. H_2O_2 (1 mL) and 3 M aq. NaOH (1 mL) also containing

EDTA (1.0 mg/mL). The biphasic mixture was stirred rapidly at 0 °C for 30 min. Full conversion was observed by TLC (hexanes/EtOAc, 90:10, CAM). The oxidation was quenched by the addition of a sodium bisulfite ($NaHSO_3$) aq. solution (1.20 g in 10 mL water) and stirred for 15 min. The mixture was transferred to a separatory funnel and diluted with diethyl ether (30 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (2 x 15 mL). The combined organic phases were washed with brine (25 mL) and then dried over magnesium sulfate, filtered, and concentrated (30 °C, 15 torr) to afford 378.4 mg of crude **109g** as an oil. The product was purified by chromatography (silica gel, 3 x 25 cm, dry load on Celite, 25-mL fractions, hexanes/EtOAc gradient elution: 95:5 (600 mL) to 90:10 (600 mL)) to afford 194.2 mg of **109g** as a yellow oil. The product was purified to an analytical standard by diffusion pump Kugelrohr distillation (80 °C ABT, 3.4 x 10^{-5} mmHg) to afford 180.3 mg (74% yield) of **109g** as a viscous, pale, yellow oil.

Data for (*S*)-(–)-**109g**:

b.p.: 80 °C (ABT, 3.4 x 10^{-5} mmHg)

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

7.48–7.43 (m, 2H, HC(5)), 7.36–7.30 (m, 4H, HC(9) and HC(6)), 7.26–7.21 (m, 3H, HC(7) and HC(10)), 7.19–7.14 (m, 1H, HC(11)), 3.54 (d, *J* = 13.3 Hz, 1H, $H_2C(1)$), 3.36 (d, *J* = 13.3 Hz, 1H, $H_2C(1)$), 2.85 (s, 1H, OH), 1.62 (s, 3H, $H_3C(3)$).

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

146.34 (C(4)), 136.65 (C(8)), 130.16 (HC(9)), 129.10 (HC(10)), 128.43 (HC(6)), 127.26 (HC(7)), 126.58 (HC(11)), 124.96 (HC(5)), 74.12 (C(2)), 49.75 ($H_2C(1)$), 29.56 ($H_3C(3)$).

IR: (neat)

3448 (w), 3058 (w), 2976 (w), 2927 (w), 1582 (w), 1493 (w), 1480 (m), 1446 (m), 1439 (m), 1373 (w), 1333 (w), 1269 (w), 1238 (w), 1179 (w), 1087 (m), 1066 (m), 1025 (m), 1000 (w), 940 (w), 911 (w), 842 (w), 765 (m), 737 (s), 716 (m), 697 (s), 689 (s), 608 (m), 581 (m), 541 (m), 473 (m).

LRMS: (EI, 70 eV)

77.1 (24), 78.1 (18), 91.1 (15), 103.1 (18), 109.0 (11), 110.0 (41), 111.0 (82), 115.1 (13), 117.1 (41), 118.1 (24), 119.1 (72), 121.1 (27), 124.1 (37), 125.1 (11), 149.1 (42), 211.1 (13), 226.1 (29), 227.1 (100), 228.1 (14), 244.1 (1), 245.2 (1).

Analysis: $C_{15}H_{16}OS$ (244.35)

Calcd: C, 73.73%; H, 6.60%

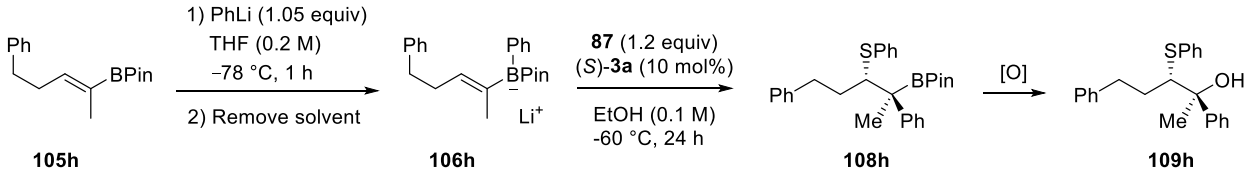
Found: C, 73.70%; H, 6.54%

TLC: R_f 0.19 (hexanes/EtOAc, 90:10, CAM)

SFC: (*S*)-**109g** t_R 18.9 min (95%); (*R*)-**109g** t_R 20.0 min (5%) (Chiralpak OD, 5-15% MeOH in CO_2 over 20 min, then hold 15% MeOH in CO_2 for 10 min, 2.0 mL/min, 220 nm, 40 °C)

Opt. Rot.: $[\alpha]_D^{24}$ –23.1 (*c* = 1.33 in 95% EtOH)

Preparation of (2*S*,3*S*)-(+)-**2,5-Diphenyl-3-(phenylthio)pentan-2-ol (**(2*S*,3*S*)-(+)-**109h)**



An oven-dried, 25-mL, Schlenk flask (**A**) equipped with a stir bar, septum, and digital thermocouple probe was charged with THF (5 mL) and (*Z*)-5-phenylpent-2-en-2-yl pinacolborane **105h** (273.0 mg, 1.00 mmol). The resulting pale, yellow solution was cooled to –78 °C using a dry ice/isopropanol bath, and then stirred for 15 min to allow the temperature to equilibrate. A solution of phenyllithium in diethyl ether (1.77 M, 595 μL, 1.05 mmol, 1.05 equiv) was added dropwise over 10 min, such that the internal temperature did not exceed –68 °C. The dark red color of the phenyllithium solution immediately disappeared upon addition to the reaction mixture. The resulting pale, yellow solution was stirred at –78 °C for 1 h. A separate, oven-dried, 25-mL, Schlenk flask (**B**) equipped with a stir bar was charged with (*S*)-**3a** (52.8 mg, 0.10 mmol, 0.10 equiv) and brought into the glovebox. To the flask was added *N*-(phenylthio)saccharin **87** (349.9 mg, 1.20 mmol, 1.20 equiv). The flask was sealed with a septum and removed from the glovebox. Absolute ethanol (5 mL) was added to flask **B**, and the resulting yellow suspension was sonicated under argon for 10 min. Flask **B** was equipped with a digital thermocouple probe and cooled to an internal temperature of –60 °C using a Cryo-Cool. Flask **A**, having been stirred for 1 h at –78 °C, was placed under vacuum (0.01 mmHg) and the cold bath was removed. The solution was stirred

rapidly under vacuum for 30 min until all of the THF was removed. The resulting beige-colored, foam solid boronate complex **106h** in flask **A** was taken up in ethanol (2.5 mL) at 25 °C, and the resulting solution was added dropwise via syringe to flask **B** over 10 min. A white suspension resulted. An additional portion of ethanol (2.5 mL) was added to flask **A** and then transferred to flask **B** as just described, to ensure complete transfer of the boronate complex. Flask **B** was stirred at –60 °C for 48 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (2.5 mL). The flask was removed from the cold bath and the biphasic mixture was allowed to warm to 25 °C. The mixture was diluted with diethyl ether (5 mL) and water (5 mL) and stirred rapidly to dissolve all solids. The biphasic mixture was transferred to a 60-mL separatory funnel and the layers were separated. The aqueous layer was washed with diethyl ether (2 x 10 mL), and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated (30 °C, 15 torr) to afford 0.60 g of crude borane **108h** as a red oil. The yield of **108h** was determined to be 81% by quantitative ^{1}H-NMR as described previously for **108a**.

A 100-mL, round-bottomed flask equipped with a stir bar was charged with crude **108h** and THF (10 mL). The turbid, red-colored solution was cooled to 0 °C with an ice bath. To this solution was added a mixture of 30% aq. H_2O_2 (1 mL) and 3 M aq. NaOH (1 mL) also containing EDTA (1.0 mg/mL). The biphasic mixture was stirred rapidly at 0 °C for 1.5 h. Full conversion was observed by TLC (hexanes/EtOAc, 90:10, CAM). The oxidation was quenched by the addition of a sodium bisulfite ($NaHSO_3$) aq. solution (1.20 g in 10 mL water) and stirred for 15 min. The mixture was transferred to a separatory funnel and diluted with diethyl ether (30 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (2 x 15 mL). The combined organic phases were washed with brine (25 mL) and then dried over magnesium sulfate, filtered, and concentrated (30 °C, 15 torr) to afford 0.53 g of crude **109h** as a pink oil. The product was purified by chromatography (silica gel, 3 x 25 cm, dry load on Celite, 25-mL fractions, hexanes/EtOAc gradient elution: 95:5 (600 mL) to 92.5:7.5 (300 mL) to 90:10 (300 mL)) to afford 307.2 mg of **109h** as a pink oil which is contaminated with 5-phenylpentan-2-one. **Note:** To remove this ketone impurity prior to distillation, the product mixture was dissolved in absolute ethanol (5 mL) and the resulting solution was cooled to 0 °C with an ice bath. Sodium borohydride (9 mg) was added, and the reaction mixture was stirred at 0 °C for 30 min. The reaction was quenched by the addition of sat. aq. NH_4Cl (1 mL). The mixture was diluted with diethyl ether (10 mL) and water (10 mL) and transferred to a 60-mL separatory funnel. The layers were separated.

The aqueous layer was extracted with diethyl ether (2 x 10 mL), and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated (30 °C, 15 torr). The residue was purified by chromatography (silica gel, 3 x 25 cm, dry load on Celite, 25-mL fractions, hexanes/EtOAc gradient elution: 95:5 (600 mL) to 92.5:7.5 (300 mL) to 90:10 (300 mL)) to afford 281.0 mg of **109h** as an oil. The product was purified to an analytical standard by diffusion pump Kugelrohr distillation (120 °C ABT, 4.0 x 10^{-5} mmHg) to afford 265.5 mg (76% yield) of **109h** as a viscous, colorless oil.

Data for (2*S*,3*S*)-(+)-**109h**:

b.p.: 120 °C (ABT, 4.0 x 10^{-5} mmHg)

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

7.46–7.42 (m, 2H, HC(11)), 7.42–7.39 (m, 2H, HC(7)), 7.30–7.19 (m, 6H, HC(9), HC(8), HC(12), HC(13)), 7.16–7.08 (m, 3H, HC(16), HC(17)), 6.82 (dd, *J* = 7.2, 1.8 Hz, 2H, HC(15)), 3.33 (dd, *J* = 11.3, 2.2 Hz, 1H, HC(3)), 3.13 (s, 1H, OH), 2.97 (ddd, *J* = 13.7, 9.1, 4.4 Hz, 1H, $H_2C(5)$), 2.50 (ddd, *J* = 13.9, 8.4 Hz, 1H, $H_2C(5)$), 1.97–1.89 (m, 1H, $H_2C(4)$), 1.78–1.70 (m, 1H, $H_2C(4)$), 1.63 (s, 3H, $H_3C(1)$).

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

144.96 (C(6)), 141.18 (C(14)), 137.18 (C(10)), 131.25 (HC(11)), 129.15 (HC(12)), 128.51 (HC(15) or HC(16)), 128.36 (HC(15) or HC(16)), 128.21 (HC(8)), 127.41 (HC(9)), 126.87 (HC(13)), 126.12 (HC(7)), 125.91 (HC(17)), 76.50 (C(2)), 65.19 (HC(3)), 34.00 ($H_2C(5)$), 33.73 ($H_2C(4)$), 24.13 ($H_3C(1)$).

IR: (neat)

3473 (w), 3059 (w), 3026 (w), 2932 (w), 2857 (w), 1602 (w), 1582 (w), 1495 (w), 1479 (w), 1446 (m), 1439 (m), 1375 (w), 1344 (w), 1182 (w), 1066 (w), 1026 (m), 1001 (w), 937 (w), 908 (m), 875 (w), 792 (w), 764 (m), 738 (s), 695 (s), 616 (m), 594 (w), 563 (w), 488 (m).

LRMS: (EI, 70 eV)

51.0 (13), 65.1 (18), 77.0 (24), 91.1 (88), 92.1 (10), 109.0 (13), 110.0 (41), 115.1 (16), 117.1 (45), 118.1 (55), 121.1 (71), 131.1 (81), 135.0 (12), 222.1 (13), 228.1 (100), 229.1 (23), 348.2 (<1).

Analysis: $C_{23}H_{24}OS$ (348.50)

Calcd: C, 79.27%; H, 6.94%

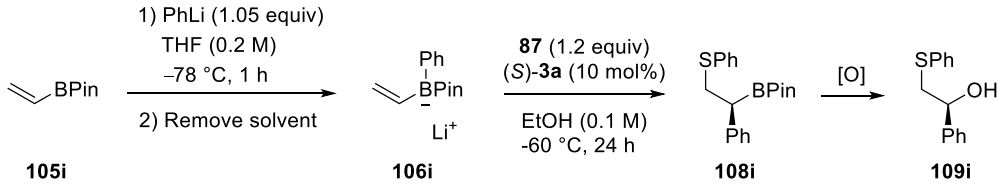
Found: C, 78.98%; H, 6.88%

TLC: R_f 0.28 (hexanes/EtOAc, 90:10, CAM)

HPLC: (2*S*,3*S*)-**109h** t_R 20.2 min (96%); (2*R*,3*R*)-**109h** t_R 21.8 min (4%) (Supelco Astec, hexanes/*i*-PrOH, 95:5, 0.5 mL/min, 220 nm, 24 °C)

Opt. Rot.: $[\alpha]_D^{24}$ +17.8 (*c* = 1.30 in 95% EtOH) (92% ee)

Preparation of (*S*)-(–)-**1-Phenyl-2-(phenylthio)ethan-1-ol (**(*S*)-(–)-**109i)**



An oven-dried, 25-mL, Schlenk flask (**A**) equipped with a stir bar, septum, and digital thermocouple probe was charged with THF (5 mL) and vinyl pinacolborane **105i** (154.3 mg, 1.00 mmol). The resulting colorless solution was cooled to –78 °C using a dry ice/isopropanol bath, and then stirred for 15 min to allow the temperature to equilibrate. A solution of phenyllithium in diethyl ether (1.77 M, 595 μL, 1.05 mmol, 1.05 equiv) was added dropwise over 10 min, such that the internal temperature did not exceed –68 °C. The dark red color of the phenyllithium solution immediately disappeared upon addition to the reaction mixture. The resulting pale, pink-brown solution was stirred at –78 °C for 1 h. A separate, oven-dried, 25-mL, Schlenk flask (**B**) equipped with a stir bar was charged with (*S*)-**3a** (51.9 mg, 0.10 mmol, 0.10 equiv) and brought into the glovebox. To the flask was added *N*-(phenylthio)saccharin **87** (350.0 mg, 1.20 mmol, 1.20 equiv). The flask was sealed with a septum and removed from the glovebox. Absolute ethanol (5 mL) was added to flask **B**, and the resulting yellow suspension was sonicated under argon for 10 min. Flask **B** was equipped with a digital thermocouple probe and cooled to an internal temperature of –60 °C using a Cryo-Cool. Flask **A**, having been stirred for 1 h at –78 °C, was placed under vacuum (0.01 mmHg) and the cold bath was removed. The solution was stirred rapidly under vacuum for 30 min until all of the THF was removed. The resulting beige-colored, foam solid boronate

complex **106i** in flask **A** was taken up in ethanol (2.5 mL) at 25 °C, and the resulting solution was added dropwise via syringe to flask **B** over 10 min. A white suspension resulted. An additional portion of ethanol (2.5 mL) was added to flask **A** and then transferred to flask **B** as just described, to ensure complete transfer of the boronate. Flask **B** was stirred at –60 °C for 16 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (2.5 mL). The flask was removed from the cold bath and the biphasic mixture was allowed to warm to 25 °C. The mixture was diluted with diethyl ether (5 mL) and water (5 mL) and stirred rapidly to dissolve all solids. The biphasic mixture was transferred to a 60-mL separatory funnel and the layers were separated. The aqueous layer was washed with diethyl ether (2 x 10 mL), and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated (30 °C, 15 torr) to afford 371.0 mg of crude borane **108i** as a yellow oil. The yield of **108i** was determined to be 65% by quantitative ^{1}H-NMR as described previously for **108a**.

A 100-mL, round-bottomed flask equipped with a stir bar was charged with crude **108i** (371.0 mg), THF (10 mL) and water (10 mL). Sodium perborate tetrahydrate (604.3 mg, 3.9 mmol) and tetra-*n*-butylammonium chloride (31.7 mg, 0.11 mmol) were added sequentially to the rapidly stirred biphasic mixture at 25 °C. The mixture was stirred rapidly for 2 h at 25 °C. Full conversion was observed by TLC (hexanes/EtOAc, 90:10, CAM). The oxidation was quenched by the addition of solid sodium bisulfite, $NaHSO_3$ (1.20 g) and the resulting mixture was stirred for 15 min. Then, aq. NaOH was added (1 M, 20 mL) and the mixture was stirred for 30 min. The mixture was transferred to a separatory funnel and diluted with diethyl ether (30 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (2 x 15 mL). The combined organic phases were washed with brine (25 mL) and then dried over magnesium sulfate, filtered, and concentrated (30 °C, 15 torr) to afford 295.7 mg of crude **109i** as an oil. The product was purified by chromatography (silica gel, 3 x 19 cm, dry load on Celite, 25-mL fractions, hexanes/EtOAc gradient elution: 95:5 (600 mL) to 90:10 (600 mL) to 85:15 (300 mL)) to afford 144.4 mg of **109i** as an oil. The product was purified to an analytical standard by diffusion pump Kugelrohr distillation (100 °C ABT, 4.2 x 10^{-5} mm Hg) to afford 137.8 mg (60% yield) of **109i** as a viscous, pale, yellow oil.

Data for (*S*)-(–)-**109i**:

b.p.: 100 °C (ABT, 4.2 x 10^{-5} mm Hg)

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

7.45–7.41 (m, 2H, HC(8)), 7.38–7.34 (m, 4H, HC(4) and HC(5)), 7.34–7.28 (m, 3H, HC(9) and HC(6)), 7.26–7.22 (HC(10)), 4.73 (dt, *J* = 9.5, 2.9 Hz, 1H, HC(1)), 3.34 (dd, *J* = 13.8, 3.5 Hz, 1H, H_2C(2)), 3.10 (dd, *J* = 13.8, 9.5 Hz, 1H, H_2C(2)), 2.82 (d, *J* = 2.4 Hz, 1H, OH).

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

142.27 (C(3)), 135.00 (C(7)), 130.42 (HC(8)), 129.30 (HC(9)), 128.72 (HC(5)), 128.15 (HC(6)), 126.97 (HC(10)), 125.99 (HC(4)), 71.81 (HC(1)), 44.26 (H_2C(2)).

IR: (neat)

3395 (w), 3059 (w), 3029 (w), 2961 (w), 2919 (w), 1950 (w), 1881 (w), 1807 (w), 1601 (w), 1582 (w), 1493 (w), 1480 (m), 1453 (w), 1438 (m), 1409 (w), 1331 (w), 1300 (w), 1272 (w), 1232 (w), 1193 (w), 1156 (w), 1086 (w), 1053 (m), 1025 (m), 1001 (m), 989 (m), 914 (w), 857 (w), 769 (w), 736 (s), 691 (s), 612 (m), 523 (m), 474 (m).

LRMS: (EI, 70 eV)

51.0 (41), 65.1 (19), 77.0 (71), 78.0 (25), 79.0 (79), 91.0 (30), 107.0 (41), 109.0 (16), 110.0 (10), 123.0 (16), 124.0 (100), 125.0 (10), 230.1 (9), 231.0 (2).

Analysis: $C_{14}H_{14}OS$ (230.32)

Calcd: C, 73.01%; H, 6.13%

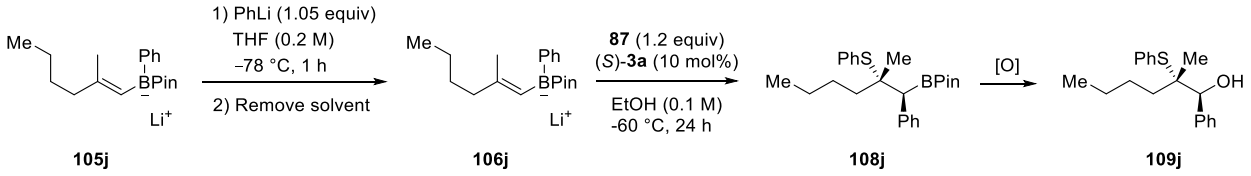
Found: C, 72.81%; H, 5.97%

TLC: R_f 0.14 (hexanes/EtOAc, 90:10, CAM)

HPLC: (*S*)-**109i** t_R 10.7 min (84%); (*R*)-**109i** t_R 12.5 min (16%) (Regis (*R*,*R*)-Whelk O1, hexanes/*i*-PrOH, 80:20, 0.5 mL/min, 220 nm, 24 °C)

Opt. Rot.: $[\alpha]_D^{24}$ –36.3 (*c* = 1.37 in 95% EtOH) (68% ee)

Preparation of (–)-2-Methyl-1-phenyl-2-(phenylthio)hexan-1-ol ((–)-109j)



An oven-dried, 50-mL, Schlenk flask (**A**) equipped with a stir bar, septum, and digital thermocouple probe was charged with THF (7.5 mL) and (*E*)-2-methylhex-1-en-1-yl pinacolborane **105j** (334.6 mg, 1.49 mmol). The resulting clear, colorless solution was cooled to –78 °C using a dry ice/isopropanol bath. A solution of phenyllithium in diethyl ether (1.77 M, 886 μL, 1.57 mmol, 1.05 equiv) was added dropwise over 10 min, such that the internal temperature did not exceed –68 °C. The dark red color of the phenyllithium solution immediately disappeared upon addition to the reaction mixture. After the addition, the resulting pale, brown solution was stirred at –78 °C for 1 h. A separate, oven-dried, 25-mL, Schlenk flask (**B**) equipped with a stir bar was charged with (*S*)-**3a** (78.3 mg, 0.15 mmol, 0.10 equiv) and brought into the glovebox. To the flask was added *N*-(phenylthio)saccharin **87** (527.4 mg, 1.81 mmol, 1.21 equiv). The flask was sealed with a septum and removed from the glovebox. Ethanol (7.5 mL) was added to flask **B**, and the resulting yellow suspension was sonicated under argon for 10 min. Flask **B** was equipped with a digital thermocouple probe and cooled to an internal temperature of –60 °C using a Cryo-Cool. At this point, flask **A**, having been stirred for 1 h at –78 °C, was placed under vacuum (0.01 mmHg) and the cold bath was removed. The solution was stirred rapidly under vacuum until all of the THF was removed (30 min). The resulting white, flaky solid boronate complex **106j** in flask **A** was taken up in ethanol (3.75 mL) at 25 °C, and the resulting solution was added dropwise via syringe to flask **B** over 10 min. A white suspension resulted. An additional portion of ethanol (3.75 mL) was added to flask **A** and then transferred to flask **B** as just described, to ensure complete transfer of the boronate complex. Flask **B** was stirred at –60 °C for 40 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (3.75 mL). The flask was removed from the cold bath and the biphasic mixture was allowed to warm to 25 °C. The mixture was diluted with diethyl ether (7.5 mL) and water (7.5 mL) and stirred rapidly to dissolve all solids. The biphasic mixture was transferred to a 60-mL separatory funnel and the layers were separated. The aqueous layer was washed with diethyl ether (2 x 15 mL), and the combined organic layers were dried over

magnesium sulfate, filtered, and concentrated (30 °C, 15 torr) to afford the crude borane **108j** as a pink, oily solid. The yield of **108j** was determined to be 33% by quantitative ^{1}H-NMR as described previously for **108a**.

A 100-mL, round-bottomed flask equipped with a stir bar was charged with crude **108j** and THF (15 mL). The turbid solution was cooled to 0 °C with an ice bath. To this solution was added a mixture of 30% aq. H_2O_2 (1.5 mL) and 3 M aq. NaOH (1.5 mL) also containing EDTA (1.0 mg/mL). The biphasic mixture was stirred rapidly at 0 °C for 3 h. Full conversion was observed by TLC (hexanes/EtOAc, 90:10, CAM). The oxidation was quenched by the addition of a sodium bisulfite ($NaHSO_3$) aq. solution (1.80 g in 15 mL water) and stirred for 15 min. The mixture was transferred to a separatory funnel and diluted with diethyl ether (45 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (2 x 25 mL). The combined organic phases were washed with brine (25 mL) and then dried over magnesium sulfate, filtered, and concentrated (30 °C, 15 torr) to afford 680.4 mg of crude **109j**. The product was purified by chromatography (silica gel, 3 x 28 cm, dry load on Celite, 25-mL fractions, hexanes/EtOAc gradient elution: 97.5:2.5 (300 mL) to 95:5 (600 mL) to 92.5:7.5 (300 mL) to 90:10 (300 mL)) to afford 135.1 mg of **109j** as an oil. The product was purified a second time by chromatography to remove an unidentified impurity (silica gel, 2 x 28 cm, dry load on Celite, 25-mL fractions, hexanes/CH_2Cl_2 gradient elution: 90:10 (200 mL) to 80:20 (200 mL) to 70:30 (200 mL) to 60:40 (200 mL) to 50:50 (200 mL) to 60:40 (200 mL)) to afford 133.6 mg of **109j**. Analytically pure product was obtained by diffusion pump Kugelrohr distillation (90 °C ABT, 4.0 x 10^{-5} mmHg) to afford 119.0 mg (27% yield) of **109j** as a viscous, colorless oil.

Data for (–)-**109j**:

b.p.: 90 °C (ABT, 4.0 x 10^{-5} mmHg)

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

7.61–7.54 (m, 2H, HC(13)), 7.45–7.41 (m, 1H, HC(15)), 7.40–7.36 (m, 2H, HC(14)), 7.31–7.23 (m, 5H, HC(8), HC(9) and HC(10)), 4.30 (s, 1H, HC(1)), 3.86 (s, 1H, OH), 1.89–1.78 (m, 1H, H_2C(4)), 1.34–1.25 (m, 1H, H_2C(4)), 1.25–1.14 (m, 4H, H_2C(5) and H_2C(3)), 1.13 (s, 3H, H_3C(11)), 0.87 (t, J = 7.2 Hz, 3H, H_3C(6)).

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

138.94 (C(7)), 137.13 (HC(13)), 130.10 (C(12)), 129.52 (HC(15)), 129.13 (HC(14)), 128.61 (HC(8) or HC(9)), 127.78 (HC(10)), 127.75 (HC(8) or HC(9)),

76.80 (HC(1)), 61.63 (C(2)), 35.45 (H_2C(3)), 26.40 (H_2C(4)), 23.07 (H_2C(5)), 17.66 (H_3C(11)), 14.35 (H_3C(6)).

IR: (neat)

3462 (w), 3061 (w), 3030 (w), 2956 (w), 2933 (w), 2870 (w), 1953 (w), 1886 (w), 1811 (w), 1604 (w), 1583 (w), 1573 (w), 1493 (w), 1474 (w), 1468 (w), 1454 (m), 1438 (m), 1378 (w), 1326 (w), 1303 (w), 1241 (w), 1187 (m), 1155 (w), 1128 (w), 1093 (w), 1044 (m), 1025 (m), 918 (w), 851 (w), 808 (w), 790 (w), 749 (s), 701 (s), 693 (s), 674 (m), 619 (w), 596 (m), 525 (m), 503 (m), 458 (m),

LRMS: (EI, 70 eV)

51.0 (17), 55.1 (69), 57.1 (17), 59.1 (15), 65.1 (22), 66.1 (10), 77.0 (63), 78.1 (13), 79.1 (55), 83.1 (70), 85.1 (10), 91.1 (63), 105.1 (29), 107.1 (35), 109.0 (56), 110.0 (65), 111.0 (18), 115.1 (20), 117.1 (37), 123.0 (70), 129.1 (13), 131.1 (36), 135.0 (10), 137.1 (94), 138.1 (12), 151.1 (25), 173.1 (27), 191.2 (15), 193.1 (100), 194.1 (92), 195.1 (39), 200.1 (14), 300.2 (1).

Analysis: $C_{19}H_{24}OS$ (300.46)

Calcd: C, 75.95%; H, 8.05%

Found: C, 75.79%; H, 7.76%

TLC: R_f 0.35 (hexanes/EtOAc, 90:10, CAM)

HPLC: (–)-**109j** t_R 12.6 min (54%); (+)-**109j** t_R 19.7 min (46%) (Regis (*R*,*R*)-Whelk O1, hexanes/*i*-PrOH, 95:5, 0.5 mL/min, 220 nm, 24 °C)

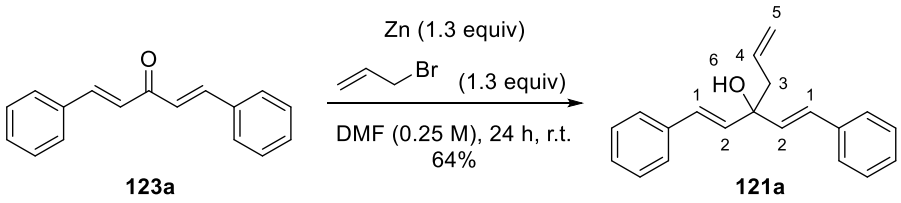
Opt. Rot.: $[\alpha]_D^{24}$ –10.2 (*c* = 1.00 in 95% EtOH) (8% ee)

Experimental for Appendix A

Literature Preparation

The following compounds from Appendix A were prepared by literature methods and characterization matched the data previously reported: dibenzylidene acetone,[144] (1*E*,4*E*)-1,5-di(pyridin-2-yl)penta-1,4-dien-3-one (**123b**),[145] 4-benzylidene-1,6-heptadien-4-ol (**127**),[146] (*E*)-4-phenyl-3-butenoic acid (**131**),[147] methyl (*E*)-4-phenyl-3-butenoate (**132**),[148] and catalyst **124c**.[157] Other catalysts **124**, **125**, and **126** were prepared previously in these laboratories. Anhydrous cerium(III) chloride was prepared according to the method described by Imamoto and co-workers.[151]

3-benzylidene-1-phenyl-1,5-hexadien-3-ol (121a)



The following procedure is a modification of a published procedure.[143] A flame-dried 50-mL Schlenk flask equipped with a stir bar was charged with zinc dust (0.36 g, 5.46 mmol, 1.3 equiv), dibenzylidene acetone **123a** (1.01 g, 4.31 mmol, 1.0 equiv), and DMF (17.1 mL). Allyl bromide (0.46 mL, 5.34 mmol, 1.3 equiv) was added dropwise and the reaction was allowed to stir at room temperature for 24 h. The reaction was quenched by the portionwise addition of sat. aqueous NH_4Cl solution. The mixture was poured into a 250-mL separatory funnel and extracted with ether (3 x 50 mL). The combined organic layers were washed with sat. aqueous NH_4Cl solution (50 mL), water (50 mL), and brine (50 mL), dried over $MgSO_4$ (~3 g), filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography using activity II neutral alumina (4 cm x 20 cm, hexanes/TBME gradient, 19:1 to 9:1 to 5:1 to 4:1 to 3:1 to 1:1) to yield 1.19 g (64%) of alcohol **121a** as a viscous yellow oil.

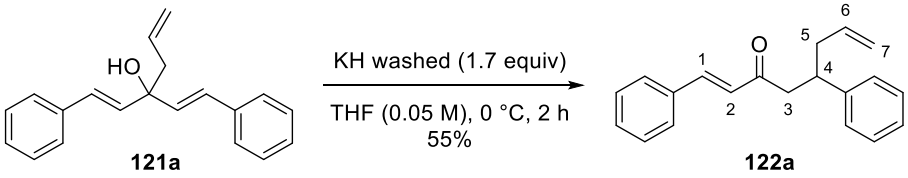
Data for **121a**:

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

7.48 – 7.41 (m, 4H, Ph), 7.40 – 7.32 (m, 4H, Ph), 7.31 – 7.24 (m, 2H, Ph), 6.72 (d, J = 16.0 Hz, 2H, CH(1)), 6.41 (d, J = 16.0 Hz, 2H, CH(2)), 5.96 – 5.84 (m, 1H, CH(4)), 5.31 – 5.21 (m, 2H, CH_2(5)), 2.62 (d, J = 7.4 Hz, 2H, CH_2(3)), 2.09 (s, 1H, OH). ^{1}H NMR peak listings match those previously reported.[143]

TLC: R_f = 0.45 (hexanes/TBME, 80:20, CAM)

Preparation of 1,5-diphenyl-1,7-octadien-3-one (122a) under traditional conditions.



The following procedure is a modification of a published procedure.[143] A 50-mL Schlenk flask was equipped with a stir bar, flame-dried, and placed under argon. Washed potassium hydride (24.9 mg, 0.62 mmol, 1.7 equiv) was added to the flask, followed by THF (4.0 mL). The suspension was cooled with an ice/water bath to an internal temperature of 0 °C and was stirred vigorously. A solution of alcohol **121a** (102.7 mg, 0.37 mmol, 1.0 equiv) in THF (4.0 mL) was added dropwise to the suspension. Stirring was continued for 2 h at 0 °C (maintained with an ice/water bath) until the reaction was complete. The reaction mixture was cooled to an internal temperature of -78 °C using a dry ice/acetone bath and was quenched by rapid injection of absolute methanol (2 mL). [**Note:** While this was never attempted, the author also suggests using a 5% solution of acetic acid in diethyl ether in place of absolute methanol for the quench, which may prevent unwanted side product formation.] The mixture was partitioned between 30 mL each of diethyl ether and sat. aqueous NH_4Cl solution. The aqueous layer was extracted with ether (3 x 30 mL) and the combined ethereal extracts were washed with brine (3 x 30 mL), dried over $MgSO_4$ (~3 g), filtered, and concentrated *in vacuo* to afford an oily yellow/white solid. The crude material was purified by column chromatography using activity II neutral alumina (2 cm x 30 cm,

hexanes/TBME gradient, 19:1 to 9:1) to yield 56.0 mg (55%) of enone **122a** as a white solid. At this point, the compound may also be recrystallized from hot isopropanol if desired.

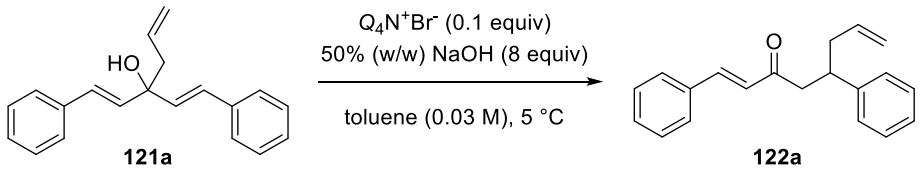
Data for **122a**:

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

7.71 – 7.04 (m, 11H, Ph and CH(1)), 6.65 (d, J = 16.2 Hz, 1H, CH(2)), 5.74 – 5.63 (m, 1H, CH(6)), 5.17 – 4.82 (m, 2H, CH_2(7)), 3.38 (pent, J = 7.5 Hz, 1H, CH(4)), 3.04 – 2.93 (m, 2H, CH_2(3)), 2.48 – 2.41 (m, 2H, CH_2(5)). ^{1}H NMR peak listings match those previously reported.[143]

TLC: R_f = 0.59 (hexanes/TBME, 80:20, CAM)

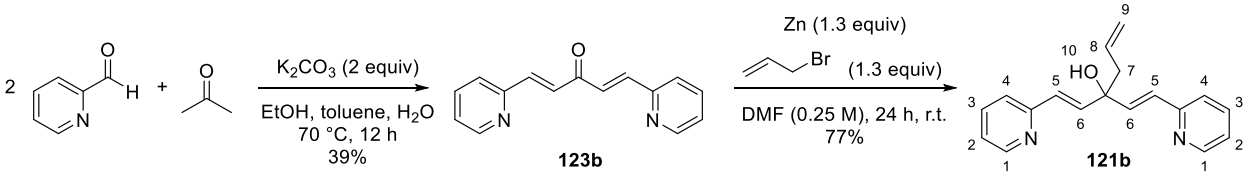
General Procedure: Rearrangement of 121a to 122a under PTC conditions.



A 4-mL, dram-sized vial was equipped with a football-shaped Teflon stir bar and charged with substrate alcohol **121a** (25.0 mg, 0.09 mmol, 1.0 equiv) and ammonium salt $Q_4N^+Br^-$ (0.009 mmol, 0.1 equiv). The vial was fitted with a lid containing a Teflon septum, placed briefly under vacuum (1 min at 0.1 mmHg), and backfilled with argon. Toluene (3 mL) containing 9.4 mg of dissolved biphenyl as an internal standard was added to the vial via syringe. [**Note:** For this purpose, a 0.0203 M stock solution was prepared by dissolving 313.4 mg biphenyl in toluene (100 mL) using a 100-mL volumetric flask.] The vial was cooled for 20 min in a cold room maintained at 5 °C with vigorous stirring (2000 rpm). A 50% (w/w) aq. NaOH solution (0.4 mL, 0.72 mmol, 8 equiv) was added to the vial with a syringe and the reaction mixture was allowed to continue stirring at 5 °C. To take an aliquot for HPLC analysis, the reaction was briefly stopped by removing the vial from the stir plate. A 30-µL aliquot was taken from the organic layer with a Hamilton syringe and placed in a 2-mL Agilent vial. This vial was placed briefly under vacuum (2 min at 0.1 mmHg) to remove toluene from the sample, and the remaining residue was dissolved in approximately 1 mL of HPLC-grade hexanes. To work up the reaction, stirring was stopped and the contents of the reaction vessel were poured into a 10-mL separatory funnel with 1 mL of water.

The layers were separated and the aqueous layer was extracted with ethyl acetate (1 mL). The combined organic extracts were filtered through sodium sulfate (30 mg) and silica gel (30 mg) in a Pasteur pipette and concentrated under reduced pressure. If desired, the crude product can be purified by column chromatography using activity II neutral alumina (1 cm x 20 cm, hexanes/TBME gradient, 19:1 to 9:1 to 4:1 to 0:1). The conversion of **121a** to **122a** was monitored by normal phase HPLC [column = (S,S)-naphthylleucine; eluent = 10:90 isopropanol/hexanes (isocratic); injection volume = 5 µL; flow rate = 1.0 mL/min; pressure = 42 bar; temperature = 22 °C; wavelength = 254 nm; run time = 8 min]. Order of elution: biphenyl (R_t = 3.2 min), alcohol **121a** (R_t = 3.7 min), enone **122a** (R_t = 4.2 min). Response factors: alcohol **121a** (0.4925), enone **122a** (2.3976). The enantiomeric ratio of enone **122a** was measured using normal phase HPLC [column = AD-H; eluent = 10:90 isopropanol/hexanes (isocratic); injection volume = 5 µL; flow rate = 1.0 mL/min; pressure = 42 bar; temperature = 22 °C; wavelength = 254 nm; run time = 13 min]. Order of elution: biphenyl (R_f = 3.6 min), enantiomers of enone **122a** (R_f = 6.8 min and 8.0 min), alcohol **121a** (R_f = 10.2 min).

Preparation of (1*E*,4*E*)-3-Allyl-1,5-di(pyridin-2-yl)penta-1,4-dien-3-ol (121b)



A flame-dried 25-mL Schlenk flask was equipped with a stir bar and placed under argon. Zinc dust (127.4 mg, 2.87 mmol, 1.3 equiv), dienone **123b** (500.5 mg, 2.12 mmol, 1.0 equiv), and DMF (8.48 mL) were added to the flask at room temperature. Allyl bromide (0.24 mL, 2.75 mmol, 1.3 equiv) was added dropwise and the reaction mixture was allowed to stir at room temperature under argon for 24 h. The reaction was quenched by the portionwise addition of sat. aqueous NH_4Cl solution (15 mL). The mixture was poured into a 125-mL separatory funnel and extracted with ether (3 x 25 mL). The combined organic layers were washed with sat. aqueous NH_4Cl solution (40 mL), water (40 mL), and brine (40 mL), dried over $MgSO_4$ (~3 g), filtered, and concentrated *in vacuo* to afford a yellow oil. The crude product was purified by column

chromatography using activity II neutral alumina (4 cm x 15 cm, MeOH in CH_2Cl_2 gradient, 0% to 0.5% to 1% to 2% to 3% to 4%) to yield **121b** (452.1 mg, 77%) as a viscous yellow oil.

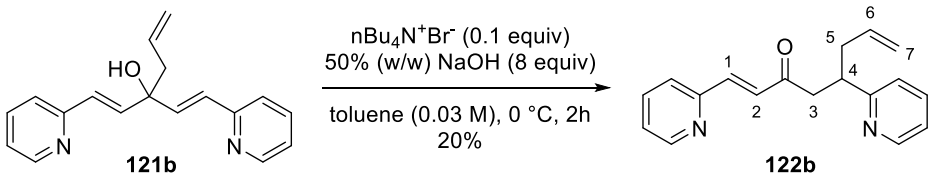
Data for **121b**:

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

8.55 (ddd, J = 5.1, 1.7, 0.9 Hz, 2H, CH(1)), 7.62 (td, J = 7.7, 1.9 Hz, 2H, CH(2/3/4)), 7.30 – 7.22 (m, 2H, CH(2/3/4)), 7.12 (ddd, J = 7.6, 4.8, 1.2 Hz, 2H, CH(2/3/4)), 6.94 (d, J = 15.7 Hz, 2H, CH(5)), 6.79 (d, J = 15.7 Hz, 2H, CH(6)), 5.96 – 5.79 (m, 1H, CH(8)), 5.32 – 5.18 (m, 2H, CH_2(9)), 2.63 (dt, J = 7.4, 1.2 Hz, 2H, CH_2(7)), 2.27 (s, 1H, OH(10)).

TLC: R_f = 0.34 (CH_2Cl_2/MeOH, 90:10, UV/$KMnO_4$)

Preparation of 1,5-di(pyridin-2-yl)-1,7-octadien-3-one (122b) under PTC conditions.



Six separate 4-mL, dram-sized vials were equipped with football-shaped Teflon stir bars. Tetra-*n*-butylammonium bromide (20.4 mg, 0.06 mmol, 0.1 equiv) was partitioned evenly among the six vials (3.4 mg per vial). A solution of tertiary alcohol **121b** (156.9 mg, 0.56 mmol, 1.0 equiv) dissolved in toluene (18.0 mL) was partitioned evenly among the six vials (3 mL per vial). The vials were cooled for 20 min in a cold room maintained at 5 °C. A 50% (w/w) aq. NaOH solution (0.24 mL, 4.51 mmol total, 8.0 equiv) was partitioned among the six vials (0.04 mL per vial) and added with a syringe. The vials were allowed to stir vigorously (2000 rpm) for 2 h at 5 °C. To workup the reaction, the contents of all six vials were combined and emptied into a 60-mL separatory funnel with 10 mL water. The layers were separated, and the toluene layer was washed with brine, dried over $MgSO_4$ (~3 g), and filtered. The aqueous layer was further extracted with dichloromethane (3 x 10 mL), and the combined extracts were washed with brine, dried over $MgSO_4$ (~3 g), and filtered. The two organic layers were combined and concentrated *in vacuo* to afford a brown oil. The crude product was purified by silica gel column chromatography (2 cm x

20 cm, MeOH in TBME gradient, 0% to 2.5% to 5% to 7.5% to 10%) to afford **122b** (67.1 mg, 43%) as a pale yellow oil. However, ^{1}H NMR spectroscopic analysis confirmed the presence of an unidentified impurity. The product was purified again by preparative thin layer chromatography (Et_2O/CH_2Cl_2, 50:50) to afford **122b** (31.3 mg, 20%) as a pale yellow oil. Additionally, the conversion of **121b** to **122b** was monitored by reverse phase HPLC [column = IC-3; eluent = 30:70 acetonitrile/water (isocratic); injection volume = 5 µL; flow rate = 2.0 mL/min; pressure = 252 bar; temperature = 22 °C; wavelength = 254 nm; run time = 25 min]. Order of elution: alcohol **121b** (R_t = 4.1 min), enone **122b** (R_t = 9.9 min), biphenyl (20.3 min). Response factors: alcohol **121b** (1.4095), enone **122b** (1.2485).

Data for **122b**:

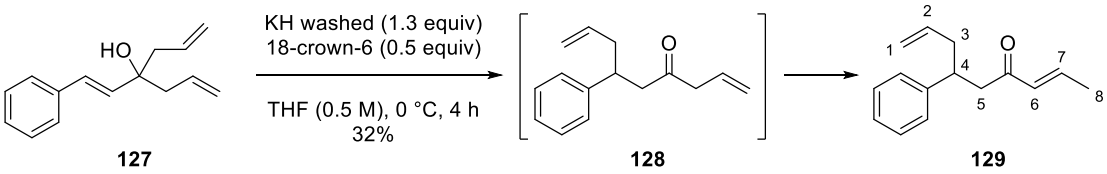
^{1}H NMR: (400 MHz, $CDCl_3$)

8.60 (d, *J* = 4.1 Hz, 1H, aryl), 8.48 (d, *J* = 4.1 Hz, 1H, aryl), 7.66 (td, *J* = 7.7, 1.7 Hz, 1H, aryl), 7.54 (td, *J* = 7.7, 1.8 Hz, 1H, aryl), 7.47 (d, *J* = 15.9 Hz, 1H, aryl), 7.38 (d, *J* = 7.8 Hz, 1H, aryl), 7.22 (dd, *J* = 7.9, 6.0 Hz, 1H, aryl), 7.18 (d, *J* = 7.8 Hz, 1H, aryl), 7.10 (d, *J* = 15.9 Hz, 1H, CH(1)), 7.04 (dd, *J* = 6.5, 4.9 Hz, 1H, CH(2)), 5.73 – 5.59 (m, 1H, CH(6)), 5.05 – 4.86 (m, 2H, CH(7)), 3.57 – 3.44 (m, 1H, CH(4)), 3.36 (dd, *J* = 17.1, 8.5 Hz, 1H, CH_2(3)), 3.01 (dd, *J* = 17.1, 5.2 Hz, 1H, CH_2(3)), 2.45 (dq, *J* = 31.2, 6.8 Hz, 2H, CH_2(5)).

TLC: R_f = 0.74 (TBME/MeOH, 95:5, UV/I_2)

R_f = 0.42 (Et_2O/CH_2Cl_2, 50:50, UV/I_2)

Preparation of 6-phenyl-2,8-nonadien-4-one (129) under traditional conditions.



Hexanes-washed potassium hydride (12.16 mg, 0.3 mmol, 1.3 equiv) was added to a flame-dried 10-mL Schlenk flask equipped with a stir bar, followed by THF (2 mL). The flask was cooled to an internal temperature of 0 °C using an ice/water bath. A solution of tertiary alcohol **127** (50 mg, 0.23 mmol, 1.0 equiv) dissolved in THF (1 mL) was added dropwise to the suspension at 0

°C. A solution of 18-crown-6 (30.83 mg, 0.12 mmol, 0.5 equiv) dissolved in THF (1.3 mL) was added dropwise to the suspension at 0 °C and the reaction was allowed to stir at this temperature for 4 h. [**Note:** The reaction was quenched before all starting material had been consumed because TLC analysis confirmed than unwanted self-condensation products were beginning to form.] The reaction was cooled to -78 C with a dry ice/acetone bath and quenched by rapid injection of absolute methanol (2 mL). [**Note:** While this was not done, the author also suggests quenching the reaction with a 5% solution of acetic acid in diethyl ether (2 mL) rather than methanol.] The mixture was partitioned between 20 mL each of diethyl ether and sat. aqueous NH_4Cl solution. The aqueous layer was extracted with ether (3 x 10 mL). The combined ethereal extracts were washed with brine (3 x 10 mL), dried over $MgSO_4$ (~3 g), filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (1 cm x 20 cm TBME in hexanes gradient, 1% to 2% to 3% to 4% to 5% to 6% to 7% to 8% to 9% to 10% to 11%) to afford **129** (19.4 mg, 32%) as a pale yellow oil.

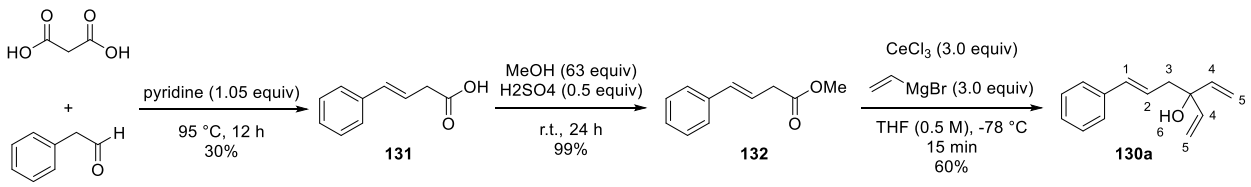
Data for **129**:

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

7.31 – 7.21 (m, 2H, Ph), 7.20 – 7.12 (m, 3H, Ph), 6.75 (dq, J = 15.7, 6.9 Hz, 1H, CH(7)), 6.03 (dd, J = 15.8, 1.6 Hz, 1H, CH(6)), 5.69 – 5.56 (m, 1H, CH(2)), 5.05 – 4.86 (m, 2H, CH_2(1)), 3.29 (pent, J = 7.2 Hz, 1H, CH(4)), 2.82 (dd, J = 7.1, 2.7 Hz, 2H, CH_2(5)), 2.41 – 2.32 (m, 2H, CH_2(3)), 1.82 (dd, J = 6.8, 1.6 Hz, 3H, CH_3(8)). ^{1}H-NMR peak listings match those previously reported.[242] Enone **34a** had been previously prepared by a different method (not via an oxy-Cope rearrangement).

TLC: R_f = 0.58 (hexanes/TBME, 80:20, UV/CAM)

Preparation of (*E*)-6-phenyl-3-vinyl-1,5-hexadien-3-ol (130a)



The following procedure for the preparation of novel alcohol **130a** was adapted from previously published literature describing the synthesis of similar compounds.[150-151] Anhydrous cerium(III) chloride (1.05 g, 4.26 mmol, 3.0 equiv) was added to a flame-dried 50-mL Schlenk flask equipped with a stir bar. The flask was cooled to an internal temperature of 0 °C using an ice/water bath. THF (7.1 mL) was added to the flask all at once at 0 °C with vigorous stirring. The suspension was allowed to stir under argon at room temperature overnight. Methyl ester **132** (251.1 mg, 1.42 mmol, 1.0 equiv) was added dropwise to the suspension at room temperature. The mixture was stirred for 1 h and then the flask was cooled with a dry ice/acetone bath to an internal temperature of -78 °C. A commercial 1.0 M solution of vinylmagnesium bromide in THF (4.27 mL) was added dropwise at -78 °C with vigorous stirring. The reaction was allowed to stir at this temperature for 15 min and was then quenched with 8 mL of a 5% solution of acetic acid in ether and allowed to warm to room temperature. The reaction mixture was transferred to a 250-mL separatory funnel, and the aqueous layer was extracted with ether (3 x 50 mL). The combined ethereal extracts were washed with brine (50 mL), sat. aq. $NaHCO_3$ (2 x 50 mL), and brine (50 mL), dried over $MgSO_4$ (~3 g), filtered, and concentrated *in vacuo* to yield a yellow oil. The crude material was purified by column chromatography using activity II neutral alumina (2 cm x 20 cm, EtOAc in hexanes gradient, 2% to 4% to 6% to 8% to 10% to 15% to 25% to 35% to 50% to 60%) to yield 169.7 mg (60%) of alcohol **130a** as a pale yellow oil.

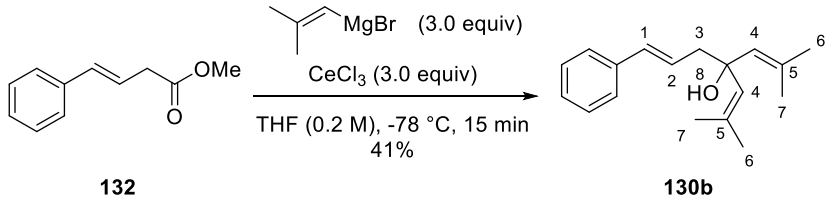
Data for **130a**:

^{1}H NMR: (500 MHz, CDCl3)

7.39 – 7.19 (m, 5H, Ph), 6.49 (d, J = 15.9 Hz, 1H, CH(1)), 6.19 (dt, J = 15.8, 7.5 Hz, 1H, CH(2)), 6.00 (dd, J = 17.3, 10.7 Hz, 2H, CH(4)), 5.31 (dd, J = 17.3, 1.2 Hz, 2H, CH_2(5)), 5.17 (dd, J = 10.7, 1.2 Hz, 2H, CH_2(5)), 2.54 (dd, J = 7.5, 1.3 Hz, 2H, CH_2(3)), 1.83 (s, 1H, OH(6)).

TLC: R_f = 0.51 (hexanes/EtOAc, 80:20, UV/CAM)

Preparation of 4-isobutenyl-6-methyl-1-phenyl-1,5-heptadien-4-ol (130b)



132 **130b**

The following procedure for the preparation of novel alcohol **130b** was adapted from previously published literature describing the synthesis of similar compounds.[150-151] Preparation of the isobutenylmagnesium bromide reagent was carried out as described by Chen and Chang without modification[243] and titrated in the usual way. Anhydrous cerium(III) chloride (1.66 g, 6.75 mmol, 3.0 equiv) was added to a flame-dried 50-mL Schlenk flask equipped with a stir bar. The flask was cooled to an internal temperature of 0 °C with an ice/water bath. THF (11.2 mL) was added to the flask all at once with vigorous stirring at 0 °C. The suspension was warmed to room temperature and allowed to stir under argon at room temperature overnight. Methyl ester **132** (396.5 mg, 2.25 mmol, 1.0 equiv) was added dropwise to the suspension at room temperature. The mixture was stirred for 1 h and then cooled with a dry ice/acetone bath to an internal temperature of -78 °C. A 0.35 M solution of isobutenylmagnesium bromide in THF (19.29 mL, 6.75 mmol, 3.0 equiv) was added dropwise at -78 °C with vigorous stirring. After 15 min, the reaction was quenched with a 5% solution of acetic acid in ether (16 mL) and allowed to warm to room temperature. The reaction mixture was transferred to a 125-mL separatory funnel and extracted with ether (3 x 25 mL). The combined ethereal extracts were washed with brine (25 mL), sat. aqueous $NaHCO_3$ (2 x 25 mL), and brine (50 mL), dried over $MgSO_4$ (~3 g), filtered, and concentrated *in vacuo* to yield a yellow oil. The product was purified with column chromatography using activity III basic alumina (2 x 25 cm, EtOAc in hexanes gradient, 0% to 1% to 2% to 4% to 6% to 8% to 10%) to yield 234.7 mg (41%) of alcohol **130b** as a pale yellow oil.

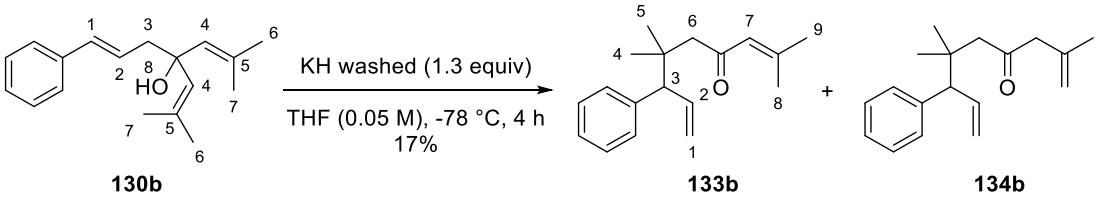
Data for **130b**:

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

7.40 – 7.18 (m, 5H, Ph), 6.48 (d, J = 15.9 Hz, 1H, CH(1)), 6.26 (dt, J = 15.9, 7.4 Hz, 1H, CH(2)), 5.54 – 5.45 (m, 2H, CH(4)), 2.53 (dd, J = 7.4, 1.2 Hz, 2H, CH_2(3)), 1.76 (s, 1H, OH(8)), 1.73 (dd, J = 6.4, 1.1 Hz, 12H, CH_3(6) and CH_3(7)).

TLC: R_f = 0.51 (hexanes/EtOAc, 80:20, UV/CAM)

Preparation of 2,6,6-trimethyl-7-phenyl-2,8-nonadien-4-one (133b).



130b **133b** **134b**

Hexanes-washed potassium hydride (10.1 mg, 0.25 mmol, 1.3 equiv) was added to a flame-dried 10-mL Schlenk flask equipped with a stir bar. THF (2 mL) was added via syringe. The suspension was cooled with a dry ice/acetone bath to an internal temperature of -78 °C. A solution of tertiary alcohol **130b** (49.1 mg, 0.19 mmol, 1.0 equiv) dissolved in THF (2 mL) was added dropwise to the stirred suspension at -78 °C. The reaction immediately turned a bright yellow color. The temperature was gradually allowed from -78 °C to –20 °C over a 4h period, during which time the reaction turned an orange-red color. The reaction was again cooled to -78 °C and quenched by rapid injection of absolute methanol (2.0 mL). [**Note:** While this was not attempted, the author also suggests quenching with a 5% solution of acetic acid in diethyl ether rather than absolute methanol.] The mixture was partitioned between 20 mL each of diethyl ether and sat. aqueous NH_4Cl solution and extracted with ether (3 x 10 mL). The combined organic extracts were washed with brine (3 x 10 mL), dried over $MgSO_4$ (~3 g), filtered, and concentrated *in vacuo* to afford a brown oil. The crude product was purified by silica gel column chromatography (1 cm x 25 cm, hexanes/EtOAc gradient, 39:1 to 19:1 to 9:1) to afford a mixture of tautomers **133b** and **134b** (8.3 mg, 17%) as a pale yellow oil.

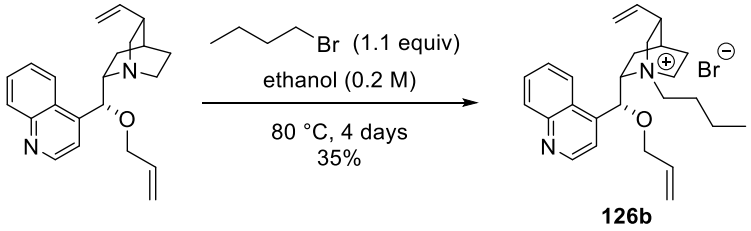
Data for **133b**:

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

7.38 – 7.11 (m, 5H, Ph), 6.38 – 6.17 (m, 1H, CH(2)), 6.01 – 5.98 (m, 1H, CH(7)), 5.22 – 5.01 (m, 2H, CH_2(1)), 3.45 (d, *J* = 9.9 Hz, 1H, CH_2(3)), 2.32 (d, *J* = 3.7 Hz, 2H, CH_2(6)), 2.15 (d, *J* = 1.3 Hz, 3H, CH_3(8/9)), 1.87 (d, *J* = 1.3 Hz, 3H, CH_3(8/9)), 1.05 (s, 3H, CH_3(4/5)), 0.99 (s, 3H, CH_3(4/5)).

TLC: R_f = 0.74 (hexanes/EtOAc, 80:20, UV/CAM)

_N_-Butyl-O-allylcinchonidinium bromide (126b)



126b

A flame-dried 5-mL round bottom flask equipped with a reflux condenser and Teflon stir bar was charged with absolute ethanol (1.5 mL), O-allylcinchonidine (95.8 mg, 0.29 mmol, 1.0 equiv), and 1-bromobutane (0.04 ml, 0.33 mmol, 1.1 equiv). [**Note:** A significant side product isolated from this reaction was protonated starting material (O-allylcinchonidinium bromide). It is recommended that 1-bromobutane be filtered through basic alumina prior to use to remove trace HBr.] The reaction was heated to reflux and stirred under argon for 72 h. The reaction flask was cooled to room temperature and placed directly on a rotary evaporator to remove solvent. The crude product was purified by silica gel column chromatography (2 cm x 10 cm, MeOH in CH_2Cl_2 gradient, 0% to 2.5% to 5% to 7.5% to 10%) to yield an oily green solid. This oily solid was triturated with hexanes to afford **126b** (46.9 mg, 35%) as a free-flowing green powder. After several weeks of storage, the color of this powder turned from green to gray, but ^{1}H NMR spectroscopic analysis of the compound revealed no decomposition.

Data for **126b**:

^{1}H NMR: (500 MHz, CD_3OD)

8.96 (d, *J* = 4.5 Hz, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.89 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.83 – 7.74 (m, 2H), 6.22 – 6.04 (m, 2H), 5.70 (ddd,

J = 17.3, 10.5, 7.0 Hz, 1H), 5.40 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.31 (dt, *J* = 10.5, 1.4 Hz, 1H), 5.15 (dt, *J* = 17.3, 1.2 Hz, 1H), 5.03 (dd, *J* = 10.6, 1.5 Hz, 1H), 4.16 – 4.11 (m, 2H), 4.07 – 3.98 (m, *J* = 4.1 Hz, 1H), 3.88 – 3.73 (m, 3H), 3.64 – 3.53 (m, *J* = 10.0, 7.0 Hz, 2H), 3.37 (ddt, *J* = 11.4, 5.3, 2.6 Hz, 1H), 2.91 – 2.81 (m, 1H), 2.45 – 2.37 (m, 1H), 2.36 – 2.27 (m, 1H), 2.13 (q, *J* = 3.1 Hz, 1H), 2.09 – 1.99 (m, 1H), 1.98 – 1.85 (m, *J* = 9.5, 5.9 Hz, 2H), 1.75 – 1.47 (m, 3H), 1.15 (t, *J* = 7.4 Hz, 3H).

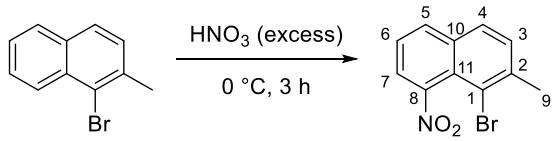
TLC: R_f = 0.19 (CH_2Cl_2/MeOH, 90:10, UV/$KMnO_4$)

Experimental for Appendix B

Literature Preparations

The following compounds from Appendix B were prepared by literature methods and characterization matched the data previously reported: 1-bromo-2-(bromomethyl)naphthalene (**156**),[182] (1-bromo-2-naphthalenyl) methyltriphenylphosphonium bromide (**157**),[183] and (*R*)-binaphtholphosphoric acid (**162**).[244]

Synthesis of 1-bromo-2-methyl-8-nitronaphthalene (152)



151 **152**

The following procedure is a modification of a published procedure.[245] A flame-dried three-necked 250-mL round bottom flask was equipped with an addition funnel, mechanical stirrer, and rubber septum. Concentrated nitric acid (56.5 mL) was added to the flask. The flask was cooled to an internal temperature of 0 °C using an ice bath. The addition funnel was charged with 1-bromo-2-methylnaphthalene **151** (35.3 ml, 226.15 mmol). This was added to the flask dropwise over the course of two hours. Moderate stirring (200 rpm) was maintained throughout, and the reaction temperature was not allowed to exceed 5 °C. After addition was complete, the mixture was allowed to stir overnight at room temperature. The mixture is initially a yellow/orange solution but eventually congeals into a thick orange paste (stir rate was reduced to 50 rpm once this was observed). The reaction was quenched at 0 °C by the slow addition of ice water (285 mL). The mixture was transferred to a separatory funnel by adding diethyl ether (285 mL) in portions to dissolve the orange paste. The layers were separated, and the ethereal layer was washed with water and brine, dried over magnesium sulfate, filtered, and concentrated to afford 65.87 g of a viscous dark orange liquid. For purification, the crude material was taken up in ethyl acetate, transferred to a 1-liter round bottom flask and adsorbed onto Celite (45 g). The total mass of the Celite mixture was roughly 110 g. The desired regioisomer was isolated by medium pressure liquid chromatography (MPLC) on a Teledyne ISCO system. A column containing 120 g silica gel was

loaded with approximately 5.5 g of the Celite mixture and eluted with 10:1:1 hexanes/EtOAc/chloroform solvent system at a flow rate of 85 mL/min for 6.5 minutes. With the 25-mL test tubes, the desired compound typically eluted in fractions 10-21. The column was flushed with ethyl acetate (6.5 min) followed by a re-equilibration with the eluent system (5 min) to prepare for the next run. Twenty consecutive runs were sufficient to separate all the material. Concentration of the fractions afforded a yellow solid (24.2 g) which was further purified by recrystallization from hot ethyl acetate to afford **152** as fine yellow needles (16.76 g, 28%).

Data for **152**:

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

δ 8.00 (dd, J = 8.0, 1.0 Hz, 1H, CH(7)), 7.84 (d, *J* = 8.3 Hz, 1H, CH(4)), 7.76 (dd, *J* = 7.4, 1.1 Hz, 1H, CH(5)), 7.52 (d, *J* = 8.4 Hz, 1H, CH(3)), 7.49 (t, *J* = 7.5 Hz, 1H, CH(6)), 2.67 (s, 3H, CH_3(9)). ^{1}H NMR peak listings match those previously reported.[245]

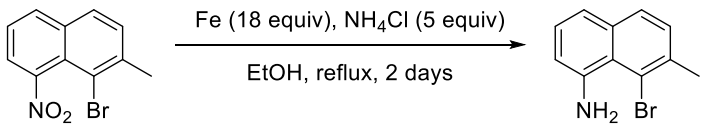
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 141.15, 134.87, 132.48, 130.47, 128.00, 124.27, 124.09, 123.57, 118.27, 25.17 (two signals overlap)

TLC: R_f = 0.40 (hexanes/EtOAc/$CHCl_3$, 10:1:1, UV/I_2)

m.p.: 102–104 °C

Synthesis of 8-bromo-7-methyl-1-aminonaphthalene (153)



152 **153**

The following procedure is a modification of a published procedure.[245] A 500-ml three-necked round bottom flask equipped with a mechanical stirrer, reflux condenser, and rubber septum was charged with absolute ethanol (200 mL). A needle was inserted into the flask and the ethanol was sparged with argon for one hour. Nitronaphthalene **152** (5.00 g), ammonium chloride (5.12 g), and iron powder (19.12 g) were added to the flask all at once and rinsed in with a small amount of additional ethanol. The mixture was heated to a vigorous reflux (bath temperature = 110

°C) and stirred at this temperature for 48 hours at 300 rpm. The reaction mixture was filtered through Celite and washed with absolute ethanol (800 mL). The red-brown solution was concentrated on a rotary evaporator to afford a brown solid. This solid was taken up in ethyl acetate (80 mL) and washed with saturated aqueous sodium bicarbonate (3 x 100 mL), water (2 x 100 mL), and brine (2 x 100 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo to afford **153** as a dry, free-flowing, easily handled brown solid which required no further purification (4.17 g, 94%).

Data for **153**:

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

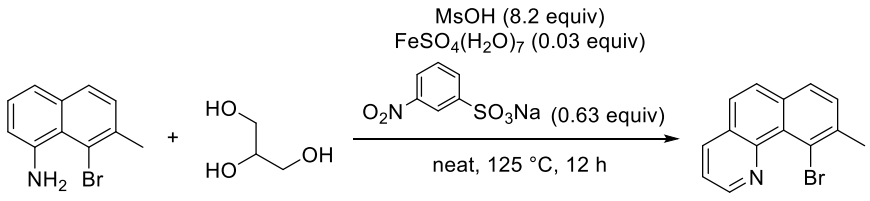
δ 7.60 (d, *J* = 8.3 Hz, 1H), 7.33 – 7.15 (m, 3H), 6.75 (dd, *J* = 6.2, 2.6 Hz, 1H), 5.25 (s, 2H, NH_2(12)), 2.55 (s, 3H, CH_3(9)). ^{1}H NMR peak listings match those previously reported.[245]

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

δ 143.50, 136.20, 136.12, 128.72, 128.64, 126.32, 121.75, 119.55, 119.23, 113.14, 25.55

TLC: R_f = 0.53 (hexanes/EtOAc/ $CHCl_3$, 10:2:1, UV/I_2)

Synthesis of 10-bromo-9-methyl-benzo[h]quinoline (154)



153 **154**

The following procedure is a modification of a published procedure.[165] A 100-ml three-necked round bottom flask equipped with a mechanical stirrer, reflux condenser, and addition funnel was flame-dried and placed under argon. The flask was charged with methanesulfonic acid (21.8 mL) and heated to 125 °C. Aminonaphthalene **153** (9.73 g, 41.21 mmol) was added portionwise, followed by sodium 3-nitrobenzenesulfonate salt (5.86 g, 26.03 mmol) and iron(II) sulfate heptahydrate (479.6 mg, 1.44 mmol). The mixture was allowed to stir for 10 minutes. The

addition funnel was charged with glycerol (9.1 ml, 123.5 mmol) which was added dropwise to the reaction at 125 °C. Stirring was continued at this temperature for three hours. The addition funnel was charged again with glycerol (9.1 ml, 123.5 mmol) which was added dropwise to the reaction at 125 °C. Stirring was continued at this temperature for 36 hours. The reaction was cooled to room temperature and diluted with water (160 mL). The solution was basified to a pH of 14 using aqueous NaOH (50% w/v). The mixture was transferred to a separatory funnel and the aqueous layer was extracted with diethyl ether (3 x 200 mL). Emulsions frequently formed during this workup but typically cleared upon standing for 10 minutes. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to afford a brown solid (9.74 g). The product was purified by silica gel chromatography (8 cm x 22 cm, 2.5% EtOAc in hexanes). Typically, 3 liters of eluent were allowed to pass through the column before collecting any fractions. When 50-mL test tubes were used, the product eluted in fractions 16-65. Removal of solvent afforded **154** as a white/off-white solid (6.75 g, 60%).

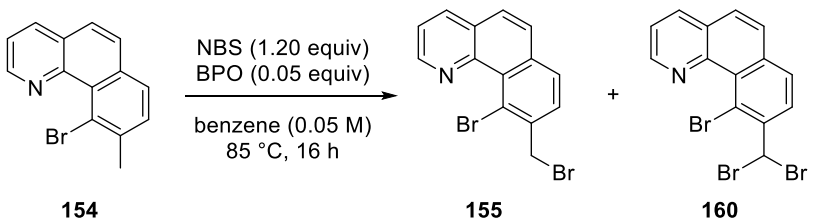
Data for **154**:

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

δ 9.09 (dd, *J* = 4.2, 1.9 Hz, 1H), 8.17 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.7 Hz, 1H), 7.65 (d, *J* = 8.7 Hz, 1H), 7.60 – 7.53 (m, 2H), 2.76 (s, 3H). ^{1}H NMR peak listings match those previously reported.[165]

TLC: R_f = 0.65 (hexanes/EtOAc/$CHCl_3$, 10:2:1, UV/I_2)

Synthesis of 10-bromo-9-(bromomethyl)-benzo[h]quinoline (155) and 10-bromo-9-(dibromomethyl)-benzo[h]quinoline (160)



154 **155** **160**

The following procedure is a modification of a published procedure.[163] An oven-dried 500-ml round bottom flask equipped with a stir bar was charged with benzo[h]quinoline **154** (3.00 g, 11.02 mmol), benzene (231 mL), and *N*-bromosuccinimide (2.35 g, 13.20 mmol). Benzoyl

peroxide (139.3 mg, 0.58 mmol) was added to the reaction mixture. The flask was equipped with a reflux condenser and refluxed (85 °C) for 16 hours. The reaction mixture was cooled to room temperature, diluted with dichloromethane (100 mL), filtered through a plug of Celite, and concentrated in vacuo to afford an off-white solid. This was taken up in dichloromethane, adsorbed onto Celite, split into three portions, and purified by silica gel column chromatography (5 cm x 16 cm, CH_2Cl_2 in hexanes gradient: 10% (500 mL) to 25% (500 mL) to 35% (500 mL) to 50% (500 mL) to 75% (1000 mL)). Typically, 1 liter of eluent was allowed to pass through the column before collecting fractions. When 50-mL test tubes were used, compound **160** typically eluted in fractions 13-20. Solvent removal afforded doubly brominated product **160** as an off-white solid (0.73 g). Compound **155** typically eluted in fractions 23-31. Solvent removal afforded singly brominated product **155** as an off-white solid (3.04 g, 78%).

Data for **155**:

^{1}H NMR: (500 MHz, CDCl3)

δ 9.12 (dd, *J* = 4.2, 1.9 Hz, 1H), 8.19 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.80 – 7.69 (m, 3H), 7.59 (dd, *J* = 8.0, 4.3 Hz, 1H), 5.05 (s, 2H). ^{1}H NMR peak listings match those previously reported.[163]

TLC: R_f = 0.47 (hexanes/CH_2Cl_2, 50:50, UV)

Data for **160**:

^{1}H NMR: (500 MHz, CDCl3)

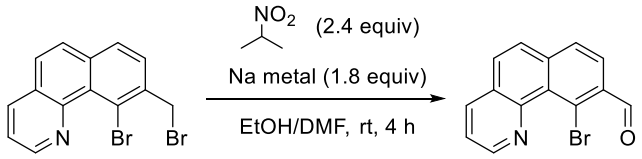
δ 9.10 (dt, *J* = 4.3, 1.3 Hz, 1H), 8.36 (d, *J* = 8.4 Hz, 1H), 8.22 – 8.17 (m, 1H), 7.99 – 7.93 (m, 1H), 7.85 (s, 1H), 7.77 (m, 2H), 7.60 (dd, *J* = 8.0, 4.2 Hz, 1H).

^{13}C NMR: (126 MHz, CDCl3)

δ 147.01, 146.61, 141.57, 136.67, 135.99, 129.62, 129.13, 128.32, 127.98, 127.86, 127.64, 122.31, 109.86, 43.05.

TLC: R_f = 0.61 (hexanes/CH_2Cl_2, 50:50, UV)

Synthesis of 10-bromo-9-carboxaldehyde-benzo[h]quinoline (148) from 155.



155 **148**

The following procedure is a modification of a published procedure.[163] A flame-dried 100-ml round bottom flask equipped with a stir bar was charged with absolute ethanol (30.5 mL) followed by sodium metal (0.36 g, 15.66 mmol). The mixture was stirred under argon until homogeneous. 2-nitropropane (1.84 ml, 20.51 mmol) was added to the solution of sodium ethoxide in ethanol. This solution was allowed to stir at room temperature for 30 minutes. In a separate flame-dried 200-ml round bottom flask, 10-bromo-9-(bromomethyl)-benzo[h]quinoline **155** (3.0 g, 8.55 mmol) was suspended in a mixture of DMF (30.5 mL) and absolute ethanol (30.5 mL). The solution of sodium ethoxide and 2-nitropropane was added dropwise to the reaction flask via cannula transfer. The reaction mixture was allowed to stir for 4 hours at room temperature. The appearance changed gradually from an off-white suspension to a hazy yellow solution. The mixture was poured into ice water (100 mL) and a large amount of fluffy white precipitate was formed. This was collected by vacuum filtration, washed with water, and rinsed with a solution of 20% diethyl ether in hexanes. The off-white solid **148** was dried for one hour under vacuum and required no additional purification (2.14 g, 88%).

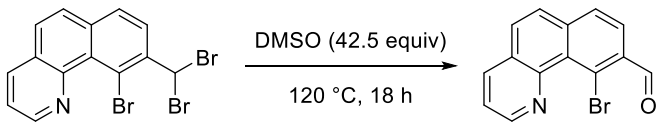
Data for **148**:

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

δ 10.92 (s, 1H), 9.13 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.22 (dd, *J* = 8.0, 1.8 Hz, 1H), 8.11 (d, *J* = 8.2 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 8.7 Hz, 1H), 7.79 (d, *J* = 8.7 Hz, 1H), 7.63 (dd, *J* = 8.0, 4.3 Hz, 1H).^{1}H NMR peak listings match those previously reported.[163]

TLC: R_f = 0.22 (hexanes/CH_2Cl_2, 50:50, UV)

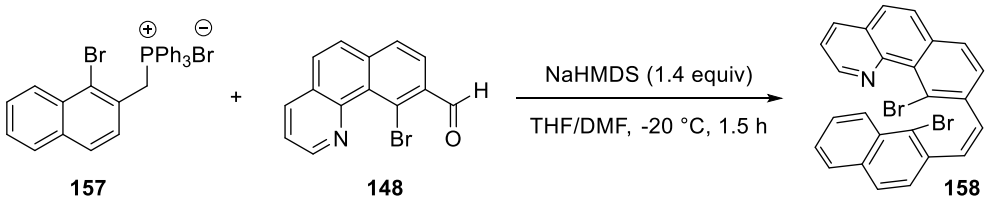
Synthesis of 10-bromo-9-carboxaldehyde-benzo[h]quinoline (148) from 160.



160 **148**

The author would like to acknowledge and thank Mr. Kuo Zhao (UIUC) for performing this reaction and keeping a detailed account of the procedure. A flame-dried 50-mL round bottom flask equipped with a stir bar was charged with geminal dibromide **160** (1.39 g, 3.23 mmol) and DMSO (9.75 mL). The flask was heated to 120 °C and maintained at this temperature for 18 hours. The reaction mixture darkened in color during this time. The mixture was allowed to cool to room temperature and water (15 mL) was added to the flask. The dark yellow solution was transferred to a separatory funnel and sat. aqueous $NaHCO_3$ was added until gas evolution ceased (20 mL). This resulted in some gas evolution. The aqueous layer was extracted with ethyl acetate (4 x 20 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford crude **148** as a yellow solid. The crude product was taken up in dichloromethane, adsorbed onto Celite, and purified by silica gel column chromatography (4 cm x 16 cm) using a 1:1 solution of CH_2Cl_2/hexanes as the eluent. Solvent removal afforded **148** as a white solid (0.67 g, 72%).

Synthesis of 10-bromo-9-[(1Z)-2-(1-bromo-2-naphthalenyl)ethenyl]-benzo[h]quinoline (158)



157 **148** **158**

The following procedure for the preparation of novel olefin **158** was adapted from previously published literature describing the synthesis of a similar compound.[163] A flame-dried 15-ml Schlenk flask equipped with a stir bar was charged with sodium hexamethyldisilylazide (2.60 g, 14.19 mmol) inside of a glove box. The flask was sealed, removed from the glove box,

and placed under argon. THF (14.5 mL) was added to dissolve the NaHMDS. In a separate flame-dried 500-ml two-necked round bottom flask, phosphonium bromide **157** (7.98 g, 14.19 mmol) and DMF (191 mL) were added. The suspension was cooled to an internal temperature of –20 °C using a 20% (w/w) aqueous calcium chloride and dry ice slush bath. Alternatively, a CryoCool could be used. The THF solution of NaHMDS was added dropwise via cannula transfer to the suspension of phosphonium bromide at –20 °C. The color immediately turned bright yellow and then orange. The mixture was allowed to stir for one hour while the temperature was maintained between –20 and –10 °C. In a third flame-dried 500-ml two-necked round bottom flask, aldehyde **148** (2.90 g, 10.14 mmol) and DMF (75 mL) were added. This solution was cooled to an internal temperature of –20 °C using the slush bath described above. The orange solution of phosphonium ylide was added dropwise via cannula transfer to the flask containing aldehyde at –20 °C. The reaction mixture was stirred at this temperature for 10 minutes before being quenched with water (323 mL) and allowed to room temperature. The mixture was poured into a separatory funnel and the aqueous layer was extracted with diethyl ether (3 x 300 mL). The combined organic layers were washed several times with a 5% (w/v) aqueous solution of lithium chloride, which assisted in the removal of DMF from the organic layer. The organic phase was washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to an off-white solid (8.29 g). The crude material was taken up in dichloromethane and adsorbed onto Celite. The Celite mixture was divided into three equal portions and purified by silica gel chromatography (5 cm x 15 cm, EtOAc/hexanes/Et_3N gradient, 15:85:1 (600 mL) to 30:70:1 (500 mL) to 60:40:1 (1000 mL)). When 50-mL test tubes were used, the product typically eluted in fractions 13-38. Solvent removal afforded **158** as an off-white solid (4.73 g, 95%) with a (*Z*:*E*) ratio of approximately 10:1 which is adequate for subsequent chemistry.

Data for **158**:

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

δ 9.14 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.37 (d, *J* = 8.6 Hz, 1H), 8.19 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.66 (m, 3H), 7.59 (m, 2H), 7.49 (m, 2H), 7.36 (d, *J* = 8.5 Hz, 1H), 7.29 (d, *J* = 11.7 Hz, 1H), 7.21 (d, *J* = 8.1 Hz, 1H), 7.15 (d, *J* = 11.7 Hz, 1H), 7.02 (d, *J* = 8.5 Hz, 1H).

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

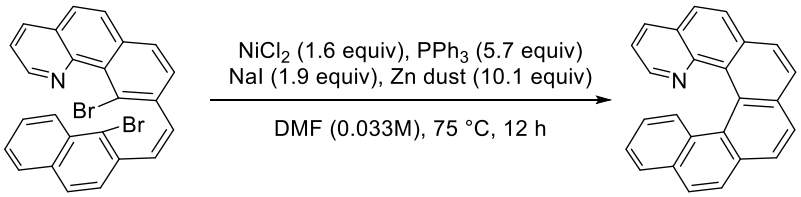
δ 146.96, 146.54, 140.11, 135.87, 135.63, 135.45, 134.37, 133.68, 132.51, 131.32, 130.70, 128.78, 128.60, 128.19, 128.00, 127.78, 127.73, 127.50, 127.26, 127.11, 126.73, 126.69, 124.27, 122.01, 121.20.

LRMS: (ESI, $[M+H]^+$)

488.0 (50), 489.0 (13), 490.0 (100), 491.0 (26), 492.0 (50), 493.0 (13), 494.0 (3)

TLC: R_f = 0.50 (EtOAc/hexanes/Et_3N, 20:80:1, UV)

Synthesis of 1-aza[6]helicene (137)



158 **137**

A flame-dried 300-ml two-necked round bottom flask equipped with a stir bar and reflux condenser was charged with DMF (116 mL) which was sparged before use. Then, the following solid reagents were added as quickly as possible: anhydrous nickel(II) chloride (0.86 g, 6.64 mmol), triphenylphosphine (6.16 g, 23.49 mmol), sodium iodide (1.14 g, 7.61 mmol), and zinc dust (2.72 g, 41.60 mmol). A small amount of DMF (8 mL) was used to rinse solids off the sides of the flask. Argon entering the condenser was kept at a high flow rate to exclude as much air as possible while adding solid reagents to the flask. The mixture was heated to 60 °C to generate the active catalyst. Right before the temperature reached 60 °C, the reaction mixture turned briefly from a grey to a yellow color and then darkened to a brownish-red color. Stirring was continued at 60 °C for one hour. Olefin **158** was added to the reaction mixture as a solid. The temperature was increased to 75 °C and the reaction was stirred at this temperature overnight. The color darkened further to nearly black. The reaction was cooled to room temperature, diluted with ether (100 mL) and filtered through Celite using a 10-micron fritted glass funnel. This filtration step was repeated until the solution no longer appeared murky. Solvent removal afforded 5.82 g of a dark oil. The crude material was taken up in dichloromethane, adsorbed onto Celite, and purified by silica gel chromatography (5 cm x 18 cm, acetone/hexanes/Et_3N gradient, 5:95:1 (1000 mL) to

7.5:92.5:1 (1000 mL) to 10:90:1 (500 mL)). When 50-mL test tubes were used, the desired product typically eluted in fractions 24-40. Removal of solvent and trituration with hexanes afforded **137** as a pale yellow powder (0.99 g, 74%).

Data for **137**:

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

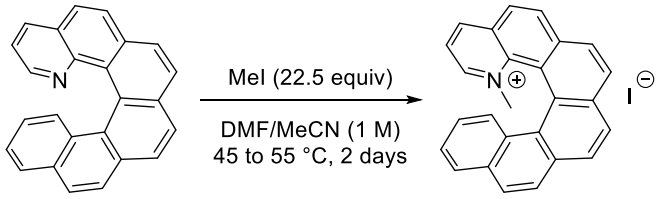
δ 8.14 – 8.09 (m, 2H), 8.05 – 7.96 (m, 4H), 7.96 – 7.91 (m, 3H), 7.89 – 7.83 (m, 2H), 7.60 – 7.55 (m, 1H), 7.19 (ddd, *J* = 8.0, 6.9, 1.2 Hz, 1H), 7.10 (dd, *J* = 8.0, 4.2 Hz, 1H), 6.60 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H). ^{1}H NMR peak listings match those previously reported for compound when prepared via an alternate route.[163]

LRMS: (ESI, $[M+H]^+$)

118.2 (45), 119.2 (3), 235.5 (3), 330.4 (100), 331.4 (26), 332.4 (3), 659.7 (10), 660.7 (5), 661.6 (2)

TLC: R_f = 0.42 (acetone/hexanes/Et_3N, 20:80:1, UV)

Synthesis of 1-aza[6]helicene-N-methyl iodide (163a)



137 **163a**

A 5-ml round bottom flask equipped with a stir bar and reflux condenser was flame-dried and placed under argon. Azahelicene **137** (100.2 mg, 0.30 mmol) was added to the vial. The system was evacuated and backfilled with argon. DMF (1.0 mL) and acetonitrile (1.0 mL) were added to the flask, followed by methyl iodide (0.28 ml, 4.56 mmol). The flask was heated to 45 °C and maintained at this temperature for 24 hours. The solution color turned from yellow to orange over time. An additional portion of methyl iodide was added (0.14 ml, 2.28 mmol) and the temperature was increased to 55 °C. The reaction was maintained at this temperature for an additional 24 hours. The mixture was allowed to cool to room temperature, diluted with methylene chloride, and transferred to a 25-mL recovery flask. Removal of solvents afforded 189.3 mg of a dark orange

oil. The crude product was purified by silica gel chromatography (2 cm x 10 cm). After an initial flush with 1:1 EtOAc/CH_2Cl_2 (50 mL), the desired salt was eluted using a MeOH/CH_2Cl_2 gradient of 1:99 (50 mL) to 3:97 (50 mL) to 5:95 (50 mL) to 7:93 (50 mL) to 10:90 (200 mL). When using 10-ml test tubes, the product typically eluted in fractions 21-58. Removal of solvents afforded a sticky orange solid, which upon trituration with hexanes afforded **163a** as a free-flowing bright orange powder (132.7 mg, 93%). This compound can be recrystallized from hot methanol if desired.

Data for **163a**:

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

δ 9.15 (dd, *J* = 8.1, 1.5 Hz, 1H), 8.93 (d, *J* = 5.2 Hz, 1H), 8.47 (d, *J* = 8.1 Hz, 1H), 8.40 (d, *J* = 8.4 Hz, 1H), 8.31 (d, *J* = 8.4 Hz, 1H), 8.26 – 8.18 (m, 3H), 8.12 – 8.03 (m, 2H), 7.98 – 7.88 (m, 2H), 7.32 – 7.27 (m, 1H), 6.63 (d, *J* = 8.4 Hz, 1H), 6.57 – 6.48 (m, 1H), 2.93 (s, 3H)

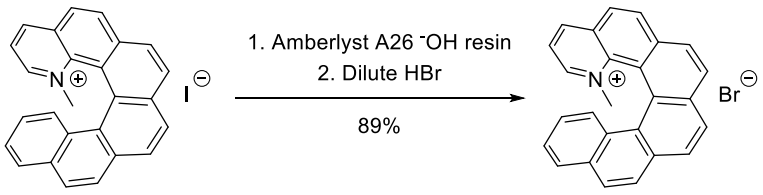
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 147.20, 144.86, 140.80, 136.64, 133.09, 132.75, 132.36, 131.90, 131.44, 129.87, 129.81, 129.70, 129.16, 127.44, 127.18, 127.16, 126.81, 126.70, 126.47, 126.39, 125.72, 123.80, 123.12, 122.68, 117.60, 50.17

LRMS: (ESI)

330.4 (26), 344.5 (100), 345.5 (30), 346.5 (5)

Synthesis of 1-aza[6]helicene-N-methyl bromide (163b)



163a **163b**

To a 1-cm diameter fritted glass column was added Amberlyst A26 (hydroxide form) resin suspended in distilled water (14.3 ml, 13.75 meq). Methanol (approximately 100 mL) was flushed through the column to remove water. Iodide salt **163a** was taken up in a 2:1 mixture of

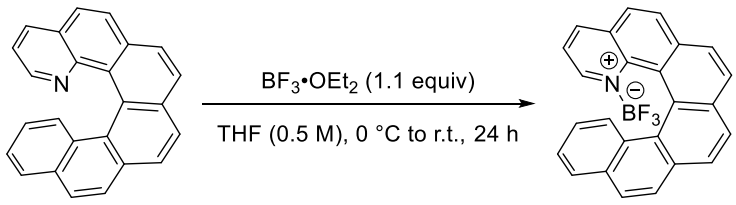
methanol:dichloromethane and added to the top of the column with a pipette. The solution was passed through the resin dropwise at a rate of 10 ml per hour. The resin was rinsed with a 1:1 solution of methanol:dichloromethane until the elution was complete (resin was visibly pink again with no orange discoloration). The volume of the collected fractions was reduced to about 20 ml on a rotary evaporator. Absence of remaining iodide salt was tested qualitatively by precipitation with 0.1 M aqueous $AgNO_3$ and 1.0 M aqueous HNO_3. To the stirred solution of hydroxide salt, 2.24 ml of a 0.25 M hydrobromic acid solution (prepared by combining 1 ml of commercial 8.9 M aqueous HBr with 34.6 ml of methanol) was added dropwise. The solution was stirred under argon overnight. Removal of solvent afforded crude **163b** as an orange/brown oil. The salt was purified by silica gel chromatography (2 cm x 10 cm). After an initial flush with 1:1 EtOAc/CH_2Cl_2 (75 mL), the desired salt was eluted using a MeOH/CH_2Cl_2 gradient of 1:99 (75 mL) to 3:97 (75 mL) to 5:95 (75 mL) to 7:93 (75 mL) to 10:90 (400 mL). When using 10-ml test tubes, the product typically eluted in fractions 34-80. Removal of solvents afforded a sticky brown solid, which upon trituration with hexanes afforded **163b** as a free-flowing brown powder (207.4 mg, 89%).

Data for **163b**:

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

δ 9.21 (d, *J* = 5.5 Hz, 1H), 9.07 (d, *J* = 7.9 Hz, 1H), 8.47 (d, *J* = 8.2 Hz, 1H), 8.39 (d, *J* = 8.4 Hz, 1H), 8.28 – 8.20 (m, 4H), 8.07 (m, 2H), 7.95 (m, 2H), 7.28 (m, 1H), 6.64 (d, *J* = 8.5 Hz, 1H), 6.52 (m, 1H), 3.00 (s, 3H)

Synthesis of 1-aza[6]helicene-BF_3 adduct (167)



137 **167**

A flame-dried 5-mL Schlenk flask equipped with a stir bar was charged with azahelicene **137** (99.2 mg, 0.30 mmol) and THF (0.6 mL). The flask was cooled to 0 °C. Boron trifluoride etherate solution was added dropwise at 0 °C and the reaction was stirred at this temperature for

15 minutes. The reaction was allowed to warm to room temperature and stirring was continued for 24 hours. Solvent was removed on a rotary evaporator to afford crude **167** as a yellow solid.

Data for **167**:

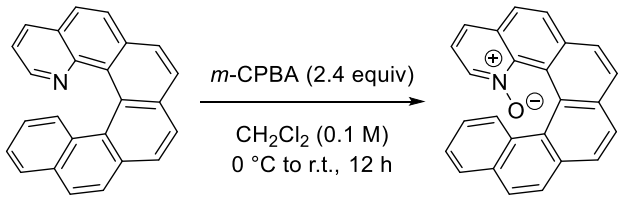
^{1}H NMR: (500 MHz, Methanol-d_4)

9.14 (d, J = 7.7 Hz, 1H), 8.51 (t, J = 9.0 Hz, 2H), 8.37 – 8.24 (m, 4H), 8.13 (s, 2H), 8.03 (d, J = 7.9 Hz, 1H), 8.00 – 7.97 (m, 1H), 7.81 – 7.76 (m, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.38 – 7.33 (m, 1H), 6.75 – 6.70 (m, 1H).

^{19}F NMR: (376 MHz, Acetonitrile-d_3)

–152.2 (not referenced).

Synthesis of 1-aza[6]helicene-N-oxide (168)



137 **168**

The following procedure is a modification of a published procedure.[163-164] A flame-dried 100-mL three-necked round bottom flask equipped with a stir bar was charged with azahelicene **137** (346.4 mg, 1.05 mmol) and dichloromethane (18 mL). The flask was cooled to 0 °C with an ice bath. *m*-CPBA (0.43 g, 2.48 mmol) was added to the reaction all at once at 0 °C. The mixture was allowed to warm gradually to room temperature and stirring was continued for 12 hours. The solution color changed from yellow to orange during this time. Although full conversion was not observed, the reaction was quenched by the addition of saturated aqueous potassium carbonate (18 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure (0.36 g). The crude product was taken up in dichloromethane, adsorbed onto Celite, and purified by silica gel column chromatography (2 cm x 18 cm) using an EtOAc/hexanes gradient: 10% (200 mL) to 25% (200 mL) to 50% (200 mL) to 75% (200 mL) to 100% (200 mL). When 10-mL test tubes were used, the desired product typically eluted in fractions

77-93. Removal of solvent and trituration with hexanes afforded N-oxide **168** as a fine yellow powder (139.7 mg, 38%). Additionally, 97.3 mg of starting azahelicene **137** was recovered from fractions 21-40 under these conditions.

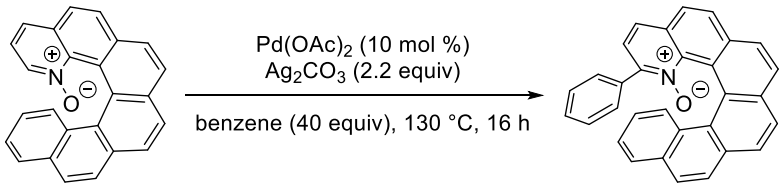
Data for **168**:

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

δ 8.23 (d, *J* = 8.1 Hz, 1H), 8.11 – 7.96 (m, 6H), 7.92 – 7.88 (m, 2H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.52 (dd, *J* = 6.3, 1.2 Hz, 1H), 7.18 (td, *J* = 7.3, 1.2 Hz, 1H), 7.06 (dd, *J* = 7.9, 6.2 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.57 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H). ^{1}H NMR peak listings match those previously reported.[163]

TLC: R_f = 0.11 (EtOAc/hexanes, 50:50, UV)

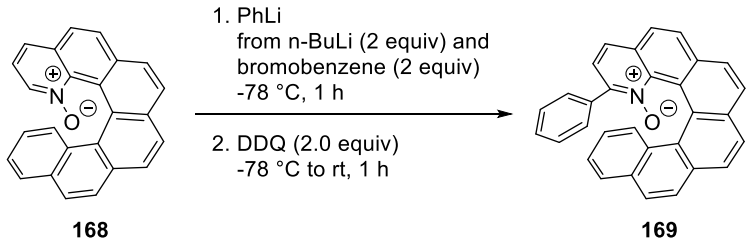
Synthesis of 2-phenyl-1-aza[6]helicene-N-oxide (169) by C–H activation.



168 **169**

A flame-dried dram-sized vial equipped with a stir bar was charged with *N*-oxide **168** (48.8 mg), palladium acetate (3.3 mg), and silver carbonate (90.2 mg). The vial was evacuated and placed under argon. Pre-sparged benzene (0.5 mL) was added to the vial. The vial was sealed and heated to 130 °C in an aluminum reaction block. This temperature was maintained for 16 hours with vigorous stirring. The reaction was cooled to room temperature, and the crude mixture was filtered through a plug of Celite and washed with ethyl acetate. The residue was concentrated under reduced pressure. The crude product was taken up in dichloromethane, adsorbed onto Celite, and purified by silica gel chromatography (2 cm x 18 cm) using an EtOAc/hexanes gradient: 10:90 (200 mL) to 25:75 (200 mL) to 50:50 (200 mL) to 75:25 (200 mL) to 100:0 (200 mL). When 10-ml test tubes are used, the product elutes in fractions 44-48. Solvent removal afforded **169** as a yellow powder (4.5 mg, 8%). Some starting material **168** was recovered in fractions 83-96 (7.9 mg).

Synthesis of 2-phenyl-1-aza[6]helicene-N-oxide (169) by organolithium addition.



A flame-dried 25-mL two-necked round bottom flask equipped with a stir bar was charged with dry THF (5.25 mL) and bromobenzene (110 μL, 1.01 mmol). The flask was cooled to an internal temperature of -78 °C with a dry ice and acetone slush bath. To the solution of bromobenzene, n-butyllithium was added dropwise at -78 °C (2.54 M, 400 μL, 1.01 mmol). The colorless solution was stirred for one hour at -78 °C. A separate flame-dried 100-mL two-necked flack equipped with a stir bar was charged with solid *N*-oxide **168** (174.4 mg, 0.50 mmol). The flask was evacuated and backfilled with argon. Dry THF (10.2 mL) was added via syringe. This flask was cooled as well to -78 °C. The organolithium reagent was cannulated to the reaction flask. The color turned dark purple immediately upon addition. The temperature was maintained at -78 °C for one hour. A solution of DDQ (237.4 mg, 1.05 mmol) in THF (10.5 mL) was added to the mixture dropwise. The mixture was allowed to warm slowly to room temperature over 45 minutes. The color changed from purple to dark green. The mixture was treated with water (30 mL) and 50% (w/v) aqueous NaOH solution (30 mL). The aqueous layer was extracted with dichloromethane (3 x 25 mL). The combined organic layers (yellow-green in color) were washed with water and brine, dried, filtered, and concentrated to afford a dark yellow solid (0.22 g). The crude product was purified by silica gel column chromatography (2 cm x 18 cm) with an EtOAc/hexanes gradient: 10% (100 mL) to 20% (400 mL) to 30% (400 mL) to 50% (200 mL). The first 200 mL of eluent were discarded before collecting fractions. When 10-mL test tubes were used, the desired product eluted in fractions 52-96. Removal of solvent and trituration with hexanes afforded **169** as a light green powder (114.4 mg, 54%).

Data for **169**:

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

δ 8.19 (d, *J* = 8.1 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 8.04 – 8.00 (m, 2H), 8.00 – 7.95 (m, 3H), 7.92 (m, 2H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.28 – 7.18 (m, 6H), 6.82 (dd, *J* = 7.9, 1.7 Hz, 2H), 6.67 (ddd, *J* = 8.1, 7.1, 1.4 Hz, 1H).

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

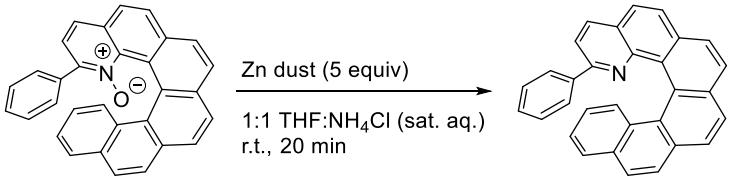
δ 146.38, 141.28, 134.29, 134.07, 132.48, 131.66, 131.08, 129.81, 129.57, 129.55, 129.44, 129.38, 128.86, 128.77, 128.66, 127.81, 127.78, 127.53, 127.32, 125.87, 125.81, 125.49, 125.42, 124.65, 123.76, 123.62, 123.49, 122.90, 120.57.

LRMS: (ESI, $[M+H]^+$)

406.2 (2), 422.2 (100), 423.2 (28), 424.2 (5), 496.2 (8), 499.2 (3), 749.3 (2)

TLC: R_f = 0.56 (EtOAc/hexanes, 50:50, UV)

Synthesis of 2-phenyl-1-aza[6]helicene (170)



169 **170**

A 25-mL round bottom flask equipped with a stir bar was charged with *N*-oxide **169** (99.8 mg, 0.24 mmol), THF (4 mL), and saturated aqueous ammonium chloride (4 mL). Zinc dust (82.6 mg, 1.26 mmol) was added to the vial and the reaction was stirred vigorously. The solution color lightened within a few minutes. Full conversion was reached in 30 minutes. The reaction was filtered through Celite, extracted with ether, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford a yellow solid (0.10 g). The product was purified by silica gel column chromatography (2 cm x 16 cm) using an acetone/hexanes/Et_3N gradient: 5:95:1 (200 mL) to 10:90:1 (200 mL) to 15:85:1 (200 mL) to 25:75:1 (200 mL). When 10-mL test tubes were used, the desired product eluted in fractions 29-68. Removal of solvent and trituration with hexanes afforded **170** as a pale yellow powder (79.7 mg, 83%).

Data for **170**:

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

δ 8.17 (d, *J* = 8.3 Hz, 1H), 8.09 (d, *J* = 8.2 Hz, 1H), 8.04 – 7.96 (m, 5H), 7.87 (dd, *J* = 8.5, 7.2 Hz, 2H), 7.79 (d, *J* = 8.6 Hz, 1H), 7.67 (d, *J* = 8.3 Hz, 1H), 7.51 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.25 – 7.19 (m, 1H), 7.18-7.12 (m, 4H), 7.01 (ddd, *J* = 7.9, 6.7, 1.2 Hz, 1H), 6.62 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H).

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

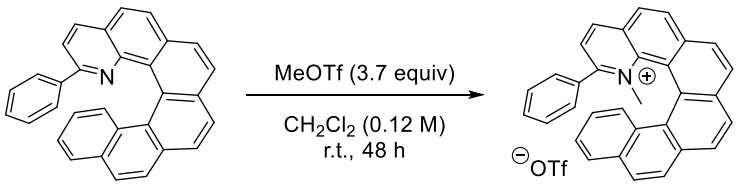
δ 153.28, 145.72, 138.17, 136.23, 133.53, 133.45, 132.29, 131.48, 131.08, 130.35, 129.20, 128.83, 128.54, 128.12, 127.89, 127.78, 127.28, 127.02, 126.77, 126.21, 126.20, 126.04, 125.29, 125.09, 124.50, 124.34, 117.26 (29 expected, 27 observed; two sets of overlapping signals).

LRMS: (ESI, $[M+H]^+$)

111.3 (8), 225.3 (8), 226.3 (2), 265.4 (2), 347.5 (2), 391.5 (5), 406.5 (100), 407.5 (60), 408.5 (10)

TLC: R_f = 0.64 (EtOAc/hexanes, 20:80, UV)

Synthesis of 2-phenyl-1-aza[6]helicene-N-methyl triflate (166c)



170 **166c**

A flame-dried dram-sized vial equipped with a stir bar was charged with azahelicene **170** (50.3 mg, 0.12 mmol). The vial was evacuated and backfilled with argon. Dichloromethane (1.0 mL) was added to vial with a syringe, followed by methyl triflate (50 μL, 0.46 mmol). The solution color immediately turned from yellow to orange. The reaction was allowed to stir at room temperature for 48 hours, and the color darkened further to a rusty orange color. The reaction mixture was transferred directly to a silica gel column using a pipette, rinsing with a minimal amount of dichloromethane. The product was purified by column chromatography (1 cm x 8 cm).

After an initial flush with 1:1 EtOAc/CH_2Cl_2 (100 mL), the desired salt was eluted with a MeOH/CH_2Cl_2 gradient: 5:95 (100 mL) to 10:90 (100 mL). When 10-mL test tubes were used, the desired product eluted in fractions 13-24. Solvent removal and trituration with hexanes afforded **166c** as a bright orange solid (52.0 mg, 74%).

Data for **166c**:

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

δ 9.37 (d, *J* = 8.2 Hz, 1H), 8.46-8.42 (m, 3H), 8.27 (d, *J* = 8.2 Hz, 1H), 8.23-8.14 (m, 3H), 8.13-8.04 (m, 2H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.51-7.45 (m, 1H), 7.41-7.35 (m, 3H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.76-6.67 (m, 3H), 2.61 (s, 3H).

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

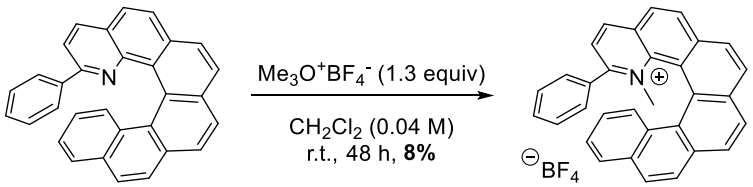
δ 158.87, 146.85, 142.84, 137.39, 133.06, 133.04, 132.94, 132.69, 131.86, 131.85, 131.43, 129.69, 129.62, 129.33, 129.30, 129.15, 128.56, 127.94, 127.86, 127.72, 127.56, 127.42, 127.40, 126.76, 126.38, 125.04, 124.22, 123.36, 118.41, 50.85.

LRMS: (ESI)

111.9 (18), 122.8 (4), 175.8 (3), 344.0 (3), 391.2 (2), 420.1 (100), 421.1 (76), 422.1 (13), 450.1 (4)

TLC: R_f = 0.39 (MeOH/CH_2Cl_2, 10:90, UV)

Synthesis of 2-phenyl-1-aza[6]helicene-N-methyl tetrafluoroborate (166d)



170 **166d**

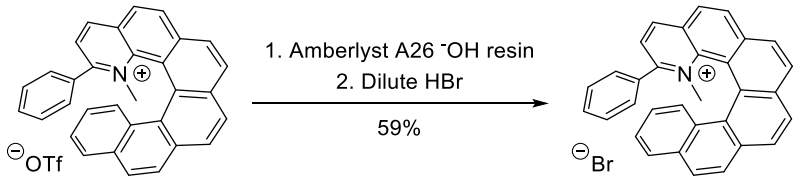
A flame-dried dram-sized vial equipped with a stir bar was charged with trimethyloxonium tetrafluoroborate (4.7 mg, 0.03 mmol) inside of a glove box. The vial was fitted with a cap with a Teflon septum and brought out of the glove box. Dichloromethane (0.2 mL) was added to the vial with a syringe, followed by a solution of azahelicene **170** (9.9 mg, 0.02 mmol) in dichloromethane (0.4 mL). The color immediately turned from a pale yellow to a brighter yellow. The reaction was stirred at room temperature for 48 hours. The reaction mixture was transferred directly to a silica

gel column using a pipette, rinsing with a minimal amount of dichloromethane. The product was purified by column chromatography (1 cm x 8 cm). After an initial flush with 1:1 EtOAc/CH_2Cl_2 (100 mL), the desired salt was eluted with a MeOH/CH_2Cl_2 gradient: 5:95 (100 mL) to 10:90 (100 mL). When 10-mL test tubes were used, the desired product eluted in fractions 13-24. Solvent removal and trituration with hexanes afforded **166d** as a dull orange solid (1.0 mg, 8%). Some starting material **170** was also recovered in fractions 1-3 (3.1 mg).

Data for **166d**:

TLC: R_f = 0.32 (MeOH/CH_2Cl_2, 10:90, UV)

Synthesis of 2-phenyl-1-aza[6]helicene-N-methyl bromide (166b)



166c **166b**

To a 1-cm diameter fritted glass column was added Amberlyst A26 (hydroxide form) resin suspended in distilled water (1.9 ml, 1.8 meq). Methanol (approximately 50 mL) was flushed through the column to remove water. The triflate salt **166c** was taken up in a 2:1 mixture of methanol:dichloromethane and added to the top of the column with a pipette. The solution was passed through the resin dropwise at a rate of 10 ml per hour. The resin was rinsed with a 1:1 solution of methanol:dichloromethane until the elution was complete (resin was visibly pink again with no orange discoloration). The combined fractions were concentrated on a rotary evaporator, and absence of remaining triflate salt was confirmed by ^{19}F NMR. To the stirred solution of hydroxide salt, 320 μL of a 0.25 M hydrobromic acid solution (prepared by combining 1 ml of commercial 8.9 M aqueous HBr with 34.6 ml of methanol) was added dropwise. The solution was stirred under argon overnight, and the color changed from a grimy yellow to a pale orange solution. Removal of solvent afforded crude **166b** as an orange oil. The salt was purified by silica gel chromatography (1 cm x 10 cm). After an initial flush with 1:1 EtOAc/CH_2Cl_2 (100 mL), the desired salt was eluted using a MeOH/CH_2Cl_2 gradient of 5:95 (100 mL) to 10:90 (100 mL). When using 10-mL test tubes, the product typically eluted in fractions 27-32. Removal of solvents

afforded a sticky orange solid, which upon trituration with TBME afforded **166b** as a free-flowing rusty orange powder (23.0 mg, 59%).

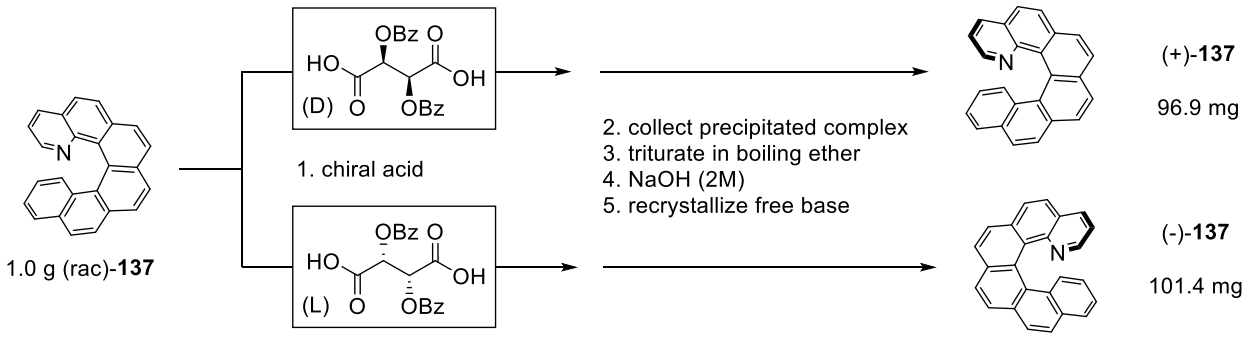
Data for **166b**:

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

δ 9.95 (d, *J* = 8.2 Hz, 1H), 8.77 (d, *J* = 8.4 Hz, 1H), 8.44 (dd, *J* = 8.3, 4.4 Hz, 2H), 8.27 (d, *J* = 8.2 Hz, 1H), 8.23 – 8.05 (m, 5H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.52 – 7.45 (m, 1H), 7.42 – 7.35 (m, 3H), 7.02 (d, *J* = 8.6 Hz, 1H), 6.78 – 6.70 (m, 3H), 2.63 (s, 3H).

TLC: R_f = 0.22 ($MeOH/CH_2Cl_2$, 10:90, UV)

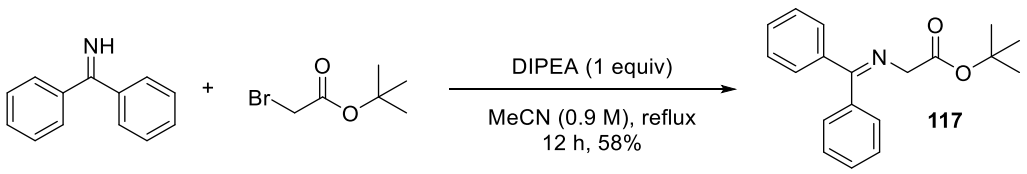
Resolution of 1-aza[6]helicene (137)



Part 1: Isolation of (+)-1-aza[6]helicene. A racemic sample of 1-aza[6]helicene **137** (1.00 g) was dissolved in warm diethyl ether (150 mL) in a 600-mL beaker containing a large stir bar. A solution of (+)-dibenzoyl-D-tartartic acid (8.0 g) in warm diethyl ether (60 mL) was poured into the solution of azahelicene. The volume was reduced from 210 mL to approximately 30 mL under stirring and heating. When nearly all of the diethyl ether was boiled away, a substantial amount of a fine vivid yellow solid precipitated out of solution. At this point, the beaker was cooled to 0 °C to encourage additional precipitation. The solid was collected by vacuum filtration. Additional precipitate was observed forming in the filtrate, and this was harvested as well and combined with the solid already collected (1.02 g total). The azahelicene-tartaric acid adduct was transferred to a 250-mL round bottom flask and suspended in diethyl ether (50 mL). The flask was equipped with a reflux condenser and the mixture was refluxed for two hours. The flask was cooled to 0 °C and the yellow solid was again collected by vacuum filtration (0.60 g). This solid was transferred to an Erlenmeyer flask and basified by the addition of 2M aqueous NaOH (50 mL). The yellow disappeared upon

mixing. The mixture was transferred to a separatory funnel (rinsing with diethyl ether), and the aqueous layer was extracted with diethyl ether (3 x 50 mL). The combined ethereal extracts were concentrated under reduced pressure to afford a pale yellow solid (0.18 g, e.r. = 95:5). The solid was recrystallized from diethyl ether and pentane to afford enantiopure (+)-1-aza[6]helicene (+)-**137** (96.9 mg, e.r. > 99:1). **Part 2: Isolation of (–)-1-aza[6]helicene.** The mother liquors and filtrates from the above steps were basified, extracted, and concentrated as previous described to afford slightly enriched (–)-1-aza[6]helicene (–)-**137** (e.r. = 27:73). This sample was dissolved in warm diethyl ether (150 mL) in a 600-mL beaker containing a large stir bar. A solution of (-)-dibenzoyl-L-tartartic acid (7.5 g) in warm diethyl ether (60 mL) was poured into the solution of azahelicene. The volume was reduced from 210 mL to approximately 30 mL under stirring and heating. When nearly all of the diethyl ether was boiled away, a substantial amount of a fine vivid yellow solid precipitated out of solution. At this point, the beaker was cooled to 0 °C to encourage additional precipitation. The solid was collected by vacuum filtration. Additional precipitate was observed forming in the filtrate, and this was harvested as well and combined with the solid already collected (1.23 g total). The azahelicene-tartaric acid adduct was transferred to a 250-mL round bottom flask and suspended in diethyl ether (50 mL). The flask was equipped with a reflux condenser and the mixture was refluxed for two hours. The flask was cooled to 0 °C and the yellow solid was again collected by vacuum filtration (0.77 g). This solid was transferred to an Erlenmeyer flask and basified by the addition of 2M aqueous NaOH (50 mL). The yellow disappeared upon mixing. The mixture was transferred to a separatory funnel (rinsing with diethyl ether), and the aqueous layer was extracted with diethyl ether (3 x 50 mL). The combined ethereal extracts were concentrated under reduced pressure to afford a pale yellow solid (0.24 g, e.r. = 4:96). The solid was recrystallized from diethyl ether and pentane to afford enantiopure (–)-1-aza[6]helicene (–)-**137** (101.4 mg, e.r. > 1:99). **HPLC Conditions.** To determine the enantiomeric ratio, an analytical HPLC sample was prepared by dissolving 0.5 mg azahelicene in 1.0 mL hexane (a few drops of isopropanol were also added to aid solubility). The sample was run on a chiral stationary phase AD-H analytical column (5 μL injection, 90:10 hexanes/isopropanol, 0.8 mL/minute, temperature not regulated, λ = 254 nm, 20 minute run time). The (+)-enantiomer eluted at t = 6.54 minutes. The (-)-enantiomer eluted at t = 9.86 minutes.

Synthesis of *tert*-butyl-*N*-(diphenylmethylene)glycinate (117)



A flame-dried 200-mL round bottom flask equipped with a stir bar and reflux condenser was charged with *tert*-butyl bromoacetate (5.30 mL, 35.9 mmol) and acetonitrile (40 mL). Benzophenone imine (6.00 mL, 35.8 mmol) and DIPEA (6.20 mL, 35.6 mmol) were added to the flask. The mixture was refluxed for 12 hours. The reaction was cooled to room temperature, and acetonitrile was removed on a rotary evaporator. The residue was partitioned between water (100 mL) and diethyl ether (200 mL). The aqueous layer was extracted with ether (3 x 200 mL). The combined ethereal extracts were concentrated on a rotary evaporator until a large amount of precipitate formed. This was collected by vacuum filtration (5.86 g, white solid). The filtrate was concentrated under reduced pressure to afford additional solid (3.00 g, yellow). Both batches of solid were recrystallized separately from isopropanol to afford **117** as small white crystals (6.16 g total, 58%).

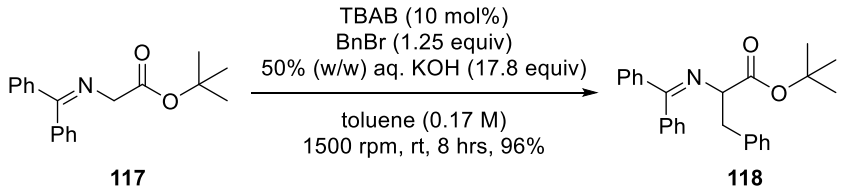
Data for **117**:

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

δ 7.68-7.63 (m, 2H), 7.49-7.43 (m, 3H), 7.42-7.36 (m, 1H), 7.36-7.30 (m, 2H), 7.20-7.16 (m, 2H), 4.12 (s, 2H), 1.46 (s, 9H).

TLC: R_f = 0.50 (TBME/hexanes, 20:80, UV)

Synthesis of *tert*-butyl-2-((diphenylmethylene)amino)-3-phenylpropanoate (118)



A dram-sized vial was charged with *t*-butyl-*N*-(diphenylmethylene)glycinate **117** (99.9 mg, 0.34 mmol) and tetra-*n*-butylammonium bromide (15.5 mg, 0.05 mmol). The vial was equipped with a stir bar and fitted with a cap containing a Teflon septum. The vial was evacuated and placed under argon. Toluene (2 mL) was added via syringe, followed by benzyl bromide (50.2 μL, 0.42 mmol). The mixture was allowed to stir for 10 minutes at room temperature (1500 rpm) before 660 μL of a 50% (w/w) aqueous potassium hydroxide solution was added to the vial. Stirring was continued for 8 hours. The organic layer was removed by syringe, concentrated under reduced pressure, and adsorbed onto Celite. The crude product was purified by silica gel column chromatography (2 cm x 12 cm) using a TBME/hexanes gradient: 2% (100 mL) to 4% (100 mL) to 8% (100 mL) to 10% (100 mL). When 10-mL fractions were used, the desired product eluted in fractions 31-44. Solvents were removed on a rotary evaporator to afford **118** which still contained hexanes even after extended drying periods (124.9 mg, 96%).

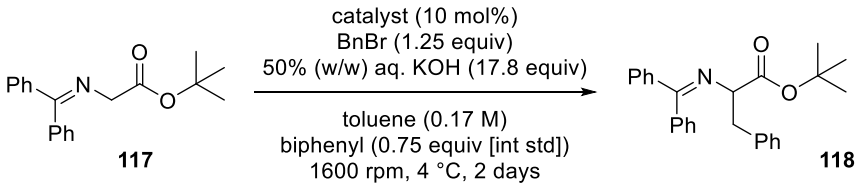
Data for **118**:

^{1}H NMR: (499 MHz, $CDCl_3$)

δ 7.59-7.55 (m, 2H), 7.40 – 7.24 (m, 6H), 7.21-7.15 (m, 3H), 7.07-7.04 (m, 2H), 6.64-6.57 (m, 2H), 4.11 (dd, *J* = 9.5, 4.5 Hz, 1H), 3.23 (dd, *J* = 13.5, 4.5 Hz, 1H), 3.16 (dd, *J* = 13.5, 9.5 Hz, 1H), 1.44 (s, 9H).

TLC: R_f = 0.64 (TBME/hexanes, 20:80, UV)

General Procedure: Alkylation of 117 to 118 (with HPLC monitoring).



A dram-sized vial (acid and base washed, oven dried) was charged with *t*-butyl-*N*-(diphenylmethylene)glycinate **117** (100 mg, 0.34 mmol) and phase transfer catalyst (0.03 mmol). The vial was equipped with a stir bar and fitted with a cap containing a Teflon septum. The vial was evacuated and placed under argon. To the vial was added 800 μL of a solution of benzyl bromide in toluene (69.3 mg, 0.41 mmol, 86.6 mg/mL) followed by 800 μL of a standard solution of biphenyl in toluene (40.8 mg, 0.26 mmol, 50.97 mg/mL). An additional 400 μL of toluene was added to the vial. The vial was maintained at 4 °C and stirred at 800 rpm for 60 minutes to allow the temperature to equilibrate. The stir rate was increased to 1600 rpm and 660 μL of a 50% (w/w) aqueous potassium hydroxide solution was added to the vial. To take aliquots from the reaction, stirring was briefly paused and the layers were allowed to separate. A 25-μL syringe was used to withdraw approximately 5 μL from the toluene layer. This was quenched into a vial containing 1 mL acetonitrile (HPLC grade) with 5 μL acetic acid. This solution was passed through a silica plug (2.5 cm) in a pipette column prior to HPLC analysis. **HPLC Conditions.** The sample was run on an achiral stationary phase Zorbax analytical column (5 μL injection, water:acetonitrile gradient elution (70:30 to 10:90 over 10 minutes, hold for 5 minutes, then 70:30 for 2 minutes), 0.6 mL/minute, temperature not regulated, λ = 254 nm, 18 minute run time). The yield of product **118** was determined by comparison of the area of the product peak (t = 12.8 minutes) to the biphenyl peak (t = 9.8 minutes) using the following equation:

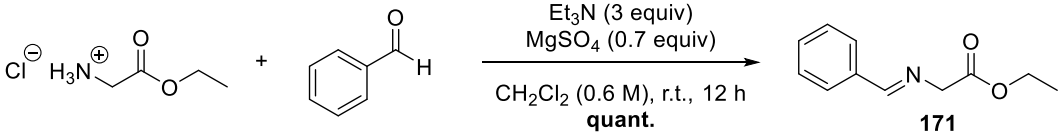
$$1.131971 = \frac{mmol\ product\ \times area\ of\ standard}{mmol\ standard\ \times area\ of\ product}$$

Isolation. Isolation of the alkylation product **118** was only necessary when wanting to measure the e.r. of an enantioselective reaction. In these cases, the organic layer was removed from the reaction vessel using a pipette and filtered through a plug of sodium sulfate. The toluene was

removed by rotary evaporation. The crude product was taken up in dichloromethane, adsorbed onto Celite, and purified by silica gel column chromatography (2 cm x 12 cm) using a TBME/hexanes gradient: 2% (100 mL) to 4% (100 mL) to 8% (100 mL) to 10% (100 mL). When 10-mL fractions were used, the desired product **118** eluted in fractions 36-42. Solvents were removed on a rotary evaporator.

HPLC Conditions. To determine the enantiomeric ratio of **118**, an analytical HPLC sample was prepared by dissolving 2.0 mg product in 1.0 mL hexane (a few drops of isopropanol were also added to aid solubility). The sample was run on a chiral stationary phase IB-3 analytical column (5 μL injection, 99:1 hexanes:isopropanol, 1.0 mL/minute, temperature not regulated, λ = 230 nm, 5 minute run time). The enantiomers eluted at 2.6 minutes and 3.0 minutes. Alternatively, the sample can be run on a chiral stationary phase Whelk analytical column (10 μL injection, 95:5 hexanes:isopropanol, 0.8 mL/minute, temperature not regulated, λ = 254 nm, 20 minute run time). The enantiomers eluted at 7.2 minutes and 14.3 minutes, in the opposite order (i.e. a sample gave an e.r. of 46:54 on the IB-3 column and an e.r. of 54:46 on the Whelk column).

Synthesis of ethyl-2-(phenylmethylene)aminoacetate (171)



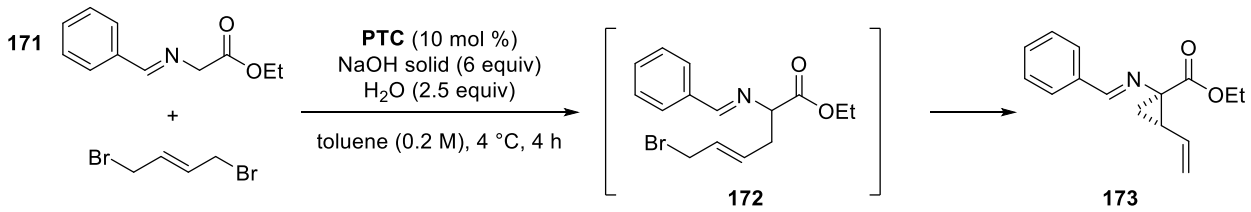
A 300-mL three-necked round bottom flask was charged with glycine ethyl ester hydrochloride (14.99 g, 107.43 mmol), anhydrous magnesium sulfate (6.00 g, 49.85 mmol), and dichloromethane (125.0 mL). Triethylamine (29.95 mL, 214.85 mmol) was added to the flask all at once. Benzaldehyde (7.28 mL, 71.62 mmol) was added dropwise and the reaction was stirred at room temperature overnight. The solution was filtered to remove magnesium sulfate and concentrated under reduced pressure. The residue (wet-looking white solid) was diluted with ether (100 mL) and washed with brine (6 x 50 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated to afford **171** as a thin pale yellow liquid requiring no further purification (14.05 g, quantitative).

Data for **171**:

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

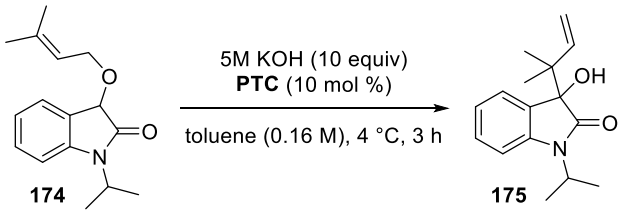
δ 8.30 (s, 1H), 7.80-7.77 (m, 2H), 7.47-7.40 (m, 3H), 4.40 (s, 2H), 4.24 (q, *J* = 7.0 Hz, 2H), 1.31 (t, *J* = 7.0 Hz, 3H).

General Procedure: Conversion of 171 to 173 under PTC conditions.



A flame-dried dram-sized vial equipped with a stir bar and was charged with catalyst (0.01 mol). The vial was sealed with a cap with a Teflon septum, evacuated, and placed under argon. A chilled solution of 2-(phenylmethylene)glycinate **171** in toluene (50 mg in 300 μL) was added to the vial. The mixture was stirred (1500 rpm) for 30 minutes at 4 °C. A chilled solution of trans-1,4-dibromo-2-butene in toluene (73 mg in 300 μL) was added to the vial. Solid sodium hydroxide (62.8 mg) was quickly added, followed by water (12 μL, 0.65 mmol). To take a reaction aliquot, stirring was briefly stopped and the layers were allowed to separate. A 20-μL aliquot was taken from the toluene layer. The sample was placed under vacuum to remove toluene and taken up in $CDCl_3$ for NMR analysis to assess conversion of **171** to **173**.

General Procedure: [2,3]-Wittig Rearrangement of 174 to 175 under PTC conditions.[142]



A dram-sized vial equipped with a stir bar and screw-on Teflon septum cap was charged with catalyst (0.01 mmol). The vial was evacuated and backfilled with argon twice. To the vial was added a solution of **174** (20.0 mg, 0.08 mmol) in pre-sparged toluene (0.2 mL). An additional

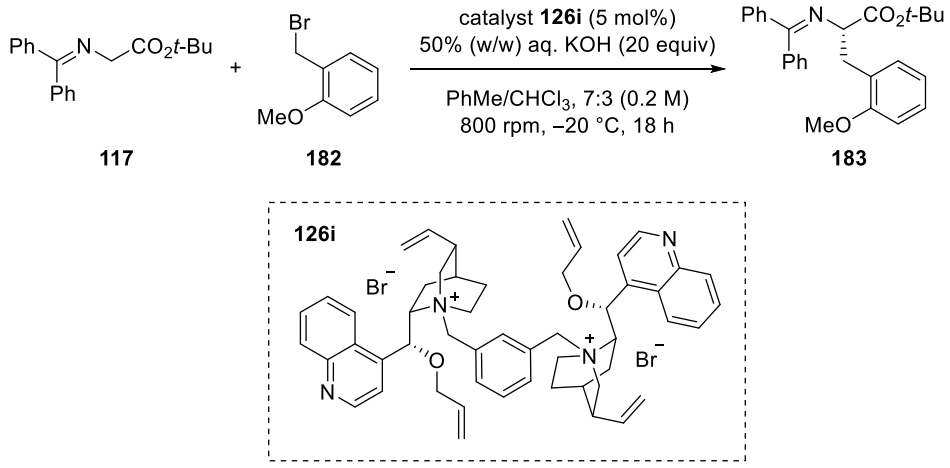
portion of pre-sparged toluene (0.28 mL) was added to the vial. The vial was stirred at 1500 rpm at 4 °C to allow the temperature to equilibrate. Stirring was halted and 5 M aqueous KOH was added (0.15 mL, 0.8 mmol). The reaction was stirred at 1500 rpm for 3 hours at 4 °C. Conversion to **175** is assessed by TLC (hexanes/EtOAc, 80:20).

Experimental for Appendix C

Literature Preparations

The following compounds were prepared by literature methods and characterization data matched those previously reported: 1-(bromomethyl)-2-methoxybenzene **182**[246] and catalyst **126i**.[204]

***tert*-Butyl (*S*)-2-((Diphenylmethylene)amino)-3-(2-methoxyphenyl)propanoate (183)**



A 500-mL, three-necked, round bottomed flask equipped with a mechanical stirrer, septum, and argon inlet adapter was charged with *tert*-butyl glycine benzophenone imine **117** (6.75 g, 22.9 mmol), phase transfer catalyst **126i** (1.07 g, 1.15 mmol, 0.05 equiv), toluene (71 mL), chloroform (31 mL), and *ortho*-anisyl bromide **182** (6.62 g, 32.9 mmol, 1.4 equiv). The flask was cooled to –20 °C using a Cryo-Cool. With vigorous stirring, 50% (w/w) aq. potassium hydroxide (34.1 mL, 13.4 M, 457 mmol, 20 equiv) was added dropwise, making sure to maintain the internal temperature below –16 °C. After the addition was complete, the biphasic mixture was stirred vigorously (800 rpm) for 18 h at –20 °C. Full conversion was observed by TLC (hexanes/TBME, 80:20). Stirring was stopped and the reaction was allowed to warm to 25 °C. The mixture was partitioned between water (200 mL) and CH_2Cl_2 (200 mL), and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford the crude product. The product was purified by chromatography (silica gel) using a hexanes/TBME gradient elution (98:2 to 96:4 to 94:6 to 92:8

to 90:10) to afford 6.80 g (72% yield, 98:2 e.r.) of **183** as a yellow powder. The product was recrystallized from TBME to afford 4.74 g (50% yield, >99:1 e.r.) of **183** as white crystals.

Data for **183**:

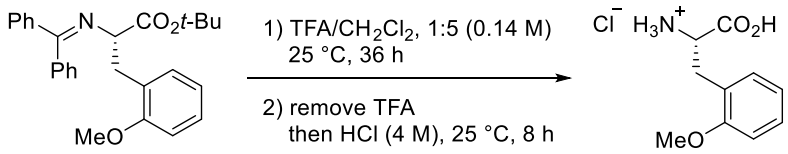
^{1}H NMR: (500 MHz, $CDCl_3$)

7.54 (d, J = 7.2 Hz, 2H), 7.37 – 7.26 (m, 6H), 7.16 – 7.07 (m, 2H), 6.78 (app. t, 1H), 6.72 – 6.60 (m, 3H), 4.28 (dd, J = 9.2, 4.4 Hz, 1H), 3.50 (s, 3H), 3.35 (dd, J = 13.1, 4.5 Hz, 1H), 3.02 (dd, J = 13.0, 9.2 Hz, 1H), 1.44 (s, 9H).

TLC: R_f 0.50 (hexanes/TBME, 80:20)

HPLC: t_R 6.4 min (2%); t_R 8.9 min (98%) (Chiralpak IB-3, hexanes/*i*-PrOH, 98:2, 1.0 mL/min, 254 nm)

2-methoxy-(*S*)-phenylalanine hydrochloride (184)



183 **184**

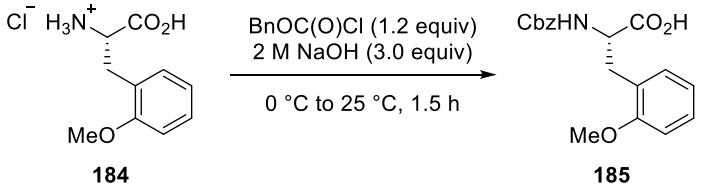
A 250-mL, round bottomed flask equipped with a stir bar was charged with imino ester **183** (4.74 g, 11.4 mmol) and CH_2Cl_2 (66 mL), resulting in a pale yellow solution. Trifluoroacetic acid (13 mL) was added to the solution, which immediately turned a bright yellow color. The solution was stirred at 25 °C for 36 h. Full conversion to the TFA adduct was assessed by ^{1}H NMR. Volatile components were removed by rotary evaporation to afford a yellow oil. Next, 4 M HCl (48 mL) was added to the flask, and the mixture was stirred at 25 °C for 8 h. The mixture was transferred to a separatory funnel, and the aqueous layer was washed with Et_2O (3 x 75 mL). The combined organic phases were discarded, and the aqueous layer was concentrated by rotary evaporation to afford 2.51 g (95%) of **184** as a white solid. No further purification was required.

Data for **184**:

^{1}H NMR: (500 MHz, CD_3OD)

7.32 (app. td, *J* = 8.3, 1.7 Hz, 1H), 7.19 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.02 (d, *J* = 8.3 Hz, 1H), 6.93 (td, *J* = 7.4, 1.0 Hz, 1H), 4.23 (dd, *J* = 7.9, 5.4 Hz, 1H), 3.88 (s, 3H), 3.38 (dd, *J* = 14.2, 5.4 Hz, 1H), 3.08 (dd, *J* = 14.2, 7.9 Hz, 1H).

_N_-Cbz-(_S_)-2-methoxyphenylalanine (185)



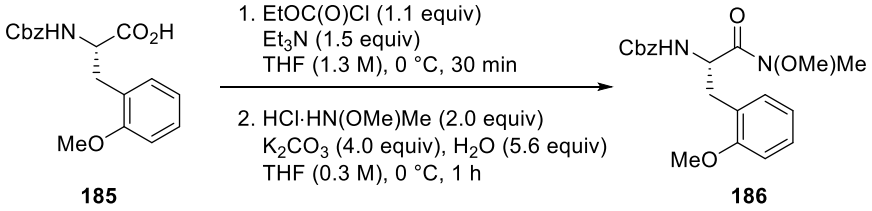
A 100-mL, round bottomed flask equipped with a stir bar was charged with amino acid HCl salt **184** (1.64 g, 7.08 mmol) and 2 M NaOH (10.6 mL). The flask was cooled to 0 °C using an ice bath. To the colorless, turbid solution was added benzyl chloroformate (1.2 mL, 8.5 mmol, 1.2 equiv) dropwise at 0 °C. A white suspension resulted. Water (10 mL) was added to thin the mixture, and stirring was continued for 30 min at 0 °C followed by 1 h at 25 °C. Upon reaching 25 °C, a colorless solution resulted. The solution was transferred to a separatory funnel, diluted with water, and washed with Et_2O. The basic aqueous phase was acidified to pH = 4 with 4 M HCl and the resulting white suspension was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to afford 2.31 g (99%) of **185** as a viscous liquid requiring no further purification. Yield is uncorrected for residual EtOAc.

Data for **185**:

^{1}H NMR: (500 MHz, CD_3OD)

7.35 – 7.19 (m, 6H), 7.11 (dd, *J* = 7.4, 1.3 Hz, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 6.83 (t, *J* = 7.4 Hz, 1H), 5.04 – 4.96 (m, 2H), 4.49 (dd, *J* = 9.4, 5.1 Hz, 1H), 3.83 (s, 3H), 3.26 (dd, *J* = 13.6, 5.1 Hz, 1H), 2.87 (dd, *J* = 13.5, 9.5 Hz, 1H).

_N_-methoxy-_N_-methyl-(_S_)-_N'_-Cbz-2-methoxyphenylalaninamide (186)



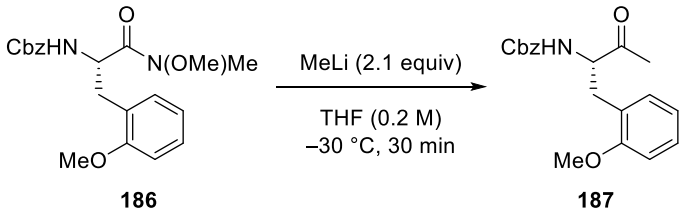
A 50-mL, round bottomed flask equipped with a stir bar was charged with carboxylic acid **185** (2.13 g, 6.47 mmol), THF (5 mL), and Et_3N (1.35 mL, 1.5 equiv). The resulting pale yellow solution was cooled to 0 °C using an ice bath. Ethyl chloroformate (0.68 mL, 7.11 mmol, 1.1 equiv) was added dropwise at 0 °C. The resulting white suspension was stirred for 30 min at 0 °C. In a separate 50-mL flask equipped with a stir bar, the following reagents were added: *N*,*O*-dimethylhydroxylamine hydrochloride (1.28 g, 13.1 mmol, 2.0 equiv), water (0.68 mL), potassium carbonate (3.57 g, 25.8 mmol, 4.0 equiv), and THF (17 mL). The mixture was stirred for 5 min at 25 °C. Stirring was stopped, and the excess potassium carbonate was allowed to settle to the bottom of the flask. The clear, colorless solution of *N*,*O*-dimethylhydroxylamine was decanted and added dropwise to the first flask (still at 0 °C). The white suspension was maintained at 0 °C for 1 h. Full conversion was observed by TLC (hexanes/EtOAc, 50:50). The reaction mixture was filtered through Celite to remove precipitates, and the filter cake was rinsed with Et_2O. The filtrate was partitioned between Et_2O (50 mL) and 10% aq. Na_2CO_3 (50 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (2 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 2.01 g of crude **186**. The product was purified by chromatography (silica gel) using a hexanes/EtOAc gradient elution (90:10 to 75:25 to 50:50 to 25:75) to afford 1.70 g (71%) of **186**. Yield is uncorrected for residual EtOAc.

Data for **186**:

^{1}H NMR: (500 MHz, $CDCl_3$)
7.36 – 7.19 (m, 6H), 7.08 (dd, *J* = 7.4, 1.5 Hz, 1H), 6.91 – 6.80 (m, 2H), 5.55 (d, *J* = 9.3 Hz, 1H), 5.08 – 4.96 (m, 3H), 3.82 (s, 3H), 3.77 (s, 3H), 3.18 (s, 3H), 3.04 – 2.95 (m, 2H).

TLC: R_f 0.43 (hexanes/EtOAc, 50:50, CAM)

(*S*)-*N*-Cbz-2-amino-1-(2-methoxy)phenyl-3-butanone (187)



186 **187**

An oven-dried, 100-mL, Schlenk flask equipped with a stir bar was charged with amide **186** (1.70 g, 4.56 mmol) and THF (22 mL). The resulting solution was cooled to –30 °C using a Cryo-Cool. A solution of methyllithium (1.6 M in Et_2O, 6.0 mL, 9.6 mmol, 2.1 equiv) was added dropwise at C. The resulting yellow solution was stirred at –30 °C for 30 min. Full conversion was observed by TLC (hexanes/EtOAc, 50:50). The reaction was quenched by pouring into a 0.04 M HCl solution (300 mL H_2O + 12 mL 1 N HCl) which had been pre-cooled to 0 °C. The biphasic solution was stirred for 2 min at 0 °C. The layers were separated, and the aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 1.55 g of crude **187**. The product was purified by chromatography (silica gel) using a hexanes/EtOAc gradient elution (90:10 to 75:25 to 50:50) to afford 1.12 g (75%) of **187** as an oil, which solidified upon trituration (sonication) with hexanes.

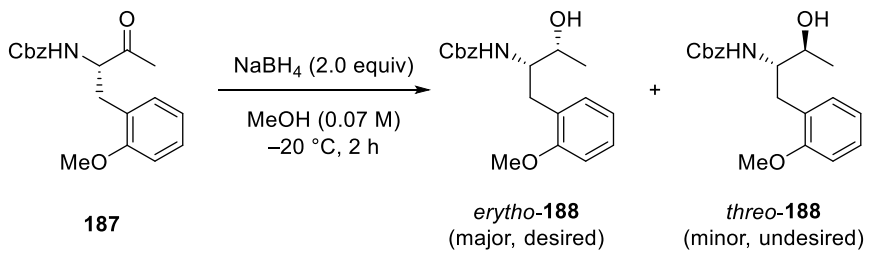
Data for **187**:

^{1}H NMR: (500 MHz, $CDCl_3$)
7.39 – 7.27 (m, 5H), 7.23 (td, *J* = 8.1, 1.7 Hz, 1H), 7.04 (dd, *J* = 7.4, 1.4 Hz, 1H), 6.91 – 6.80 (m, 2H), 5.51 (d, *J* = 6.8 Hz, 1H), 5.12 – 4.99 (m, 2H), 4.59 (q, *J* = 6.7 Hz, 1H), 3.79 (s, 3H), 3.15 – 2.96 (m, 2H), 2.21 (s, 3H).

TLC: R_f 0.70 (hexanes/EtOAc, 50:50)

HPLC: t_R 7.4 min (2%); t_R 8.5 min (98%) (Chiralpak IB-3, hexanes/*i*-PrOH, 90:10, 1.0 mL/min, 220 nm)

_N_-Cbz-(2_R_,3_S_)-3-amino-4-(2-methoxyphenyl)butan-2-ol (188)



187

erytho-**188** (major, desired)

threo-**188** (minor, undesired)

An oven-dried, 200-mL, Schlenk flask equipped with a stir bar was charged with amino ketone **187** (0.90 g, 2.75 mmol) and methanol (45 mL). The resulting colorless solution was cooled to –20 °C and $NaBH_4$ (0.21 g, 5.5 mmol, 2.0 equiv) was added in one portion. The reaction was stirred for 2 h at –20 °C. Full conversion was observed by TLC (hexanes/EtOAc, 50:50). The reaction was quenched by the addition of water (90 mL). Most of the methanol was removed by rotary evaporation, and the remaining mixture was partitioned between EtOAc and water. The layers were separated. The aqueous phase was extracted with EtOAc (1 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.88 g (97% yield, 73:27 d.r.) of **188** as a white solid. The diastereomers were separated by chromatography (silica gel) using a hexanes/EtOAc gradient elution (90:10 to 80:20 to 70:30 to 60:40 to 50:50 to 25:75) to afford 0.16 g (18%) of undesired *threo*-**188** (>95:5 d.r.) and 0.54 g (59%) of desired *erythro*-**188** (>98:2 d.r.).

Data for *erythro*-**188**:

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

7.38 – 7.26 (m, 5H), 7.25 – 7.20 (m, 1H), 7.11 (dd, J = 7.4, 1.6 Hz, 1H), 6.94 – 6.83 (m, 2H), 5.14 (d, J = 6.3 Hz, 1H), 5.07 – 4.99 (m, 2H), 3.96 – 3.75 (m, 5H), 3.12 (d, J = 5.1 Hz, 1H), 2.88 (dd, J = 13.7, 8.9 Hz, 1H), 2.78 (dd, J = 13.9, 4.5 Hz, 1H), 1.22 (d, J = 6.3 Hz, 3H).

TLC: R_f 0.42 (hexanes/EtOAc, 50:50, UV)

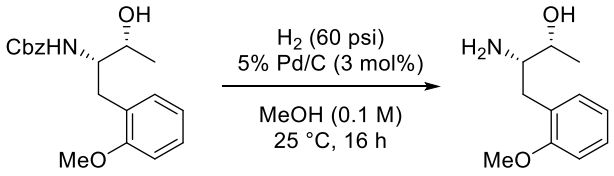
Data for *threo*-**188**:

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

7.39 – 7.29 (m, 5H), 7.25 – 7.19 (m, 2H), 6.99 – 6.86 (m, 2H), 5.22 (d, *J* = 8.9 Hz, 1H), 5.09 (s, 2H), 3.85 (s, 3H), 3.75 – 3.64 (m, 2H), 2.93 (dd, *J* = 13.3, 9.1 Hz, 1H), 2.85 (dd, *J* = 13.4, 6.7 Hz, 1H), 2.78 (d, *J* = 3.9 Hz, 1H), 1.13 (d, *J* = 6.3 Hz, 3H).

TLC: R_f 0.47 (hexanes/EtOAc, 50:50, UV)

(2*R*,3*S*)-3-Amino-4-(2-methoxyphenyl)butan-2-ol (189)



erytho-**188** (2*R*,3*S*)-**189**

A 50-mL, recovery flask equipped with a stir bar was charged with carbamate **188** (0.56 g, 1.71 mmol) and methanol (13 mL). Argon gas was bubbled through the solution for 10 min, and then 5% palladium on carbon (0.11 g, 0.05 mmol Pd, 0.03 equiv) was added in one portion. The flask was placed in a bomb which was charged with hydrogen gas (60 psi). The reaction was stirred at 25 °C for 16 h. The bomb was opened, and full conversion was observed by TLC (hexanes/EtOAc, 50:50). The reaction mixture was filtered through a finely-packed Celite pad to remove the catalyst, and the filtrate was concentrated to afford 0.32 g (98%) of **189** as an oil, which solidified upon drying. No further purification was required.

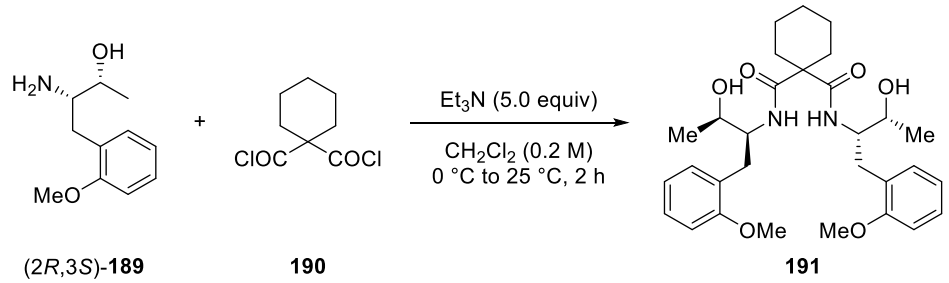
Data for **189**:

^{1}H NMR: (500 MHz, CD_3OD)

7.24 – 7.18 (m, 1H), 7.15 (dd, *J* = 7.4, 1.4 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.89 (t, *J* = 7.4 Hz, 1H), 3.83 (s, 3H), 3.69 (qd, *J* = 6.4, 4.4 Hz, 1H), 3.05 (dt, *J* = 9.0, 4.6 Hz, 1H), 2.91 (dd, *J* = 13.4, 5.1 Hz, 1H), 2.53 (dd, *J* = 13.4, 8.8 Hz, 1H), 1.21 (d, *J* = 6.4 Hz, 3H).

TLC: R_f 0.00 (hexanes/EtOAc, 50:50, CAM)

_N_1,_N_1'-Bis[(1_S_,2_R_)-2-hydroxy-1-[(2-methoxyphenyl)methyl]propyl]cyclohexane-1,1-dicarboxamide (191)



(2*R*,3*S*)-**189** **190** **191**

An oven-dried, 100-mL, Schlenk flask was charged with amino alcohol **189** (595 mg, 3.05 mmol), CH_2Cl_2 (15 mL), and Et_3N (2.1 mL, 15.2 mmol, 5.0 equiv). The mixture was cooled to 0 °C. A solution of freshly distilled cyclohexane-1,1-dicarbonyl dichloride **190** (319 mg, 1.5 mmol, 0.5 equiv) in CH_2Cl_2 (5 mL) was added dropwise to the reaction flask. The reaction mixture was allowed to warm to 25 °C and stirring was continued for 2 h. Full conversion was observed by ^{1}H NMR analysis of a reaction aliquot or by TLC (hexanes/EtOAc, 50:50). The mixture was diluted with CH_2Cl_2, transferred to a separatory funnel, and washed with 1 N HCl (2 x 10 mL). The organic phase was then washed with sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.74 g of crude **191** as a yellow foam. The product was purified by chromatography (silica gel) using a hexanes/EtOAc gradient elution (75:25 to 50:50 to 25:75 to 0:100) to afford 579.9 mg (72%) of **191** as a white solid (after trituration with hexanes).

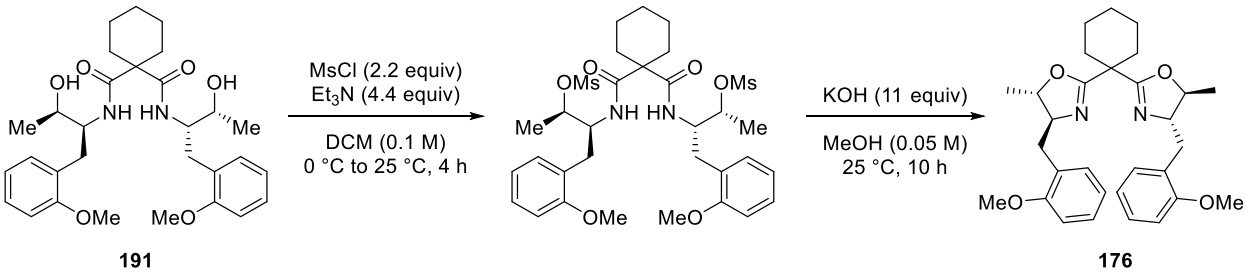
Data for **191**:

^{1}H NMR: (500 MHz, CD_3OD)

7.19 – 7.13 (m, 2H), 7.11 (dd, *J* = 7.4, 1.5 Hz, 2H), 6.94 – 6.84 (m, 4H), 6.82 (td, *J* = 7.4, 0.9 Hz, 2H), 4.16 – 4.08 (m, 2H), 3.83 (s, 6H), 3.81 – 3.75 (m, 2H), 2.95 (dd, *J* = 13.8, 3.9 Hz, 2H), 2.69 (dd, *J* = 13.8, 11.2 Hz, 2H), 1.74 – 1.60 (m, 2H), 1.48 – 1.36 (m, 2H), 1.18 (d, *J* = 6.5 Hz, 6H), 1.15 – 1.08 (bm, 4H), 1.05 – 0.94 (bm, 2H).

TLC: R_f 0.06 (hexanes/EtOAc, 50:50, CAM)

(4*S*,4'*S*,5*S*,5'*S*)-2,2'-(Cyclohexane-1,1-diyl)bis(4-(2-methoxybenzyl)-5-methyl-4,5-dihydrooxazole) (176)



A flame-dried, 100-mL, Schlenk flask equipped with a stir bar was charged with bis(amide) **191** (574 mg, 1.09 mmol), CH_2Cl_2 (10 mL), and Et_3N (0.67 mL, 4.8 mmol, 4.4 equiv). The solution was cooled to 0 °C, and mesyl chloride (0.19 mL, 2.4 mmol, 2.2 equiv) was added dropwise. The reaction was allowed to warm to 25 °C over 1 h, and stirring was continued at this temperature for 3 h. Full conversion was observed by TLC (hexanes/EtOAc, 50:50) or by ^{1}H NMR analysis of a reaction aliquot. The mixture was poured in sat. aq. NH_4Cl (30 mL), and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to afford 700.6 mg of crude bis(mesylate) as an off-white solid, which was used directly in the next reaction.

A 50-mL, round bottomed flask equipped with a stir bar was charged with crude bis(mesylate) and a 4% (w/v) solution of KOH in methanol (720 mg potassium hydroxide pellets in 18 mL methanol). The resulting yellow suspension was stirred at 25 °C for 10 h. Full conversion was observed by TLC (hexanes/EtOAc, 50:50) or by ^{1}H NMR analysis of a reaction aliquot. The reaction mixture was diluted with water and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 492.9 mg of crude **176** as a yellow residue. The product was purified by chromatography (silica gel) using a hexanes/EtOAc gradient elution (90:10 to 70:30 to 50:50 to 25:75) to afford 362.7 mg (76% over 2 steps) of bisoxazoline **176** as a yellow oil.

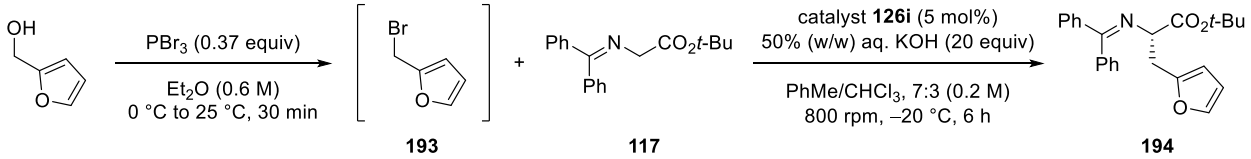
Data for **176**:

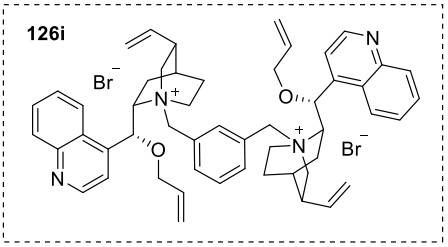
^{1}H NMR: (500 MHz, CD_3OD)

7.21 – 7.13 (m, 4H), 6.87 (t, *J* = 7.4 Hz, 2H), 6.84 (d, *J* = 8.2 Hz, 2H), 4.31 (p, *J* = 6.1 Hz, 2H), 3.95 (dt, *J* = 10.0, 5.2 Hz, 2H), 3.80 (s, 6H), 3.13 (dd, *J* = 13.3, 4.9 Hz, 2H), 2.56 (dd, *J* = 13.3, 9.2 Hz, 2H), 2.15 – 2.06 (m, 2H), 1.98 – 1.89 (m, 2H), 1.76 – 1.64 (m, 2H), 1.52 – 1.41 (m, 4H), 1.01 (d, *J* = 6.2 Hz, 6H).

TLC: R_f 0.56 (hexanes/EtOAc, 50:50, UV)

(*S*)-*tert*-Butyl 2-(Benzhydrylideneamino)-3-(2-furyl)propanoate (194)





A flame-dried, 100-mL, recovery flask equipped with a stir bar was charged with freshly distilled furfuryl alcohol (1.08 mL, 12.4 mmol) and Et_2O (17 mL). The colorless solution was cooled to 0 °C with an ice bath. In a separate flask, neat PBr_3 (0.43 mL, 4.55 mmol, 0.37 equiv) was added to Et_2O (5 mL) to form a 0.9 M solution. The PBr_3 solution was added dropwise to the reaction flask at 0 °C over 10 min. A small amount of blue/black solid was observed on the bottom of the flask. The solution itself remained colorless. The ice bath was removed, and the mixture was allowed to stand (no stirring) for 30 min at 25 °C, before decanting into a clean Erlenmeyer flask. The flask was cooled to 0 °C, and aq. KOH (5 M, 5.4 mL) was slowly added (*exothermic*). The aqueous phase became quite dark in color, while the organic phase became a turbid, pale yellow color. The layers were separated, and the organic phase was treated with a few pellets of solid KOH, which removed the cloudy appearance. The pale, yellow solution of furfuryl bromide **193** in Et_2O should be used immediately. According to Zanetti, "the solution may be estimated to

contain 70% of the original furfuryl alcohol as bromide." By this estimation, the solution is 0.4 M (8.8 mmol of **193** in 22 mL Et_2O).

A 250-mL, three-necked, round bottomed flask equipped with a mechanical stirrer, septum, and argon inlet adapter was charged with glycine imine **117** (2.00 g, 6.77 mmol) and catalyst **126i** (0.32 g, 0.34 mmol, 0.05 equiv). The solution of furfuryl bromide **193** just prepared (0.4 M, 22 mL, 8.8 mmol, 1.3 equiv) was diluted with toluene (47 mL), and Et_2O was removed by rotary evaporation (25 °C, 30 mmHg). Following this solvent swap, the solution of furfuryl bromide in toluene was added to the reaction flask, along with chloroform (20 mL). The mixture was cooled to –20 °C using a Cryo-Cool. To this rapidly stirred solution was added 50% (w/w) aq. KOH (10 mL, 135 mmol, 20 equiv) dropwise over several minutes. The biphasic mixture was stirred rapidly (600 rpm) for 6 h, at which point it was determined by TLC (hexanes/TBME, 80:20) that the reaction had stalled before reaching full conversion. Stirring was stopped and the reaction was allowed to warm to 25 °C. The mixture was partitioned between water (100 mL) and CH_2Cl_2 (100 mL), and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford the crude product. The product was purified by chromatography (silica gel) using a hexanes/TBME gradient elution (98:2 to 96:4 to 94:6 to 92:8 to 90:10) to afford 1.49 g (59% yield, 95:5 e.r.) of **194** as an oil. The product is contaminated with a small quantity of benzophenone, which is easily removed after the next step.

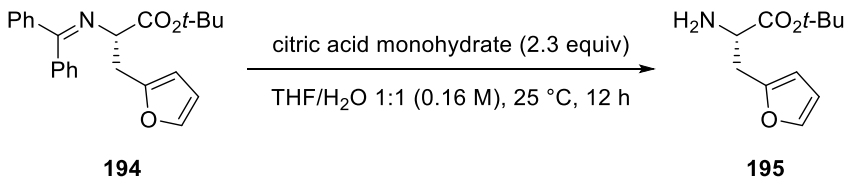
Data for **194**:

^{1}H NMR: (500 MHz, $CDCl_3$)
7.61 – 7.56 (m, 2H), 7.41 – 7.34 (m, 4H), 7.33 – 7.28 (m, 2H), 7.24 – 7.21 (m, 1H), 6.87 (d, J = 7.1 Hz, 2H), 6.23 (dd, J = 3.1, 1.9 Hz, 1H), 6.01 (d, J = 3.1 Hz, 1H), 4.22 (dd, J = 8.9, 4.4 Hz, 1H), 3.29 – 3.16 (m, 2H), 1.44 (s, 9H).

TLC: R_f 0.57 (hexanes/TBME, 80:20)

HPLC: t_R 7.5 min (95%); t_R 13.3 min (5%) (Whelk, hexanes/*i*-PrOH, 95:5, 0.8 mL/min, 254 nm)

(*S*)-*tert*-Butyl 2-Amino-3-(2-furyl)propanoate (195)



194 **195**

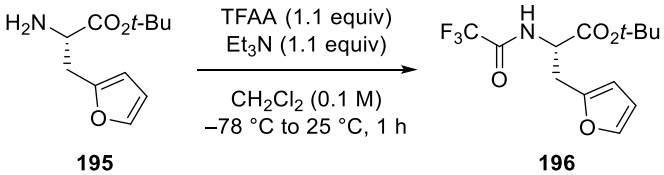
A 100-mL, round bottomed flask equipped with a stir bar was charged with imine **194** (1.49 g, 3.97 mmol), THF (12.6 mL), and a solution of citric acid monohydrate (1.95 g, 9.28 mmol, 2.3 equiv) in water (12.6 mL). The reaction was stirred (800 rpm) at 25 °C for 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 86:14). [**Note:** The disappearance of **194** and the generation of benzophenone is monitored by TLC. The product **195** remains in the acidic aqueous phase.] The reaction mixture was diluted with 1 M HCl (15 mL) and transferred to a separatory funnel. The aqueous layer was washed with Et_2O (2 x 30 mL). The aqueous layer was basified by the addition of 3 M NaOH, resulting in a white precipitate. The aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 691.4 mg (83%) of **195** as a thin, yellow oil requiring no further purification.

Data for **195**:

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

7.35 – 7.31 (m, 1H), 6.31 – 6.28 (m, 1H), 6.13 – 6.09 (m, 1H), 3.67 – 3.62 (m, 1H), 3.04 (dd, *J* = 14.9, 5.4 Hz, 1H), 2.96 (dd, *J* = 14.9, 7.0 Hz, 1H), 1.45 (s, 9H).

(*S*)-*tert*-Butyl 3-(2-Furyl)-2-[(2,2,2-trifluoroacetyl)amino]propanoate (196)



195 **196**

A flame-dried, 100-mL, two-necked, round bottomed flask equipped with a stir bar was charged with amino ester **195** (690 mg, 3.27 mmol), CH_2Cl_2 (25 mL), and Et_3N (0.50 mL, 3.59 mmol, 1.1 equiv). The flask was cooled to –78 °C, and trifluoroacetic anhydride (0.50 mL, 3.59

mmol, 1.1 equiv) was added dropwise, maintaining the internal temperature below –65 °C. After the addition, the cold bath was removed and the mixture was allowed to warm to 25 °C. Stirring was continued for 30 min, at which point full conversion was observed by TLC (hexanes/EtOAc, 80:20). The reaction was quenched by the addition of sat. aq. $NaHCO_3$ (30 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with 1 M HCl and sat. aq. $NaHCO_3$, dried, filtered, and concentrated to afford 1.01 g (quant.) of **196** as a yellow oil requiring no further purification.

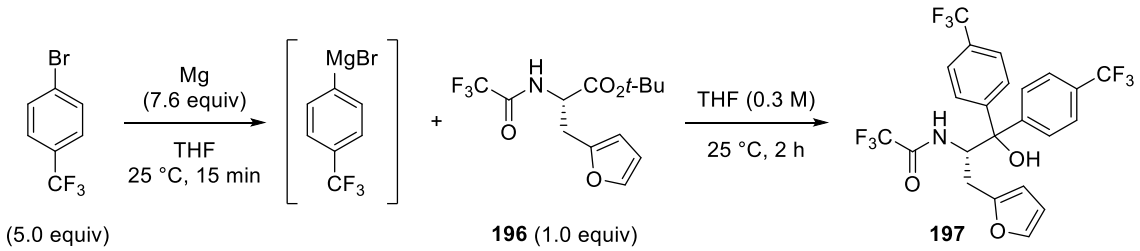
Data for **196**:

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

7.33 – 7.32 (m, 1H), 6.96 (bs, 1H), 6.34 – 6.26 (m, 1H), 6.09 (d, J = 3.2 Hz, 1H), 4.69 (dt, J = 7.4, 5.1 Hz, 1H), 3.33 – 3.17 (m, 2H), 1.47 (s, 9H).

TLC: R_f 0.53 (hexanes/EtOAc, 80:20)

(*S*)-2,2,2-Trifluoro-*N*-[1-(2-furylmethyl)-2-hydroxy-2,2-bis[4-(trifluoromethyl)phenyl]ethyl] acetamide (197)



The following procedure is not optimized. A flame-dried, 25-mL, two-necked round bottomed flask equipped with a stir bar was charged with mechanically activated magnesium turnings (607 mg, 25.1 mmol) and a chip of iodine. The flask was evacuated and placed under argon. Dry THF (6.3 mL) was added to the flask, resulting in a yellow solution. Neat 4-(trifluoromethyl)bromobenzene (2.32 mL, 16.6 mmol) was added dropwise to the flask, and the mixture was stirred at room temperature under argon. Within 1 minute, the yellow color disappeared, and a significant exotherm was observed as the solution turned a dark red color [**Note**: The use of a reflux condenser and/or external cooling source during this operation is recommended.] The reaction mixture was stirred for 15 min and used immediately. A solution of amino ester **196** (1.01 g, 3.29 mmol) in THF (6.3 mL) was added dropwise to the pot of Grignard

reagent at 25 °C. The mixture was stirred at 25 °C for 2 h. Full conversion was observed by TLC (hexanes/EtOAc, 80:20). The reaction was quenched by the addition of sat. aq. NH_4Cl. The mixture was poured into water and CH_2Cl_2. The resulting brown-red emulsion was filtered through a pad of Celite. The biphasic filtrate was transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 1.71 g of crude **197** as a brown, oily solid. The product was purified by chromatography (silica gel) using a hexanes/EtOAc/Et_3N gradient elution (95:5:1 to 90:10:1 to 80:20:1 to 60:40:1) to afford 363.0 mg (21%) of **197**.

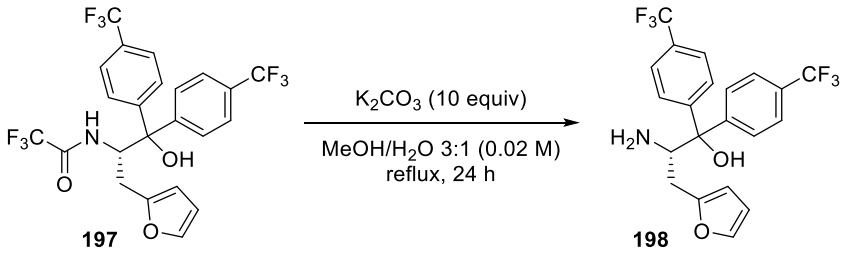
Data for **197**:

^{1}H NMR: (500 MHz, $CDCl_3$)
7.67 (app. s, 4H), 7.61 – 7.55 (m, 4H), 7.37 – 7.34 (m, 1H), 6.70 (d, *J* = 9.4 Hz, 1H), 6.29 (dd, *J* = 3.0, 1.6 Hz, 1H), 6.02 (d, *J* = 3.2 Hz, 1H), 5.34 (dt, *J* = 9.7, 5.9 Hz, 1H), 3.50 (bs, 1H), 2.95 (d, *J* = 5.9 Hz, 2H).

TLC: R_f 0.26 (hexanes/EtOAc, 80:20)

HPLC: t_R 4.8 min (6%); t_R 5.3 min (94%) (Supelco Astec, hexanes/*i*-PrOH, 90:10, 1.0 mL/min, 220 nm)

(2*S*)-2-Amino-3-(2-furyl)-1,1-bis[4-(trifluoromethyl)phenyl]propan-1-ol (198)



A 50-mL, round bottomed flask equipped with a stir bar and reflux condenser was charged with acetamide **197** (353 mg, 0.67 mmol). A solution of potassium carbonate (932 mg, 6.74 mmol, 10.0 equiv) in methanol (21.2 mL) and water (7.1 mL) was added to the flask. The mixture was heated to reflux overnight. Full conversion was observed by TLC (hexanes/EtOAc, 80:20) or by ^{1}H NMR analysis of a reaction aliquot. The reaction mixture was cooled to 25 °C, and the majority of the methanol was removed by rotary evaporation. The remaining residue was partitioned

between water and CH_2Cl_2, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 204.5 mg (71%) of **198** as a dark orange, oily solid. Despite the presence of some impurities, further purification by chromatography was not attempted, owing to the anticipated instability of **198** on silica gel.

Data for **198**:

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

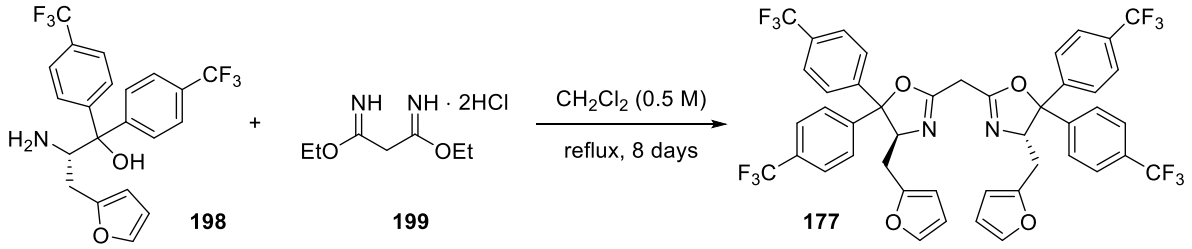
7.77 (d, *J* = 8.3 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.59 (app. t, *J* = 8.1 Hz, 4H), 7.34 (d, *J* = 1.8 Hz, 1H), 6.31 – 6.27 (m, 1H), 6.07 (d, *J* = 3.1 Hz, 1H), 4.69 (bs, 1H), 4.34 (dd, *J* = 10.2, 3.0 Hz, 1H), 2.58 (dd, *J* = 15.2, 10.2 Hz, 1H), 2.52 (dd, *J* = 15.0, 3.0 Hz, 1H).

TLC: R_f 0.36 (hexanes/EtOAc, 80:20, UV/CAM)

LRMS: (ESI, $[M+H]^+$)

430.1 (100), 431.1 (30).

Bisoxazoline 177



The following procedure is not optimized. A flame-dried, 5-mL, round bottomed flask equipped with a stir bar and reflux condenser was charged with a solution of amino alcohol **198** (109 mg, 0.26 mmol) in CH_2Cl_2 (0.6 mL). Diethyl malonimidate dihydrochloride **199** (29.4 mg, 0.13 mmol, 0.5 equiv) was added in one portion, and the reaction mixture was heated to reflux for 8 days. Roughly 80% conversion was observed by ^{1}H NMR analysis of a reaction aliquot. The reaction mixture was diluted with water and extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to afford 110.9 mg of crude **177**. The product was purified by chromatography (silica gel) using a

hexanes/EtOAc gradient elution (90:10 to 85:15 to 80:20 to 75:25 to 70:30) to afford 57.4 mg (51%) of **177** as an oily, orange solid. Yield is not adjusted for purity or for residual EtOAc. The product is approx. 85% pure.

Data for **177**:

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

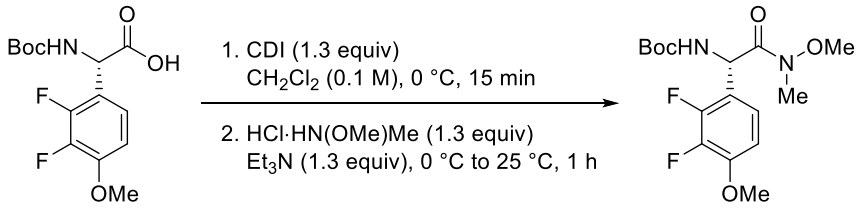
7.64 (d, *J* = 8.4 Hz, 4H), 7.54 (d, *J* = 8.3 Hz, 4H), 7.43 (d, *J* = 8.4 Hz, 4H), 7.30 (d, *J* = 1.7 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 4H), 6.23 (dd, *J* = 3.0, 1.9 Hz, 2H), 5.76 (d, *J* = 3.1 Hz, 2H), 5.25 – 5.18 (m, 2H), 3.69 (s, 2H), 2.59 (dd, *J* = 15.5, 8.4 Hz, 2H), 2.51 (dd, *J* = 15.4, 6.3 Hz, 2H).

TLC: R_f 0.33 (hexanes/EtOAc, 80:20, CAM)

LRMS: (ESI, $[M+H]^+$)

430.4 (50), 456.4 (35), 512.5 (10), 526.5 (25), 638.5 (10), 891.5 (100), 892.5 (45), 893.5 (10).

tert-Butyl _N_-[(_S_)-1-(2,3-Difluoro-4-methoxy-phenyl)-2-[methoxy(methyl)amino]-2-oxoethyl] carbamate (201)



200 **201**

A flame-dried, 50-mL, three-necked flask equipped with a stir bar and septum was charged with amino acid **200** (589 mg, 1.86 mmol) and CH_2Cl_2 (17 mL). The resulting solution was cooled to 0 °C using an ice bath. Carbonyldiimidazole (CDI) (395 mg, 2.44 mmol) was added in one portion. [**Note:** As CDI is prone to hydrolysis, this compound should be recrystallized from THF before use. Dissolution, crystallization, filtration, and drying should all be performed under an inert atmosphere for best results.] The added CDI dissolved within 3 min to afford a pale yellow solution. The reaction mixture was stirred at 0 °C for 15 min. Full conversion to the mixed anhydride was observed by IR (carbonyl stretch shifts from 1715 cm^{-1} to 1691 cm^{-1}). *N*,*O*-Dimethylhydroxylamine hydrochloride (244 mg, 2.50 mmol, 1.35 equiv) was added in one portion

at 0 °C, immediately followed by Et_3N (0.34 mL, 2.41 mmol, 1.30 equiv). The reaction mixture was maintained at 0 °C for 1 h and then allowed to warm to 25 °C. Full conversion was observed by TLC (hexanes/EtOAc, 50:50). The mixture was transferred to a separatory funnel and washed with 1 M HCl (2 x 20 mL), sat aq. $NaHCO_3$ (1 x 20 mL), and brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated to afford 0.44 g (66%) of **201** as a white solid requiring no further purification. Additional extractions of the aqueous phase did not afford any more product. [**Note**: Compound **201** is hygroscopic and should be stored in a desiccator, as water is detrimental to the next reaction in the sequence.]

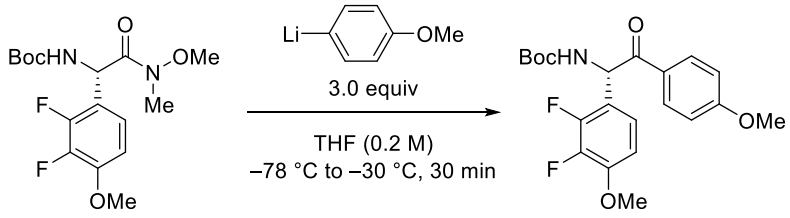
Data for **201**:

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

7.10 – 6.93 (m, 1H), 6.79 – 6.63 (m, 1H), 5.81 (bd, J = 10.1 Hz, 2H), 3.88 (s, 3H), 3.56 (s, 3H), 3.16 (s, 3H), 1.41 (s, 9H).

TLC: R_f 0.56 (hexanes/EtOAc, 50:50, UV)

tert-Butyl _N_-[(1_S_)-1-(2,3-Difluoro-4-methoxy-phenyl)-2-(4-methoxyphenyl)-2-oxo-ethyl] carbamate (202)



201 **202**

A flame-dried, 100-mL, three-necked, round bottomed flask equipped with a stir bar was charged with 4-bromoanisole (0.60 mL, 4.82 mmol, 3.1 equiv) and THF (20 mL). The solution was cooled to –78 °C with a dry ice/acetone bath. _n_-Butyllithium (2.03 M in hexanes, 2.3 mL, 4.66 mmol, 3.0 equiv) was added dropwise, and the solution was stirred for 40 min at –78 °C. Completeness of lithium-halogen exchange was confirmed by GC analysis of a reaction aliquot quenched into methanol (HP-1 column, 100 °C (3 min) → ramp 20 °C/min (8 min) → hold 260 °C (1 min), _Rt_ = 2.7 min (anisole) and 5.7 min (4-bromoanisole)). A separate 250-mL, Schlenk flask equipped with a stir bar was charged with Weinreb amide **201** (0.560 g, 1.55 mmol) and THF (16 mL), and the resulting solution was cooled to –78 °C. The freshly prepared solution of 4-

methoxyphenyllithium was cannulated into the flask containing **201** at –78 °C. The resulting yellow-orange solution was stirred at –78 °C for 15 min. Full conversion was observed by TLC (hexanes/EtOAc, 50:50). The reaction was quenched at –78 °C by the addition of 1 M phosphate buffer (pH = 7, 120 mL), and the mixture was allowed to warm to 25 °C with stirring. The mixture was transferred to a separatory funnel and diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 758.1 mg of a mixture of crude **202** (e.r. = 92:8) and anisole (approx. 1:2 molar ratio). Due to concerns about the potential of **202** to racemize, the crude material was immediately subjected to the next reaction.

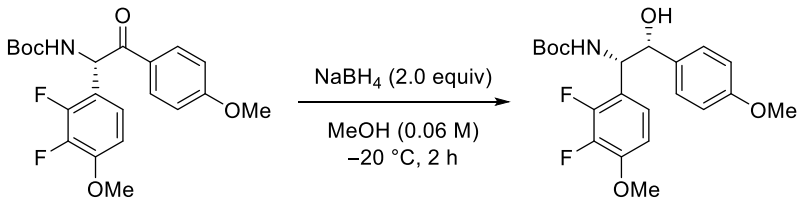
Data for **202**:

^{1}H NMR: (500 MHz, $CDCl_3$)
7.97 (d, *J* = 8.9 Hz, 2H), 6.98 (t, *J* = 7.7 Hz, 1H), 6.91 (d, *J* = 8.6 Hz, 2H), 6.73 – 6.65 (m, 1H), 6.40 (d, *J* = 7.0 Hz, 1H), 6.12 (d, *J* = 6.6 Hz, 1H), 3.86 (s, 6H), 1.45 (s, 9H).

TLC: R_f 0.75 (hexanes/EtOAc, 50:50, UV)

HPLC: t_R 10.3 min (92%); t_R 15.2 min (8%) (Supelco Astec, hexanes/*i*-PrOH, 90:10, 1.0 mL/min, 254 nm)

tert-Butyl _N_-[(1_S_,2_R_)-1-(2,3-Difluoro-4-methoxy-phenyl)-2-hydroxy-2-(4-methoxyphenyl)ethyl]carbamate (203)



202 **203**

A flame-dried, 100-mL, round bottomed flask equipped with a stir bar was charged with crude ketone **202** (758 mg) and MeOH (20 mL). The resulting pale yellow solution was cooled to –20 °C using an aq. $CaCl_2$/dry ice slush bath. Sodium borohydride (93.6 mg, 2.5 mmol, 2.1 equiv) was added in two portions, and the reaction mixture was stirred at –20 °C for 2 h. Full conversion

was observed by TLC (hexanes/EtOAc, 50:50). The reaction was quenched by the addition of water (45 mL). Much of the methanol was removed by rotary evaporation. The remaining residue was partitioned between EtOAc and water, and the layers were separated. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated to afford 620.8 mg of crude **203** as a white solid. The product was purified by chromatography (silica gel) using a hexanes/EtOAc gradient elution (75:25 to 50:50 to 25:75) to afford 499.1 mg (79% over two steps) of **203**. The yield is not adjusted for impurities remaining after chromatography.

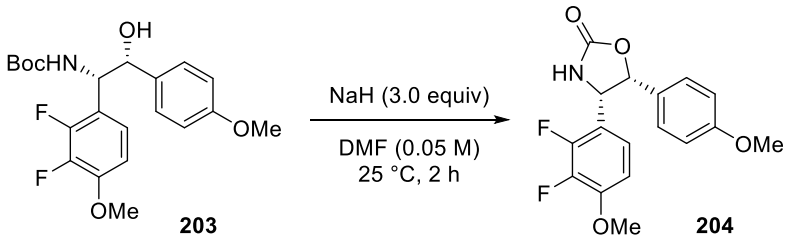
Data for **203**:

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

7.07 – 7.01 (m, 2H), 6.89 – 6.77 (m, 3H), 6.66 (bt, *J* = 7.5 Hz, 1H), 5.32 (bs, 1H), 5.11 (bs, 1H), 5.03 – 4.96 (m, 1H), 3.88 (s, 3H), 3.78 (s, 3H), 2.25 (bs, 1H), 1.38 (bs, 9H).

TLC: R_f 0.58 (hexanes/EtOAc, 50:50, UV/CAM)

(4*S*,5*R*)-4-(2,3-Difluoro-4-methoxy-phenyl)-5-(4-methoxyphenyl)oxazolidin-2-one (204)



A flame-dried, 100-mL, Schlenk flask equipped with a stir bar was charged with sodium hydride (62.8 mg, 2.62 mmol, 3.1 equiv, hexanes-washed) inside of the glovebox. The flask was sealed, removed from the glovebox, and charged with DMF (14 mL). Amino alcohol **203** (347 mg, 0.85 mmol) was added portionwise, as a solid, at 25 °C. Any solid stuck to the walls/neck of the flask was rinsed in with additional DMF (4 mL). The suspension was stirred at 25 °C for 2 h. Full conversion was observed by TLC (hexanes/EtOAc, 50:50). The reaction was quenched by the cautious addition of water (gas evolution was observed). The mixture was partitioned between water and EtOAc, and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with water and aq. LiCl (5% w/v), and then

dried over $MgSO_4$, filtered, and concentrated to afford 280.4 mg of crude **204** as a white, foam solid. The product was purified by chromatography (silica gel) using a hexanes/EtOAc gradient elution (75:25 to 50:50 to 25:75 to 0:100) to afford 205.1 mg (72%) of *cis*-**204** as a white, foam solid.

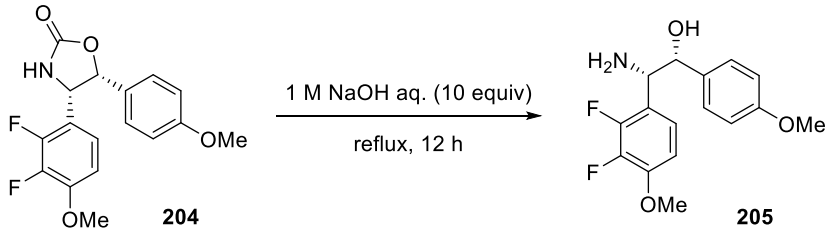
Data for *cis*-**204**:

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

6.97 (d, J = 8.5 Hz, 2H), 6.89 – 6.82 (m, 1H), 6.68 (d, J = 8.7 Hz, 2H), 6.59 (t, J = 8.0 Hz, 1H), 5.94 (d, J = 8.2 Hz, 1H), 5.45 (d, J = 8.2 Hz, 1H), 5.27 (bs, 1H), 3.82 (s, 3H), 3.72 (s, 3H).

TLC: R_f 0.29 (hexanes/EtOAc, 50:50, CAM)

(1*R*,2*S*)-2-Amino-2-(2,3-difluoro-4-methoxy-phenyl)-1-(4-methoxyphenyl)ethanol (205)



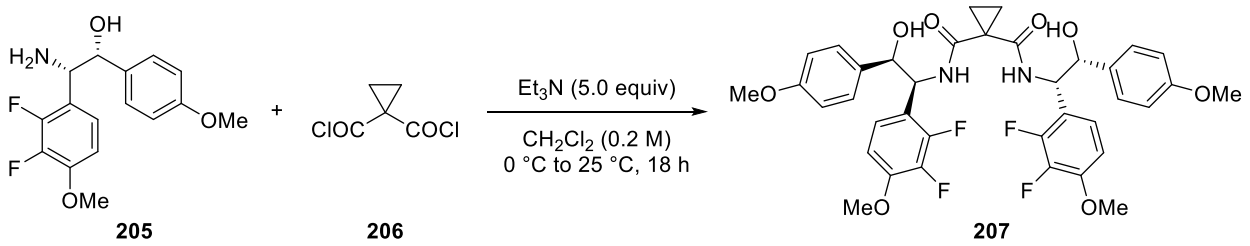
A 50-mL, round bottomed flask equipped with a stir bar and reflux condenser was charged with oxazolidinone **204** (204.7 mg, 0.61 mmol) and 1 M sodium hydroxide (6.1 mL, 6.1 mmol, 10 equiv). The resulting white suspension was heated to reflux for 12 h. The mixture was cooled to room temperature, diluted with water, and extracted with EtOAc (4 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 166.0 mg (88%) of **205** as a white solid in >90% purity (estimated from ^{1}H NMR). The product was combined with **205** from a small-scale experiment and recrystallized from EtOAc/hexanes to afford 137.3 mg of pure, crystalline **205** (approx. 70% recovery).

Data for **205**:

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

7.15 – 7.09 (m, 2H), 6.98 – 6.90 (m, 2H), 6.86 – 6.79 (m, 3H), 6.72 – 6.66 (m, 1H), 4.79 (d, J = 5.9 Hz, 1H), 4.44 (d, J = 6.1 Hz, 1H), 3.89 (s, 3H), 3.80 (s, 3H).

_N_1,_N_1'-Bis[(1_S_,2_R_)-1-(2,3-difluoro-4-methoxy-phenyl)-2-hydroxy-2-(4-methoxyphenyl) ethyl]cyclopropane-1,1-dicarboxamide (207)



A flame-dried, 5-mL, Schlenk flask equipped with a stir bar was charged with amino alcohol **205** (137 mg, 0.44 mmol), CH_2Cl_2 (0.8 mL), and Et_3N (0.31 mL, 5.0 equiv), and the resulting suspension was cooled to 0 °C. Freshly distilled cyclopropane-1,1-dicarbonyl chloride **206** (37 mg, 0.22 mmol, 0.50 equiv) was dissolved in CH_2Cl_2 (0.8 mL), and this solution was added dropwise to the reaction mixture at 0 °C. The resulting turbid solution was allowed to warm to 25 °C and stirring was continued for 12 h. Incomplete conversion was observed by ^{1}H NMR analysis of a reaction aliquot. The reaction mixture was cooled to 0 °C and an additional portion of **206** (9 mg, 0.055 mmol, 0.125 equiv) dissolved in CH_2Cl_2 (0.2 mL) was added dropwise. The reaction mixture was allowed to warm to 25 °C and stirring was continued for 6 h. Full conversion was observed by ^{1}H NMR analysis of a reaction aliquot. The reaction was quenched by the addition of sat. aq. $NaHCO_3$, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to afford 168.5 mg (quant.) of amide **207** as a white solid. No further purification was performed. Yield is not adjusted for impurities.

Data for **207**:

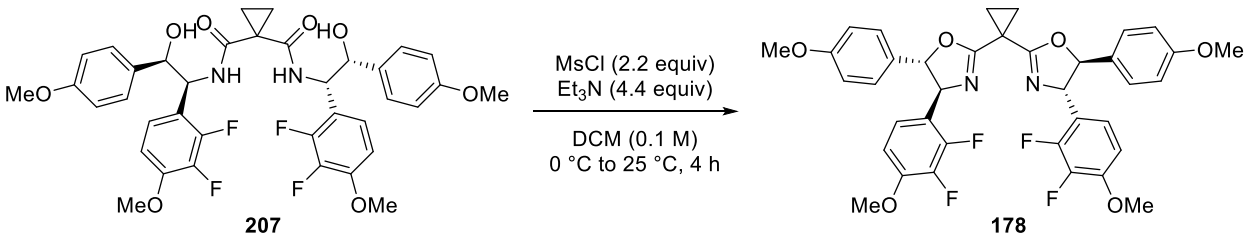
^{1}H NMR: (500 MHz, $CDCl_3$)

7.81 (d, *J* = 7.9 Hz, 2H), 7.02 (d, *J* = 8.5 Hz, 4H), 6.80 (d, *J* = 8.7 Hz, 4H), 6.79 – 6.72 (m, 2H), 6.64 – 6.57 (m, 2H), 5.40 (dd, *J* = 8.3, 4.9 Hz, 2H), 5.01 (d, *J* = 4.6 Hz, 2H), 3.86 (s, 6H), 3.78 (s, 6H), 1.31 (s, 4H).

LRMS: (ESI, $[M–OH]^+$)

677.2 (65), 695.2 (100), 696.2 (45).

Bisoxazoline 178



A flame-dried, 10-mL, Schlenk flask equipped with a stir bar was charged with bis(amide) **207** (165 mg, 0.23 mmol), CH_2Cl_2 (2 mL), and Et_3N (0.14 mL, 1.02 mmol, 4.4 equiv). The suspension was cooled to 0 °C, and mesyl chloride (0.040 mL, 0.51 mmol, 2.2 equiv) was added dropwise. The resulting solution was allowed to warm to 25 °C over 1 h, and stirring was continued at this temperature for 3 h. Full conversion was observed by TLC (hexanes/EtOAc, 50:50). The mixture was poured in sat. aq. NH_4Cl (30 mL), and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to afford 146.9 mg of crude **178**. ^{1}H NMR analysis of the crude mixture suggested that bisoxazoline **178** was the major species, with no detectable amount of any mesylated intermediates. The crude product was subjected to chromatography (silica gel) using a hexanes/EtOAc gradient elution (90:10 to 75:25 to 50:50 to 25:75) to afford 79.3 mg (51%) of **178** in approx. 75% purity (estimated from ^{1}H NMR). [**Note**: The product is partially unstable to silica gel chromatography. Components were isolated which were not present in the ^{1}H NMR of crude **178** prior to chromatography.] The product was recrystallized from TBME/hexanes to afford 37.5 mg (24%) of **178** in approx. 80% purity. Yield not adjusted for purity.

Data for **178**:

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

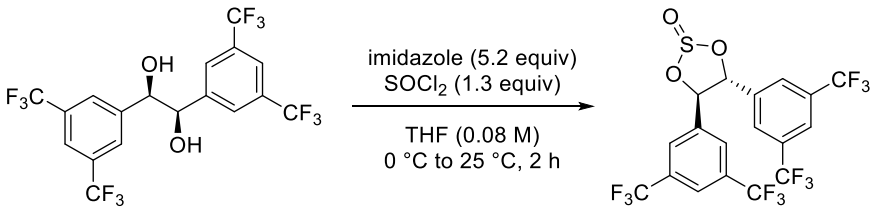
7.29 – 7.24 (m, 4H), 7.00 – 6.95 (m, 2H), 6.83 – 6.78 (m, 4H), 6.66 – 6.61 (m, 2H), 5.29 (d, *J* = 6.5 Hz, 2H), 5.24 (d, *J* = 6.6 Hz, 2H), 3.88 (s, 6H), 3.78 (s, 6H), 1.77 (q, *J* = 4.4 Hz, 2H), 1.58 – 1.54 (m, 2H).

LRMS: (ESI, $[M+H]^+$)

677.2 (100), 678.2 (40), 679.2 (10).

TLC: R_f 0.45 (hexanes/EtOAc, 50:50, UV/CAM)

(4*S*,5*S*)-4,5-Bis[3,5-bis(trifluoromethyl)phenyl]-1,3,2-dioxathiolane 2-oxide (209)



208 **209**

A flame-dried, 100-mL, round bottomed flask equipped with a stir bar was charged with imidazole (1.46 g, 21.4 mmol, 5.2 equiv) and THF (33 mL). The flask was cooled to 0 °C and thionyl chloride (0.39 mL, 5.3 mmol, 1.3 equiv) was added dropwise, immediately resulting in a milky, white suspension. This is indicative of the formation of sulfonyl diimidazole *in situ* with concomitant precipitation of imidazole hydrochloride. A second, flame-dried, 200-mL, round bottomed flask equipped with a stir bar was charged with diol **208** (1.99 g, 4.1 mmol) and THF (21 mL). This solution was also cooled to 0 °C. The freshly prepared solution of sulfonyl diimidazole in THF was added dropwise at 0 °C to the flask containing diol **208** by means of cannula filtration. Once the addition was complete, the ice bath was removed and the reaction mixture was allowed to warm to 25 °C. Stirring was continued for 2 h. Full conversion was observed by TLC (hexanes/EtOAc, 80:20). The mixture was diluted with an equal volume of EtOAc and filtered through a pad of silica gel. The pad was rinsed with EtOAc, and the filtrate was concentrated to afford 2.02 g (93%) of **209** as an oily residue. ^{1}H NMR indicates the presence of residual imidazole and EtOAc as the sole impurities, which are not expected to interfere with the next step. No further purification was performed. Yield is not adjusted for purity.

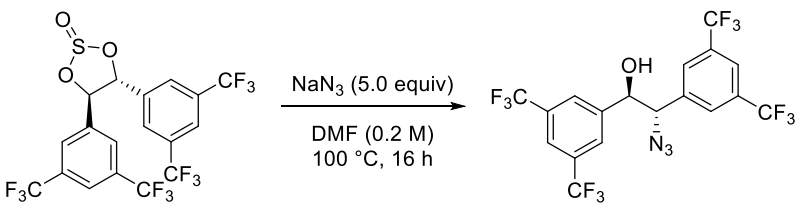
Data for **209**:

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

8.00 (d, J = 5.8 Hz, 2H), 7.77 (s, 2H), 7.70 (s, 2H), 5.78 (d, J = 9.3 Hz, 1H), 5.27 (d, J = 9.3 Hz, 1H).

TLC: R_f 0.79 (hexanes/EtOAc, 80:20, UV/CAM)

(1*S*,2*R*)-2-Azido-1,2-bis[3,5-bis(trifluoromethyl)phenyl]ethanol (210)



209 **210**

A 100-mL, round bottomed flask equipped with a stir bar and reflux condenser was charged with cyclic sulfite **209** and DMF (19 mL). Sodium azide was added in one portion (*caution*: toxic and shock-sensitive reagent). The resulting yellow suspension was heated to 100 °C for 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 80:20) or by ^{1}H NMR analysis of a reaction aliquot. The reaction mixture was cooled to 25 °C and diluted with 1M HCl (100 mL). The mixture was extracted with EtOAc (5 x 50 mL). The combined organic extracts were washed with 5% (w/v) aq. LiCl solution (2 x 50 mL) and brine (2 x 50 mL), and then dried over $MgSO_4$, filtered, and concentrated to afford 2.03 g of crude **210** as a yellow liquid. The product was purified by chromatography (silica gel) using a hexanes/EtOAc gradient elution (95:5 to 92.5:7.5 to 90:10 to 87.5:12.5 to 85:15) to afford 697.8 mg (36%) of azido alcohol **210** as a pale, yellow oil.

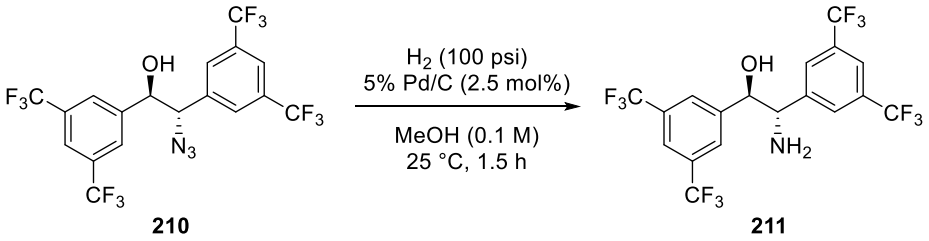
Data for **210**:

^{1}H NMR: (500 MHz, $CDCl_3$)
7.86 (d, *J* = 14.0 Hz, 2H), 7.63 (d, *J* = 12.0 Hz, 4H), 5.07 (dd, *J* = 5.6, 3.0 Hz, 1H), 4.87 (d, *J* = 5.8 Hz, 1H), 2.52 (d, *J* = 3.4 Hz, 1H).

IR: (neat)
2110 (m), diagnostic azide stretching frequency.

TLC: R_f 0.53 (hexanes/EtOAc, 80:20, UV)

(1*R*,2*S*)-2-Amino-1,2-bis[3,5-bis(trifluoromethyl)phenyl]ethanol (211)



A 50-mL, round bottomed flask equipped with a stir bar was charged with azido alcohol **210** (505 mg, 0.99 mmol), degassed MeOH (10 mL), and 5% palladium on carbon (54.2 mg, 0.025 mmol, 0.025 equiv). The flask was placed in a bomb and charged with hydrogen gas (100 psi). The reaction was stirred at 25 °C for 1.5 h. The bomb was vented, and full conversion was observed by TLC (hexanes/EtOAc, 80:20). The reaction mixture was filtered through a pad of Celite to remove the catalyst, and the pad was rinsed with CH_2Cl_2. The filtrate was concentrated to afford 446.7 mg (93%) of amino alcohol **211** as an off-white solid requiring no further purification.

Data for **211**:

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

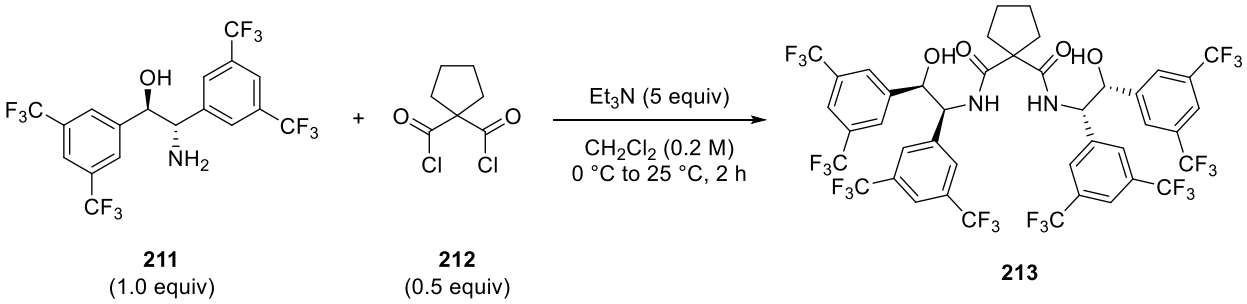
7.77 (s, 2H), 7.51 (s, 4H), 5.01 (d, J = 4.7 Hz, 1H), 4.41 (d, J = 4.8 Hz, 1H), 3.24 (s, 1H), 1.69 (s, 2H).

LRMS: (ESI, $[M+H]^+$)

468.1 (40), 486.1 (100), 487.1 (65), 488.1 (15).

TLC: R_f 0.18 (hexanes/EtOAc, 80:20, UV)

_N_1,_N_1'-Bis[(1_S_,2_R_)-1,2-bis[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-ethyl]cyclopentane-1,1-dicarboxamide (213)



211 (1.0 equiv) **212** (0.5 equiv) **213**

A flame-dried, 10-mL, Schlenk flask equipped with a stir bar was charged with amino alcohol **211** (439 mg, 0.90 mmol), CH_2Cl_2 (1.8 mL), and Et_3N (0.63 mL, 4.5 mmol, 5.0 equiv). The resulting yellow solution was cooled to 0 °C. A solution of freshly distilled cyclopentane-1,1-dicarbonyl chloride **212** (88.2 mg, 0.45 mmol, 0.5 equiv) in CH_2Cl_2 (1.8 mL) was added dropwise to the reaction mixture at 0 °C. The reaction was allowed to warm to 25 °C and stirring was continued for 2 h. Full conversion was observed by ^{1}H NMR analysis of a reaction aliquot. The reaction was quenched with sat. aq. $NaHCO_3$, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to afford 562.5 mg of crude **213** as a white solid. The product was purified by chromatography (silica gel) using a hexanes/EtOAc gradient elution (90:10 to 75:25 to 50:50 to 25:75 to 0:100) to afford 280.1 mg (57%) of **213** as a white solid.

Data for **213**:

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

7.79 (s, 2H), 7.71 (s, 2H), 7.56 (d, *J* = 7.9 Hz, 2H), 7.42 (s, 4H), 7.28 (s, 4H), 5.34 (s, 2H), 5.20 (dd, *J* = 7.9, 4.1 Hz, 2H), 2.95 (bs, 2H), 2.28 – 2.13 (m, 4H), 1.80 – 1.69 (m, 4H).

(500 MHz, CD_3OD)

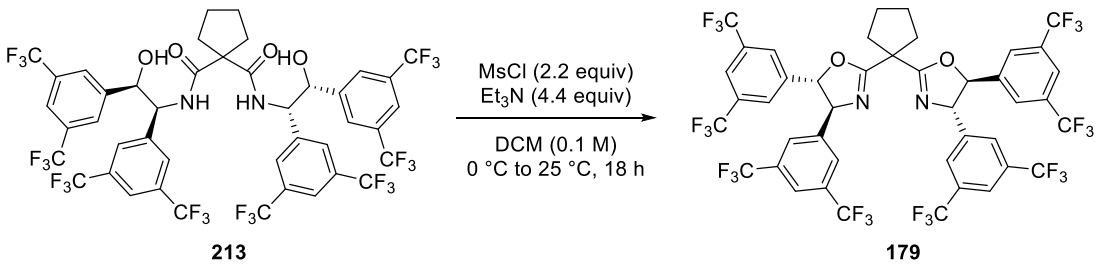
7.84 (s, 2H), 7.80 (s, 4H), 7.66 (s, 2H), 7.61 (s, 4H), 5.22 (d, *J* = 6.9 Hz, 2H), 5.05 (d, *J* = 6.9 Hz, 2H), 2.15 – 2.06 (m, 2H), 1.79 – 1.70 (m, 2H), 1.40 – 1.29 (m, 4H).

LRMS: (ESI, $[M+H]^+$)

1093.2 (65), 1110.2 (100), 1111.2 (40), 1115.0 (15).

TLC: R_f 0.11 (hexanes/EtOAc, 80:20, UV)

Bisoxazoline 179



213 **179**

A flame-dried, 5-mL, Schlenk flask equipped with a stir bar was charged bis(hydroxyamide) **213** (170 mg, 0.16 mmol), CH_2Cl_2 (2 mL), and Et_3N (95 μL, 0.69 mmol, 4.4 equiv). The resulting pale, yellow solution was cooled to 0 °C and mesyl chloride (26 μL, 0.34 mmol, 2.2 equiv) was added dropwise. The reaction mixture was allowed to warm to 25 °C and stirring was continued for 18 h. Full conversion was observed by TLC (hexanes/EtOAc, 80:20). The mixture was poured into sat. aq. NH_4Cl (3 mL), and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated to afford 147.3 mg of crude **179** as a foam solid. The crude product was purified by chromatography (silica gel) using a hexanes/EtOAc gradient elution (95:5 to 90:10 to 80:20 to 60:40 to 25:75) to afford 73.9 mg (45%) of **179** as a solid.

Data for **179**:

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

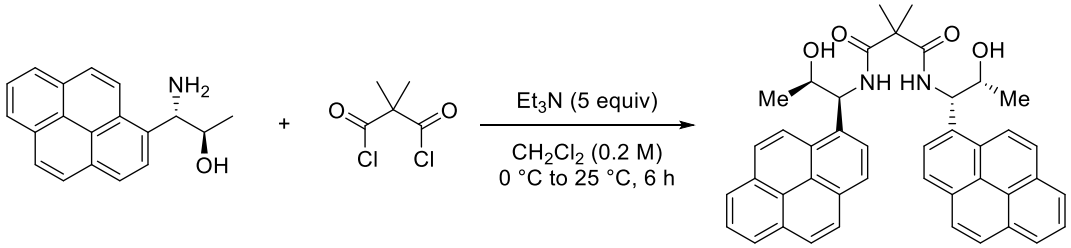
7.85 (s, 4H), 7.77 (s, 4H), 7.66 (s, 4H), 5.39 (d, J = 6.1 Hz, 2H), 5.23 (d, J = 6.1 Hz, 2H), 2.60 (tq, J = 13.2, 6.9 Hz, 4H), 2.03 – 1.95 (m, 4H).

LRMS: (ESI, $[M+H]^+$)

391.5 (15), 520.6 (15), 564.2 (15), 1057.1 (100), 1058.1 (40), 1059.1 (10), 1135.0 (10).

TLC: R_f 0.69 (hexanes/EtOAc, 80:20, UV)

***N*,*N*'-Bis[(1*S*,2*R*)-2-hydroxy-1-pyren-1-yl-propyl]-2,2-dimethyl-propanediamide (216)**



214 (1.0 equiv) **215** (0.5 equiv) **216**

A flame-dried, 10-mL, Schlenk flask equipped with a stir bar was charged with amino alcohol **214** (201 mg, 0.73 mmol), CH_2Cl_2 (3 mL), and Et_3N (0.51 mL, 3.64 mmol, 5.0 equiv). The resulting yellow suspension was cooled to 0 °C. A solution of 2,2-dimethylpropanedioyl dichloride **215** (48 μL, 0.36 mmol, 0.5 equiv) in CH_2Cl_2 (1 mL) was added dropwise at 0 °C. The resulting solution was allowed to warm to 25 °C and stirring was continued for 4 h. Approx. 93% conversion was observed by ^{1}H NMR analysis of a reaction aliquot. The reaction mixture was again cooled to 0 °C, and an additional portion of **215** (3 μL, neat) was added. The reaction mixture was stirred for 2 h at 25 °C. Full conversion was observed by ^{1}H NMR analysis of a reaction aliquot. The mixture was transferred to a separatory funnel, diluted with CH_2Cl_2, and washed with 1 N HCl (2 x 5 mL). The organic phase was washed with sat. aq. $NaHCO_3$ (2 x 5 mL) and brine (5 mL), and then dried over $MgSO_4$, filtered, and concentrated to afford 204.0 mg (87%) of **216** as a pale yellow solid requiring no further purification.

Data for **216**:

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

8.39 (d, *J* = 9.4 Hz, 2H), 8.18 (d, *J* = 7.5 Hz, 2H), 8.11 (d, *J* = 7.4 Hz, 2H), 8.05 (d, *J* = 9.3 Hz, 2H), 8.03 – 7.96 (m, 4H), 7.75 (dd, *J* = 10.6, 8.5 Hz, 4H), 7.71 – 7.62 (m, 4H), 6.19 (dd, *J* = 7.9, 4.4 Hz, 2H), 4.41 (s, 2H), 2.53 (s, 2H), 1.59 (s, 6H), 1.07 (d, *J* = 6.4 Hz, 6H).

(500 MHz, DMSO–d_6)

8.55 (d, *J* = 9.5 Hz, 2H), 8.27 (d, *J* = 7.6 Hz, 2H), 8.23 (d, *J* = 7.6 Hz, 2H), 8.19 – 8.10 (m, 6H), 8.04 (t, *J* = 7.6 Hz, 2H), 7.94 (d, *J* = 8.9 Hz, 2H), 7.89 (d, *J* = 8.1 Hz, 2H), 7.78 (d, *J* = 8.1 Hz, 2H), 5.87 (t, *J* = 7.5 Hz, 2H), 4.87 (d, *J* = 5.3 Hz, 2H), 4.21 (hex, *J* = 6.1 Hz, 2H), 1.35 (s, 6H), 1.04 (d, *J* = 6.2 Hz, 6H).

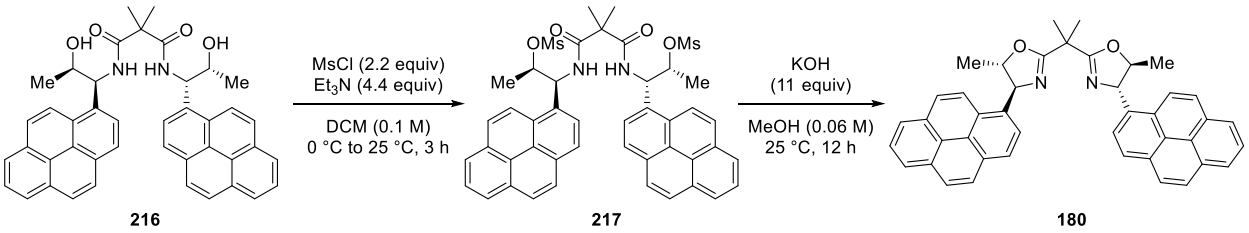
LRMS: (ESI, $[M+H]^+$)

241.1 (15), 259.1 (45), 389.2 (15), 445.2 (15), 459.3 (15), 647.3 (100), 648.3 (50), 649.3 (10).

IR: (neat)

3405 (bw), 1660 (m), 1504 (m), 840 (s).

(4*S*,4'*S*,5*S*,5'*S*)-2,2'-(Propane-2,2-diyl)bis(5-methyl-4-(pyren-1-yl)-4,5-dihydrooxazole) (180)



216 **217** **180**

A flame-dried, 10-mL, Schlenk flask equipped with a stir bar was charged with bis(hydroxyamide) **216** (190.2 mg, 0.29 mmol), CH_2Cl_2 (3 mL), and Et_3N (0.18 mL, 1.3 mmol, 4.4 equiv). The mixture was cooled to 0 °C, and mesyl chloride (50 μL, 0.65 mmol, 2.2 equiv) was added dropwise. The reaction was allowed to warm to 25 °C and stirring was continued for 3 h at 25 °C. Nearly full conversion was observed by TLC (hexanes/EtOAc, 50:50) or by ^1H NMR analysis of a reaction aliquot. The mixture was poured in sat. aq. NH_4Cl (10 mL), and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to afford 227.2 mg of crude **217** as a yellow solid, which was used directly in the next reaction.

A 15-mL, round bottomed flask equipped with a stir bar was charged with crude bis(mesylate) **217** and a 4% (w/v) solution of KOH in methanol (163 mg potassium hydroxide pellets in 5 mL methanol). The resulting thick, beige suspension was stirred at 25 °C for 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 50:50). The reaction mixture was diluted with water and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 160 mg of crude **180**. The product was purified by chromatography (silica gel) using a hexanes/EtOAc gradient elution (90:10 to 80:20 to 65:35 to 50:50 to 25:75) to afford 101.2 mg (60% over 2 steps) of bisoxazoline **180** as an off-white solid.

Data for **180**:

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

8.31 (d, *J* = 9.3 Hz, 2H), 8.19 (d, *J* = 7.6 Hz, 2H), 8.16 (d, *J* = 7.6 Hz, 2H), 8.13 – 8.09 (m, 4H), 8.07 – 8.03 (m, 4H), 8.03 – 7.98 (m, 4H), 5.91 (d, *J* = 6.2 Hz, 2H), 4.75 (p, *J* = 6.2 Hz, 2H), 1.90 (s, 6H), 1.74 (d, *J* = 6.2 Hz, 6H).

LRMS: (ESI, $[M+H]^+$)

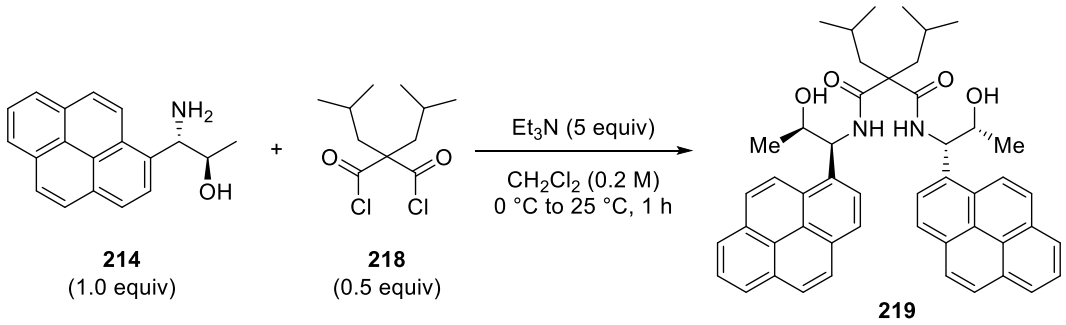
611.4 (100), 612.4 (50), 613.4 (10).

IR: (neat)

1655 (m), 837 (s), 714 (m).

TLC: R_f 0.76 (hexanes/EtOAc, 50:50, UV)

***N*,*N*'-Bis[(1*S*,2*R*)-2-hydroxy-1-pyren-1-yl-propyl]-2,2-diisobutyl-propanediamide (219)**



A flame-dried, 10-mL, Schlenk flask equipped with a stir bar was charged with amino alcohol **214** (161 mg, 0.59 mmol), CH_2Cl_2 (1.6 mL), and Et_3N (0.41 mL, 2.93 mmol, 5.0 equiv). The resulting suspension was cooled to 0 °C. A solution of 2,2-diisobutylpropanedioyl dichloride **218** (74 μL, 0.37 mmol, 0.6 equiv) in CH_2Cl_2 (1.6 mL) was added dropwise at 0 °C. The resulting yellow solution was allowed to warm to 25 °C and stirring was continued for 1 h. Full conversion was observed by TLC (hexanes/EtOAc, 50:50) or by ^{1}H NMR analysis of a reaction aliquot. The mixture was transferred to a separatory funnel, diluted with CH_2Cl_2, and washed with 1 N HCl (2 x 5 mL). The organic phase was washed with sat. aq. $NaHCO_3$ (2 x 5 mL) and brine (5 mL), and then dried over $MgSO_4$, filtered, and concentrated to afford 234.6 mg (87%) of crude **219**. The product was purified by chromatography (silica gel) using a hexanes/EtOAc gradient elution (90:10 to 75:25 to 50:50 to 25:75 to 0:100) to afford 162.8 mg (76%) of **219**.

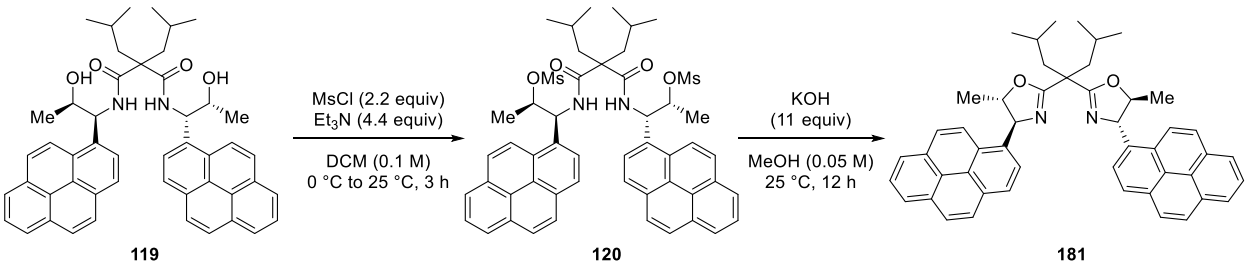
Data for **219**:

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

8.87 (bd, *J* = 7.6 Hz, 2H), 8.49 (d, *J* = 9.4 Hz, 2H), 8.18 – 8.13 (m, 4H), 8.09 (app. dd, *J* = 11.2, 8.7 Hz, 4H), 8.04 – 7.94 (m, 8H), 6.30 (dd, *J* = 7.8, 4.2 Hz, 2H), 4.43 (hex, *J* = 6.3 Hz, 2H), 2.37 (d, *J* = 6.0 Hz, 2H), 1.90 (qd, *J* = 14.2, 6.6 Hz, 4H), 1.51 (hept, *J* = 6.5 Hz, 2H), 1.15 (d, *J* = 6.4 Hz, 6H), 0.68 (app. dd, *J* = 11.2, 6.6 Hz, 12H).

TLC: R_f 0.22 (hexanes/EtOAc, 50:50, UV)

(4*S*,4'*S*,5*S*,5'*S*)-2,2'-(2,6-Dimethylheptane-4,4-diyl)bis(5-methyl-4-(pyren-1-yl)-4,5-dihydrooxazole) (181)



A flame-dried, 10-mL, Schlenk flask equipped with a stir bar was charged with bis(hydroxyamide) **119** (190 mg, 0.26 mmol), CH_2Cl_2 (3 mL), and Et_3N (0.16 mL, 1.1 mmol, 4.4 equiv). The mixture was cooled to 0 °C, and mesyl chloride (44 μL, 0.57 mmol, 2.2 equiv) was added dropwise. The reaction was allowed to warm to 25 °C and stirring was continued for 3 h at 25 °C. Full conversion was observed by TLC (hexanes/EtOAc, 50:50) or by ^{1}H NMR analysis of a reaction aliquot. The mixture was poured in sat. aq. NH_4Cl (10 mL), and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to afford 222.3 mg of crude **120** as a yellow solid, which was used directly in the next reaction.

A 15-mL, round bottomed flask equipped with a stir bar was charged with crude bis(mesylate) **120** (222 mg, 0.25 mmol) and a 4% (w/v) solution of KOH in methanol (148 mg potassium hydroxide pellets in 5 mL methanol). The resulting beige suspension was stirred at 25 °C for 12 h. The suspension was observed to become more homogenous over time. Full conversion

was observed by TLC (hexanes/EtOAc, 50:50). The reaction mixture was diluted with water and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 174.4 mg of crude **181**. The product was purified by chromatography (silica gel) using a hexanes/EtOAc gradient elution (95:5 to 90:10 to 85:15 to 80:20 to 75:25 to 70:30) to afford 50.4 mg (29% over 2 steps) of bisoxazoline **181** as an off-white solid.

Data for **181**:

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

8.37 (d, *J* = 9.4 Hz, 2H), 8.20 – 8.13 (m, 6H), 8.13 – 8.08 (m, 4H), 8.06 – 7.97 (m, 6H), 5.87 (d, *J* = 8.2 Hz, 2H), 4.71 (dq, *J* = 7.9, 6.2 Hz, 2H), 2.42 – 2.35 (m, 4H), 2.00 (dp, *J* = 12.9, 6.6 Hz, 2H), 1.80 (d, *J* = 6.2 Hz, 6H), 1.17 (d, *J* = 6.6 Hz, 6H), 1.10 (d, *J* = 6.7 Hz, 6H).

LRMS: (ESI, $[M+H]^+$)

130.3 (20), 695.5 (100), 696.5 (50), 697.5 (15).

IR: (neat)

1647 (m), 840 (s), 716 (m).

TLC: R_f 0.89 (hexanes/EtOAc, 50:50, UV)