Chapter 3

Progress Towards the Total Synthesis of Cylindrocyclophane F.
Investigations into a Novel B-alkyl Suzuki Cross-Coupling.

I. Introduction to the Cylindrocyclophanes.

i. Isolation and structure determination.


The [7.7]paracyclophanes were isolated in 1990 by Moore and co-workers from two species of terrestrial blue-green algae, *Cylindrospermum licheniforme* Kutzing and *Nostoclickia* (Roth) Bornet. The cylindrocyclophanes were found to be the major cytotoxic component in three different strains of *Cylindrospermum licheniforme*; cylindrocyclophane A exhibited moderate toxicity against KB and LoVo tumor cell lines (IC$_{50}$ = 0.5 µg/mL). In fact, all of the cyclophanes have an IC$_{50}$ between 0.5–5.0 µg/mL but they are not selective for human solid tumor cell lines in the Corbett assay. The structurally similar chlorinated nostocyclophanes were found to be the major cytotoxic component of *Nostoclickia* (Fig. 1).
The absolute configuration of cylindrocyclophane A was determined by detailed NMR spectral analysis. It was assigned the molecular formula of $C_{36}H_{56}O_6$ based on the mass spectrum ($MH^+ = 584$), however only 18 carbons appeared in the $^{13}$C spectrum. Therefore it was concluded that the molecule had a two-fold axis of symmetry. $^1$H NMR and DEPT experiments confirmed atom connectivity and the absolute configuration was determined by analysis of the ($R$)- and ($S$)-Mosher esters of the benzylic alcohols (eq. 1). An additional chemical correlation of cylindrocyclophanes B and D to cylindrocyclophane A was done under basic hydrolysis to remove the acetoxy groups in order to confirm that functionality.

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The relative and absolute stereochemistry of nostocyclophane D was determined by single crystal X-ray analysis (Figure 2). The crystal structure incorporates a molecule of ethanol within the cyclophane core. This type of host-guest interaction with cyclophanes has long been recognized and has received considerable attention in the literature.\(^5\)

\[\text{cylindrocyclophane A} \rightarrow \begin{array}{c}
\text{1. CH}_2\text{N}_2 (34\%) \\
\text{2. (R)- or (S)-MTPA acid} \\
\text{DCC, DMAP (43\%)}
\end{array} \rightarrow \text{cylindrocyclophane D}
\]

**Figure 2. X-ray structure of nostocyclophane D.**

**ii. Proposed biosynthesis of the cylindrocyclophanes**

Moore and co-workers have studied the biosynthetic pathway of cylindrocyclophane D by feeding \(^2\)H, \(^{13}\)C, and \(^{18}\)O-labeled sodium acetates to *Cylindrospermum lichenforme* cultures.\(^6\)

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Very detailed and elegant NMR analysis of the isolated metabolites resulted in the proposed biosynthetic pathway shown in figure 3. Nonaketide 3 is the product of successive polyketide synthase (PKS)-mediated Claisen condensations of one acetyl-CoA (1) and eight malonyl-CoA (2) units. The PKS enzyme complex processes the intermediates of each Claisen condensation to adjust oxidation states of the polyketide as necessary. Full processing involves a carbonyl reduction-dehydration-olefin reduction sequence to give the saturated alkyl framework. The trans olefin of 3 is formed by a reduction-dehydration sequence in what is known as partial processing. Nonaketide 3 undergoes sequential intramolecular aldol condensations to form the six-membered ring 4, and subsequent dehydration, enolization, and decarboxylation to furnish resorcinol 5.
The methyl group is incorporated to the framework of 6 through a series of modifications, which is postulated to include a malonate condensation. Cylindrocyclophane D (7) is envisioned to arise by dimerization of the two resorcinol fragments 6, presumably through electrophilic aromatic substitution at C(7) with an olefin. It is unclear, however, whether the incorporation of the methyl group and reduction of the benzylic ketone occurs before or after the dimerization event.

II. Previous Synthetic Efforts to the Cylindrocyclophanes.

i. Albizati’s approach to a cylindrocyclophane model.

Albizati and Martin designed their approach to cylindrocyclophane A based on X-ray and NMR data that suggested that all six substituents on the macrocycle occupied equatorial positions. With the assumption that the natural product was the most thermodynamically favored of the isomers, they set out to use a two step procedure to equilibrate the methyl groups in bisketone 8 followed by a catalyst-controlled chiral reduction of the carbonyl to give cylindrocyclophane A (9) (Fig. 4). Alternatively, equilibration of the diastereomeric mixture 10 under Meerwein-Ponndorf-Verley conditions should also provide access to the diastereopure natural product. Model system

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11, which is devoid of the chiral butyl groups, was targeted in order to test this equilibration hypothesis.

Figure 4. Albizati’s equilibration hypothesis for the cylindrocyclophanes.

In order to avoid a high dilution dimerization event, Albizati and Martin chose to adopt a two step approach: a free radical-mediated closing macrocyclization of 12 followed by oxidation/epimerization of the methyl stereocenter (Fig. 5). The same methodology would be employed to couple enone 14 and alkyl halide 13. Both of these substrates are available from aryl bromide 15, which was derived in four steps from the commercially available benzoic acid 16.
Both alkyl halides 13 and 14 are available from a common intermediate in the synthesis (Scheme 1). Lithiation of aryl bromide 14 followed by trapping with 4-chloro-1-butanal generated the benzylic alcohol, which was dehydrated under acidic conditions to give trans olefin 17. Hydrogenation, deprotection, oxidation, and isoprenyllithium addition furnished alkyl chloride 19. This intermediate was then transformed to the alkyl iodide under Finkelstein conditions to give alkyl iodide 13. It was also subjected to Swern oxidation to give enone 14.

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The intermolecular coupling of iodide 13 and enone 14 was effected by using conditions developed by Luche\textsuperscript{10} (Scheme 2). Excess iodide 13 was added to a solution of enone 14 and activated zinc/copper couple under sonication to provide the coupled product 20 in good yields. After iodination and subsequent oxidation, the same free radical-mediated intramolecular coupling was attempted. The previously successful Luche conditions and the more standard Bu\textsubscript{3}SnH/AIBN conditions failed to afford the

desired macrocycle 12. There has been no further communication regarding this synthesis from the Albizati group.

Scheme 2. Attempts at a free radical-mediated macrocyclization.

ii. Trost’s approach to cylindrocyclophane A.

Schnaderbeck and Trost attempted to exploit the C₂-symmetry of cylindrocyclophane A and employ a dimerization event to assemble the 22-membered macrocycle. In a retrosynthetic sense, the natural product would arise from functionalization of macrocyclic tetraene 22, which is a product of a ruthenium-catalyzed

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Alder-Ene reaction\textsuperscript{12} of enyne 23. The Alder-Ene substrate is available from functionalized aromatic core 24.

![Figure 6. Trost's retrosynthetic analysis of cylindrocyclophane A.](image)

Electron-rich aryl system 24, derived from 3,5-dihydroxybenzoic acid (16), was converted via a two-step sequence to ketone 25 (Scheme 3). Installation of the butyl group furnished tertiary alcohol 26. Subsequent deprotection of the dioxolane under acidic conditions provided a separable mixture of eliminated (28) and non-eliminated (27) products. Both of these compounds were carried to dimerization precursors 29 and 30 by addition of TMS-alkynyl lithium to the aldehyde and followed by removal of the silyl group.

Despite the precedence that the Trost group has shown for the formation of macrocycles via the ruthenium-catalyzed Alder-ene reaction, the desired system was resistant to the reaction conditions. The use of different ruthenium catalysts under various reaction conditions only resulted in polymerization or the recovery of starting materials.
materials (eq. 2). The lack of reactivity was attributed to lack of coordinating functionality on the molecule distant to the reacting site, a characteristic that was noted earlier in the thesis work of Schnaderbeck to be necessary for a macrocyclization event to occur.

\[
\begin{align*}
\text{HO} & \quad \text{Ru} \quad \text{Cl} \\
\text{MeO} & \quad \text{Ru} \quad \text{Cl} \\
\text{Me} & \quad \text{O} \\
\text{Me} & \quad \text{OH} \\
\text{or} & \\
\text{HO} & \quad \text{Ru} \quad \text{Cl} \\
\text{MeO} & \quad \text{Ru} \quad \text{Cl} \\
\text{Me} & \quad \text{O} \\
\text{Me} & \quad \text{OH} \\
\text{Ru \ cat.} & \quad \text{polymerization} \\
& \quad \text{and} \\
& \quad \text{recovered SM}
\end{align*}
\]

(2)

iii. Hoye’s approach to cylindrocyclophane A.

Hoye, Humpal, and Moon recently reported a strategy towards cylindrocyclophane A. They chose to exploit the C2-symmetry of 9 by incorporating a late-stage Horner-Wadsworth-Emmons coupling of phosphonate ester 32 to provide access to cyclic dimer 31 (Fig. 7). Macrocyclizations using these type of phosphonate esters under the mild conditions are well-precedented. The lone stereocenter in 32 was envisioned to arise from a diastereoselective Ireland-Claisen rearrangement of 33. Allyl enolate 34 was derived in several steps from benzaldehyde 35, which in turn originated from 3,5-dihydroxybenzoic acid (16).

Similar to Trost’s work, Hoye’s synthesis commences with the elaboration of functionalized resorcinol derivative 35 (Scheme 4). Horner-Wadsworth-Emmons olefination followed by borohydride reduction under Luche conditions\textsuperscript{16} afforded exclusively the \textit{trans} allylic alcohol 37.

Installation of the chiral butyl group presented a major challenge in Hoye’s synthesis (Fig. 8). Early attempts to add butyl cuprates to enone 38 proved difficult.\(^{17}\) Alkylation strategies with chiral oxazolidinone 40 likewise were unsuccessful.

Figure 8. Unsuccessful incorporation of the butyl group.

Intermolecular rearrangements were then pursued due to the lack of reactivity of systems 38 and 40. The enolate Claisen rearrangement depicted in Scheme 4 was conceived to overcome this problem. Racemic alcohol 37 was resolved to enantiopure acetate 34 using the commercially available lipase enzyme (Amano P-30) lipase from *Pseudomonas fluorescens*.\(^{18}\) Acetate 34 was recovered in a 93% yield after separation from recovered allylic alcohol (–)-37. Exposure of acetate 34 to KHMDs and trapping with TBS chloride provided the TBS-silyl ketene acetal, which underwent a [3,3]-sigmatropic rearrangement upon warming to ambient temperature to provide ester 33 as a single enantiomer.


Elaboration of silyl ester 33 commenced with reduction of the ester and hydrogenation of the olefin to provide primary alcohol 42 (Scheme 5). Oxidation of this alcohol was followed by installation of the \( \alpha,\beta \)-unsaturated ester of 43 via a Horner-Wadsworth-Emmons olefination. After reduction of ester 43 and formation of the corresponding allylic chloride, S\( _{\text{N}} \)2 displacement of the chloride with trimethyl phosphonoacetate gave stabilized phosphonate 44. Deprotection, hydrogenation, and oxidation were required in order to complete the dimerization precursor 45.
Scheme 5. Synthesis of saturated phosphonate ester 45.

As shown in scheme 6, optimized conditions for the Horner-Wadsworth-Emmons dimerization provided the macrocycle in good yield.\textsuperscript{19} The ester functionality of 46 then converted to the methyl group of the natural product. This was accomplished in a three-step sequence consisting of reduction, bromination of the allylic alcohol and hydride displacement in overall excellent yield. Finally, diastereoselective hydroboration with isopinocampheylborane (IpcBH\textsubscript{2}) and deprotection of the phenolic methyl groups provided cylindrocyclophane A in 24 overall linear steps.

iv. Smith’s synthesis of cylindrocyclophanes A and F.

In 1999, Smith, Kozmin, and Paone reported an initial first-generation synthesis of cylindrocyclophane F. This synthesis established the capability of ring-closing olefin metathesis to form the 22-membered macrocycle (Scheme 7) of the natural product. Using Myers’ reductive alkylation protocol, the carbon-carbon bond of 50 was formed between alkyl iodide 48 and silylated tosyl hydrazone 49. Deprotection of the MOM group, oxidation of the resultant alcohol, and one carbon homologation with the methyl Wittig reagent furnished diene 51. This diene was subjected to the first-generation

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21 For recent reviews, see: (a) Grubbs, R. H.; Chang, S. Tetrahedron 1998, 54, 4413. (b)
Grubbs catalyst to afford the completed macrocycle 52 in 88% yield. Finally, hydrogenation and deprotection of the phenolic methyl ethers provided cylindrocyclophane F (53) in 20 linear steps.

Scheme 7. Smith’s first-generation approach to cylindrocyclophane F.

A year later, in the communication immediately following that of Hoye and coworkers, Smith, Kozmin, Adams, and Paone reported a more efficient synthesis to cylindrocyclophanes A and F that featured a remarkable olefin metathesis dimerization
strategy of dienes such as 54 (Fig. 9). Diene 54 is accessible from resorcinol derivative 55, which is available in one step as the product of a Danheiser annulation with siloxyacetylene 56 and cyclobutenone 57.

Figure 9. Smith’s retrosynthetic plan for cylindrocyclophanes A and F.

Smith’s synthesis of cylindrocyclophane A began with synthesis of the appropriate cyclobutenone 60, which was available in two steps from alkyne 58 (Scheme 8).

Scheme 8. Synthesis of cyclobutenone 60.

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Synthesis of siloxyacetylene 56 began with alkylated Evans oxazolidinone 61, available in three steps from the corresponding oxazolidinone. Reduction to the carboxylic acid followed by conversion to the ethyl ester furnished 62 in excellent yield. Alkyne 56 was obtained via a Kowalski ester homologation in which the oxyacetylene rearrangement product is trapped with TIPSOTf (Scheme 9).

**Scheme 9. Synthesis of siloxyacetylene 56.**

Assembly of the aromatic moiety 63 was accomplished by heating acetylene 56 with cyclobutenone 60 to effect the Danheiser benzannulation. The aromatic stannane was converted to the aryl iodide followed by TIPS deprotection and reprotection of both phenols as methyl ethers completed formation of aryl iodide 64 in good overall yield for the four step sequence (Scheme 10). Installation of the northern fragment commenced with the lithium/halogen exchange of 64 and subsequent addition into the Myers amide furnished a ketone. This ketone was then diastereoselective reduced to the corresponding

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alcohol with (+)-B-chlorodiisopinocampheylborane (19:1 d.r.) and silyl-protected to complete synthesis of diene 65.

**Scheme 10. Elaboration to an RCM dimerization precursor.**

![Scheme 10](image)

Synthesis of the corresponding diene 67 for cylindrocyclophane F proceeded in a similar sequence of events from alkyne 56 and cyclobutenone 66 (eq. 3).

![Equation 3](image)

After a survey of the Grubbs ruthenium metathesis catalysts and the Schrock molybdenum metathesis catalyst, the Schrock catalyst was found to effect the dimerization in good yields (Fig. 10). Despite the fact that a mixture of olefin isomers and head-to-head and head-to-tail dimers were all possible products from this reaction, only the *trans* head-to-tail dimer was observed. This truly remarkable example of the
reversible nature of the cross-metathesis was elegantly investigated in a full article from the Smith group in 2001.  

![Diagram](image)

**Figure 10.** RCM dimerization to form the cylindrocyclophane macrocycle.

Elaboration of macrocycles 68 and 69 required few steps to reach the final synthetic targets (Scheme 11). Hydrogenation and deprotection of 69 provided cylindrocyclophane F (53) in 11 linear steps. Deprotection of the TES group, hydrogenation and nucleophilic deprotection of the methyl ethers furnished cylindrocyclophane A (9) in 16 linear steps.

![Scheme 11](image)

**Scheme 11.** Smith’s second-generation endgame to the cylindrocyclophanes.

III. First-generation Approach to Cylindrocyclophane F.

In choosing a natural product target within our laboratories, we look for molecules of biological importance and architectural complexity that will highlight methodologies that have been developed by our group. When this project began late in 2002, the group had been extensively exploring the utility of iminium activation technologies and a new area of MacMillan group methodology was emerging: a nickel-catalyzed cross-coupling between aryl boronic acids and trimethylanilinium salts.\(^{30}\) Cylindrocyclophane F appeared to be an architecturally intriguing target to expand the scope of this nickel-catalyzed cross-coupling to the B-alkyl Suzuki coupling. However, before embarking upon a total synthesis, the B-alkyl Suzuki cross-coupling of aryltrimethylammonium salts had to be developed.

i. Suzuki cross-couplings of aryltrimethylammonium salts.

Transition metal-catalyzed cross-coupling reactions have emerged as a powerful tool for carbon-carbon bond formation.\(^{31}\) In this context, aryl iodides, triflates, bromides, and chlorides have found broad utility as electrophilic cross-coupling partners. However, simple aryl amines have not yet been widely used as electrophilic oxidative insertion partners. This is surprising considering the widespread availability of aryl amines and


their application as \( \cdots \)-nucleophiles in a variety of synthetic transformations. One such example of insertion into an aryl-nitrogen bond is the cross-coupling of aryl diazonium salts, which requires derivitization of the primary aryl amine to the diazotized compound (eq. 4).\(^{32}\)

\[
\text{Classical Diazotization Sequence}
\]

\[
\text{Trialkylanilinium Salt Sequence (Wenkert)}
\]

In 1988, Wenkert reported the nickel(II)-catalyzed Kumada cross-coupling of aryltrimethylammonium iodides (eq. 5).\(^{33}\) While the scope of the reaction was very limited in terms of both reacting partners and the yields were less than optimal, this research introduced the concept that dialkylanilines might be utilized as oxidative insertion substrates via a simple nitrogen quaternization. It is presumed that the metal insertion is facilitated by lengthening and concomitant weakening of the C–N bond that occurs upon quaternization.


Our lab reported in 2003 that this catalytic concept could be applied to a Suzuki cross-coupling with aryltrimethylammonium triflates and aryl boronic acids using a novel IMes•Ni(0) catalyst complex.\textsuperscript{30} Ni(COD)\textsubscript{2} was found to be uniquely effective when employed in combination with IMes•HCl as the ligand with CsF as the requisite base conducted in dioxane. Under these conditions, this new Suzuki variant was found to provide excellent yields for a very broad range of both anilinium salts and boronic acids (eq. 6).

\textit{Trialkylanilinium Salt Sequence (MacMillan and Blakey)}

\begin{align*}
\text{NMe}_2 & \xrightarrow{\text{MeOTf}} \text{NMe}_2\text{OTf} \\
\text{Ar–B(OH)_2} & \xrightarrow{\text{Ni(COD)}_2 \text{IMes•HCl, CsF}} \text{Ar} \\
\text{dioxane, 80 °C} & \text{79–98% yields}
\end{align*}

ii. \textit{B-alkyl Suzuki cross-coupling investigations.}

A model system resembling the electron-rich resorcinol in the natural product was chosen to investigate the alkyl Suzuki cross-coupling.\textsuperscript{34} Starting from commercially available 3,5-dimethoxyaniline, anilinium salt 72 was prepared in two steps (Scheme 12). Bismethylation of aniline 70 followed by quaternization of the nitrogen with methyl triflate\textsuperscript{35} provided trimethylanilinium salt 72 in 83% yield for the sequence.


Scheme 12. Synthesis of trimethylanilinium salt.

The $B$-alkyl borane used in Table 1 was synthesized via hydroboration of the corresponding olefin with the dimer of 9-borabicyclononane (9-BBN). This alkyl borane moiety was chosen because alkyl boranes are known to be more reactive than their boronic acid and boronic ester counterparts.\textsuperscript{31a} They are, however, not stable to isolation and were thus generated in situ and added to the reaction mixture as a solution of known concentration.

Unfortunately, the conditions developed for the aryl boronic acid Suzuki coupling (eq. 5) were not efficient for the analogous alkyl boronate cross-coupling with 72. An initial base screen showed little reactivity in all cases, however, cesium fluoride did affect some carbon-carbon bond formation (Table 1, entry 1).
Table 1. Base screen for cross-coupling with model system.

<table>
<thead>
<tr>
<th>Entry</th>
<th>base</th>
<th>% conversion to 73</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CsF</td>
<td>~5</td>
</tr>
<tr>
<td>2</td>
<td>CsOH</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>KF</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>K₂CO₃</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>K₃PO₄</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>NaOt-Bu</td>
<td>trace</td>
</tr>
<tr>
<td>7</td>
<td>KOH</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>KOEt</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>NaOH</td>
<td>trace</td>
</tr>
<tr>
<td>10</td>
<td>NaOMe</td>
<td>0</td>
</tr>
</tbody>
</table>

A screen of phosphine and N-heterocyclic carbene ligands\(^{36}\) proved more rewarding. Still employing Ni(COD)\(_2\) and cesium fluoride as a base, most of the tested ligands provided some level of reactivity, with the exception of tri(tert-butyl)phosphine. The best results for the cross-coupling were obtained with tricyclohexylphosphine and the biphenylphosphine ligand L3 (Table 2, entries 5 and 7).\(^{37}\)

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Table 2. Ligand screen in the cross-coupling.

<table>
<thead>
<tr>
<th>Entry</th>
<th>ligand</th>
<th>% conversion to 73</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IMes•HCl</td>
<td>~5</td>
</tr>
<tr>
<td>2</td>
<td>sIMes•HCl</td>
<td>~5</td>
</tr>
<tr>
<td>3</td>
<td>L1</td>
<td>&lt;10</td>
</tr>
<tr>
<td>4</td>
<td>L2</td>
<td>&lt;10</td>
</tr>
<tr>
<td>5</td>
<td>L3</td>
<td>~10</td>
</tr>
<tr>
<td>6</td>
<td>Pt-Bu3</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>PCy3</td>
<td>25</td>
</tr>
<tr>
<td>8</td>
<td>none</td>
<td>0</td>
</tr>
</tbody>
</table>

The other reaction parameters were also investigated. A screen of nickel sources [NiCl2(dppf), NiCl2(dppp), Ni(acac)2, NiCl2(PPh3)2, Ni(PPh3)2(CO)2] showed Ni(COD)2 to be superior. A survey of solvents and reaction temperatures also did not increase the yield of this reaction. Finally, other transmetalating metals like magnesium and zinc (Fig. 11) were not effective in this cross-coupling system. Alkyl boronic acids and esters are generally more stable but less reactive cross-coupling reagents than trialkyboranes, and were found to be less reactive transmetalation partners.
While the reaction yield for the model system remained moderate (eq. 7), the concept of carbon-carbon bond formation via a $B$-alkyl Suzuki cross-coupling with trimethylanilinium salt 72 was proven to be feasible. It was at this point that the decision to proceed with the total synthesis of cylindrocyclophane F was made. It was foreseen that the Suzuki dimerization to the natural product would require the most focus in the development of optimal reaction conditions.

iii. Proposed catalytic cycle to explain nickel-catalyzed demethylation.

Blakey and MacMillan’s initial report of this novel Suzuki reaction did not include mechanistic investigations. The catalytic cycle put forth here is based upon the precedent of other nickel-catalyzed cross-couplings\textsuperscript{38} and observations made within this

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study.\textsuperscript{39} This section will consider the $B$-alkyl variant of the Suzuki cross-coupling investigated herein. It is important to note that the rate-determining step of the $B$-alkyl Suzuki cross-coupling tends to be the transmetalation step, whereas sp\textsuperscript{2} boronic acids undergo rapid transmetalation and the rate-determining step is generally oxidative addition.\textsuperscript{31,40} Figure 12 shows the proposed catalytic cycle for alkyl boranes (RBX\textsubscript{2}). Oxidative insertion of nickel(0) into the C–N bond of the trimethylanilinium species results in the release of trimethylamine. Addition of a fluoride X-type ligand completes the formation of a nickel(II) intermediate. Transmetalation via a four-centered transition state is facilitated by activation of the borane by another equivalent of the fluoride counterion. The nickel(II) product of transmetalation ultimately undergoes reductive elimination to release the desired product and nickel(0).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{catalytic_cycle.png}
\caption{Proposed catalytic cycle for $B$-alkyl Suzuki cross-coupling.}
\end{figure}


The common byproduct observed in the cross-coupling reactions of trimethylanilinium salts is demethylation of the starting material to form \(N,N\)-dimethylaniline. This is presumably the result of a nickel-catalyzed pathway or it is possibly promoted by exogenous base present in the reaction. In order to test this hypothesis, a simple experiment shown in figure 13 was conducted. Exposure of the anilinium salt to the reaction conditions displayed rapid demethylation, yet insignificant amounts of the dimethylaniline 71 were observed when nickel was not present.

![Figure 13. Nickel-catalyzed demethylation of trimethylanilinium salt.](image)

One possible explanation of this may be considering where the positive charge of the quaternized anilinium actually resides. For example, for the tetramethylammonium ion (Fig. 14), the formal positive charge is drawn on nitrogen because it is tetravalent (A). However, calculations have indicated that the nitrogen is essentially neutral and the positive charge actually is distributed evenly among the methyl groups, as shown in B.41

By analogy, the positive charge in the quaternized anilinium ions is distributed between the aryl and the three methyl groups.

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Figure 14. Charge distribution in the tetramethylammonium ion.

In the system at hand, there are two different C–N bonds into which the nickel can insert. It can either insert on the aryl-nitrogen bond (green arrow, Fig. 15) leading to the desired cross-coupled product or alternatively insert into the methyl–nitrogen bond (red arrow, Fig. 15) to form the dimethylaniline byproducts observed in these reactions. Because transmetalation is the rate-determining step and oxidative addition is reversible in B-alkyl Suzuki cross-couplings, this insertion into the nitrogen–methyl becomes a competitive side reaction.

Figure 15. Competing oxidative addition pathways on trimethylanilinium salts.
iv. **Retrosynthetic strategy for cylindrocyclophane F.**

Like our predecessors in this synthetic endeavor towards cylindrocyclophanes F, we chose to exploit the C2-symmetry of this molecule and perform a late stage dimerization to assemble the macrocycle (Fig. 16). In our retrosynthetic strategy, we envisioned using an in situ $B$-alkyl Suzuki coupling to dimerize trimethylanilinium salt 74 with a tethered alkyl boronate, giving rise to alkyl iodide precursor 75. Disconnection between C4 and C5 provides two enantiopure fragments: Wittig salt 77 and aldehyde 76. The latter is the direct product of an organocatalytic 1,4-addition of an electron-rich aniline into 2-heptenal. The Wittig salt 77 can be derived from enantiopure furan adduct 78, which is also the product of an organocatalytic 1,4-addition into crotonaldehyde with 2-methylfuran.

![Figure 16. Retrosynthetic plan.](image)

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Following the retrosynthetic route outlined in figure 17, the first step forward was to access the two enantiopure fragments 76 and 78 by the organocatalytic 1,4-conjugation addition of \( - \)-nucleophiles into \( \alpha,\beta \)-unsaturated aldehydes. In a forward sense, the addition of 3,5-dimethoxy-\( N,N \)-dimethylaniline (71) into heptenal, which would set the benzylic stereocenter of 76, needed to be verified. The reaction was not expected to be problematic, based on the wide scope of aniline nucleophiles in the work done by Paras and MacMillan.\(^{42} \) However, the steric bulk from both meta positions of the nucleophile would test the limits of this methodology. The first reaction proceeded to give the desired product using the reported optimal conditions though only in a 10% isolate yield (eq. 8). The reaction pathway was found to be operative, but optimization of solvent, co-catalyst, concentration, and temperature was necessary.

![Synthesis Diagram](image)

An initial temperature screen with HCl as the co-catalyst and methylene chloride as the solvent at \(-40 \, ^{\circ}\text{C}\) gave a 70% ee with full conversion (Table 3, entry 1), while higher temperatures gave lower enantioselectivities and lower temperatures gave lower conversions. In a subsequent solvent screen, however, chloroform, toluene, and THF emerged as the most effective solvents for this transformation (entries 2, 3, and 4).
Table 3. Solvent screen for organocatalytic aniline addition.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>conversion (%)</th>
<th>% ee&lt;sup&gt;a&lt;/sup&gt;</th>
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<td>1</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>74</td>
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<td>CHCl&lt;sub&gt;3&lt;/sub&gt;</td>
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<td>5</td>
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<tr>
<td>6</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>59</td>
<td>63</td>
</tr>
<tr>
<td>7</td>
<td>MeOH</td>
<td>59</td>
<td>41</td>
</tr>
<tr>
<td>8</td>
<td>Et&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>74</td>
<td>49</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by HPLC analysis of the corresponding alcohol

Meanwhile, a co-catalyst study was run in methylene chloride at −40 °C. Triflic acid, dichloroacetic acid, and 2,4-dinitrobenzoic acid imparted good enantioselectivities and/or good conversion to the reaction (Table 4, entries, 1, 4, and 5) so they were screened with the optimal solvents from Table 3 (Table 5).

Table 4. Representative co-catalyst screen.

<table>
<thead>
<tr>
<th>Entry</th>
<th>HX</th>
<th>pK&lt;sub&gt;a&lt;/sub&gt;</th>
<th>conversion (%)</th>
<th>% ee&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TfOH</td>
<td>−14</td>
<td>48</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>HCl</td>
<td>−8</td>
<td>63</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>TFA</td>
<td>−0.25</td>
<td>51</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>DCA</td>
<td>1.29</td>
<td>66</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>DNBA</td>
<td>1.86</td>
<td>58</td>
<td>83</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by HPLC analysis of the corresponding alcohol
Table 5. Survey of a combination of co-catalyst and solvent conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>HX</th>
<th>Solvent</th>
<th>conversion (%)</th>
<th>% ee(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCA</td>
<td>CHCl₃</td>
<td>83</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>DCA</td>
<td>THF</td>
<td>57</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>DCA</td>
<td>toluene</td>
<td>94</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>DNBA</td>
<td>CHCl₃</td>
<td>59</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>DNBA</td>
<td>THF</td>
<td>78</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>DNBA</td>
<td>toluene</td>
<td>85</td>
<td>91</td>
</tr>
<tr>
<td>7</td>
<td>TiOH</td>
<td>CHCl₃</td>
<td>52</td>
<td>89</td>
</tr>
<tr>
<td>8</td>
<td>TiOH</td>
<td>THF</td>
<td>82</td>
<td>73</td>
</tr>
<tr>
<td>9</td>
<td>TiOH</td>
<td>toluene</td>
<td>85</td>
<td>85</td>
</tr>
</tbody>
</table>

\(^a\) Determined by HPLC analysis of the corresponding alcohol

In chloroform, DCA and 2,4-DNBA had high enantioselectivities (Table 5, entries 1 and 4, 94% ee), but DCA showed a higher conversion. The reaction utilizing dichloroacetic acid in chloroform has been run on gram scale multiple times and consistently affords aldehyde 76 in excellent yield and enantioselectivity (eq. 9).

The organocatalytic addition of 2-methyl furan into crotonaldehyde had been developed previously in the lab.\(^{43}\) It was found that in situ reduction with sodium borohydride provided higher isolated yields of the alcohol 80, with an isolated 98% yield.
and 94% ee (Scheme 13). With alkylated furan 80 in hand, a suitable protecting group for the free hydroxyl was needed in order to withstand the subsequent oxidation of the furan ring.

Scheme 13. Undesired oxidation products of furan oxidation protocols.

A benzyl protecting group was installed, and on a small scale the reaction proceeded to afford the benzylated product 81. However, larger scale reactions (>50 mg) imparted a mixture of desired product 82 and overoxidized product 83, all present in different mixtures depending on the oxidation system (Ru(III), Ru(IV), ozone) that was used. Thus, to avoid the problem of overoxidation, a benzyol protecting group was installed and the oxidation via ozonolysis proceeded efficiently with a 70% yield to afford carboxylic acid 83 (Scheme 14).
Scheme 14. Successful ozonolysis of the furan to give acid 83.

Once carboxylic acid 83 was in hand, mild reduction conditions using borane-dimethyl sulfide complex reduced the acid to the alcohol while leaving the benzoyl ester intact in an 87% yield (eq. 10). Protection of the free alcohol with benzyloxymethyl ether (BOM) was followed by removal of the benzoyl protecting group using 1% NaOH in methanol. Subsequent iodide formation on the free hydroxyl provided iodide 85 with a yield of 55% over four steps.

\[
\begin{align*}
\text{Me} & \quad \text{O} & \quad \text{Me} \\
\text{O} & \quad \text{Me} & \quad \text{OH} \\
80 & \quad \text{BzCl, Et}_3\text{N} & \quad 98\% \text{ yield} \\
\text{Me} & \quad \text{O} & \quad \text{Me} \\
\text{O} & \quad \text{Me} & \quad \text{O} \\
84 & \quad \text{O}_3, \text{MeOH} & \quad \sim-78 ^\circ \text{C} \quad 70\% \text{ yield} \\
\text{HO} & \quad \text{Me} & \quad \text{O} \\
\text{O} & \quad \text{Me} & \quad \text{O} \\
83 & \quad 84 & \quad 85
\end{align*}
\]

\[
\text{Me} \quad \text{O} \quad \text{Me} \\
\text{O} \quad \text{Me} \quad \text{O} \\
83 \quad \text{BH}_3\text{-SMe}_2 \\
\text{BOMCl, DIPEA} \\
1\% \text{NaOH/MeOH} \\
PPh_3, I_2, \text{imid. CH}_3\text{CN/Et}_2\text{O} \\
85 \quad 83 \quad 85a
\]

vi. Myers’ reductive alkylation strategy.

A Myers reductive alkylation \cite{22} was used to forge the C4–C5 bond using alkyl iodide 85 and its TIPS protected analog 85a. First, formation of silylated tosyl hydrazone 86 was accomplished in two steps from aldehyde 76 (eq. 11). Next, the alkyl lithiiums produced from lithium/halogen exchange of iodides 85 and 85a were added to hydrazone 86 at –78 °C (eq. 12). Finally, the addition of acetic acid in trifluoroethanol was used to
promote the reductive alkylation to form the saturated product 87. However, no product could be isolated from the reaction mixture.

Consideration of the mechanism (Fig. 17) revealed that acetic acid is necessary for protodesilylation, which in turn initiates the reaction sequence. It was believed that the basic aniline moiety might be consuming the acetic acid necessary for protodesilylation. Thus, excess acetic acid was added to effect quaternization of the aniline moiety and facilitate desilylation. However, despite this effort none of the desired product 87 was observed. As a further testament to the poor reactivity of this system, n-butyllithium was added in an analogous fashion with no success. At this point, a different carbon-carbon bond formation event was investigated.

Figure 17. Myers’ reductive alkylation mechanism.
vii. Wittig olefination strategy.

It was realized that installation of an olefin at C4–C5 would not change the number of chemical transformations in the synthesis so long as the protecting group was susceptible to hydrogenation conditions. The BOM protecting group was therefore targeted as the appropriate protecting group in the olefination strategy. To iodide 85, triphenylphosphine was added in different solvents to form Wittig reagent 88 upon heating. Removal of the solvent furnished the desired olefination partner 88 (eq. 14). It was found that the upcoming Wittig olefination was more effective if the reagent was prepared from ether or THF rather than chlorinated solvents.

\[
\text{BOMO}_3\text{Me}_1 \text{I} \xrightarrow{\text{PPh}_3, \text{Et}_2\text{O}} \text{BOMO}_3\text{Me}_1^+ \text{PPh}_3^- \quad (13)
\]

The intermolecular olefination (Scheme 15) was completed using the iodide Wittig salt 88 to give olefin 89 in low yield. If the temperature was kept at \(-78^\circ\text{C}\) throughout the reaction, completing decomposition pathways were suppressed and the yield improved to 40%. The bromide Wittig salt of 88 is also reactive, however the reaction was not as efficient. With olefinated product 89 in hand, removal of the BOM group and reduction of the olefin could be accomplished under hydrogen pressure with a palladium catalyst. Surprisingly, the removal of the BOM protecting group was sluggish and low yields were obtained. Furthermore, the subsequent iodination protocol of the primary alcohol resulted in electrophilic substitution on the aromatic moiety before completion of the iodination.
While the above protecting group strategy was being investigated, the same Wittig olefination sequence was performed bringing in the furan moiety as phosphonium salt 92 (Scheme 16). The olefination proved to be more efficient; however, the hydrogenation required elevated pressure, and reduction of the olefin was concomitant with reduction of the furan to tetrahydropyran 94, albeit in low yields. The remainder of the mass was not recovered and decomposition was observed under these forcing conditions. Additionally, the Wittig reaction was unreliable with low yields occurring at times.

In search of a more reliable olefination, the nucleophilic and electrophilic moieties in the Wittig olefination were reversed; aldehyde 76 was transformed into Wittig salt 95. This unstabilized phosphonium salt proved to be unexpectedly unstable, and upon exposure to a variety of bases at –78 °C, β-elimination occurred and a mixture of olefinic products was isolated (eq. 15). The Wittig olefination approach was eliminated as a route to cylindrocyclophane F due to inconsistencies in the reaction and low yields associated with the subsequent protecting group removals.
viii. **Julia-Lythgoe olefination strategy.**

The Julia-Lythgoe olefination, traditionally, is a two-step carbon-carbon bond formation that results in olefinic linkages. This coupling procedure has the benefits of utilizing readily available \( \text{[\text{-sulfonyl carbanions}} \) and giving predominately \( E \) olefins (Fig. 18). The reducing conditions that are commonly used to cleave the \( \text{-oxysulfonate products} \) are not mild and thus functional group compatibility can be problematic for this procedure.

![Julia-Lythgoe Olefination](image)

![Julia-Kocienski Olefination](image)

**Figure 18. The Julia olefination.**

The modified Julia olefination, or the Julia-Kocienski olefination, has been reported in order to avoid the second reducing step that is required to eliminate the aryl sulfone (Fig. 8). The phenyl groups of the sulfone were ingeniously replaced with heteroaromatic system, like the benzothiozyl shown in equation 17. With small

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counterions, the addition of the sulfonyl carbanion into an aldehyde generates a closed transition state that eliminates in situ.

The one-step Julia-Kocienski olefination was first attempted. However, addition of octylsulfonyl phenyltetrazole model system\textsuperscript{46} into aldehyde \textit{76} did not form the desired olefin and only starting material was recovered (eq. 15).

\begin{equation}
\begin{array}{c}
\text{MeO} \quad \text{NMe}_2 \\
\text{Me} \quad \text{MeO} \\
\text{Me} \quad \text{OMe} \\
\text{C}_7\text{H}_{15} \quad \text{SO} \quad \text{N} \\
\text{N} \quad \text{N} \\
\text{Ph} \quad \text{base} \\
\end{array}
\quad \begin{array}{c}
\text{no reaction} \\
(15)
\end{array}
\end{equation}

Analogous to the Wittig investigations reported in the previous section, the reaction partners were reversed in an effort to attain reactivity for the olefination. In order to convert the aldehyde to the sulfone, thiol \textit{96} was prepared under Mitsunobu conditions and a mild oxidant was used to attempt oxidation of the thiol to the sulfone (Scheme 17). However, the basic \textit{N,N}-dimethylaniline proved to be problematic once again as it outcompeted the sulfone for oxidation and formed the undesired \textit{N}-oxide \textit{97} instead of the desired sulfone \textit{98}

Scheme 17. Oxidation sequence forms N-oxide.

Because of the inability of this system to under selective thiol oxidation, the two-step Julia olefination sequence was attempted. Synthesis of phenylsulfone 101 was accomplished in three steps from aldehyde 76 (Scheme 18). Sodium borohydride reduction of the aldehyde gave alcohol 99 in excellent yield. Iodination of the alcohol followed by nucleophilic displacement of the alkyl iodide with sodium benzenesulfinate provided phenylsulfone 101 in good yield.

Meanwhile, preparation of olefination partners with began with chiral aldehyde 107a (R = OPMB) as a target (Scheme 19). Drawing from the chiral pool, (R)-Roche ester 102 was protected as its para-methoxybenzyl ether 103, which was then subjected to a two-step Kowalski ester homologation in which dibromoketone 104 was isolated en route to the one-carbon homologation product 105. Reduction of the ethyl ester in 105 was followed by oxidation of the primary alcohol with TEMPO to afford the desired aldehyde 107a containing a PMB-protected alcohol.

The detailed mechanism for the Kowalski ester homologation is shown in figure 19. The methyl ester 103 was converted to the dibromoketone 104, which was then converted to the vinyl dibromide. Lithium/halogen exchange in the presence of butyllithium yields a dianion, which upon warming causes rearrangement to the acetylene and concomitant bromide displacement. The ynolate anion is then protonated in acidic
ethanol. The resulting enol is in equilibrium with the ketene, which is eventually consumed by the acidic ethanol, affording the one-carbon homologated product 105.

Figure 19. Mechanism of the Kowalski rearrangement.

Preparation of the siloxy analogue of 107 was completed using novel reaction methodology developed within the MacMillan lab at the same time as this research. The enantioselective organocatalytic 1,4-hydride reduction of enals reported in early 2005 was applied in the synthesis of compound 107b. The reduction of the TIPS-protected enal 108 was performed using Hantzsch ester in the presence of chiral tert-butyl imidazolidinone catalyst to provide the desired product in 74% yield and 90% ee (eq. 16).

\[ \text{O\text{MeOTIPS}} \quad 108 \quad \text{O\text{EtO}} \quad 107b \]

(eq. 16)

The nucleophilic addition of the carbanion of sulfone 101 into aldehydes 107a or 107b (R = OPMB or OTIPS) proceeded in 74% yield to give adducts 109 after in situ acetylation. However, when acetates 109 were subjected to sodium/mercury amalgam,48 samarium diiodide,44e,49 or magnesium/mercuric chloride,50 the desired elimination product was not observed as the system slowly decomposed under the reaction conditions. It was hypothesized that the ether groups could be problematic so the acetoxy sulfone 109c derived from addition of 101 into isovaleraldehyde (107c, R = H) was subjected to the reducing conditions. Even with a large excess of reagent at elevated temperature, this system was also resistant to elimination and slowly decomposed. Decomposition pathways produced a variety of alkyl side products, which was suggestive that the aniline moiety was a possible reason for the failure of this system to produce the desired olefin product.

Scheme 20. Julia olefination two-step sequence.


The proposed mechanism involves a one electron transfer from the Na(Hg) or SmI₂ to reduce the vinyl sulfone to the vinyl radical, which is further reduced to the vinyl carbanion (Fig. 20).44

![Figure 20. Proposed mechanism for cleavage of acetoxy sulfones.](image)

It is plausible that the dimethoxyaniline moiety accepts the electrons being donated to the system by the Na(Hg) amalgam or SmI₂, giving rise to an intermediate (Fig. 21) that was inert to further reduction. Extended reaction times resulted in the slow cleavage of the aromatic carbon and C1 of the alkyl chain, which would explain the various hydrocarbon side products that were observed as decomposition products.

![Figure 21. An unreactive intermediate under one electron reducing conditions.](image)
IV. Second-generation Approach to Cylindrocyclophane F.

i. Revised retrosynthetic strategy.

During the course of these efforts, another more efficient route to 75 was successfully pursued in order to bring through larger amounts of material with which to test the dimerization key step. The C4–C5 olefination strategy was abandoned in favor of a new strategy that would eliminate this disconnection entirely. The same dimerization of alkylborane intermediate 74 was targeted, however synthesis of iodide precursor 75 was revised. It was established in section III (vide infra) of this chapter that the organocatalytic addition of dimethylaniline 71 was a very efficient method to forge the aryl carbon bond. It was envisioned that a fully functionalized α,β-unsaturated aldehyde like 110 could be easily synthesized and be subjected to the previously developed organocatalytic 1,4-addition conditions to access dimerization precursor 75 (Fig. 22).

![Figure 22. Alternate retrosynthetic strategy.](image-url)
Scheme 21. Successful synthesis of the dimerization precursor.

Starting with the commercially available (R)-Roche ester 102, homologation to \( \text{a,b-unsaturated aldehyde 110} \) commenced with a four-step sequence that had literature precedent (Scheme 21). Protection of the Roche ester 102 followed by reduction furnished benzyl ether 111 in good yield.\(^{51}\) Conversion of the free hydroxyl of 111 to tosylate 112\(^{52}\) followed by subsequent five-carbon homologation with the cuprate of 4-


pentenylmagnesium bromide gave olefin 113.\textsuperscript{53} Cross-metathesis\textsuperscript{54} of 113 with crotonaldehyde using the second-generation Grubbs metathesis catalyst gave an excellent yield of \textit{E}-enal 110.

The organocatalytic addition of aniline 71 to aldehyde 110 under the conditions previously described gave excellent yield of a single diastereomer 114. Two-carbon homologation followed by simultaneous deprotection and olefin reduction yielded alcohol 90. Finally, an efficient two-step iodide formation provided dimerization precursor 75 and, more importantly, provided access to sufficient quantities of material to test the cross-coupling dimerization outlined in Figure 21.

\textbf{ii. Investigations into the Suzuki dimerization.}

The proposed Suzuki dimerization sequence involves three steps: (i) lithium/halogen exchange to form an alkyl borane by nucleophilic addition into 9-BBN-X where X is a leaving group such as OMe, OTf, iodide or bromide, (ii) quaternization of the aniline moiety with methyl triflate, and (iii) cross-coupling dimerization under the nickel(0)-catalyzed conditions developed in section II of this chapter.


Consideration of the necessary alkyl borane for the desired dimerization reveals that an asymmetric hydroboration would have to be performed in order to set the desired stereochemistry at C6 of the alkyl chain. However, there are no asymmetric methods to do an enantioselective hydroboration on a 1,1-disubstituted terminal olefin to date (Fig. 23).\(^{55}\) Instead, the alkyl borane must be generated in situ starting with the corresponding alkyl iodide. Lithium/halogen exchange of the alkyl iodide with subsequent addition of the resulting alkyl lithium into BBN–X (where X is a leaving group) provides complementary access to alkyl boranes.

Figure 23. Access to \(\text{\(\mathbb{D}\)}\)-stereogenicity on the alkyl borane.

This approach to generate \(\text{\(\mathbb{D}\)}\)-chiral boranes has been applied to natural product synthesis. In 1998, Marshall employed this in his total synthesis of discodermolide to form the trisubstituted olefin (Fig. 24).\(^{56}\) In a similar manner, Lee used the same system to form the trisubstituted olefin in route to the total synthesis of kendomycin.\(^{57}\)

---


Using the same lithiation/transmetalation sequence reported by Marshall and later by Lee, alkyl iodide 75 was converted to alkyl borane 115 at −78 °C in THF by addition to 9-BBN-OMe (Scheme 22). To this reaction mixture, methyl triflate was added at 0 °C and warmed to room temperature, at which point the solvent was removed and dioxane was added. This dioxane solution of 116 was then cannulated into a flame-dried vial containing Ni(COD)$_2$, PCy$_3$, and CsF. The heterogeneous mixture was then heated to 80 °C for 12–16h. Analysis of the reaction mixture only showed the formation of the protodeborylated product 118a and trace amounts of eliminated product 118b. Despite variation in ligand, base, borane counterion (9-BBN-X), and/or solvent, the desired cross-coupled dimerization product 117 was never observed. In fact, there was no evidence for
any carbon-carbon bond formation. In order to confirm that the desired intermediates 115 and 116 were indeed being formed, NMR was used to monitor the individual steps. Formation of the alkyl borane 115 was observed by a chemical shift of about 88 ppm in the $^{11}$B NMR. Quaternization of the aniline 116 was seen in the downfield shifts of the aryl hydrogens and N-methyl hydrogens in the $^1$H NMR spectrum.

Scheme 22. Key Suzuki cross-coupling dimerization sequence.

The most notable difference between this system and the model system previously explored was the preparation of the alkyl borane. The model system was generated via hydroboration whereas the real system utilized a lithiation/transmetalation procedure that generated an equivalent of lithium methoxide as a byproduct. Metal-catalyzed cross-
couplings are notoriously sensitive and very particular for tailored reaction conditions, thus it was hypothesized that lithium methoxide was poisoning the reaction.

iii. Reassessment of the B-alkyl Suzuki cross-coupling.

In order to test effects of the method in which the alkyl boranes were prepared, the initial model system was reinvestigated (Table 6). The alkyl 9-BBN-derivative prepared via hydroboration of the terminal olefin (prep A) gave the cross-coupled product 73 in 25% yield, the same result that was previously observed (entry 1). The alkyl borane that was formed by lithiation/transmetalation onto 9-BBN-OMe (prep B) did not provide any of the desired cross-coupled product (entry 2). However, when lithium methoxide was added to the reaction conditions in entry 1 the cross-coupling was shut down, thus confirming that lithium methoxide is not tolerated in this procedure. In order to rectify this issue of counterion compatibility, the lithiation/transmetalation sequence was performed with 9-BBN-OTf. The triflate counterion was proven to be a spectator in this reaction as it was the counterion for trimethylanilinium salt 72. Surprisingly, the cross-coupling still did not work (entry 4) though it was plausible that the triflate should not affect the reaction.
Table 6. Probing the counterion effect in the Suzuki cross-coupling.

<table>
<thead>
<tr>
<th>Entry</th>
<th>alkyl borane prep</th>
<th>additives</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>none</td>
<td>25%</td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>none</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>LiOMe (1 equiv)</td>
<td>no reaction</td>
</tr>
<tr>
<td>4</td>
<td>C</td>
<td>none</td>
<td>no reaction</td>
</tr>
</tbody>
</table>

A: hydroboration

B: lithiation/transmetalation onto 9-BBN-OMe

C: lithiation/transmetalation onto 9-BBN-OTf

The lack of reactivity seen for the procedure in table 6, entry 4 was unexpected and prompted a boron NMR study in order to ascertain the exact nature of the different boron intermediates. Figure 25 shows boron NMR shifts that will be of importance in this study.58

Literature precedent suggested that the nucleophilic addition of an alkyl lithium into 9-BBN-OMe leads to the formation of the boron “ate” complex,\textsuperscript{56,57} which would be expected to have an \(^{11}\text{B}\) NMR chemical shift equal to or less than zero. As shown in equation 17, it was discovered that the addition produced the trialkylborane, characterized by a clean NMR signal of 88 ppm. This also explains the full dissociation of methoxide counterion to form lithium methoxide in the reaction.

Interestingly, the addition of the same alkyl lithium species into 9-BBN-OTf did not produce a signal for the trialkylborane (80–90 ppm) or the boron “ate” (<0 ppm). Instead, a chemical shift of 56 ppm was observed, which is indicative of a dialkylborate species. Rearrangements of trialkylboron “ate” complexes have been reported,\textsuperscript{59} and the product of this reaction is proposed to be the 9-OBBD derivative shown in equation 18. This intermediate, however, has not been conclusively identified.

It was presented in this chapter that substrates less reactive than trialkylboranes were not compatible as transmetalating partners in the nickel(0)-catalyzed cross-coupling reaction with trimethylanilinium salts. Even though the triflate counterion should be inert to the reaction conditions, the less reactive dialkylborate in equation 18 did not participate in cross-coupling.

**Conclusion.**

A novel $B$-alkyl Suzuki cross-coupling with trimethylanilinium salts was observed under nickel(0)-catalysis. Using this methodology, a $B$-alkyl Suzuki cross-coupling dimerization strategy was employed in the total synthesis of cylindrocyclophane F in order to assemble the $C_2$-symmetric macrocycle. Synthesis of a dimerization precursor was accomplished in ten steps and featured an organocatalytic conjugate addition of an electron-rich aniline to an $\alpha,\beta$-unsaturated aldehyde to set the benzylic stereocenter with excellent stereocontrol. Access to cylindrocyclophane F via a $B$-alkyl Suzuki cross-coupling dimerization was not feasible due to incompatibility of the preparation of the requisite trialkyl borane with the cross-coupling conditions. At this point, a new synthetic strategy needed to be devised in order to identify a more efficient reaction partner for the cross-coupling.
Supporting Information.

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego. Dimethylformamide was obtained from EM Science in a DriSolv™ container and used as supplied. Non-aqueous reagents were transferred under nitrogen via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using an ice-water bath. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method of Still. Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or by anisaldehyde stain.

\(^{1}\)H and \(^{13}\)C NMR spectra were recorded on a Mercury 300 Spectrometer (300 MHz and 75 MHz) as noted, and are internally referenced to residual protio solvent signals (CDCl\(_3\) = 7.26 ppm, C\(_6\)D\(_6\) = 7.16 ppm, D\(_6\)-acetone = 2.05 ppm). Data for \(^{1}\)H NMR are reported as follows: chemical shift (\(\delta\) ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for \(^{13}\)C NMR are reported in terms of chemical shift. Data for \(^{11}\)B NMR are reported in terms of chemical shift and referenced to BF\(_3\)OEt\(_2\) (\(\delta = 0\)). IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm\(^{-1}\)). Mass spectra were obtained from the California Institute of Technology mass spectral facility. Gas liquid chromatography (GLC) was

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performed on Hewlett-Packard 6850 and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using a Bodman Chiraldex □-DM (30 m x 0.25 mm) column or a Chiraldex □-TA (30 m x 0.25 mm) as noted. High pressure liquid chromatography (HPLC) was performed on Hewlett-Packard 1100 Series chromatographs using a Chiralcel AD column (25 cm) and AD guard (5 cm) or a Chiralcel OD-H column (25 cm) and OD-H guard (5 cm) as noted. Optical rotations were recorded on a Jasco P-1010 polarimeter, and \( [\alpha]_D \) values are reported in 10\(^{-1}\) dg cm\(^2\) g\(^{-1}\); concentration (c) is in g/100 mL.

**3,5-Dimethoxy-N,N,N-trimethylanilinium triflate (72).** To a 0.5 M solution of 3,5-dimethoxy-N,N-dimethylaniline 71 (1.81 g, 10 mmol) in dichloromethane (20 mL) was added trifluoromethanesulfonate via syringe (1.08 mL, 10.5 mmol). The reaction was stirred at room temperature for 15 minutes, after which pentanes or hexanes was added until a white solid precipitated from solution. The solid was filtered and washed with pentanes or hexanes to afford the anilinium salt 72 as a white solid (3.46 g, quantatative).

IR (film) 1658, 1625, 1261, 1163 1033, 640 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) 6.83 (d, 2H, \( J = 1.5\) Hz, ArH), 6.53 (t, 1H, \( J = 1.8\) Hz, ArH), 3.86 (s, 6H, OCH\(_3\)), 3.69 (s, 9H, NCH\(_3\)) \( ^{13}\)C NMR (125 MHz, CDCl\(_3\)) 162.1, 142.7, 101.8, 98.2, 57.4, 56.2. \(^{19}\)F NMR (282 MHz, CDCl\(_3\)) –78.5. HRMS (FAB+) exact mass calculated for [MH – OTf]\(^+\) (C\(_{11}\)H\(_{18}\)NO\(_2\)) requires \( m/z \) 196.1338, found \( m/z \) 196.1338.
1,3-Dimethoxy-5-(2-methyl-4-phenylbutyl)benzene (73). The reagents and glassware in this reaction were thoroughly dried prior to use. Dioxane was prepared by freeze-pump thaw deoxygenation. A 0.6M stock solution of the alkyl BBN derivative was prepared as follows: To a flame-dried flask charged with 9-BBN dimer (329 mg, 1.35 mmol) under argon at ambient temperature, 3-methyl-4-phenyl-1-butene\(^{62}\) (395 mg, 2.7 mmol) was added in 4.5 mL dioxane via syringe. This mixture was stirred until all of the BBN dimer dissolved, at which point the hydroboration was complete.

To a flame-dried 2-dram vial equipped with stir bar and septa-filled cap, anilinium salt 73 (51.8 mg, 0.15 mmol), bis(cyclooctadiene)nickel (4.3 mg, 0.015 mmol), and cesium fluoride (68 mg, 0.45 mmol) were added in a glove box under inert atmosphere. Upon being removed from the glove box, the reaction vessel was placed under a dry argon atmosphere in order to add tricyclohexylphosphine (150 \(\mu\)L of a 0.1 M stock solution in dioxane), alkyl borane (0.5 mL of the stock solution prepared above, 0.30 mmol), and dioxane (0.95 mL) (3.46 g, quantatative). The reaction was sealed and heated to 80 °C for 15 h. The reaction was quenched with 5 mL saturated ammonium chloride and extracted with ethyl acetate (3 x 5 mL). The organic layers were dried with magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography (gradient elution from 0 to 5% EtOAc/hexane) provided the desired compound as the major

component in a mixture of other side products. Silica gel chromatography was done a second time to afford the title compound 73 as an oil with about 80% purity (10 mg, approx. 25% yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.14-7.32 (m, 5H, PhH), 6.53 (d, 2H, $J$ = 1.8 Hz, ArH), 6.36 (t, 1H, $J$ = 1.8 Hz, ArH), 3.77 (s, 6H, OCH$_3$), 2.56-2.78 (m, 2H, ArCHHCH), 2.37 (dd, 1H, $J$ = 9.0, 12.6 Hz, ArCHH), 1.35-1.94 (m, 4H, PhCH$_2$CH$_2$), 0.95 (d, 3H, $J$ = 7.2 Hz, CHCH$_3$).

(S)-3-(4-(Dimethylamino)-2,6-dimethoxyphenyl)heptanal (76). A solution of 3,5-dimethoxy-$N,N$-dimethylaniline$^{63}$ (1.81 g, 10 mmol), imidazolidinone DCA salt ($R,R$)-79•DCA (668 mg, 2 mmol) in chloroform (20 mL, 0.5M) was cooled to –60 °C. (E)-2-Heptenal (4 mL, 30 mmol) was added via syringe. The reaction was stirred at –60 °C for 48 h, at which point the reaction mixture was concentrated and loaded onto a silica gel column. Flash chromatography (5% EtOAc/pentanes) provided the enantioenriched aldehyde 76 as an orange oil (2.65 g, 91% yield, 92% ee). IR (film) 2956, 2930, 2856, 1720, 1613, 1568, 1507, 1427, 1390, 1279, 1255, 1207, 1129, 1007, 797, 638 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.59 (t, 1H, $J$ = 3.0 Hz, CHO); 5.91 (s, 2H, ArH); 3.78 (s, 6H, OCH$_3$); 3.77 (m, 1H, ArCH); 2.95 (s, 6H, NCH$_3$); 2.81 (ddd, 1H, $J$ = 3.0, 9.0, 16.5 Hz, CHHCHO); 2.66 (ddd, 1H, $J$ = 3.0, 6.6, 16.2 Hz, CHHCHO); 1.76–1.92 (m, 1H, CHHCH); 1.50–1.62 (m, 1H, CHHEt); 1.04–1.3 (m, 4H, CH$_2$CH$_2$CH$_3$); 0.82 (t, 3H, $J$ = 7.2 Hz, CH$_2$CH$_3$); $^{13}$C

NMR (125 MHz, CDCl₃) δ 204.7, 159.1, 150.3, 107.8, 89.5, 55.4, 48.2, 40.6, 33.5, 30.1, 29.2, 22.7, 14.1; HRMS (EI+) exact mass calculated for [M•]+ (C₁₈H₂₆O₄) requires m/z 293.1991, found m/z 293.1994; [α]D = −5.37 (c = 0.95, CHCl₃). The enantiomeric ratio was determined by HPLC analysis of the corresponding alcohol 80, obtained by sodium borohydride of the aldehyde, using a Chiralcel AD and AD guard column (1.0% ethanol/hexanes, 254 nm, 1.0 mL/min); (S) isomer tᵣ = 24.7 min, (R) isomer tᵣ = 21.7 min.

(S)-3-(5-Methylfuran-2-yl)butan-1-ol (80). Sodium borohydride (4.16 g, 110 mmol) was added to a solution of furan adduct 78 (15.2 g, 100 mmol) in 200 mL of CH₂Cl₂/EtOH (3:1 v:v) at 0 °C. The reaction was stirred for 90 minutes before it was carefully quenched with saturated NaHCO₃ at 0 °C. The biphasic mixture was warmed to ambient temperature and extracted with CH₂Cl₂ (3 x 150 mL). The organic layers were dried with sodium sulfate, filtered, and concentrated via rotary evaporation. Flash chromatography provided the alcohol as a slightly yellow oil (14.9 g, 97% yield). IR (film) 3342 (broad), 2967, 2933, 2878, 1567, 1454, 1380, 1221, 1047, 1020, 940, 780 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.84 (m, 2H, ArH), 3.65 (m, 2H, CH₂OH), 2.93 (app sex, 1H, J = 7.2 Hz, CHCH₃), 2.24 (s, 3H, CH₃furan), 1.85 (m, 1H, CHHCH₂OH), 1.76 (m, 1H, CHHCH₂OH), 1.25 (d, 3H, J = 6.6 Hz, CHCH₃). ¹³C NMR (125 MHz, CDCl₃) δ 158.1, 150.2, 105.6, 104.2, 60.8, 38.7, 29.8, 19.3, 13.4; HRMS (EI+) exact mass calculated for [M•]+ (C₉H₁₀O₂) requires m/z 154.0994, found m/z 154.0991. [α]D = +21.6 (c = 1.2, CHCl₃).
(S)-3-(5-Methylfuran-2-yl)butyl benzoate (84). Triethylamine (11.7 mL, 84.2 mmol) and catalytic DMAP was added to a solution of alcohol 80 (12.4 g, 80.2 mmol) in 160 mL CH₂Cl₂ at 0 °C under an argon atmosphere. Benzoyl chloride (9.8 mL, 84.2 mmol) was added and the reaction was slowly warmed to room temperature. It was stirred at room temperature until judged complete by TLC analysis. The reaction was diluted with EtOAc and washed sequentially with 2.0 N HCl, saturated NaHCO₃, then brine. The reaction was washed over a large silica plug and the solvents were removed in vacuo to afford the title compound 84 as a yellow oil (20.3 g, 98% yield). IR (film) 2968, 1716, 1602, 1567 1452, 1385, 1314, 1275, 1113, 1070, 1026, 939, 781, 711 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.03 (m, 2H, PhH), 7.56 (tt, 1H, J = 1.8, 7.5 Hz, PhH), 7.43 (m, 2H ArH), 5.84 (m, 2H, ArH), 4.34 (m, 2H, CH₂OBz), 3.00 (app sex, 1H, J = 7.2 Hz, CHCH₃), 2.22 (s, 3H, CH₃furan), 2.13 (ddt, 1H, J = 6.6, 7.8, 13.8 Hz, CHHCH₂OH), 1.98 (ddt, 1H, J = 6.6, 7.2, 13.8 Hz, CHHCH₂OH), 1.25 (d, 3H, J = 6.6 Hz, CHCH₃). ¹³C NMR (125 MHz, CDCl₃) δ 166.4, 157.2, 150.2, 132.7, 130.2, 129.4, 128.1, 105.6, 104.5, 63.1, 34.6, 30.3, 19.4, 13.6; HRMS (EI⁺) exact mass calculated for [M⁺]⁺ (C₁₆H₁₈O₃) requires m/z 258.1256, found m/z 258.1262. [α]D = +39.7 (c = 1.14, CHCl₃).
(S)-2-Methyl-4-(phenylcarbonyloxy)butanoic acid (83). A solution of benzoyl ether 84 (20.2 g, 78.1 mmol) in methanol (250 mL) was cooled to −78 °C. Ozone was bubbled through the reaction until the starting material was consumed as judged by TLC analysis. The reaction was purged with oxygen for 20 minutes and slowly warmed to room temperature (ozone is potentially explosive: do this behind a blast shield or sash). The acidic mixture was made basic with 4N NaOH. The aqueous layer was washed with ether and separated. The aqueous layer was then acidified with 1N HCl and extracted with EtOAc (3 x 200 mL). The organic layers were dried with sodium sulfate, filtered, and concentrated in vacuo to furnish the carboxylic acid as a yellow oil (12.3 g, 70% yield). IR (film) 2975, 1722, 1453, 1276, 1176, 1114, 1071, 1027 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.41 (bs, 1H, COOH), 8.02 (m, 2H, PhH), 7.55 (m, 1H, PhH), 7.43 (m, 2H ArH), 4.35 (dt, 2H, J = 1.2, 6.6 Hz, CH₂OBz), 2.67 (app sex, 1H, J = 7.2 Hz, CHCH₃), 2.18 (m, 1H, J = CHHCH₂OBz), 1.88 (m, 1H, CHHCH₂OBz), 1.24 (d, 3H, J = 7.2 Hz, CHCH₃). ¹³C NMR (125 MHz, CDCl₃) δ 176.2, 166.2, 132.8, 129.4, 128.2, 105.6, 62.8, 51.7, 36.6, 32.4, 17.3; HRMS (FAB+) exact mass calculated for [MH]⁺ (C₁₂H₁₅O₄) requires m/z 223.0970, found m/z 223.0964. [α]D = +18.8  (c = 1.0, CHCl₃).
(S)-4-(Benzyloxymethoxy)-3-methylbutan-1-ol. Carboxylic acid 83 (12.3 g, 55.4 mmol) was taken up in 110 mL diethyl ether and cooled to 0 °C under a nitrogen atmosphere. Borane-dimethyl sulfide adduct (42 mL, 83.1 mmol) was added to the solution at 0 °C and the mixture was allowed to warm to ambient temperature for 2 h. The reaction was quenched with saturated NaHCO₃. The aqueous layer was separated and extracted with diethyl ether (2 x 100 mL). The organic layers were dried with sodium sulfate and concentrated to provide the free alcohol, which was used directly in the next step.

One gram of the crude alcohol (4.81 mmol) was taken up in 10 mL CH₂Cl₂ and diiso-propylethylamine (1.68 mL, 9.62 mmol) was added. Benzyloxymethyl chloride (2 mL, 14.43 mmol) was added via syringe and stirred at ambient temperature for 22 h. The reaction was diluted with ethyl acetate and washed over a silica pad with excess EtOAc. The EtOAc layer was removed via rotary evaporator. The product was inseparable from excess BOMCl, thus it was carried on to the next step without further purification.

The crude reaction residue was dissolved in 20 mL methanol. Sodium hydroxide (1.15 g, 28.8 mmol) was added and the reaction was stirred at room temperature for 16 h. 50 mL water was added to the reaction, which was then extracted with ethyl acetate (3 x 50 mL). The organic layers were dried with sodium sulfate, filtered, and the solvents removed in vacuo. Flash chromatography provided the alcohol as a colorless oil (708 mg, 58% yield over 3 steps). IR (film) 3409 (broad), 2931, 2877, 1455, 1380, 1109,
1047, 738, 698 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.34 (m, 5H, ArH), 4.77 (s, 2H, OCH$_2$O), 4.61 (s, 2H, PhCH$_2$O), 3.69 (m, 2H, CH$_2$OH), 3.48 (dd, 1H, $J = 6.3$, 12.0 Hz, BOMOCHH), 3.44 (dd, 1H, $J = 6.3$, 12.0 Hz, BOMOCHH), 2.11 (bs, 1H, OHOH), 1.91 (app sex, 1H, $J = 6.3$ Hz, CHCH$_3$), 1.66 (m, 1H, CHHCH$_2$OH), 1.50 (m, 1H, CHHCH$_2$OH), 0.97 (d, 3H, $J = 6.9$ Hz, CHCH$_3$). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 137.7, 128.4, 127.8, 127.7, 94.7, 73.5, 69.4, 60.9, 37.3, 30.8, 17.4; HRMS (FAB+) exact mass calculated for [MH]$^+$ (C$_{13}$H$_{19}$O$_3$) requires m/z 225.1491, found m/z 225.1493. $[\alpha]_D = – 3.87$ (c = 1.0, CHCl$_3$).

(S)-(((4-Iodo-2-methylbutoxy)methoxy)methyl)benzene (85). 4-(Benzylxymethoxy)-3-methylbutan-1-ol (224 mg, 1.0 mmol), triphenylphosphine (275 mg, 1.05 mmol), and imidazole (72 mg, 1.05 mmol) were dissolved in 2 mL Et$_2$O and 0.6 mL acetonitrile at room temperature. Once the mixture turned homogenous, it was cooled to 0 °C and iodine (254 mg, 1.0 mmol) was added. The reaction was stirred for 3 h at 0 °C, then filtered over silica with ether and the solvents were removed in vacuo. Rapid flash chromatography (10% EtOAc/hexanes) provided iodide 85 as a clear oil (326 mg, 98% yield). (IR (film) 2957, 2876, 1455, 1380, 1234, 1176, 1112, 1047, 737, 698 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.42 (m, 5H, ArH), 4.80 (s, 2H, OCH$_2$O), 4.65 (s, 2H, PhCH$_2$O), 3.48 (m, 2H, BOMOCH$_2$), 3.28 (m, 2H, CH$_2$I), 2.08 (m, 1H, CHHCH$_2$I), 1.94 (app sex, 1H, $J = 6.3$ Hz, CHCH$_3$), 1.75 (m, 1H, CHHCH$_2$I), 0.99 (d, 3H, $J = 6.6$ Hz, CHCH$_3$). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 137.8, 128.3, 127.8, 127.6, 94.7, 72.2, 69.3,
37.6, 34.4, 16.2, 4.6; HRMS (FAB+) exact mass calculated for [MH]+ (C_{13}H_{18}O_{2}) requires m/z 333.0352, found m/z 333.0359. [α]_D = -6.66  (c = 1.1, CHCl₃).

(S)-N'-(3-(4-(Dimethylamino)-2,6-dimethoxyphenyl)heptylidene)-4-methylbenzene-sulfonohydrazide.\textsuperscript{64} p-Toluenesulfonyl hydrazone (768 mg, 4.12 mmol) was added to a solution of aldehyde 76 (1.1 g, 3.75 mmol) in THF (18.75 mL, 0.2M). A catalytic amount of p-toluenesulfonic acid was added. The reaction was stirred for 10 h at room temperature, after which it was filtered over a pad of silica gel and the solvent was removed in vacuo. Flash chromatography (30% EtOAc/hexanes) provided the tosyl hydrazone as a yellow oil (1.114 g, 64% yield). IR (film) 3216, 2954, 2930, 2857, 1613, 1567, 1465, 1336, 1256, 1209, 1166, 1129, 1007, 670 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, CDCl₃) δ 7.87 (bs, 1H, NH), 7.73 (d, 2H, J = 8.4 Hz, ArH); 7.63 (d, 2H, J = 8.4 Hz, ArH); 7.26 (d, 2H, J = 8.1 Hz, ArH); 7.19 (d, 2H, J = 8.1 Hz, ArH); 6.97 (dd, 1H, J = 5.4, 6.3 Hz, CH=N); 6.68 (dd, 1H, J = 5.1, 7.2 Hz, CH=N); 5.85 (s, 2H, ArH); 5.83 (s, 2H, ArH); 3.74 (s, 6H, OCH₃); 3.69 (s, 6H, OCH₃); 3.35 (m, 1H, ArCH); 2.93 (s, 6H, NCH₃); 2.92 (s, 6H, NCH₃); 2.79 (m, 1H, CHHC=N); 2.56 (m, 1H, CHHC=N); 2.40 (s, 3H, C₆H₄CH₃); 2.37 (s, 3H, C₆H₄CH₃); 2.28 (dt, 1H, J = 5.4, 12.0 Hz, CHCHHCH₂); 1.64-1.85 (m, 1H, CHCHHCH₂); 0.92-1.5 (m, 4H, CH₃CH₂CH₃); 0.79 (t, 3H, J = 7.2 Hz, CH₃CH₃); 0.76 (t, 3H, J = 7.2 Hz, CH₃CH₃); \textsuperscript{13}C NMR (125 MHz, CDCl₃) δ 170.8, 159.1,

\textsuperscript{64} 5:4 rotamer ratio complicated interpretation of the spectra. Minor peaks noted in \textit{italics} where applicable.
154.6, 151.6, 143.3, 135.4, 129.3, 129.2, 127.7, 127.6, 107.2, 89.7, 60.4, 55.8, 40.7, 40.6, 36.7, 33.6, 33.1, 32.4, 32.2, 31.7, 30.2, 30.1, 22.8, 22.7, 21.6, 21.1, 14.2, 14.1; HRMS (FAB+) exact mass calculated for [MH]⁺ (C₂₄H₃₆N₃O₄S) requires m/z 462.2427, found m/z 462.2411.

(S,E)-N-(tert-Butyldimethylsilyl)-N’-(3-(4-(dimethylamino)-2,6-dimethoxyphenyl)-heptylidene)-4-methylbenzenesulfonylhydrazide (86). Triethylamine (0.50 mL, 3.59 mmol) was added to a solution of tosyl hydrazone (1.11 g, 2.76 mmol) in 13.8 mL THF at −78 °C under argon. tert-Butyldimethylsilyl trifluoromethanesulfonate (0.76 mL, 3.32 mmol) was added via syringe. The reaction was stirred for 15 min and the excess TBSOTf was quenched with 0.23 mL methanol. The cold reaction was diluted with hexanes and then washed sequentially with saturated NaHCO₃ and brine. The hexanes layer was dried with magnesium sulfate, filtered, and the solvent was removed in vacuo. Flash chromatography (25% EtOAc/hexanes) provided the silyl hydrazone 86 as an amorphous solid (1.29 g, 90% yield). IR (film) 2955, 2930, 2858, 1613, 1568, 1506, 1465, 1334, 1255, 1159, 1093, 937 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) [6] 7.62 (m, 2H, ArH); 7.25 (m, 2H, ArH); 5.87 (s, 2H, ArH); 3.73 (s, 6H, OC₃H₃); 3.43 (m, 1H, ArCH); 2.93 (s, 6H, NCH₃); 2.80 (m, 1H, CHHC=N); 2.61 (m, 1H, CHHC=N); 2.38 (s, 3H, C₆H₄CH₃); 1.68-1.82 (m, 1H, CHCHHCH₂); 1.42-1.54 (m, 1H, CHCHHCH₂); 1.01-1.33

[^2]: Rotomers around the imine bond caused proton NMR to be an indecipherable mixture at some chemical shifts.
(m, 4H, \(\text{CH}_2\text{CH}_3\)); 0.89 (s, 9H, SiMe_2(CH_3)_3); 0.79 (t, 3H, \(J = 7.2\) Hz, \(\text{CH}_2\text{CH}_3\)); 0.20 (d, 3H, \(J = 12.0\) Hz, SiCH_3); 0.12 (d, 3H, \(J = 12.0\) Hz, SiCH_3). \(^{13}\)C NMR (125 MHz, CDCl_3) \[173.8, 159.8, 150.7, 142.7, 129.3, 127.6, 126.2, 108.2, 90.1, 55.5, 53.7, 41.1, 37.9, 33.8, 32.2, 30.4, 27.1, 26.0, 25.9, 23.0, 21.8, 19.6, 14.4, -3.3, -4.2 \]; HRMS (FAB+) exact mass calculated for [MH]^+ \((\text{C}_{30}\text{H}_{50}\text{N}_3\text{O}_4\text{SiS})\) requires \(m/z\) 576.3291, found \(m/z\) 576.3315.

\[ \text{BOMO} \quad \text{Me} \quad \text{1.} \quad \text{PPh}_3 \quad \text{2.} \quad \text{n-BuLi, 76} \]

4-((5S,10S)-11-(Benzyloxymethoxy)-10-methylundec-7-en-5-yl)-3,5-dimethoxy-N,N-dimethylaniline (89).\(^{66}\) Triphenylphosphine (40 mg, 0.15 mmol) was added to a solution of iodide 85 (50 mg, 0.15 mmol) in dry acetonitrile (0.38 mL, 0.4 M). The reaction was heated to reflux in a sealed vial for 4 h, after which excess acetonitrile was removed in vacuo. The Wittig salt 88 was then azeotroped with benzene to remove excess water to provide the salt as an amorphous white solid that was unstable and used immediately in the subsequent Wittig olefination.

The Wittig salt 88 was dissolved in 0.5 mL dry THF and cooled to \(-78\) °C under an argon atmosphere. \(n\)-BuLi (61 \(\mu\)L, 0.145 mmol) was added, resulting in a reddish orange solution that was stirred for an hour at \(-78\) °C. Aldehyde 76 (15 mg, 0.05 mmol) was added via syringe at \(-78\) °C and it was stirred as this temperature for three hours,

\(^{66}\) Chemical shifts of minor trans isomer noted in italics.
during which time the solution turned yellow then brownish orange. The reaction was then warmed to \(-20 \, ^\circ\text{C}\) for another 3 h, after which it was loaded directly onto a silica gel column. The desired product was obtained after flash chromatography (10 % EtOAc/hexanes) as a clear oil (13.1 mg, 54% yield). IR (film) 2954, 2930, 2857, 1613, 1568, 1463, 1460, 1254, 1206, 1123, 1047, 797, 735, 698 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.34 (m, 5H, PhH), 5.96 (s, 2H, ArH), 5.34 (m, 2H, CH=CH), 4.79 4.75 (s, 2H, OCH\(_2\)O), 4.64 4.62 (s, 2H, PhCH\(_2\)O), 3.83 3.80 (s, 6H, OCH\(_3\)), 3.50 (dd, 2H, J = 6.0, 9.6 Hz, BOMOCHH), 3.40 (dd, 2H, J = 6.9, 9.3 Hz, BOMOCHH), 3.24 (m, 1H, ArCH), 2.98 2.97 (s, 6H, NCH\(_3\)), 2.45 (m, 2H, CHCH\(_2\)), 2.16 (m, 1H, =CHCHH), 1.92 (m, 1H, =CHCHH), 1.52-1.85 (m, 2H, CH(alkyl)), 1.75 (m, 3H, CH(alkyl)), 0.94 (d, 3H, J = 6.6 Hz, CHCH\(_3\)), 0.85 (t, 3H, J = 7.2 Hz, CH\(_2\)CH\(_3\)). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 150.0, 138.0, 131.4, 128.4, 127.9, 127.6, 127.0, 110.6, 94.7, 90.3, 73.1, 69.2, 60.4, 55.6, 40.7, 34.9, 34.0, 33.8, 33.2, 31.8, 31.2, 30.5, 22.9, 17.0, 14.1; HRMS (FAB+) exact mass calculated for [MH]\(^+\) (C\(_{30}\)H\(_{46}\)O\(_4\)N) requires m/z 484.3427, found m/z 484.23423. [\(\alpha\)]\(_D\) = \(-\)1.95 (c = 1.0, CHCl\(_3\)).

(S)-3-(4-(Dimethylamino)-2,6-dimethoxyphenyl)heptan-1-ol (99). Aldehyde 76 (2.65 g, 9.1 mmol) was taken up in 5 mL EtOH and 20 mL CH\(_2\)Cl\(_2\). Sodium borohydride (1.8g, 45.5 mmol) was added in portions and stirred for 2 h at ambient temperature. The reaction was quenched with saturated NaHCO\(_3\). The aqueous layer was separated and
extracted with EtOAc (2 x 50 mL). The organic layers were dried with sodium sulfate and the solvent was removed in vacuo. Flash chromatography (gradient elution: 10 to 40% EtOAc/hexanes) provided the primary alcohol 99 as a yellow oil (2.67 g, quantitative). IR (film) 3420 (bs), 2954, 2931, 2857, 1613, 1568, 1506, 1465, 1253, 1207, 1127, 1107, 798 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.93 (s, 2H, ArH); 3.78 (s, 6H, OCH₃); 3.47 (m, 1H, ArCH); 3.31 (m, 2H, CH₂OH); 2.95 (s, 6H, NCH₃); 2.04 (bs, 1H, OH); 1.87 (m, 1H, CHHCHCH₂); 1.58 (m, 1H, CHHCHCH₂); 1.04-1.3 (m, 4H, CH₂CH₂CH₃); 0.83 (t, 3H, J = 7.2 Hz, CH₂CH₃); ¹³C NMR (125 MHz, CDCl₃) δ 159.3, 150.3, 108.5, 90.4, 61.8, 55.5, 40.7, 36.6, 33.6, 30.8, 30.6, 22.8, 14.1; HRMS (FAB+) exact mass calculated for [MH]⁺ (C₁₇H₂₉NO₃) requires m/z 295.2147, found m/z 295.2143; [α]D = −5.57 (c = 1.0, EtOH).

(S)-4-(1-Iodoheptan-3-yl)-3,5-dimethoxy-N,N-dimethylaniline (100). Iodine (2.42g, 9.55 mmol) was added to a mixture of triphenylphosphine (2.71g, 10.3 mmol) and imidazole (694 mg, 10.3 mmol) in 80 mL CH₂Cl₂ at 0 °C. Alcohol 99 (2.35g, 7.96 mmol) was added dropwise. The reaction was stirred at 0 °C for 30 min. and warmed to 23 °C for 1 h. The reaction was quenched with 150 mL saturated NH₄Cl, which was then extracted with CH₂Cl₂ (3 x 100 mL). The organic layers were dried with sodium sulfate and the solvents were removed in vacuo. Flash chromatography (0 to 15 to 30% Et₂O/pentanes, silica pretreated with Et₃N) provided the product as a viscous oil (2.38 g,
74% yield). The molecule proved to be unstable to prolonged storage, so it is best to store it at low temperatures under argon. IR (film) 2954, 2930, 2856, 1613, 1568, 1506, 1464, 1147, 1115, 1009, 796 cm\(^{-1}\); \(^1\)H NMR (300 MHz, C\(_6\)D\(_6\)) \[5.84 (s, 2H, ArH); 3.62 (tt, 1H, \(J = 5.4, 9.9\) Hz, ArCH); 3.41 (broad s, 6H, OCH\(_3\)); 3.00-3.14 (m, 2H, CH\(_2\)I); 2.71 (m, 1H, CH\(_3\)CHCH\(_2\)); 2.59 (s, 6H, NCH\(_3\)); 2.28 (m, 1H, CHHCHCH\(_2\)); 2.08 (m, 1H, CH\(_2\)CHHH); 1.70 (m, 1H, CH\(_2\)CHCHH); 1.24-1.44 (m, 4H, CH\(_2\)CH\(_2\)CH\(_3\)); 0.86 (t, 3H, \(J = 7.2\) Hz, CH\(_2\)CH\(_3\)); \(^{13}\)C NMR (125 MHz, C\(_6\)D\(_6\)) \[160.2, 150.8, 108.1, 90.4, 55.1, 40.4, 39.3, 36.3, 34.0, 30.8, 23.3, 14.4, 6.6; HRMS (FAB+) exact mass calculated for [MH]\(^+\) (C\(_{17}\)H\(_{28}\)INO\(_2\)) requires m/z 405.1165, found m/z 405.1156; \([\alpha]\)\(_D\) = +29.1 (c = 1.0, EtOH).

(S)-3,5-Dimethoxy-\(N,N\)-dimethyl-4-(1-(phenylsulfonyl)heptan-3-yl)aniline (101). The sodium salt of benzene sulfinic acid (PhSO\(_2\)Na, 446 mg, 2.72 mmol) dried under vacuum at 50 °C for 2h. It was then added to a solution of iodide 100 (1 g, 2.27 mmol) in DMF (15 mL, 0.16 M) at room temperature and stirred for 48 h. The reaction was diluted with 50 mL diethyl ether and the biphasic mixture was stirred for 2 h. The layers were separated and the ether layer was washed with 100 mL water and 100 mL brine. The ether layer was dried and concentrated. The crude residue was subjected to flash chromatography to provide the sulfone 101 as a viscous oil (591 mg, 57% yield). IR (film) 2932, 1613, 1568, 1507, 1447, 1305, 1248, 1206, 1142, 1008 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \[7.84 (m, 2H, PhH); 7.62 (m, 1H, PhH), 7.52 (m, 2H, PhH), 5.83 (s, 2H,
ArH); 3.64 (broad s, 6H, OCH₃); 3.14 (m, 1H, ArCH); 2.94 (m, 1H, CHHS); 2.93 (s, 6H, NCH₃); 2.82 (ddd, 1H, J = 4.8, 12.6, 14.1 Hz, CHHS), 2.17 (m, 1H, CHHCHCH₂); 1.87 (m, 1H, CHHCHCH₂); 1.72 (m, 2H, CH₂CHCHH); 1.45 (m, 1H, CH₂CHCHH); 0.96-1.32 (m, 5H, CH₂CHCHH and CH₃CH₂CH₃); 0.78 (t, 3H, J = 7.2 Hz, CH₃); ¹³C NMR (125 MHz, CDCl₃) δ 159.8, 150.4, 139.2, 133.1, 128.9, 128.0, 107.0, 89.5, 55.4, 40.6, 33.6, 33.5, 31.5, 30.1, 22.7, 14.1; HRMS (FAB+) exact mass calculated for [MH]⁺ (C₂₃H₃₃NO₄S) requires m/z 419.2130, found m/z 419.2131; [α]D = –7.78 (c = 1.0, EtOH).

(R)-Methyl 3-(4-methoxybenzylxylo)-2-methylpropanoate (103). PMBO-trichloroacetimidate was prepared by the following sequence: p-Methoxybenzyl alcohol (5.8 mL, 46.55 mmol) was slowly added to a slurry of sodium hydride (60%, 373 mg, 9.31 mmol) in 12 mL diethyl ether at 0 °C. Trichloroacetonitrile (14 mL, 0.140 mol) was added over 5 minutes. The reaction was warmed to room temperature and stirred for an additional 2 h. The solvents were removed via rotary evaporator. 0.5 mL methanol in 150 mL pentane was added to the reaction slurry. A precipitate formed and the mixture was then filtered over Celite and concentrated in vacuo to an orange oil that was used in the following protection reaction.

PMB-acetimidate (14.4 g, 50.97 mmol) was added to a solution of (R)-Roche ester 102 (5 g, 42.0 mmol) in 187 mL diethyl ether at 0 °C. Catalytic triflic acid (30 μL, 0.168 mmol) was added via syringe. The reaction was warmed to ambient temperature
and stirred for 12 h. Additional portions of 30 \( \text{mL} \) triflic acid were added every 2 h until the reaction stopped progressing, as indicated by TLC analysis. The reaction was quenched with 150-200 mL saturated NaHCO\(_3\). The aqueous layer was separated and extracted with pentanes (3 x 100 mL). The collected organic layers were washed with brine, dried with sodium sulfate and the solvents were removed in vacuo. Flash chromatography (15% Et\(_2\)O/pentanes) provided the title compound as a yellow oil (8.2 g, 82% yield). IR (film) 1737, 1612, 1513, 1454, 1302, 1247, 1174, 1096, 1033, 819 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.25 (m, 2H, ArH), 6.88 (m, 2H, ArH), 4.46 (s, 2H, CH\(_2\)OPMB), 3.81 (s, 3H, OCH\(_3\)), 3.70 (s, 3H, OCH\(_3\)), 3.64 (dd, 1H, \( J = 7.5, 9.3 \) Hz, CHHOPMB), 3.47 (dd, 1H, \( J = 6.0, 9.3 \) Hz, CHHOPMB), 2.78 (ddq, 1H, \( J = 6.0, 7.2, 7.5 \) Hz, CHCH\(_3\)), 1.18 (d, 3H, \( J = 7.2 \) Hz, CHCH\(_3\)). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 175.3, 159.1, 130.2, 129.1, 113.7, 72.7, 71.6, 55.2, 51.6, 40.1, 13.9; HRMS (El+) exact mass calculated for [M\(^+\)] (C\(_{13}\)H\(_{18}\)O\(_4\)) requires \( m/z \) 238.1205, found \( m/z \) 238.1196. \([\alpha]_D^\circ = -8.23 \) (c = 1.0, CHCl\(_3\)).

(R)-1,1-Dibromo-4-(4-methoxybenzyloxy)-3-methylbutan-2-one (104). LiTMP was generated in a flame-dried round bottom flask at 0 \(^\circ\)C under argon by the addition of \( n-\text{BuLi} \) (2.5M, 4 mL, 10.0 mmol) to a solution of tetramethylpiperidine (1.85 mL, 11.0 mmol) in 15 mL THF. The LiTMP was transferred via cannula to a solution of methyl ester 103 (1.19 gm 5.00 mmol) and dibromomethane (0.7 mL, 10.0 mmol) in 20 mL THF also at 0 \(^\circ\)C. The reaction was stirred at 0 \(^\circ\)C for an additional 20 minutes, at which point
it was quenched with 50 mL 1N HCl and warmed to room temperature. The biphasic mixture was separated and the aqueous layer was extracted with 10% ether/pentanes. The organic layers were washed with brine and dried with sodium sulfate. The solvents were removed in vacuo. Flash chromatography (10% Et$_2$O/pentanes) provided -dibromoketone 104 as a yellowish-orange oil (1.40 g, 73% yield). (IR (film) 2923, 1738, 1613, 1514, 1452, 1248, 1200, 1175, 1089, 820 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$7.21 (m, 2H, ArH), 6.88 (m, 2H, ArH), 6.09 (s, 1H, CHBr$_2$), 4.40 (s, 2H, CH$_2$OPMB), 3.81 (s, 3H, OCH$_3$), 3.70 (s, 3H, OCH$_3$), 3.48 (m, 3H, CH$_2$OPMB and CHCH$_3$), 1.21 (d, 3H, J = 6.3 Hz, CHCH$_3$). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$198.3, 159.3, 129.5, 129.2, 113.8, 73.0, 72.8, 55.2, 44.4, 41.6, 14.5; HRMS (EI+) exact mass calculated for [M$^+$]$^+$ (C$_{13}$H$_{16}$O$_3$Br$_2$) requires m/z 379.9446, found m/z 379.9438. $[\alpha]_D$ = −129.6 (c = 1.0, CHCl$_3$).

(S)-Ethyl 4-(4-methoxybenzyloxy)-3-methylbutanoate (105). LiHMDS was freshly generated by adding n-BuLi (1.6 mL, 4.00 mmol) to a solution of HMDS (0.87 mL, 4.18 mmol) in 18 mL THF at 0 °C under argon. This LHMDS solution was transferred via syringe to an addition funnel that was equipped to a flask already cooled to −78 °C and charged with dibromoketone 104 (1.395 g, 3.67 mmol) in 18 mL THF. LHMDS was slowly added dropwise over 20 minutes, and the reaction was stirred for an additional 20 minutes at −78 °C. 3.2 mL n-BuLi (8.07 mmol) was added and the reaction was stirred at −78 °C for 30 minutes. This reaction was transferred dropwise via cannula to an acidic solution of acetyl chloride (14 mL) in ethanol (72 mL). Upon completion of the addition
the reaction was quenched with water. The aqueous layer was separated and extracted with diethyl ether (3 x 50 mL). The organic extracts were washed with brine, dried with magnesium sulfate, and the solvents removed in vacuo. Flash chromatography (1:6.5 Et₂O/pentanes) provided the homologated ester 105 as a slightly yellow oil (721 mg, 74% yield). IR (film) 2960, 2859, 1732, 1613, 1514, 464, 1373, 1302, 1248, 1180, 1094, 1035, 820 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 7.25 (d, 2H, J = 6.0 Hz, ArH), 6.87 (d, 2H, J = 5.7 Hz, ArH), 4.42 (s, 2H, CH₂OPMB), 4.10 (q, 2H, J = 7.2 Hz, OCH₂CH₃), 3.80 (s, 3H, OCH₃), 3.70 (s, 3H, OCH₃), 3.34 (dd, 1H, J = 5.4, 9.3 Hz, CHHOPMB), 3.26 (dd, 1H, J = 6.9, 9.3 Hz, CHHOPMB), 2.47 (dd, 2H, J = 5.7, 15.0 Hz, CHHCO₂Et), 2.29 (m, 1H, CHCH₂), 2.13 (dd, 2H, J = 8.1, 15.0 Hz, CHHCO₂Et), 1.23 (t, 3H, J = 7.2 Hz, OCH₂CH₃), 0.96 (s, 3H, J = 6.3 Hz, CHCH₃). ¹³C NMR (125 MHz, CDCl₃) 173.0, 159.1, 130.6, 129.1, 113.7, 74.5, 72.6, 60.1, 55.2, 38.7, 30.8, 16.9, 14.2; HRMS (EI+) exact mass calculated for [M⁺]⁺ (C₁₅H₂₂O₄) requires m/z 266.1518, found m/z 266.1508. [⁰]D = −3.34 (c = 1.0, CHCl₃).

(S)-4-(4-Methoxybenzyloxy)-3-methylbutan-1-ol (106). Lithium aluminum hydride (154 mg, 4.06 mmol) was added to a solution of ester 105 (721 mg, 2.71 mmol) in 13.6 mL diethyl ether at 0 °C. The reaction was stirred for 1 h. A saturated aqueous Na/K tartrate solution was added and the biphasic mixture was stirred at ambient temperature until all solids were dissolved. The aqueous layer was separated and extracted with diethyl ether (3 x 20 mL). The organic layers were filtered over a silica pad and the
solvents were removed in vacuo to provide alcohol 106 as a clear oil (400 mg, 66% yield). IR (film) 3390 (broad), 2927, 1613, 1514, 1452, 1362, 1302, 1248, 1174, 1087, 1036, 820 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) □ 7.25 (d, 2H, J = 5.7 Hz, ArH), 6.87 (d, 2H, J = 5.7 Hz, ArH), 4.44 (s, 2H, CH₂OPMB), 3.79 (s, 3H, OCH₃), 3.62 (m, 2H, CH₂OH), 3.34 (dd, 1H, J = 4.8, 9.0 Hz, CHHOPMB), 3.27 (dd, 1H, J = 7.5, 9.3 Hz, CHHOPMB), 2.55 (bs, 1H, OH), 1.90 (m, 1H, CHCH₂), 1.57 (m, 2H, CH₂CH₂OH), 0.93 (d, 3H, J = 6.9 Hz, CHCH₃). ¹³C NMR (125 MHz, CDCl₃) □ 159.2, 130.1, 129.3, 113.8, 75.7, 72.8, 61.0, 55.2, 38.0, 31.4, 17.6; HRMS (EI⁺) exact mass calculated for [M⁺]+ (C₁₃H₂₀O₃) requires m/z 224.1413, found m/z 224.1421. [α]D = −4.48 (c = 1.0, CHCl₃).

(S)-4-(4-Methoxybenzyloxy)-3-methylbutanal (107a). Bisacetoxyiodosobenzene (95 mg, 0.295 mmol) was added to a solution of alcohol 106 (60 mg, 0.269 mmol) in 0.54 mL CH₂Cl₂. TEMPO (6 mg, 0.0384 mmol) was added and the reaction was stirred for 3 h at room temperature. The reaction was quenched with 3 mL saturated Na₂S₂O₅. The aqueous layer was separated and extracted with diethyl ether (3 x 5 mL). The organic layers were dried with magnesium sulfate and concentrated via rotary evaporator. Flash chromatography (10% to 20% Et₂O/pentanes) provided the aldehyde as a clear oil (41 mg, 70% yield). IR (film) 3390 (broad), 2838, 1722, 1612, 1513, 1463, 1362, 1302, 1247, 1174, 1090, 1034, 820 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) □ 9.76 (t, 1H, J = 2.1 Hz, CHO), 7.25 (d, 2H, J = 8.4 Hz, ArH), 6.89 (d, 2H, J = 8.4 Hz, ArH), 4.43 (s, 2H, CH₂OPMB), 3.81 (s, 3H, OCH₃), 3.40 (dd, 1H, J = 5.4, 9.3 Hz, CHHOPMB), 3.23 (dd,
$1H, J = 7.5, 9.0 \text{ Hz}, \text{CHHOPMB}$), 2.54 (ddd, $1H, J = 2.1, 6.0, 15.6 \text{ Hz}, \text{CHHCHO}$), 2.41 (m, $1H, \text{CHCH}_{2}$), 2.28 (ddd, $1H, J = 2.1, 6.9, 15.9 \text{ Hz}, \text{CHHCHO}$), 0.99 (d, $3H, J = 6.6 \text{ Hz}, \text{CHCH}_{3}$).

$\text{^{13}C\text{NMR (125 MHz, CDCl}}_3)$ $\square$ 202.4, 159.1, 130.3, 129.1, 113.7, 74.6, 72.7, 55.2, 48.4, 29.1, 17.0; HRMS (EI+) exact mass calculated for $[M^{+}]^+$ ($C_{13}H_{18}O_3$) requires $m/z$ 222.1256, found $m/z$ 222.1258. $[\square]_D = -13.4 \ (c = 1.0, \text{CHCl}_3)$.

(R)-Methyl 3-(benzyloxy)-2-methylpropanoate. To a solution of the (R)-Roche ester 102 (5g, 42.3 mmol) and benzyl trichloroacetimidate (13.28g, 52.8 mmol) in cyclohexane/CH$_2$Cl$_2$ (160 mL, 2:1 v:v) at 23 °C under an argon atmosphere, triflic acid (0.38 mL, 4.23 mmol) was added via syringe. The reaction mixture was stirred for 17 h, during which time CCl$_3$CONH$_2$ precipitated out of solution. The heterogeneous reaction mixture was filtered and washed with cold CH$_2$Cl$_2$. The filtrate was then washed with water, NaHCO$_3$(aq), and brine. The organic layers were dried with magnesium sulfate and concentrated. Silica gel chromatography (1:6 EtOAc/hexanes) provided the desired product as a yellow oil (14.16g, 83% yield). IR (film), 2951, 2862, 1739, 1494, 1455, 1364, 1252, 1200, 1094, 738 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$). $\square$ 7.33 (m, 5H, ArH); 4.52 (s, 2H, CH$_2$OBn); 3.70 (s, 3H, CO$_2$CH$_3$); 3.70 (s, 3H, CO$_2$CH$_3$); 3.66 (dd, 1H, $J = 7.2, 9.0 \text{ Hz}, \text{CHHOBn}$); 3.49 (dd, 1H, $J = 6.0, 9.0 \text{ Hz}, \text{CHHOBn}$); 2.78 (m, 1H, CHCH$_3$); 1.18 (d, 3H, $J = 6.9 \text{ Hz}, \text{CHCH}_{3}$); $^{13}$C NMR (75 MHz, CDCl$_3$). $\square$ 175.3, 138.1, 128.3(x2), 127.5(x2), 127.5, 73.1, 76.6, 51.7, 40.1, 14.0; HRMS (EI+) exact mass
calculated for [M•]+ (C_{13}H_{18}O_4) requires m/z 208.1100, found m/z 208.1095; [α]_D = −11.45 (c = 1.23, CHCl₃).

(S)-3-(Benzyloxy)-2-methylpropan-1-ol (111). Lithium aluminum hydride (3.86 g, 101.7 mmol) was suspended in 68 mL of ether at 0 °C. (R)-methyl 3-(benzyloxy)-2-methylpropanoate (14.16 g, 67.8 mmol) was added dropwise via addition funnel as a solution in 68 mL of ether. When the addition was complete, the reaction was warmed to room temperature at which point the reaction was judged complete by TLC analysis. 2.5 mL H₂O, 5.5 mL 2N NaOH, and then 12.5 mL H₂O were added very carefully (note: gas evolution). The reaction was swirled by hand and diluted in ether. The gray mixture turned yellowish-red. The aqueous layer was removed and the ether layer dried with magnesium sulfate. The solvent was removed in vacuo. Silica gel chromatography (1:1 EtoAc/hexanes) provided the alcohol 111 as a yellow oil (9.25 g, 77% yield). IR (film). 3393 (broad), 3026, 2686, 1452, 1363, 1095, 1040, 752, 734 cm⁻¹. ¹H NMR (300 MHz, CDCl₃). [δ] 7.33 (m, 5H, Ar H); 4.52 (s, 2H, CH₂OBn); 3.61 (m, 2H, CH₂OBn); 3.54 (dd, 1H, J = 4.5, 9.0 Hz, CHHOH); 3.43 (dd, 1H, J = 8.1, 9.0 Hz, CHHOH); 2.64 (app q, H, J = 9.0 Hz, OH); 2.0 (m, 1H, CHCH₃); 0.89 (d, 3H, J = 7.5 Hz, CHCH₃); ¹³C NMR (75 MHz, CDCl₃). [δ] 138.0, 1218.4(x2), 127.7, 127.5(x2), 75.3, 73.3, 67.7, 35.6, 13.4; HRMS (EI+) exact mass calculated for [M•]+ (C_{13}H_{16}Br₂O₃) requires m/z 180.1150, found m/z 180.1144; [α]_D = −16.09 (c = 1.36, CHCl₃).
(R)-3-(benzyl oxy)-2-methylpropyl 4-methylbenzenesulfonate (112).  

Toluenesulfonyl chloride (12.9 g, 67.5 mmol) was added to a solution of alcohol 111 (9.25 g, 51.9 mmol) in 200 mL pyridine at 0 °C. The reaction was stirred at room temperature for 13 h. The reaction was poured into ice-cooled 1N HCl (200 mL). The aqueous mixture was extracted with diethyl ether (3 x 150 mL). The organic layers were washed with saturated CuSO₄ then brine. The ether layers were dried and the solvents removed in vacuo. Flash chromatography (20% EtOAc/hexanes) furnished the desired product 112 (9.37 g, 54% yield). IR (film), 3024, 2849, 1598, 1454, 1356, 1174, 1094, 936, 809, 665, 554 cm⁻¹. ¹H NMR (300 MHz, CDCl₃).  δ 7.87 (m, 2H, ArH); 7.30 (m, 2H, ArH); 7.22–7.36 (m, 5H, CH₂Ph); 6.87 (m, 2H, ArH); 4.40 (s, 2H, CH₂OBn); 4.05 (dd, 1H, J = 5.4, 9.3 Hz, CHHOTs); 3.99 (dd, 1H, J = 5.7, 9.3 Hz, CHHOTs); 3.34 (ddd, 2H, J = 5.4, 9.6, 12.9 Hz, CH₂OBn); 2.42 (s, 2H, ArCH₃); 2.11 (m, 1H, CHCH₃); 2.12 (dd, 1H, J = 8.1, 15.0Hz, CHHCO₂Et); 0.94 (d, 3H, J = 6.6 Hz, CHCH₃); ¹³C NMR (75 Mhz, CDCl₃).  δ 144.6, 138.2, 133.0, 128.8(x2), 128.3(x2), 127.9(x2), 127.5, 127.4(x2), 73.0, 72.2, 71.1, 33.7, 21.6, 13.6; HRMS (EI⁺) exact mass calculated for [M⁺]+ (C₁₅H₂₂O₄) requires m/z 334.1239, found m/z 334.1231; [α]D = −6.42 (c = 1.06, CHCl₃).
(S)-((2-Methyloct-7-enyloxy)methyl)benzene (113). 5-Bromopentene (2.2 mL, 18.7 mmol) was added to magnesium turnings (509 mg, 20.9 mmol) in 9.4 mL dry THF. A small crystal of iodine was added before the reaction was refluxed at 65 °C for 2 h. The reaction was cooled to ambient temperature to produce a cloudy gray solution. This mixture was transferred via cannula to a –78 °C solution of tosylate 112 (2.5 g, 7.48 mmol) and Li$_2$CuCl$_4$ (0.5 mL, 0.1 M in hexanes, 0.0501 mmol) in THF (12.5 mL, 0.6 M) under argon. The yellow-gray solution was stirred at –78 °C for 1 h and slowly warmed to room temperature where it was stirred for an additional 12 h. The reaction was quenched with 75 mL of a 2:1 (v:v) mixture of 1N HCl (50 mL) and sat. NH$_4$Cl (25mL). The reaction was diluted with ether and stirred vigorously until all solids dissolved. The biphasic mixture was separated and the aqueous layer extracted with ether (2 x 50 mL). The organic layers were washed sequentially with 1N HCl, water, saturated NaHCO$_3$, and brine. The layers were dried with magnesium sulfate and the solvents removed in vacuo. Flash chromatography (8% Et$_2$O/hexanes) delivered the homologated product 113 as a clear oil (1.47g, 85% yield). (IR (film) 2916, 2855, 1640, 1452, 1363, 1100, 933, 909, 734 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.21-7.38 (m, 5H, ArH); 5.82 (ddt, 1H, $J$ = 3.0, 3.6, 6.6 Hz, CH$_2$CH=CH$_2$); 4.97 (m, 2H, $J$ = CH$_2$CH=CH$_2$); 4.51 (s, 2H, CH$_2$OBn); 3.34 (dd, 1H, $J$ = 6.0, 9.0 Hz, CHHOBn); 3.25 (dd, 1H, $J$ = 6.6, 9.0, CHHOBn); 2.06 (dt, 2H,
$ J = 6.3, 7.2$ Hz, $\text{CH}_2=\text{CHCH}_2$); $1.77$ (m, $1\text{H}$, $ J = 5.7$ Hz, $\text{CHMe}$); $1.23-1.50$ (m, $5\text{H}$, $\text{CH}$(alkyl)); $1.09-1.19$ (m, $1\text{H}$, $\text{CH}$(alkyl)); $0.94$ (d, $3\text{H}$, $ J = 6.9$ Hz, $\text{CHCH}_3$); $^{13}\text{C}$ NMR (125 MHz, CDCl$_3$) $\delta$ 194.1, 158.8, 138.7, 133.0, 128.3(x2), 127.4, 75.8, 73.0, 33.3, 33.3, 32.7, 28.0, 26.4, 17.0; HRMS (EI+) exact mass calculated for $[\text{M}^+]^+$ ($\text{C}_{18}\text{H}_{26}\text{O}_4$) requires $m/z$ 232.1827, found $m/z$ 232.1822; $[\alpha]D = -0.31$ (c = 1.50, CHCl$_3$).

(5, E)-9-(Benzyloxy)-8-methylnon-2-enal (110). The second-generation Grubbs catalyst (268 mg, 0.317 mmol) was added to a solution of olefin 113 (1.47 g, 6.33 mmol) and crotonaldehyde (2.62 mL, 31.7 mmol) in CH$_2$Cl$_2$ (31 mL, 0.2M). The reaction was heated to 40 °C for 18 h. The crotonaldehyde and solvent were evaporated in vacuo. The crude reaction residue was subjected to silica gel flash chromatography (20% Et$_2$O/hexanes), which provided [E]-unsaturated aldehyde 110 as a clear oil (1.43 g, 87% yield, 23:1 $E:Z$). IR (film) 2922, 2856, 1692, 1637, 1453, 1363, 1100, 737 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.50 (d, $1\text{H}$, $ J = 7.5$ Hz, $\text{CHO}$); 7.25-7.35 (m, $5\text{H}$, Ar$\text{H}$); 6.84 (dt, $1\text{H}$, $ J = 6.8$, 15.6 Hz, $\text{CHOCH}=\text{CH}$); 6.11 (ddt, $1\text{H}$, $ J = 1.5, 7.2$, 15.6 Hz, $\text{CHOCH}=\text{CH}$); 4.50 (s, 2H, CH$_2$OBn); 3.31 (dd, $1\text{H}$, $ J = 6.0, 9.0$ Hz, CHHOBn); 3.25 (dd, $1\text{H}$, $ J = 5.7, 9.0$, CHHOBn); 2.33 (dt, 2H, $ J = 6.3, 7.2$ Hz, $\text{CH}_2=\text{CHCH}_2$); 1.75 (m, 1H, CHMe); 1.26-1.56 (m, 5H, CH$_{\text{alkyl}}$); 1.09-1.19 (m, 1H, CH$_{\text{alkyl}}$); 0.92 (d, 3H, $ J = 6.6$ Hz, CHCH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 194.1, 158.8, 138.7, 133.0, 128.3(x2), 127.4, 75.8, 73.0, 33.3, 33.3, 32.7, 28.0, 26.4, 17.0; HRMS (EI+) exact mass
calculated for [M•+] (C₁₈H₂₆O₄) requires m/z 260.1776, found m/z 260.1781; [α]D = -2.50 (c = 1.21, CHCl₃).

(3R,8S)-9-(Benzyloxy)-3-(4-(dimethylamino)-2,6-dimethoxyphenyl)-8-methyl-nonanal (114). 3,5-Dimethoxy-N,N-dimethylaniline (181 mg, 1 mmol) was added to a solution of imidazolidinone (S,S)-79 • DCA (75 mg, 0.2 mmol) in 4 mL CHCl₃. The reaction was cooled to -60 °C, at which point [α]-unsaturated aldehyde 110 (520 mg, 2 mmol) was added via syringe. The reaction was stirred at -60 °C for 48 h. The solvents were removed in vacuo, and residue was loaded onto a silica gel column. Flash chromatography (5 to 10% EtOAc/hexanes) provided the title compound as an orange oil (428 mg, 97% yield). IR (film) 2929, 2854, 2718, 1721, 1613, 1568, 1507, 1454, 1255, 1204, 1129, 1107, 1108, 797 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.59 (t, 1H, J = 5.7 Hz, CHO); 7.25-7.33 (m, 5H, ArH); 5.89 (s, 2H, ArH); 4.48 (s, 2H, CH₂OBn); 3.77 (s, 6H, OMe); 3.76 (m, 1H, ArCH); 3.30 (dd, 1H, J = 6.0, 9.0 Hz, CHHOBn); 3.19 (dd, 1H, J = 7.2, 9.0, CHHOBn); 2.94 (s, 6H, NCH₃); 2.80 (ddd, 1H, J = 2.4, 7.5, 15.9 Hz, CHHCHO); 2.65 (ddd, 1H, J = 3.0, 6.6, 15.9 Hz, CHHCHO); 1.82 (m, 1H, CHMe); 1.70 (m, 1H); 1.56 (m, 1H); 1.01-1.40 (m, 6H, CH(alkyl)); 0.89 (d, 3H, J = 6.6 Hz, CHCH₃); ¹³C NMR (125 MHz, CDCl₃) δ 204.9, 159.3, 150.6, 138.9, 128.3(x2), 127.5(x2), 127.3,
107.9, 89.7, 76.0, 72.9, 55.4, 48.2, 40.6, 33.7, 33.6, 33.5, 29.2, 28.1, 26.9, 17.1; HRMS (FAB+) exact mass calculated for [MH]+ (C27H37NO4) requires m/z 441.868, found m/z 441.2879; [□]D = –2.50 (c = 1.21, CHCl3). The enantiomeric ratio was determined by HPLC analysis of the corresponding alcohol, obtained by sodium borohydride of the aldehyde, using a Chiralcel AD and AD guard column (3.0% ethanol/hexanes, 254 nm, 1.0 mL/min); (S) isomer tᵣ = 18.36 min, (R) isomer tᵣ = 16.17 min.

4-((5R,10S)-11-(Benzyloxy)-10-methylundec-2-en-5-yl)-3,5-dimethoxy-N,N-dimethylaniline. (Minor chemical shifts of (E)-olefin are in parentheses.) n-BuLi (4.52 mL, 11.32 mmol) was added to a heterogeneous mixture of ethyl triphenylphosphonium bromide (4.2 g, 11.32 mmol) in 45 mL THF at 0 °C under an argon atmosphere. The bright red ylid mixture was stirred for 30 min, then aldehyde 110 (2.0 g, 4.53 mmol) was added via syringe as a solution in 18 mL THF. The reaction was warmed to room temperature and then heated to 60 °C for 12 h. Upon cooling to ambient temperature, saturated NH4Cl was added and stirred until homogeneity was reached. The aqueous layer was separated and extracted with EtOAc (3 x 50 mL). The organic layers were washed with brine and dried with magnesium sulfate. The solvents were removed in vacuo. Flash chromatography provided 4-((5R,10S)-11-(benzyloxy)-10-methylundec-2-en-5-yl)-3,5-dimethoxy-N,N-dimethylaniline as a yellow oil as approximately a 2:1
mixture of cis:trans olefin isomers (1.53 g, 75% yield). IR (film) 2929, 2854, 1612, 1566, 1503, 1452, 1359, 1254, 1203, 1130, 1107, 1008, 797, 735, 698 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 7.25-7.33 (m, 5H, ArH); 5.92 (s, 2H, ArH); 5.33 (m, 2H, CH=CH), 4.48 (s, 2H, CH₂OBn); 3.77 (s, 6H, OCH₃); 3.30 (dd, 1H, J = 5.7, 9.0 Hz, CHHOBn); 3.23 (m, 1H, ArCH); 3.19 (dd, 1H, J = 6.0, 9.0, CHHOBn); 2.94 (s, 6H, NCH₃); 2.3-2.5 (m, 2H, CH₂CH=CH); 1.65-1.85 (m, 2H, CHMe and CH(alkyl)); 1.56(1.58) (d, 3H, J = 7.2 Hz, CH₃CH=CH); 1.01-1.40 (m, 6H, CH(alkyl)); 0.89 (d, 3H, J = 6.6 Hz, CHCH₃); ¹³C NMR (125 MHz, CDCl₃) 150.0, 138.9, (131.9) 131.0; 128.3, 127.5, 127.3, (124.3) 123.2, 110.7, (90.5) 90.4, 76.1, 72.9, 55.7, 40.7 (37.4), (35.1) 35.0, 33.7, 33.5, 33.4 (33.2), 31.4, 28.6, 27.1, (18.0) 17.2, 12.8; HRMS (FAB+) exact mass calculated for [MH]⁺ (C₂₉H₄₄NO₃) requires m/z 454.3321, found m/z 454.3335

(2S,7S)-7-(4-(Dimethylamino)-2,6-dimethoxyphenyl)-2-methylundecan-1-ol (90). 4-((5R,10S)-11-(Benzylxy)-10-methylundec-2-en-5-yl)-3,5-dimethoxy-N,N-dimethyl-aniline (1.5 g, 3.30 mmol) was taken up 24 mL MeOH and 8 mL trifluoroacetic acid. Pearlman’s catalyst (Pd(OH)₂, 30 mg) was added. The atmosphere was evacuated and purged with hydrogen gas three times, after which the reaction was stirred at ambient temperature under 1 atm of hydrogen gas for 12 h. The reaction was neutralized with 2N NaOH. The reaction was extracted with ethyl acetate (3 x 25 mL). The organic layers
were dried with magnesium sulfate and passed through a plug of silica to provide the title compound as an orange oil (1.235 g, quantitative). IR (film) 3373 (broad), 2930, 2857, 1615, 1562, 1509, 1459, 1255, 1205, 1135, 1113, 1109, 800 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \[ 5.96 (s, 2H, ArH); 3.77 (s, 6H, OCH\(_3\)); 3.47 (dd, 1H, \( J = 6.0, 7.5\) Hz, CHHOH); 3.37 (dd, 1H, \( J = 6.6, 7.5\) Hz, CHHOH); 3.14 (ddt, 1H, \( J = 6.0, 9.3, 11.7\) Hz, ArCH); 2.95 (s, 6H, NCH\(_3\)); 1.69-1.83 (m, 3H, CH(alkyl)); 1.47-1.60 (m, 3H, OH and CH(alkyl)); 1.01-1.40 (m, 10H, CH(alkyl)); 0.89 (d, 3H, \( J = 6.6\) Hz, CHCH\(_3\)); 0.82 (t, 3H, \( J = 7.2\) Hz, CH\(_2\)CH\(_3\)); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \[ 149.8, 128.8, 111.1, 90.5, 68.4, 55.7, 40.8, 35.8, 34.5, 34.0, 33.8, 33.1, 30.6, 29.7, 28.5, 27.8, 27.0, 22.9, 16.6, 14.1; HRMS (FAB+) exact mass calculated for [MH]\(^+\) (C\(_{22}\)H\(_{39}\)NO\(_3\)) requires \( m/z \) 365.2930, found \( m/z \) 365.2937.

4-((5S,10S)-11-Iodo-10-methylundecan-5-yl)-3,5-dimethoxy-N,N-dimethylaniline (75). \( p\)-Toluenesulfonyl chloride (313 mg, 1.64 mmol) was added to a solution of alcohol 90 (200 mg, 0.547 mmol), triethylamine (0.45 mL, 3.28 mmol), and DMAP (194 mg, 0.602 mmol) in 5.5 mL CH\(_2\)Cl\(_2\) at ambient temperature. The reaction was monitored by TLC analysis for completion (3 h). The reaction was quenched with 20 mL saturated NaHCO\(_3\). It was then diluted with about 150 mL of water. The aqueous layers were extracted with CH\(_2\)Cl\(_2\) (3x 150 mL). The organic layers were washed with sat. CuSO\(_4\)
and brine. The CH$_2$Cl$_2$ layers were dried with magnesium sulfate, filtered, and the solvent removed in vacuo.

The crude residue was taken up in 3.3 mL acetone. Sodium iodide (445 mg, 2.97 mmol) was added and the mixture was heated to 50 °C for 6 h. The reaction was filtered and the solvent removed in vacuo. Flash chromatography (10% EtOAc/hexanes on silica pretreated with Et$_3$N) provided the product 75 as an oil (241mg, 93% yield). $^1$H NMR (300 MHz, C$_6$D$_6$) $\delta$ 5.93 (s, 2H, ArH), 3.65 (tt, 1H, $J = 5.1, 9.3$ Hz, ArCH), 3.52 (s, 6H, OCH$_3$), 2.83 (dd, 1H, $J = 5.1, 9.9$ Hz, CHH), 2.72 (dd, 1H, $J = 5.7, 9.3$ Hz, CHH), 2.62 (s, 6H NCH$_3$), 2.24 (m, 2H, CHCH$_2$), 1.85 (m, 2H, CH$_2$CH), 0.9-1.56 (m, 11H, CH(alkyl)), 0.92 (t, 3H, $J = 7.2$ Hz, CH$_2$CH$_3$), 0.75 (d, 3H, $J = 6.0$ Hz, CH$_3$CH). $^{13}$C NMR (125 MHz, CD$_6$D$_6$) $\delta$ 160.2, 150.8, 108.2, 90.5, 55.0, 40.1, 36.3, 34.3, 34.2, 34.2, 30.9, 27.3, 26.8, 23.1, 20.3, 17.8, 14.1.

**Reaction procedure for the cross-coupling Suzuki dimerization:**

In a flame-dried Schlenk tube under Ar, a solution of iodide 75 (20 mg, 0.0420 mmol) in dried diethyl ether (0.84 mL, 0.05M) was added and cooled to $-78$ °C. Titrated t-BuLi (1.7M in hexanes, 0.0863 mmol) was added at $-78$ °C and stirred for 3 min. 9-BBN-OMe or 9-BBN-OTf (0.0420 mmol) was added and this reaction solution was stirred for 30 min at $-78$ °C. The reaction tube was evacuated to remove the diethyl ether and hexanes solvents and warmed to 0 °C under vacuum to give the alkyl borane salt 115 as a while amorphous solid.
Meanwhile, Ni(COD)$_2$ (12.0 mg, 0.0420 mmol), tricyclohexylphosphine (23.5 mg, 0.0840 mmol), and cesium fluoride (16 mg, 0.105 mmol) were added to a flame-dried Schlenk tube in a glovebox.

2.7 mL dioxane (0.01 M, prepared using the freeze-pump thaw method) was added to the alkyl borane salt. Trifluoromethanesulfonate was added to the solution via syringe (4.3 μL, 0.0420 mmol). This solution was then transferred via cannula to the Schlenk that was charged with the metal, ligand, and base. The vial was rinsed with an excess 0.2 mL dioxane. The Schlenk was sealed and heated to 80 °C for 24 h.

The reaction was cooled to ambient temperature and filtered over Celite. Crude NMRs were taken to judge the composition of the crude reaction mixture. Flash chromatography provided the protodeborylated product 118a as the major identifiable product from the reaction mixture.

(S)-3,5-Dimethoxy-N,N-dimethyl-4-(10-methylundecan-5-yl)aniline (118a). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.97 (s, 2H, ArH), 3.80 (s, 6H, OCH$_3$), 3.17 (m, 1H, ArCH), 2.98 (s, 6H NCH$_3$), 1.77 (m, 3H, CH(alkyl)), 1.52 (m, 1H, CH(alkyl)), 1.04-1.32 (m, 11H, CH(alkyl)), 0.86 (d, 6H, $J = 6.3$ Hz, (CH$_3$)$_2$CH), 0.85 (t, 3H, $J = 7.2$ Hz, CH$_2$CH$_3$).