C h a p t e r   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.[1] 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 limes (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.[2] The structucally similar chlorinated nostocyclophanes[3] were found to be the major cytotoxic component of *Nostoclickia* (Fig. 1).

[1] Moore, B. S.; Chen, J.-L.; Patterson, G. M.; Moore, R. M.; Brinen, L. S.; Kato, Y.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 4061.

[2] LoRusso, P.; Wozniak, A. J.; Polin, L.; Capps, D.; Leopold, W. R.; Werbel, L. M.; Biernat, L.; Dan, M. E.; Corbett, T. N. *Cancer Res.* **1990**, *50*, 4900.

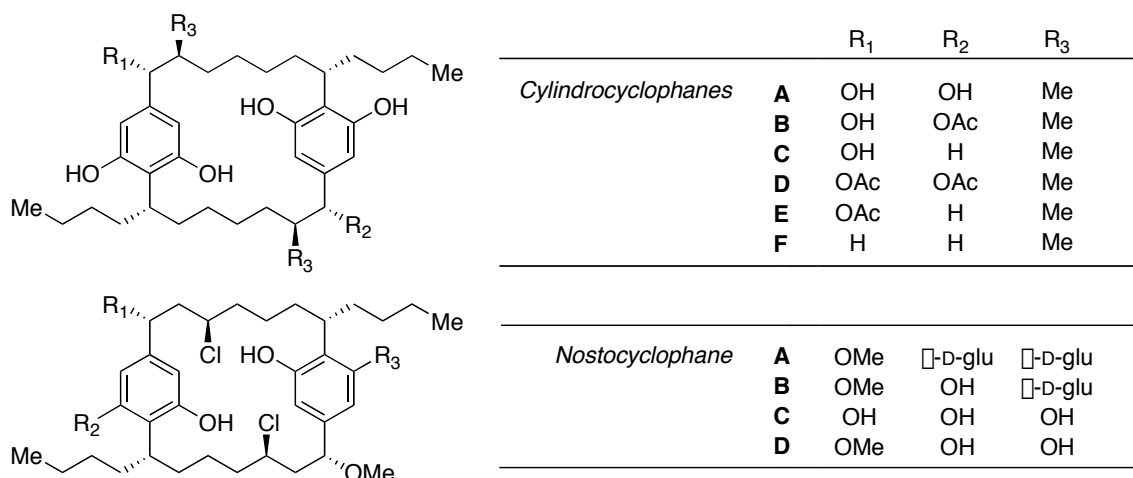[3] Chen, J. L.; Moore, R. E.; Patterson, G. M. L. *J. Org. Chem.* **1992**, *56*, 4360.

			R_1	R_2	R_3
Cylindrocyclophanes		A	OH	OH	Me
		B	OH	OAc	Me
		C	OH	H	Me
		D	OAc	OAc	Me
		E	OAc	H	Me
		F	H	H	Me
Nostocyclophane		A	OMe	β-D-glu	β-D-glu
		B	OMe	OH	β-D-glu
		C	OH	OH	OH
		D	OMe	OH	OH

Figure 1. Structures of the cylindrocyclophanes and nostocyclophanes.

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. ^1H 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).[4] 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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[4] Moore, B. S.; Chen, J. L.; Patterson, G. M. L.; Moore, R. E. *Tetrahedron* **1992**, *48*, 3001.

cylindrocyclophane A

1. CH_2N_2 (34%)

2. (R)- or (S)-MTPA acid DCC, DMAP (43%)

(1)
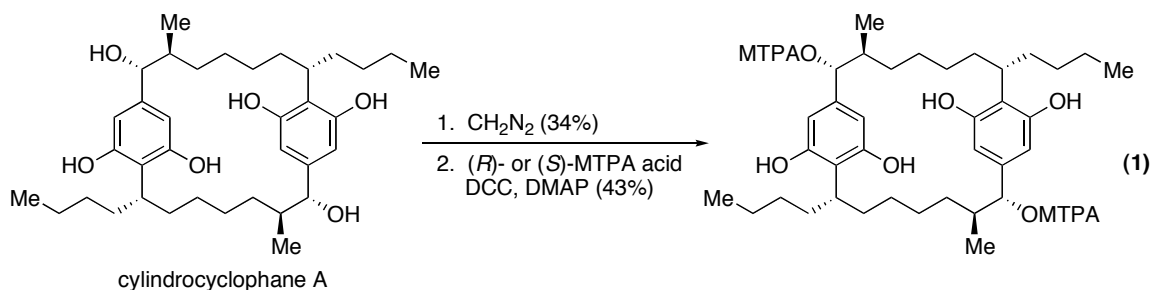
The relative and absolute stereochemistry of nostocyclophane D was determined by single crystal X-ray analysis (Figure 2). The crystal structure incorporates a molecule of ethanol within the cyclophane core. This type of host-guest interaction with cyclophanes has long been recognized and has received considerable attention in the literature.[5]
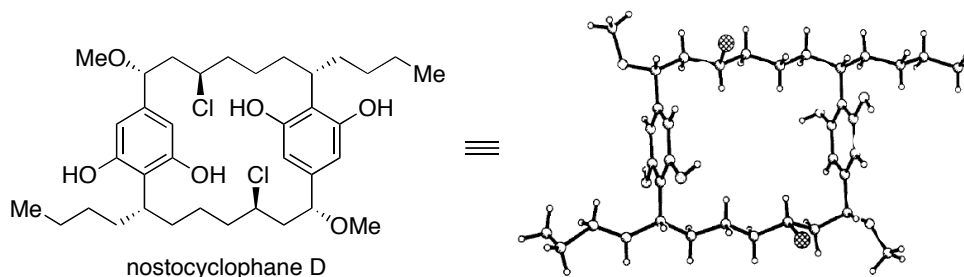

nostocyclophane D

$\equiv$

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]

[5] For reviews in cyclophane host-guest interactions, see: (a) *Cyclophanes*. Keehn, P. M.; Rosenfeld, S. M., Eds.; Academic: New York, 1983; Vol. 2, Chapter 11. (b) Tabushi, I.; Yamamura, K. In *Topics in Current Chemistry*; Vogtle, F., Ed.; Springer-Verlag:New York, 1983; Vol. 113, pp 146-182. (c) Vogtle, F. *Cyclophane Chemistry*; Wiley: New York, 1993; Chapter 12.

[6] Moore, R. E.; Bobzin, S. C. *Tetrahedron* **1993**, *49*, 7615.
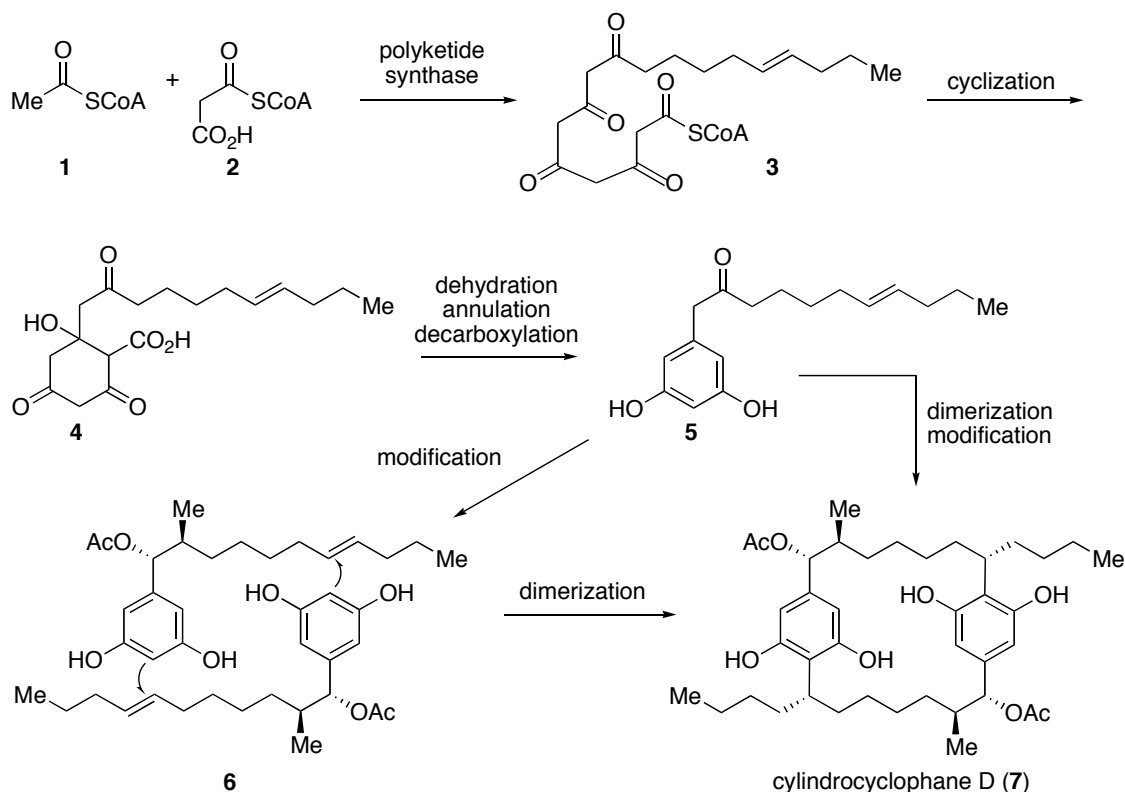
Figure 3. Proposed biosynthetic pathway.

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.[7] 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[8] conditions should also provide access to the diastereopure natural product. Model system

[7] Martin, V. A. Ph.D. Thesis, Wayne State University, 1992.

[8] (a) Meerwein, H.; Schmidt, R. *Justus Liebigs Ann. Chem.* **1925**, *444*, 221. (b) Ponndorf, W. *Angew. Chem.* **1926**, *39*, 138. (c) Verley, M. *Bull. Soc. Chim. Fr.* **1925**, *37*, 871.

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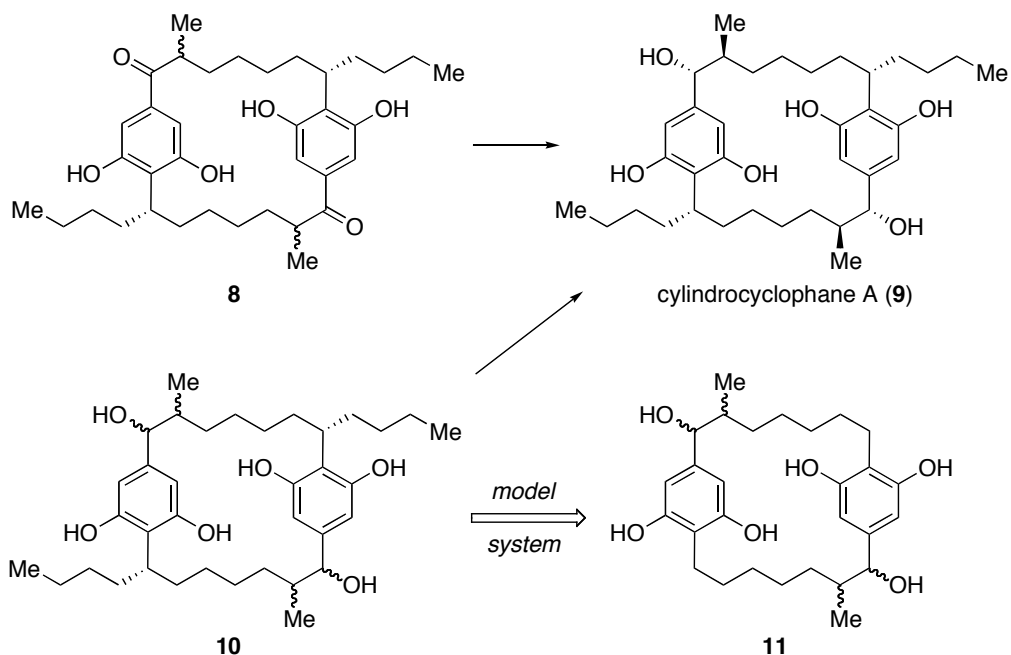

Figure 4. Albizati's equilibration hypothesis for the cylindrocyclophanes.

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**.
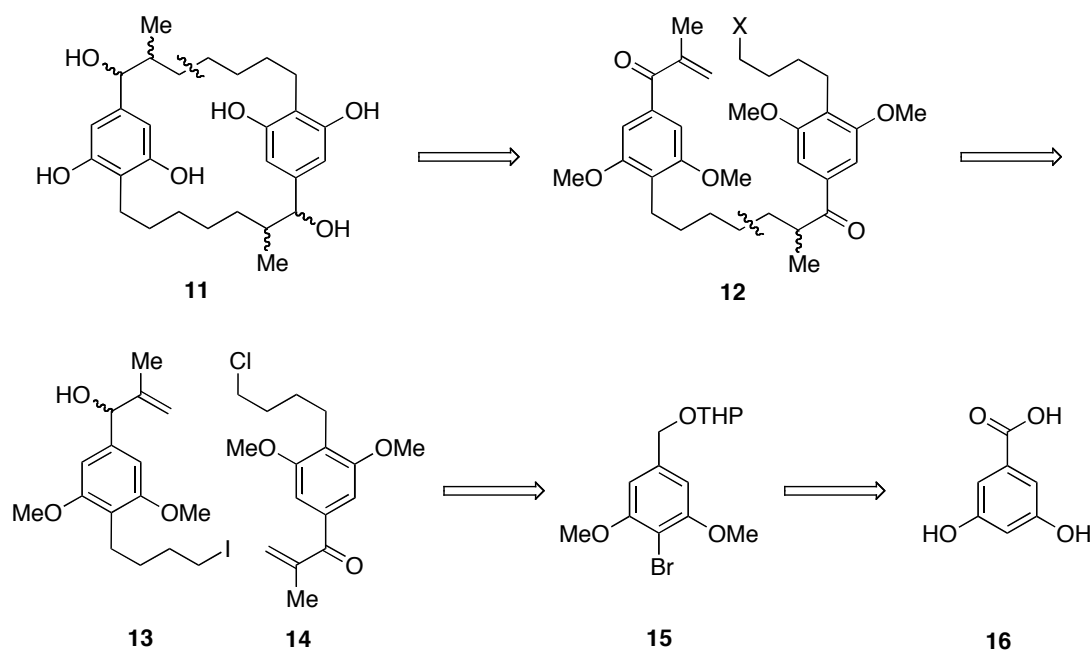
Figure 5. Albizati's retrosynthetic analysis of the model system.

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[9] to give alkyl iodide **13**. It was also subjected to Swern oxidation to give enone **14**.

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[9] (a) Finkelstein, H. *Ber.* **1910**, *43*, 1528. (b) Sharts, C. M.; Shappard, W. A. *Org. React.* **1974**, *21*, 125.

**Scheme 1. Synthesis of radical coupling precursors.**
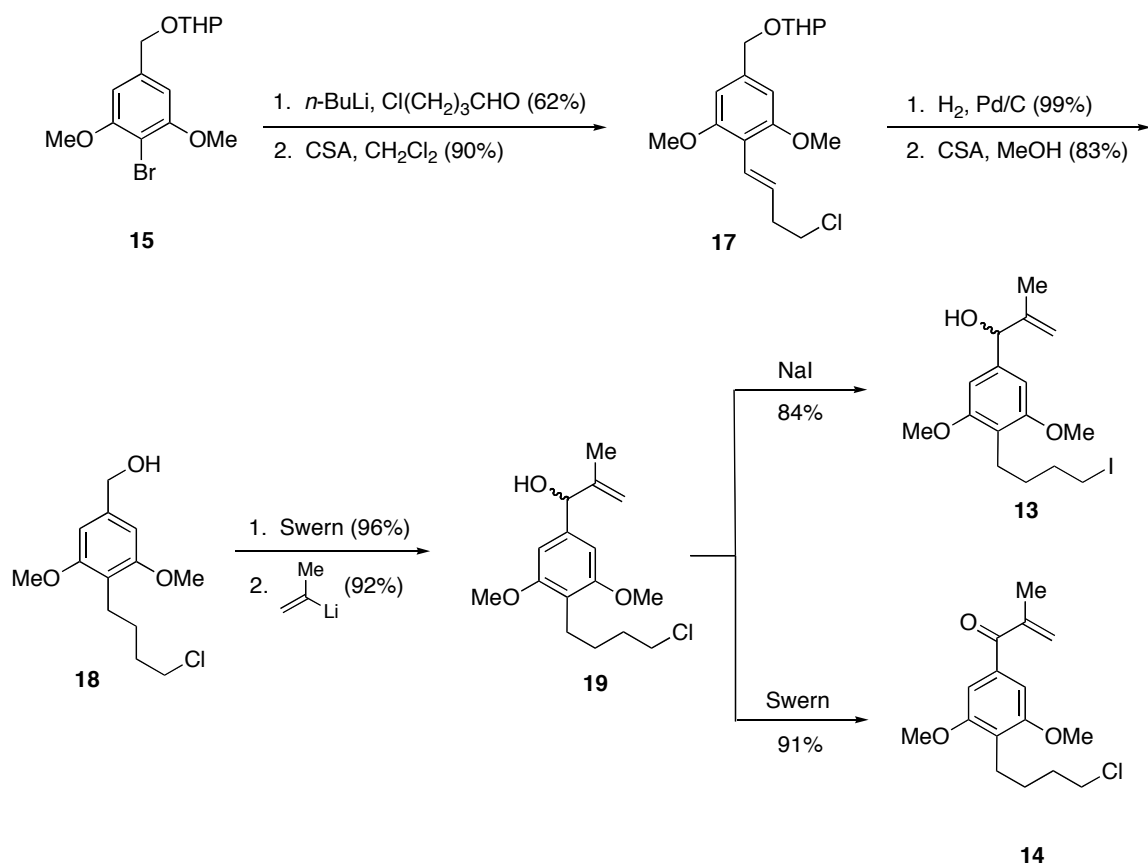
The intermolecular coupling of iodide **13** and enone **14** was effected by using

conditions developed by Luche[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 Bu₃SnH/AIBN conditions failed to afford the

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[10] (a) Petrier, C.; Dupuy, C.; Juche, J. L. *Tetrahedron Lett.* **1986**, *27*, 3149. (b) Petrier, C.; Dupuy C.; Luche, J. L. *Tetrahedron Lett.* **1984**, *25*, 3463.

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.
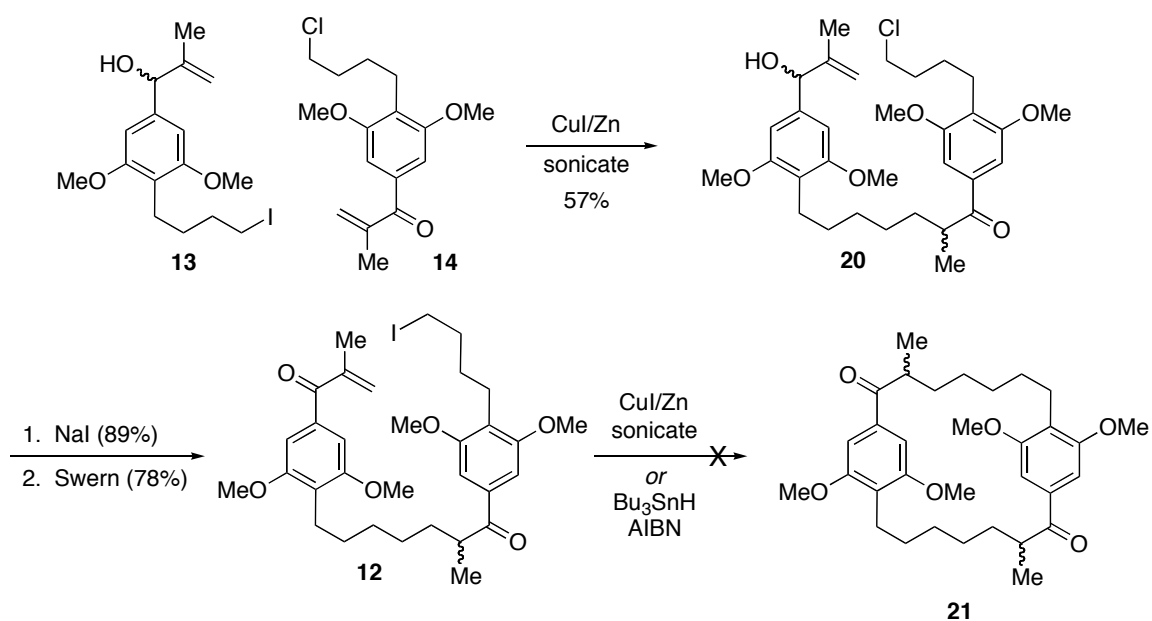
ii. *Trost's approach to cylindrocyclophane A.*

Schnaderbeck and Trost attempted to exploit the C_2-symmetry of cylindrocyclophane A and employ a dimerization event to assemble the 22-membered macrocycle.[11]   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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[11] Schnaderbeck, Matthew J. Ph.D. thesis, Stanford University, 1998.

Alder-Ene reaction[12] of enyne **23**. The Alder-Ene substrate is available from functionalized aromatic core **24**.
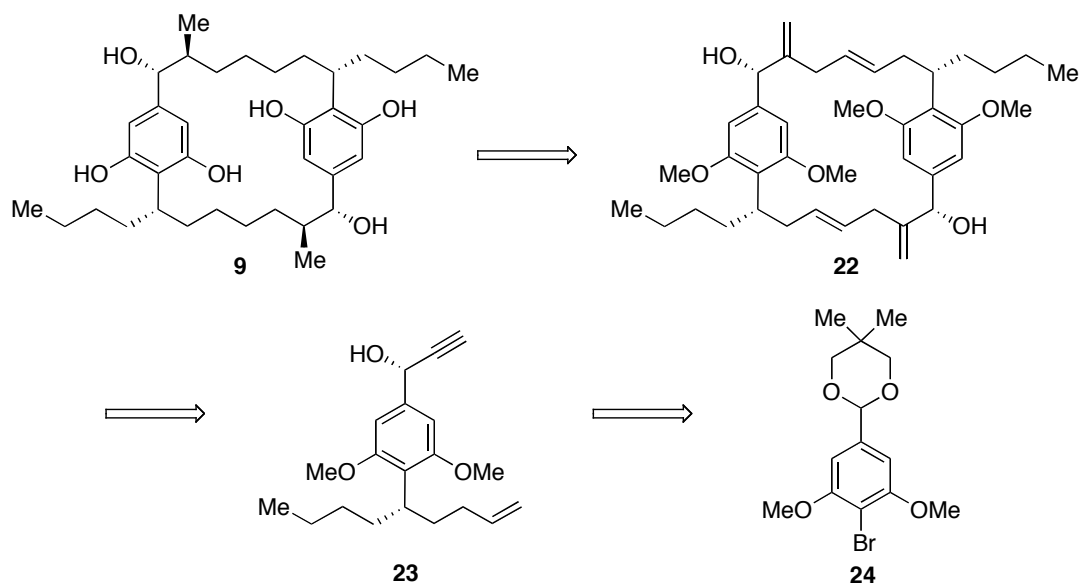

Figure 6. Trost's retrosynthetic analysis of cylindrocyclophane A.

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.

[12] For reviews on the Alder-ene reaction, see: (a) Hoffmann, H. M. R. *Angew. Chem. Int. Ed.* **1969**, *8*, 556. (b) Oppolzer, W.; Snieckus, V. *Angew. Chem. Int. Ed.* **1978**, *17*, 476. (c) Snider, B. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; pp 1-28 and 527-561. (d) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021. (e) Brummond, K. M.; McCabe, J. M. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, Germany, 2005; pp 151-172.

Scheme 3. Synthesis of macrocyclic Alder-Ene precursors.
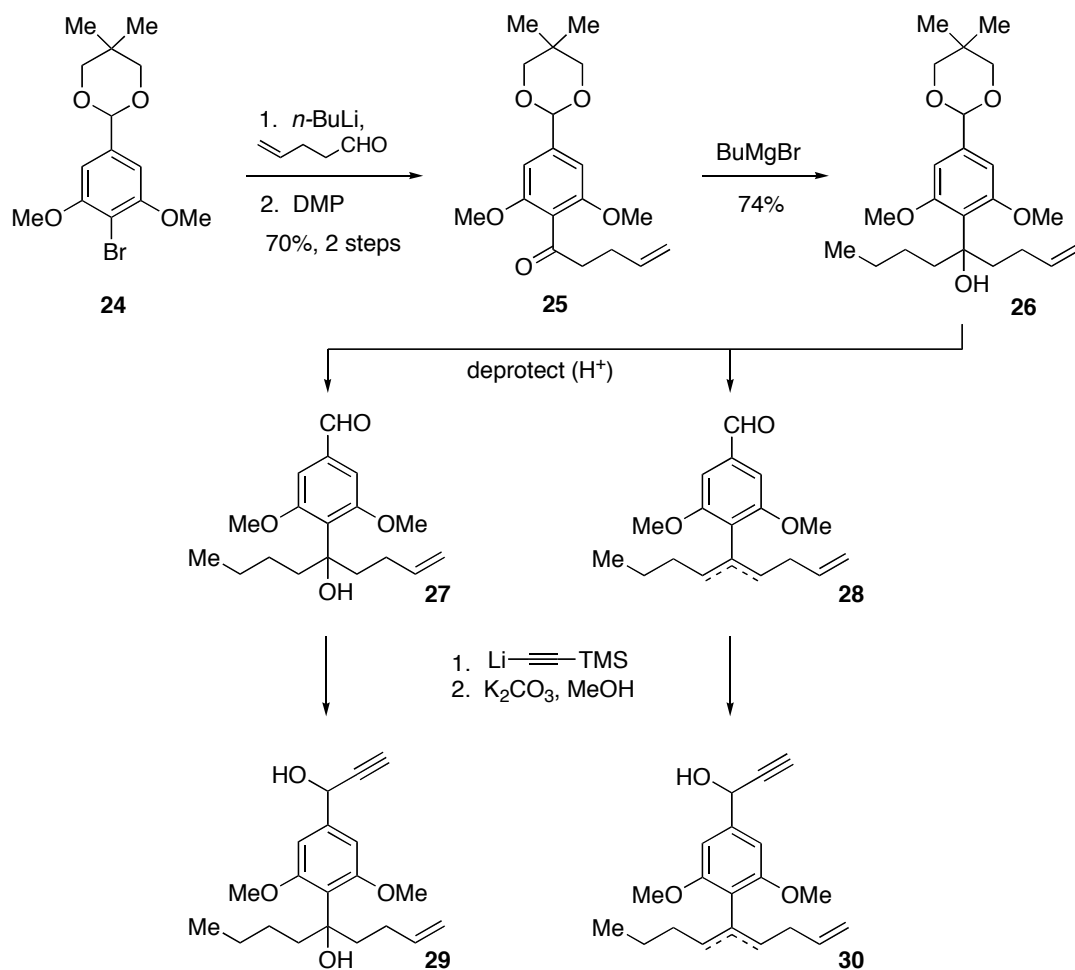
Despite the precedence that the Trost group has shown for the formation of macrocycles via the ruthenium-catalyzed Alder-ene reaction,[10] the desired system was resistant to the reaction conditions. The use of different ruthenium catalysts under various reaction conditions only resulted in polymerization or the recovery of starting

materials (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.
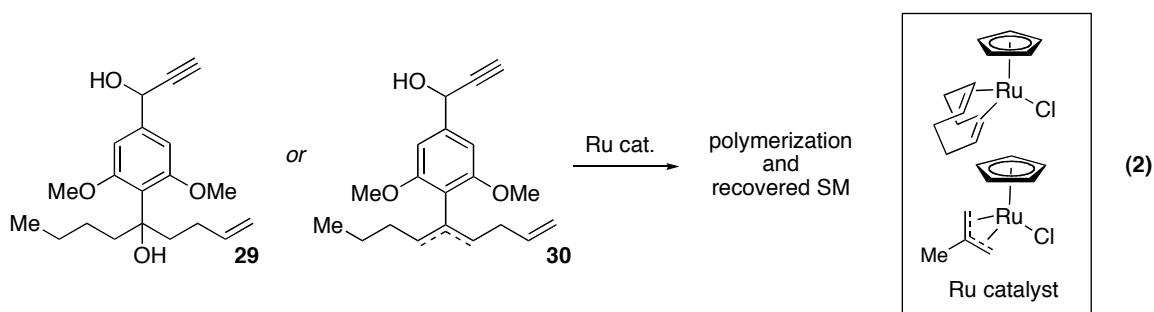
iii. *Hoye's approach to cylindrocyclophane A.*

Hoye, Humpal, and Moon recently reported a strategy towards cylindrocyclophane A.[13] They chose to exploit the C_2-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.[14] The lone stereocenter in **32** was envisioned to arise from a diastereoselective Ireland-Claisen rearrangement[15] of **33**. Allyl enolate **34** was derived in several steps from benzaldehyde **35**, which in turn originated from 3,5-dihydroxybenzoic acid (**16**).

[13] Hoye, T. R.; Humpal, P. E.; Moon, B. J. *J. Am. Chem. Soc.* **2000**, *122*, 4982.

[14] Sanchez, C. C.; Keck, G. E. *Org. Lett.* **2005**, *7*, 3053. (b) Gonzalez, M. A.; Pattenden, G. *Angew. Chem. Int. Ed.* **2003**. *42*, 1255. (c) Mulzer, J.; Pichlmair, S.; Green, M. P.; Marques, M. M. B.; Martin, H. J. *Proc. Nat. Acad. Sci.* **2004**, *101*, 11980. (e) Suzuki, T.; Usui, K.; Miyake, Y.; Namikoshi, M.; Nakada, M. *Org. Lett.* **2004**, *6*, 553.

[15] (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2668. (b) Rathke, M. W.; Sullivan, D. F. *Synth. Commun.* **1973**, *3*, 67.
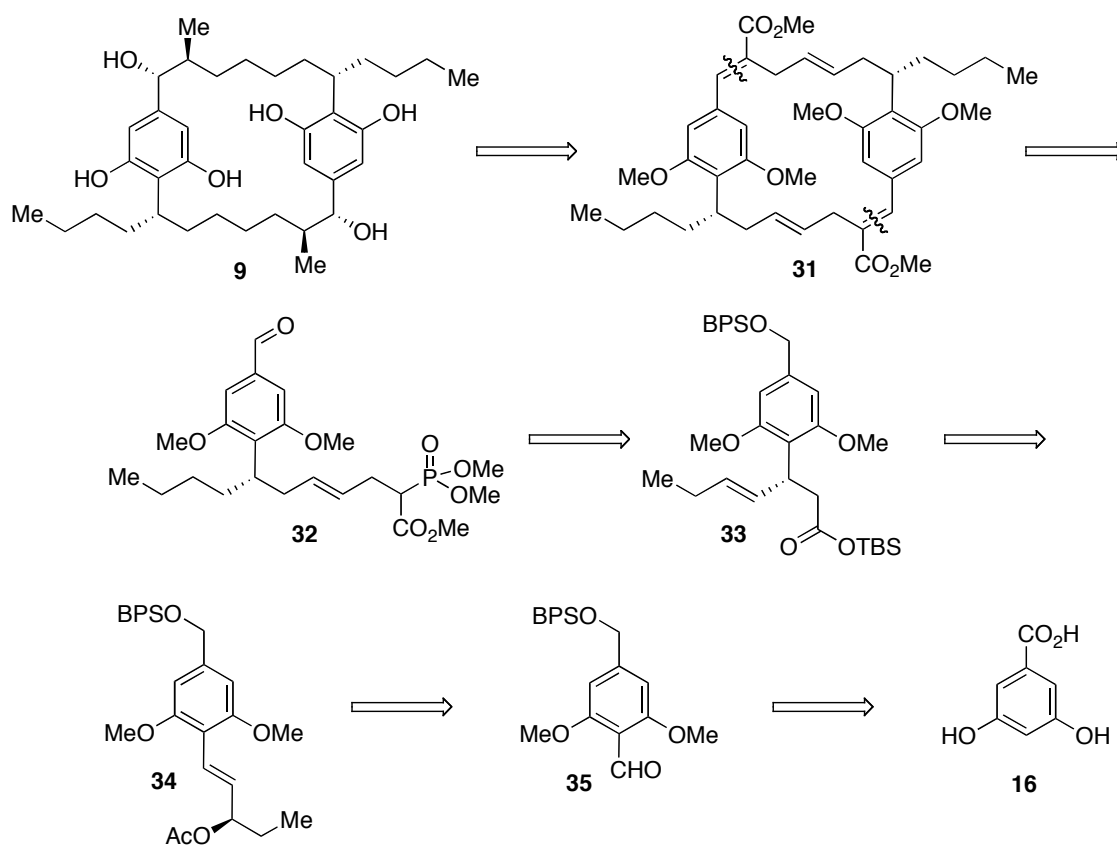
Figure 7. Hoye's retrosynthetic analysis of cylindrocyclophane A.

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[16] afforded exclusively the *trans* allylic alcohol **37**.

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[16] Gernal, A. L.; Luche, A. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

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.
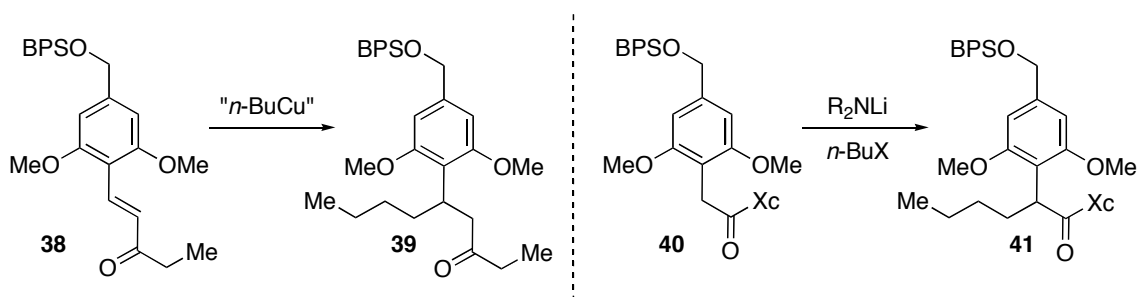

Figure 8. Unsuccessful incorporation of the butyl group.

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 fluorscens*.[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.

17 Humpal, P. E. Ph.D. thesis. University of Minnesota, 1996.

18 (a) Burgess, K.; Jennings, L. D.; *J. Am. Chem. Soc.* **1991**, *113*, 6129. (b) Johnson, C. R.; Golebiowski, A.; McGill, T. K.; Steensma, D. H.; *Tetrahedron Lett.* **1991**, *32*, 2597. (c) Boland, W.; Frobl, C.; Lorenz, M. *Synthesis* **1991**, *12*, 1049. (d) Kazlauskas, R. L.; Weissfloch, A. N. E.; Rapport, A. T.; Cuccia, A. T. *J. Org. Chem.* **1991**, *56*, 2656. (e) Wong, C.-H.; Whitesides, G. M. In *Enzymes in Synthetic Organic Chemistry.* Baldwin, J. E.; Magnus, P. D., Eds.; Tetrahedron Organic Chemistry Series; Permagon : New York, 1994; Vol. 12, pp. 82-93.

Scheme 4. Installation of chiral butyl group via an Ireland-Claisen rearrangement.
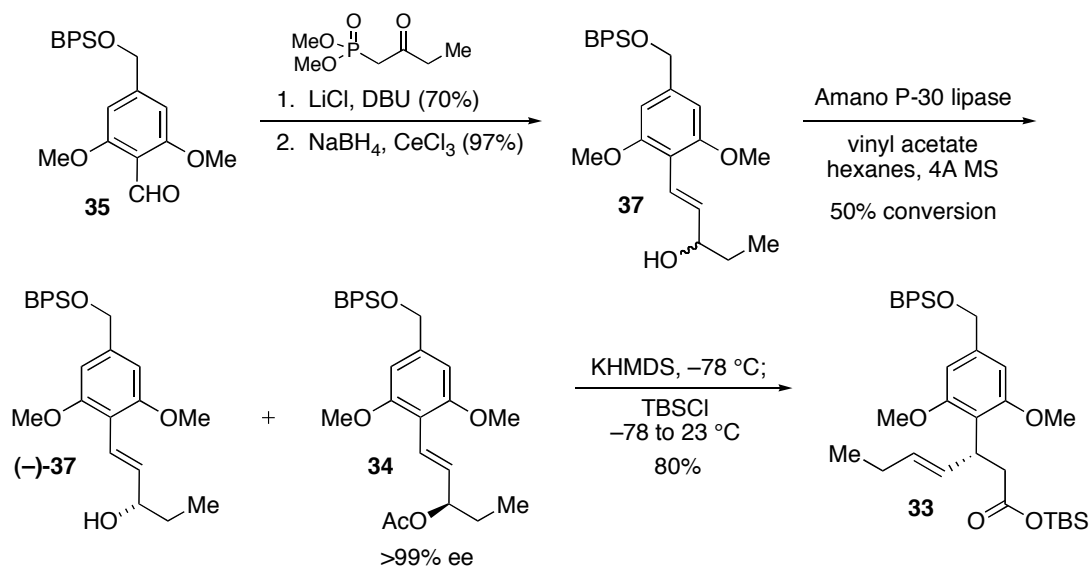
Elaboration of silyl ester **33** commenced with reduction of the ester and hydrogenation of the olefin to provide primary alcohol **42** (Scheme 5). Oxidation of this alcohol was followed by installation of the α,β-unsaturated ester of **43** via a Horner-Wadsworth-Emmons olefination. After reduction of ester **43** and formation of the corresponding allylic chloride, S_N2 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.
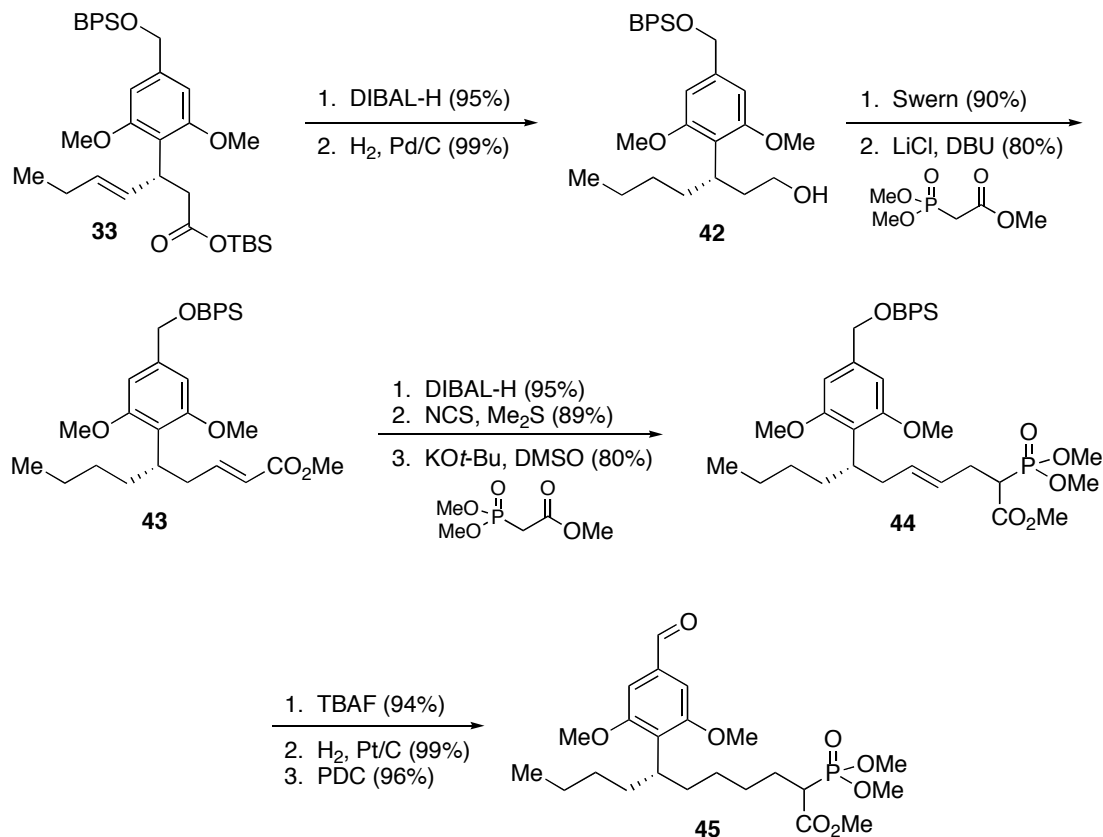
As shown in scheme 6, optimized conditions for the Horner-Wadsworth-Emmons dimerization provided the macrocycle in good yield.[19] The ester functionality of **46** then converted to the methyl group of the natural product. This was accomplished in a three-step sequence consisting of reduction, bromination of the allylic alcohol and hydride displacement in overall excellent yield. Finally, diastereoselective hydroboration with isopinocampheylborane (IpcBH$_2$) and deprotection of the phenolic methyl groups provided cylindrocyclophane A in 24 overall linear steps.

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[19] Moon, B. E. Ph.D. thesis. University of Minnesota, 1998.

Scheme 6. Hoye's endgame approach to cylindrocyclophane A.
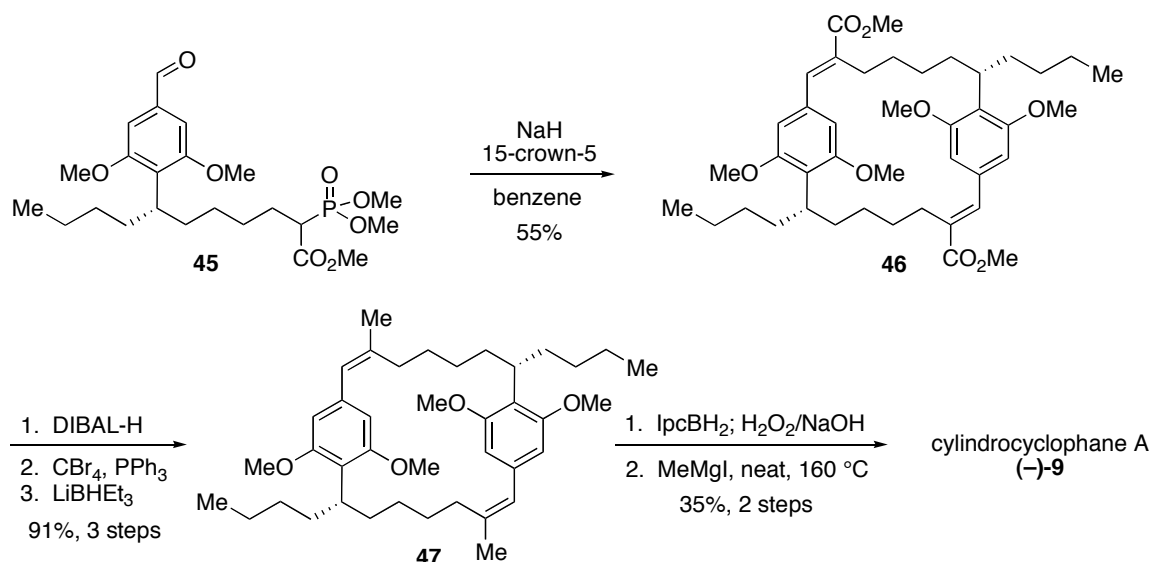
iv. *Smith's synthesis of cylindrocyclophanes A and F.*

In 1999, Smith, Kozmin, and Paone reported an initial first-generation synthesis of cylindrocyclophane F.[20] This synthesis established the capability of ring-closing olefin metathesis[21] to form the 22-membered macrocycle (Scheme 7) of the natural product. Using Myers' reductive alkylation protocol,[22] 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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[20] Smith, A. B. III.; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **1999**, *121*, 7423.

[21] For recent reviews, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b)

[22] Myers, A. G.; Movassaghi, M. *J. Am. Chem. Soc.* **1998**, *120*, 8891.

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.
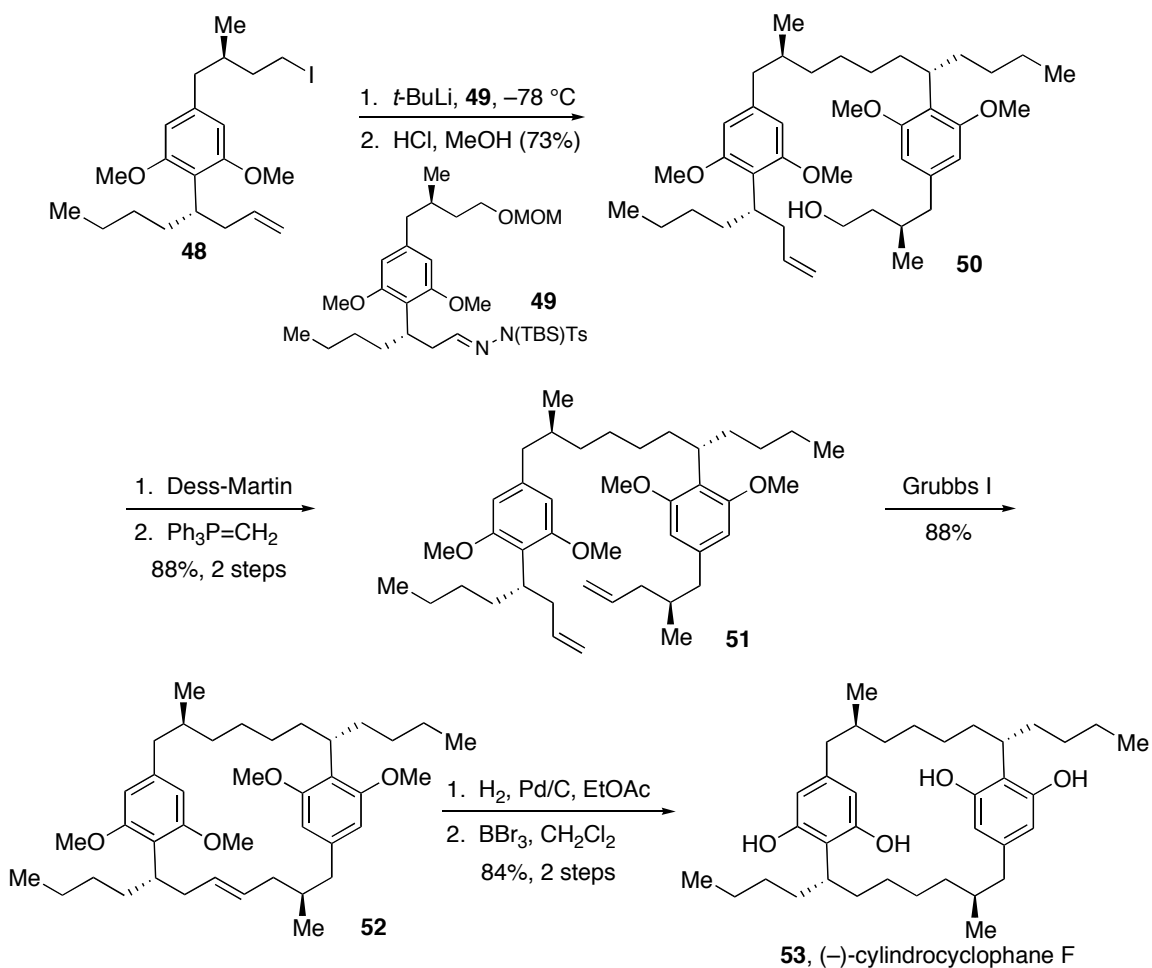
A year later, in the communication immediately following that of Hoye and coworkers,[13] Smith, Kozmin, Adams, and Paone reported a more efficient synthesis to cylindrocyclophanes A and F that featured a remarkable olefin metathesis dimerization

strategy of dienes such as **54** (Fig. 9).[23] Diene **54** is accessible from resorcinol derivative **55**, which is available in one step as the product of a Danheiser annulation[24] with siloxyacetylene **56** and cyclobutenone **57**.
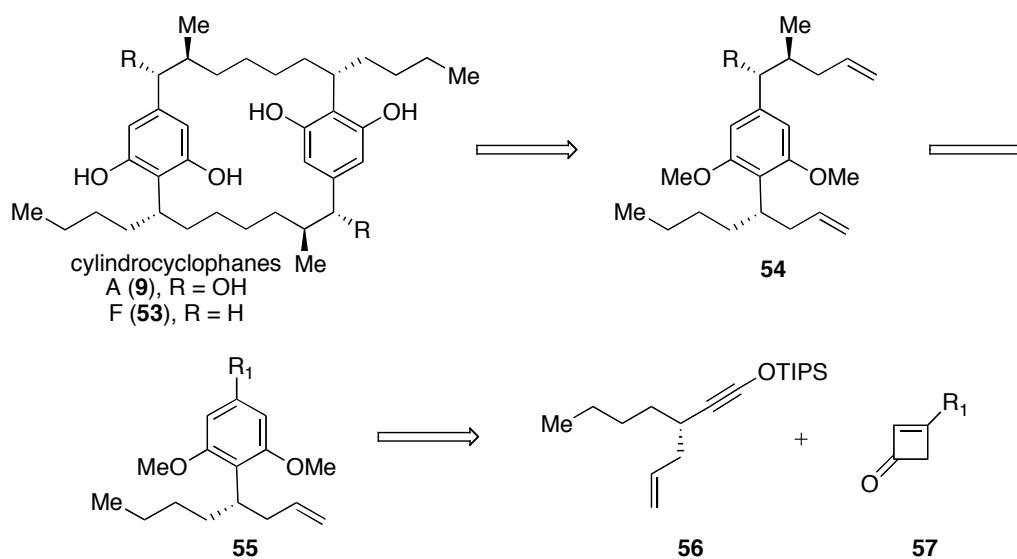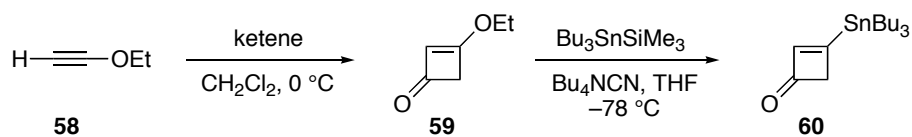

Figure 9. Smith's retrosynthetic plan for cylindrocyclophanes A and F.

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).[25]

**Scheme 8. Synthesis of cyclobutenone 60.**

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[23] Smith, A. B. III; Kozmin, S. A.; Adams, C. M.; Paone, D. V. *J. Am. Chem. Soc.* **2000**, *122*, 4984.

[24] (a) Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984***, 49,* 1672. (b) Danheiser, R. L.; Gee, S. K.; Perez, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 806. (c) Danheiser, R. L.; Nishida, A.; Savariar, S.; Trova, M. P. *Tetrahedron Lett.* **1988**, *29*, 4917. (d) Danheiser, R. L.; Casebier, D. S.; Huboux, A. H. *J. Org. Chem.* **1994**, *59*, 4844.

[25] Liebeskind, L. S.; Stone, G. B.; Zhang, S. *J. Org. Chem.* **1994**, *59*, 7917.

Synthesis of siloxyacetylene **56** began with alkylated Evans oxazolidinone **61**, available in three steps from the corresponding oxazolidinone.[26] 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[27] in which the oxyacetylene rearrangement product is trapped with TIPSOTf (Scheme 9).

Scheme 9. Synthesis of siloxyacetylene 56.
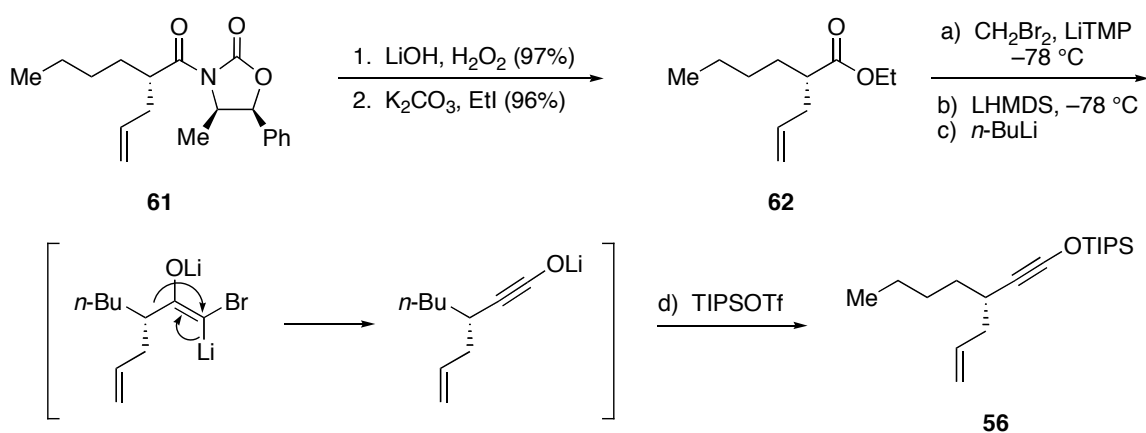
Assembly of the aromatic moiety **63** was accomplished by heating acetylene **56** with cyclobutenone **60** to effect the Danheiser benzannulation. The aromatic stannane was converted to the aryl iodide followed by TIPS deprotection and reprotection of both phenols as methyl ethers completed formation 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[28] furnished a ketone. This ketone was then diastereoselective reduced to the corresponding

[26] Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506.

[27] (a) Kowalski, C. J.; Haque, M. S.; Fields, K. W. *J. Am. Chem. Soc.* **1985**, *107*, 1429. (b) Kowalski, C. J.; Lal, G. S.; Haque, M. S. *J. Am. Chem. Soc.* **1986**, *108*, 7127. (c) Kowalski, C. J.; Lal, G. S. *J. Am. Chem. Soc.* **1988**, *110*, 3693.

[28] Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.

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.
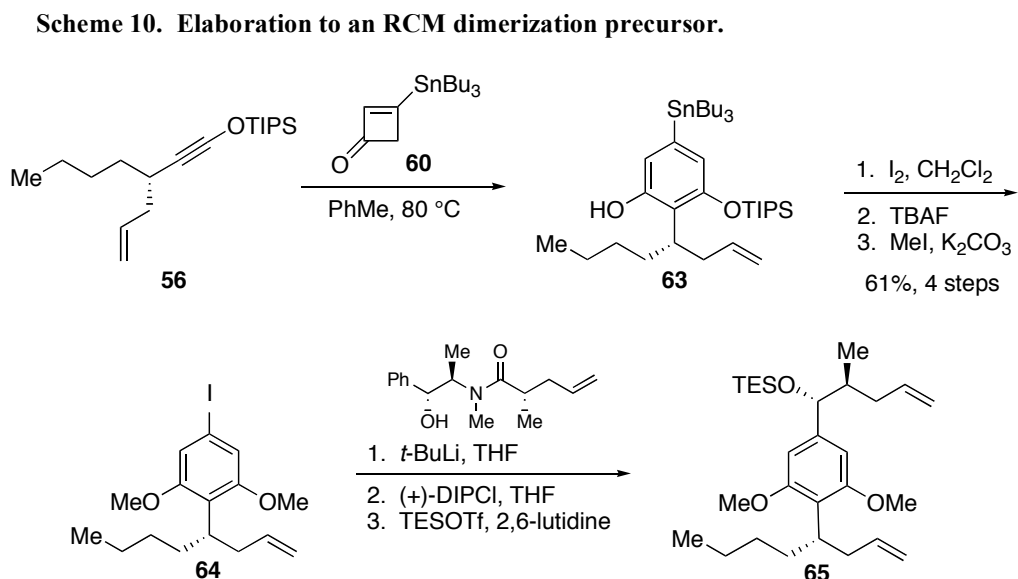
Synthesis of the corresponding diene **67** for cylindrocyclophane F proceeded in a similar sequence of events from alkyne **56** and cyclobutenone **66** (eq. 3).
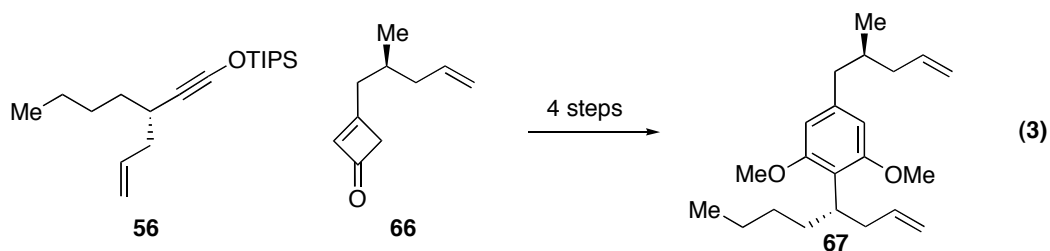
After a survey of the Grubbs ruthenium metathesis catalysts and the Schrock molybdenum metathesis catalyst, the Schrock catalyst was found to effect the dimerization in good yields (Fig. 10). Despite the fact that a mixture of olefin isomers and head-to-head and head-to-tail dimers were all possible products from this reaction, only the *trans* head-to-tail dimer was observed. This truly remarkable example of the

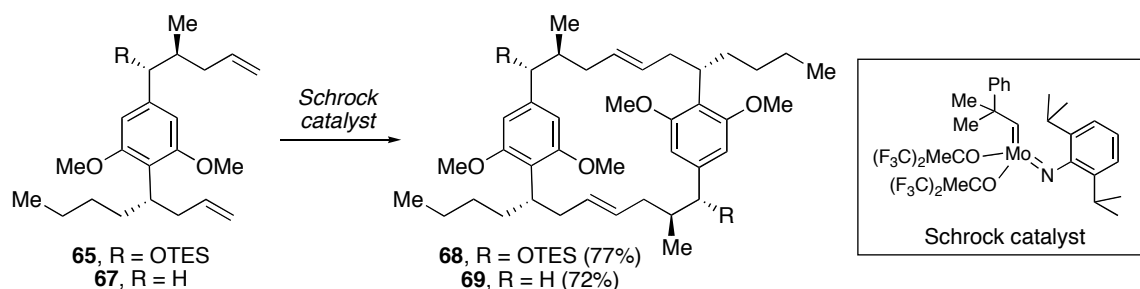reversible nature of the cross-metathesis was elegantly investigated in a full article from the Smith group in 2001.[29]

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. Smith's second-generation endgame to the cylindrocyclophanes.
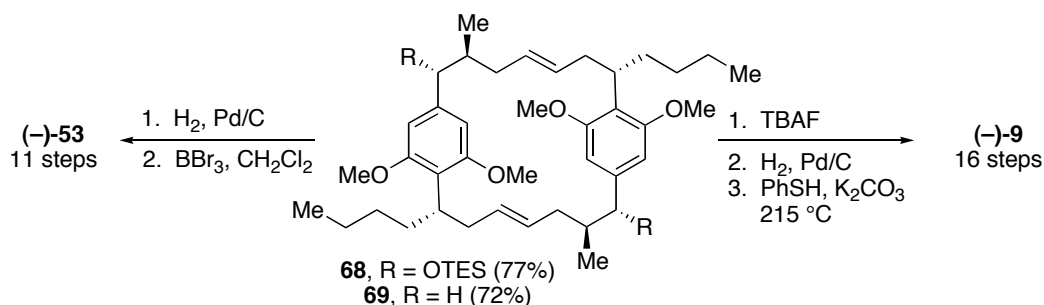
[29] Smith, A. B. III; Adams, C. M.; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 5925.

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.

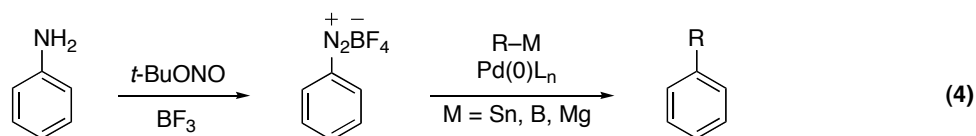### i. *Suzuki cross-couplings of aryltrimethylammonium salts.*

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

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30 Blakey, S. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 6046.

31 For reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Ed.; Wiley-VCH: Weinheim, 2004.

their application as π-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]

Classical Diazotization Sequence

$$(4)$$

Trialkylanilinium Salt Sequence (Wenkert)

$$(5)$$
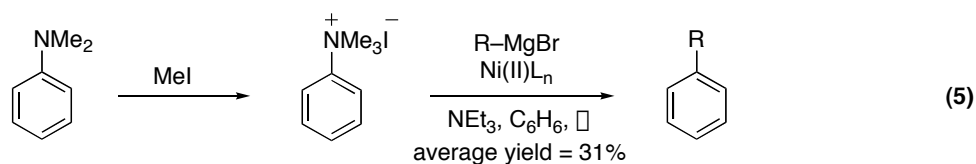
In 1988, Wenkert reported the nickel(II)-catalyzed Kumada cross-coupling of aryltrimethylammonium iodides (eq. 5).[33] While the scope of the reaction was very limited in terms of both reacting partners and the yields were less than optimal, this research introduced the concept that dialkylanilines might 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.

[32] (a) Willis, D. M.; Strongin, R. M. *Tetrahedron Lett.* **2000**, *41*, 6271. (b) Sengupta, S.; Bhattacharyya, S. *J. Org. Chem.* **1997**, *62*, 3405. (c) Darses. S.; Jeffrey, J. P.; Genet, J. P.; Brayer, J. L.; Demoute, J. P. *Tetrahedron Lett.* **1996**, *37*, 3857. (d) Kikukawa, K.; Kono, K.; Wada, F.; Matsuda, T. *J. Org. Chem.* **1983**, *48*, 1333.

[33] Wenkert, E.; Han, A.-L.; Jenny, C.-J. *J. Chem. Soc., Chem. Commun.* **1988**, 975.

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.[30]   Ni(COD)$_2$ 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).

Trialkylanilinium Salt Sequence (MacMillan and Blakey)
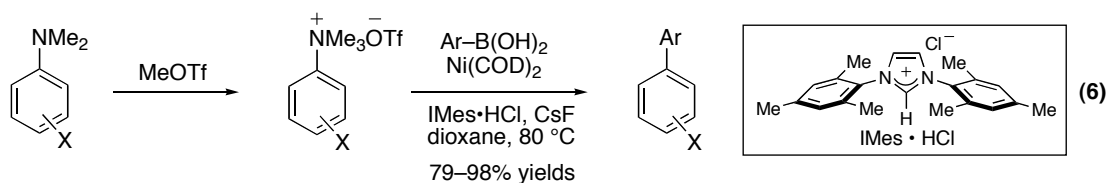

ii. B-*alkyl Suzuki cross-coupling investigations.*

A model system resembling the electron-rich resorcinol in the natural product was chosen to investigate the alkyl Suzuki cross-coupling.[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[35] provided trimethylanilinium salt **72** in 83% yield for the sequence.

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[34] For a review on *B*-alkyl Suzuki cross-couplings, see: Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 4544.

[35] Langer, O.; Dollé, F.; Valette, H.; Halldin, C.; Vaufrey, F.; Fuseau, C.; Coulton, C.; Ottaviani, M.; Någren, K.; Bottlaender, M.; Maziére, B.; Crouzel, C. *Bioorg. Med. Chem.* **2001**, *9*, 677.

Scheme 12. Synthesis of trimethylanilinium salt.
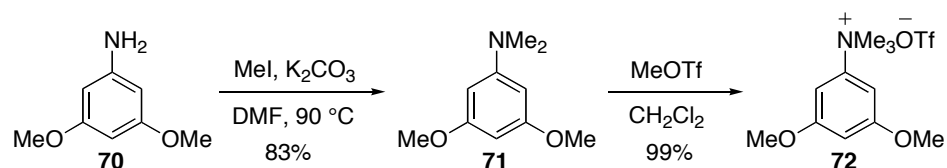
The *B*-alkyl borane used in Table 1 was synthesized via hydroboration of the corresponding olefin with the dimer of 9-borabicyclononane (9-BBN). This alkyl borane moiety was chosen because alkyl boranes are known to be more reactive than their boronic acid and boronic ester counterparts.[31a] They are, 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.
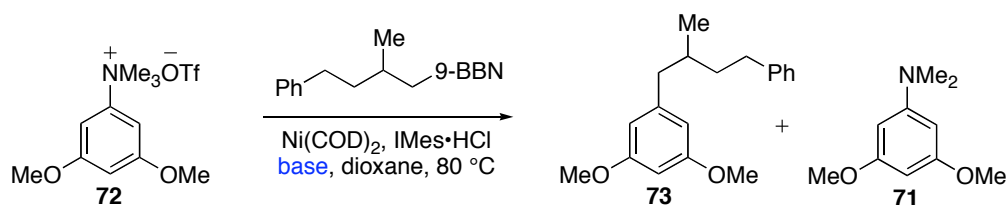
| Entry	base	% conversion to 73
1	CsF	~5
2	CsOH	0
3	KF	0
4	K$_2$CO$_3$	0
5	K$_3$PO$_4$	0
6	NaOt-Bu	trace
7	KOH	0
8	KOEt	0
9	NaOH	trace
10	NaOMe	0

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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[36] For reviews on *N*-heterocyclic carbenes, see: (b) Herrmann, W. A.; Kocher, C. *Angew. Chem. Int. Ed.* **1997**, *36*, 2182. (c) Herrmann, W. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1290. (d) Jafarpour, L.; Nolan, S. P. *Adv Organomet. Chem.* **2001**, *46*, 181. (e) Arduengo, A. J. III. *Acc. Chem. Res.* **1999**, *32*, 913.

[37] For a general review, see: (a) Schlummer, B.; Scholz, U. *Adv. Synth. Cat.* **2004**, *346*, 1599. For references on ligands **L1**, **L2**, and **L3**, see: (b) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **1999**, *38*, 2413. (c) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722. (d) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.

Table 2. Ligand screen in the cross-coupling.
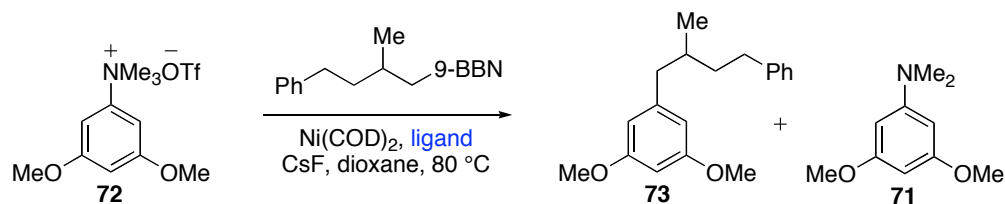
Entry	ligand	% conversion to **73**
1	IMes·HCl	~5
2	sIMes·HCl	~5
3	**L1**	<10
4	**L2**	<10
5	**L3**	~10
6	Pt-Bu$_3$	0
7	PCy$_3$	25
8	none	0
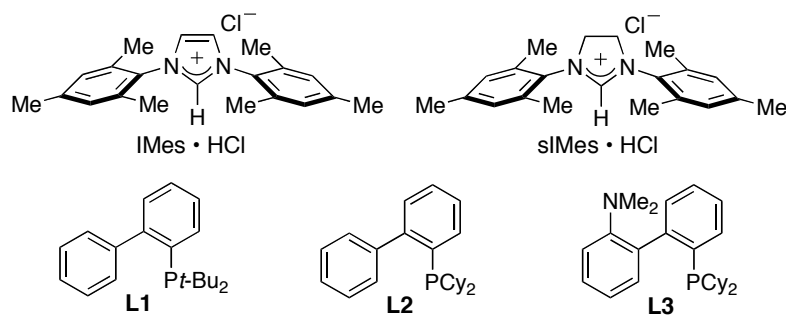
The other reaction parameters were also investigated. A screen of nickel sources [NiCl$_2$(dppf), NiCl$_2$(dppp), Ni(acac)$_2$, NiCl$_2$(PPh$_3$)$_2$, Ni(PPh$_3$)$_2$(CO)$_2$] showed Ni(COD)$_2$ to be superior. A survey of solvents and reaction temperatures also did not increase the yield of this reaction. 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.
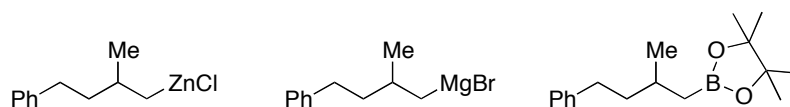
Figure 11. Ineffective transmetaling partners in the cross-coupling reaction.

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.

$$(7)$$
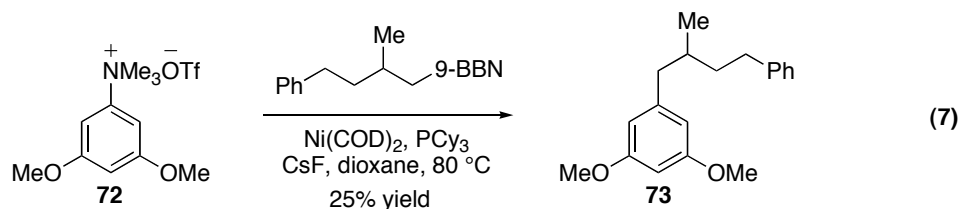
iii. *Proposed catalytic cycle to explain nickel-catalyzed demethylation.*

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[38] and observations made within this

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[38] Neigishi, E.; Takahashi, T.; Baba, S.; Van Horn, D. E.; Okukado, N. *J. Am. Chem. Soc.* **1987**, *109*, 2393.

study.[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^2 boronic acids undergo rapid transmetalation and the rate-determining step is generally oxidative addition.[31,40] Figure 12 shows the proposed catalytic cycle for alkyl boranes (RBX_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).

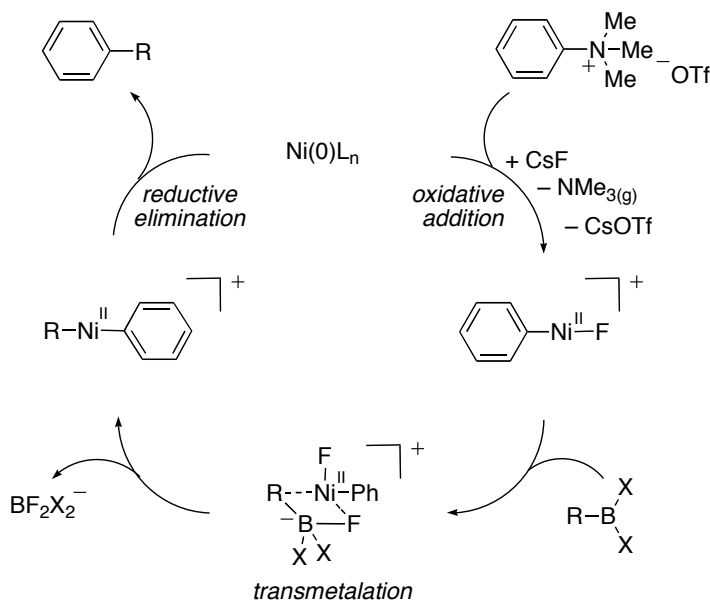**Figure 12. Proposed catalytic cycle for *B*-alkyl Suzuki cross-coupling.**

[39] For a review on nickel-catalyzed cross-couplings, see: Negishi, E.; Zeng, X.; Tan, Z.; Qian, M.; Hu, Q.; Huang, Z. In *Metal-Catalyzed Cross-Coupling Reactions (2nd Edition)*. De Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004. pp. 815-889.

[40] Zim, D.; Lando, V. R.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2001**, *3*, 3049.

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.
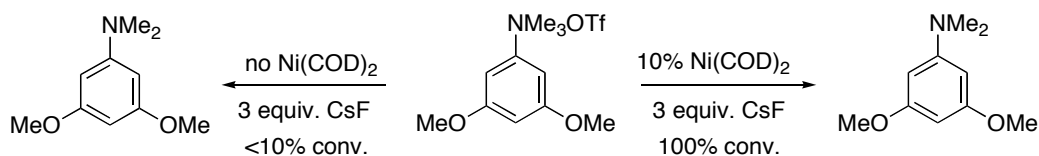

Figure 13. Nickel-catalyzed demethylation of trimethylanilinium salt.

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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[41] Anslyn, E. V.; Dougherty, D. A. In *Modern Physical Organic Chemistry.* University Science Books: **2006**, p. 7.
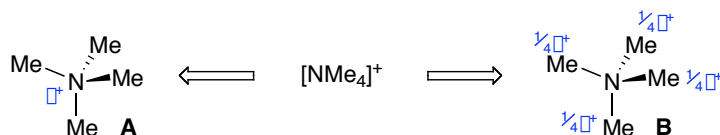
Figure 14. Charge distribution in the tetramethylammonium ion.

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.
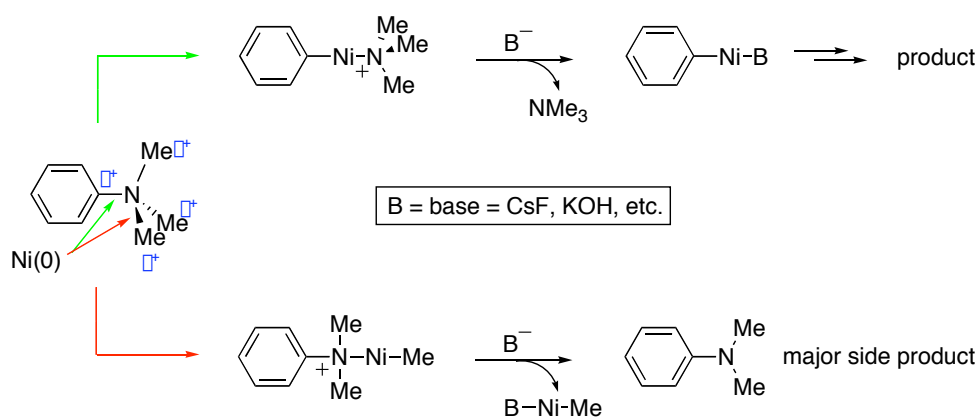

Figure 15. Competing oxidative addition pathways on trimethylanilinium salts.

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.[42] 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.[43]
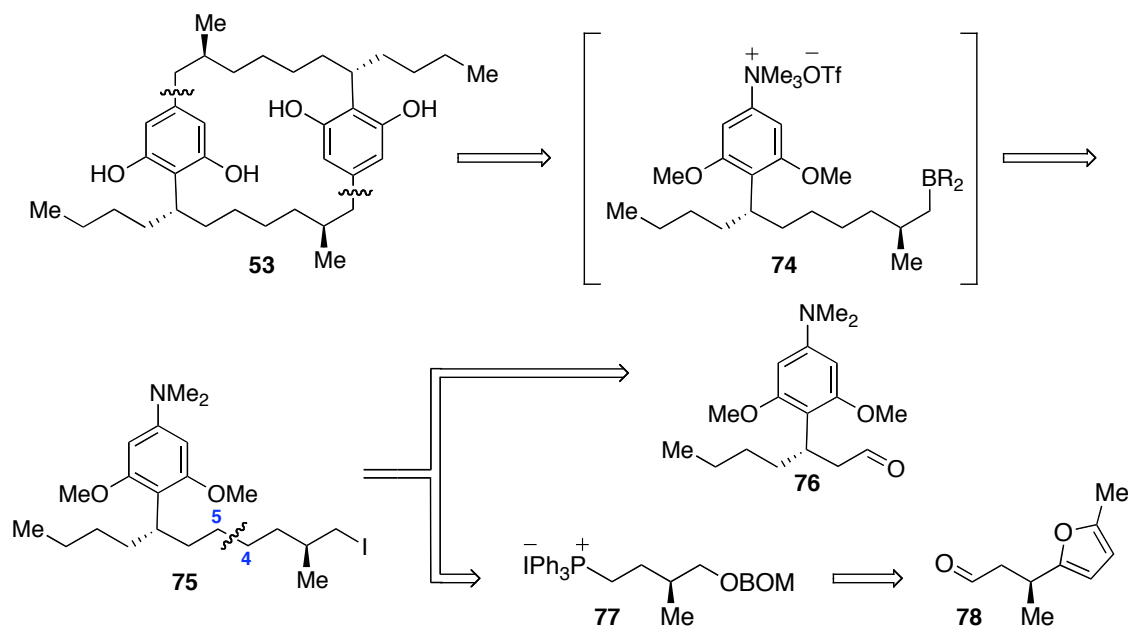

Figure 16. Retrosynthetic plan.

[42] Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894.

[43] Brown, S. P. Ph.D. thesis. California Institute of Technology, 2005.

v. *Synthesis of a dimerization precursor.*

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 π-nucleophiles into α,β-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.

(8)
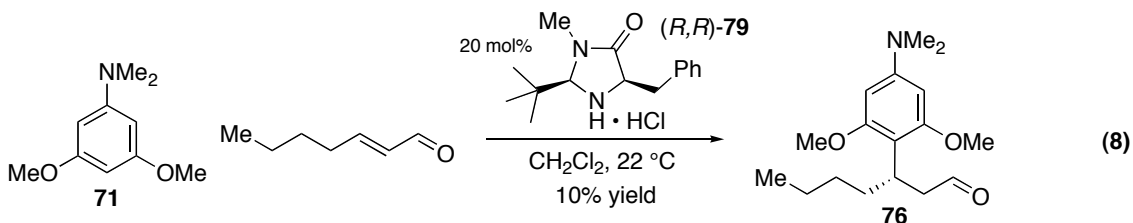
An initial temperature screen with HCl as the co-catalyst and methylene chloride as the solvent at –40 °C gave a 70% ee with full conversion (Table 3, entry 1), while higher temperatures gave lower enantioselectivities and lower temperatures gave lower conversions. In a subsequent solvent screen, however, 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.
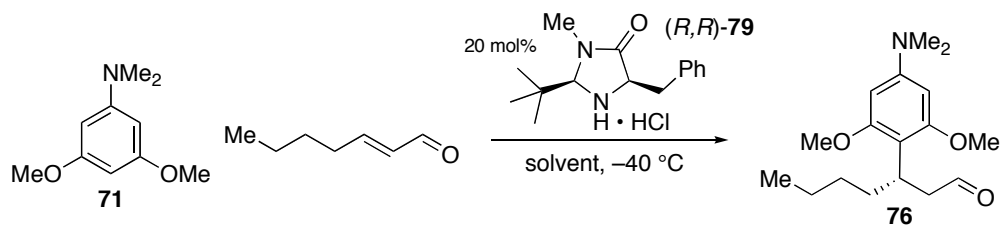
Entry	Solvent	conversion (%)	% ee[a]
1	CH$_2$Cl$_2$	74	74
2	CHCl$_3$	79	88
3	toluene	67	88
4	THF	79	80
5	DMF	75	46
6	CH$_3$CN	59	63
7	MeOH	59	41
8	Et$_2$O	74	49

[a] 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.
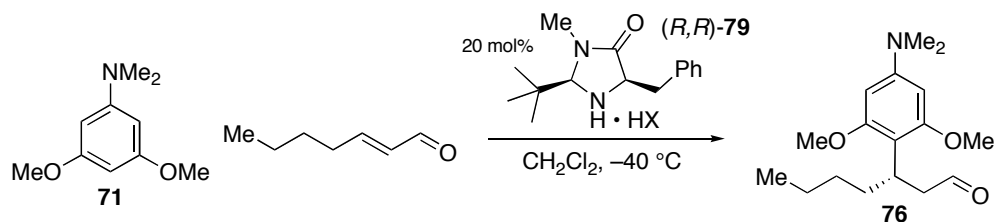
Entry	HX	pK$_a$	conversion (%)	% ee[a]
1	TfOH	–14	48	79
2	HCl	–8	63	72
3	TFA	–0.25	51	72
4	DCA	1.29	66	78
5	DNBA	1.86	58	83

[a] Determined by HPLC analysis of the corresponding alcohol

Table 5. Survey of a combination of co-catalyst and solvent conditions.
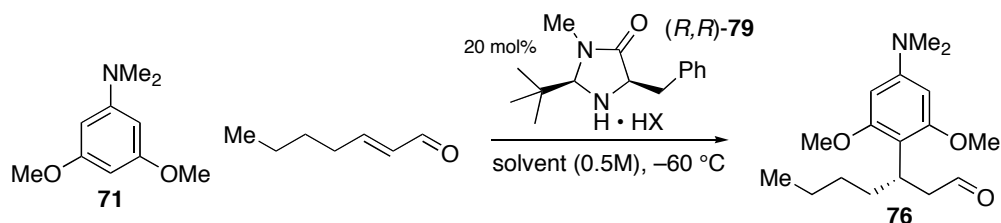
| Entry	HX	Solvent	conversion (%)	% ee[a]
1	DCA	CHCl$_3$	83	94
2	DCA	THF	57	86
3	DCA	toluene	94	89
4	DNBA	CHCl$_3$	59	94
5	DNBA	THF	78	90
6	DNBA	toluene	85	91
7	TfOH	CHCl$_3$	52	89
8	TfOH	THF	82	73
9	TfOH	toluene	85	85

[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).

(9)
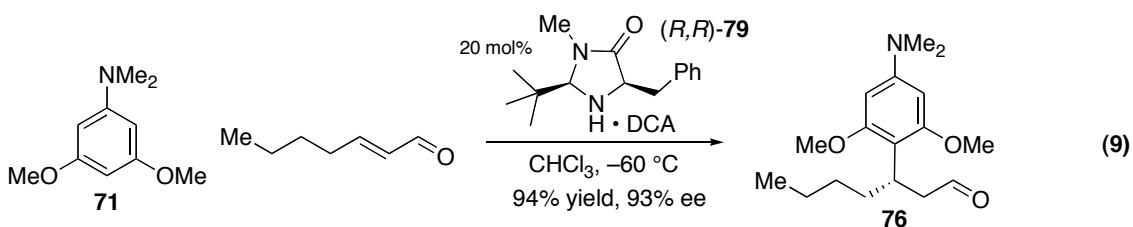
The organocatalytic addition of 2-methyl furan into crotonaldehyde had been developed previously in the lab.[43] It was found that in situ reduction with sodium borohydride provided higher isolated yields of the alcohol **80**, with an isolated 98% yield

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.
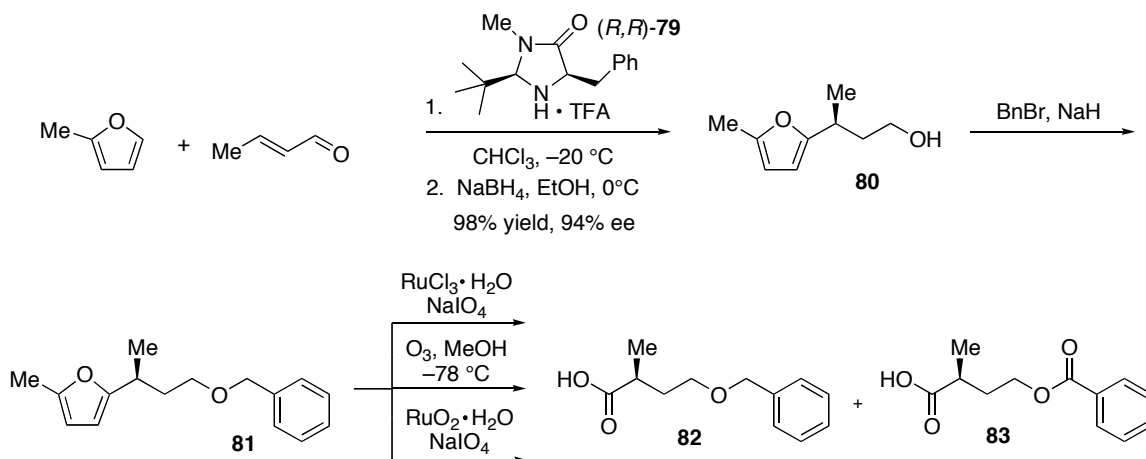
A benzyl protecting group was installed, and on a small scale the reaction proceeded to afford the benzylated product **81**. However, larger scale reactions (>50 mg) imparted a mixture of desired product **82** and overoxidized product **83**, all present in different mixtures depending on the oxidation system (Ru(III), Ru(IV), ozone) that was used. Thus, to avoid the problem of overoxidation, a benzoyl 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.
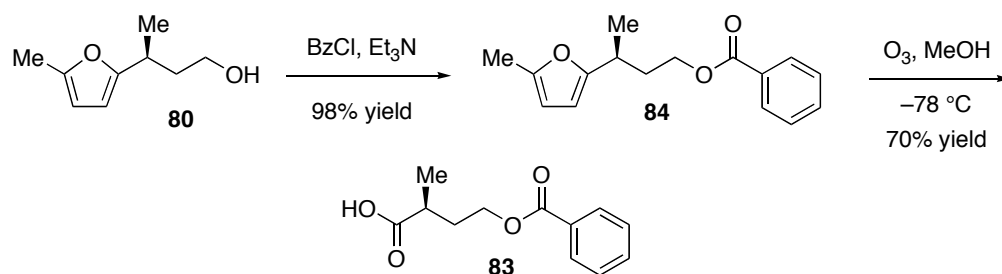
Once carboxylic acid **83** was in hand, mild reduction conditions using borane-dimethyl sulfide complex reduced the acid to the alcohol while leaving the benzoyl ester intact in an 87% yield (eq. 10). Protection of the free alcohol with benzyloxymethyl ether (BOM) was followed by removal of the benzoyl protecting group using 1% NaOH in methanol. Subsequent iodide formation on the free hydroxyl provided iodide **85** with a in 55% yield over four steps.

$$(10)$$
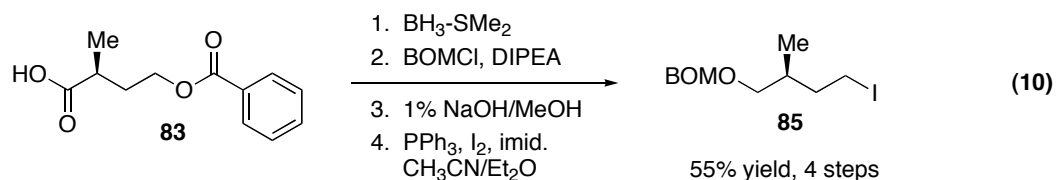
vi. *Myers' reductive alkylation strategy.*

A Myers reductive alkylation[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 lithiums 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.
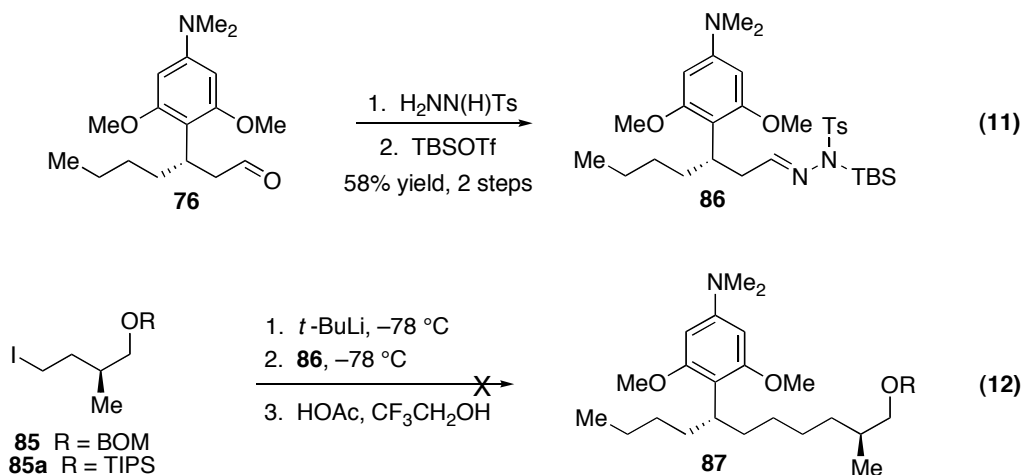
Consideration of the mechanism (Fig. 17) revealed that acetic acid is necessary for protodesilylation, which in turn initiates the reaction sequence. It was believed that the basic aniline moiety might be consuming the acetic acid necessary for protodesilylation. Thus, excess acetic acid was added to 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.
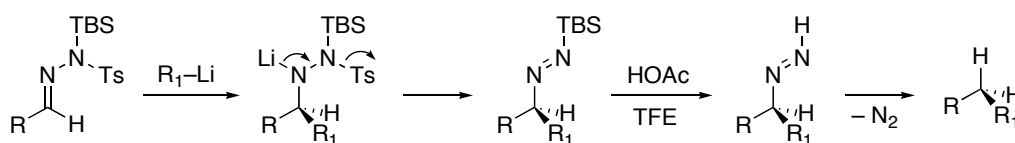

**Figure 17. Myers' reductive alkylation mechanism.**

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.

$$\text{BOMO} \overset{\text{Me}}{\underset{85}{\diagdown}} \text{I} \quad \xrightarrow[\text{quantitative}]{\text{PPh}_3,\ \text{Et}_2\text{O}} \quad \text{BOMO} \overset{\text{Me}}{\underset{88}{\diagdown}} \overset{+}{\text{PPh}_3}\bar{\text{I}} \qquad \textbf{(13)}$$

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 °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.

Scheme 15. First-generation Wittig olefination.
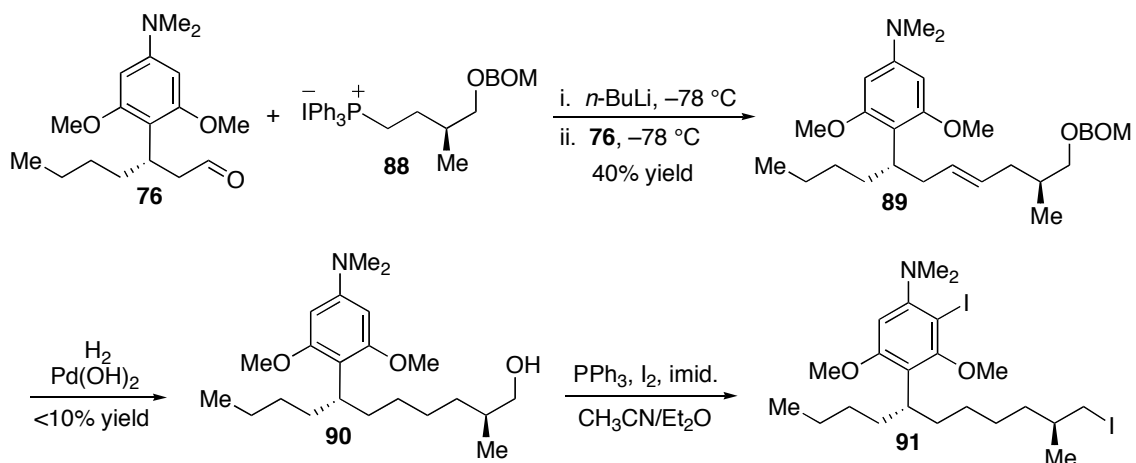
While the above protecting group strategy was being investigated, the same Wittig olefination sequence was performed bringing in the furan moiety as phosphonium salt **92** (Scheme 16). The olefination proved to be more efficient; however, the hydrogenation required elevated pressure, and reduction of 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.

Scheme 16. Second-generation Wittig olefination.
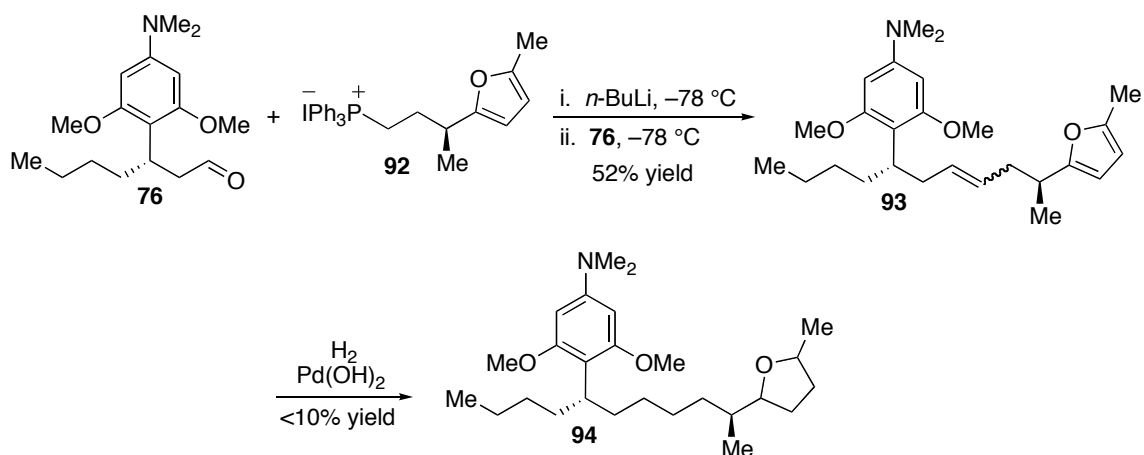
In search of a more reliable olefination, the nucleophilic and electrophilic moieties in the Wittig olefination were reversed; aldehyde **76** was transformed into Wittig salt **95**. This unstabilized phosphonium salt proved to be unexpectedly unstable, and upon exposure to a variety of bases at −78 °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.

(14)
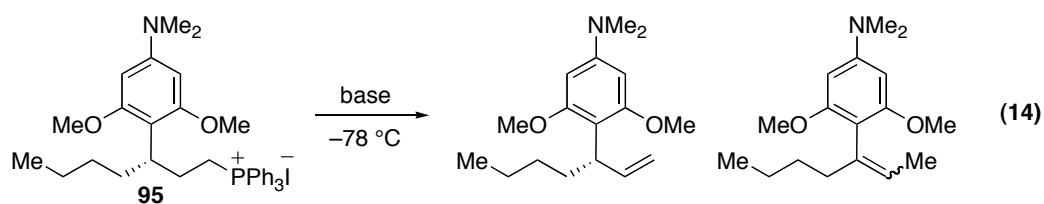
viii. *Julia-Lythgoe olefination strategy.*

The Julia-Lythgoe olefination, traditionally, is a two-step carbon-carbon bond formation that results in olefinic linkages.[44] This coupling procedure has the benefits of utilizing readily available α-sulfonyl carbanions and giving predominately *E* olefins (Fig. 18). The reducing conditions that are commonly used to cleave the β-oxysulfonate products are not mild and thus functional group compatibility can be problematic for this procedure.

Julia-Lythgoe Olefination

Julia-Kocienski Olefination
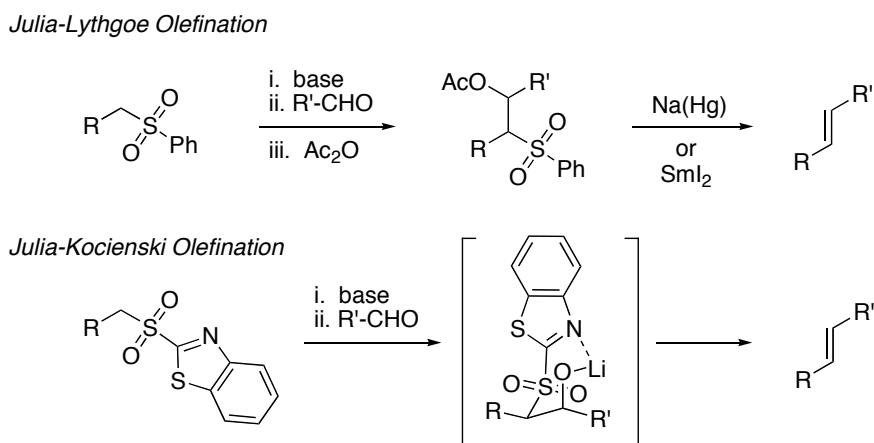
Figure 18. The Julia olefination.

The modified Julia olefination, or the Julia-Kocienski olefination,[45] 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

[44] (a) Julia, M.; Arnold, D. *Bull. Soc. Chim. Fr.* **1973**, 743. (b) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, *49*, 4833. (c) Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. I* **1978**, 829. (d) Kocienski, P. J.; Lythgoe, B.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. I* **1980**, 1045. (e) Keck, G. E.; Savin, K. A.; Weglarz, M. *J. Org. Chem.* **1995**, *60*, 3194.

[45] Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, *107*, 26.

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[46] into aldehyde **76** did not form the desired olefin and only starting material was recovered (eq. 15).
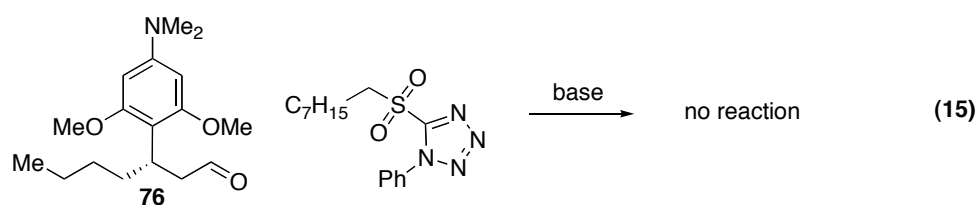
Analogous to the Wittig investigations reported in the previous section, the reaction partners were reversed in an effort to attain reactivity for the olefination. In order to convert the aldehyde to the sulfone, thiol **96** was prepared under Mitsunobu conditions and a mild oxidant was used to attempt oxidation of the thiol to the sulfone (Scheme 17). However, the basic *N,N*-dimethylaniline proved to be problematic once again as it outcompeted the sulfone for oxidation and formed the undesired *N*-oxide **97** instead of the desired sulfone **98**

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[46] McAlonan, H.; Potts, D.; Stevenson, P. J.; Thompson, N. *Tetrahedron Lett.* **2000**, *41*, 5411.

Scheme 17. Oxidation sequence forms *N*-oxide.
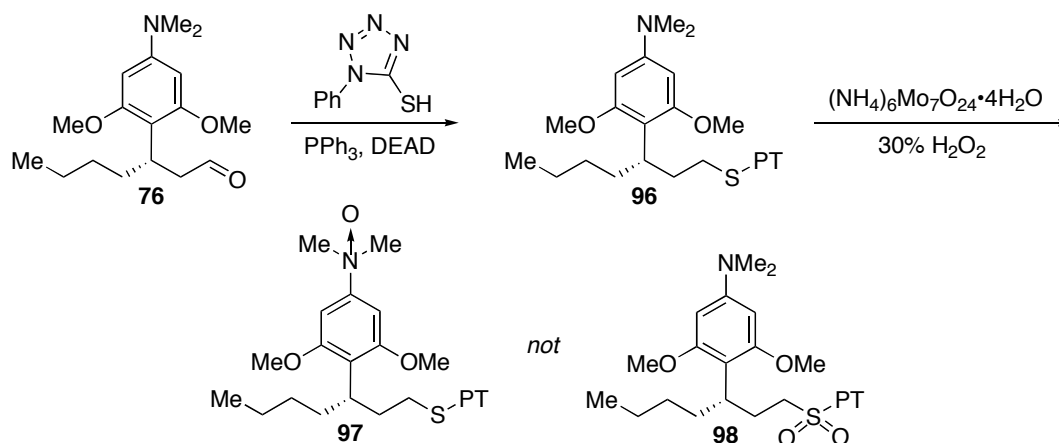
Because of the inability of this system to under selective thiol oxidation, the two-step Julia olefination sequence was attempted. Synthesis of phenylsulfone **101** was accomplished in three steps from aldehyde **76** (Scheme 18). Sodium borohydride reduction of the aldehyde gave alcohol **99** in excellent yield. Iodination of the alcohol followed by nucleophilic displacement of the alkyl iodide with sodium benzenesulfinate provided phenylsulfone **101** in good yield.

Scheme 18. **Synthesis of phenyl sulfone 101.**
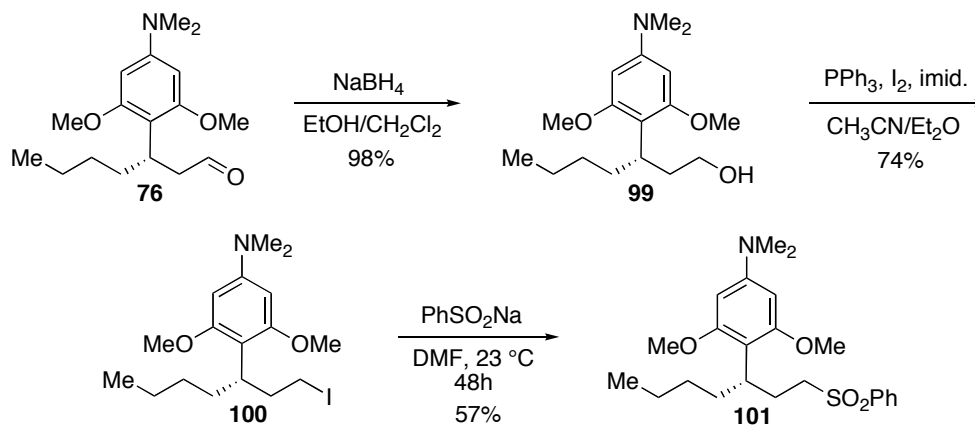
Meanwhile, preparation of olefination partners with began with chiral aldehyde **107a** (R = OPMB) as a target (Scheme 19). Drawing from the chiral pool, (*R*)-Roche ester **102** was protected as its *para*-methoxybenzyl ether **103**, which was then subjected to a two-step Kowalski ester homologation 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.

Scheme 19. Synthesis of chiral aldehyde 107a for use in the Julia olefination.
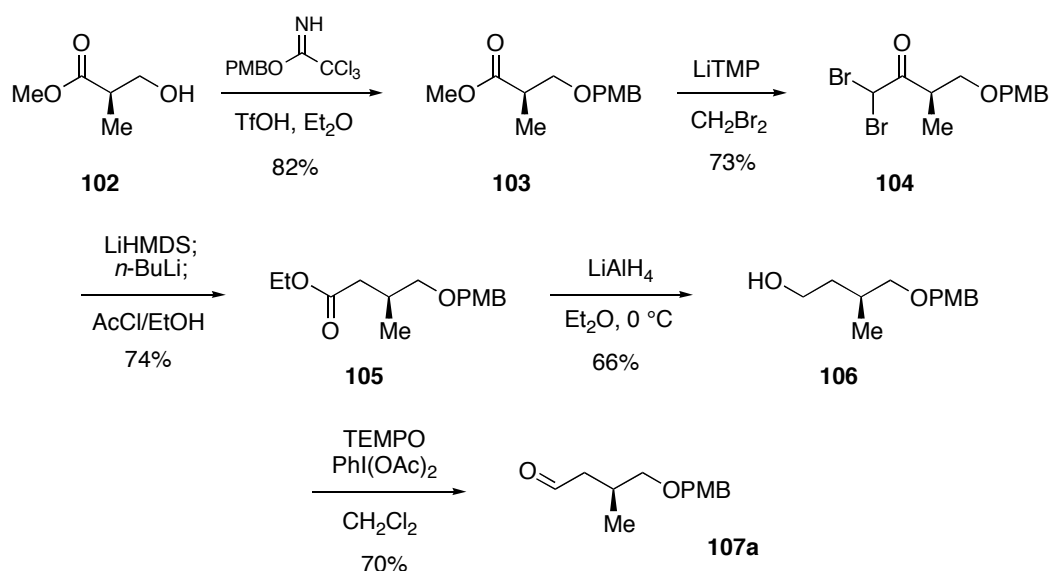
The detailed mechanism for the Kowalski ester homologation is shown in figure 19.[27] The methyl ester **103** was converted to the dibromoketone **104**, which was then converted to the vinyl dibromide. Lithium/halogen exchange in the presence of butyllithium yields a dianion, which upon warming causes rearrangement to the acetylene and concomitant bromide displacement. The ynolate anion is then protonated in acidic

ethanol. The resulting ynol is in equilibrium with the ketene, which is eventually consumed by the acidic ethanol, affording the one-carbon homologated product **105**.
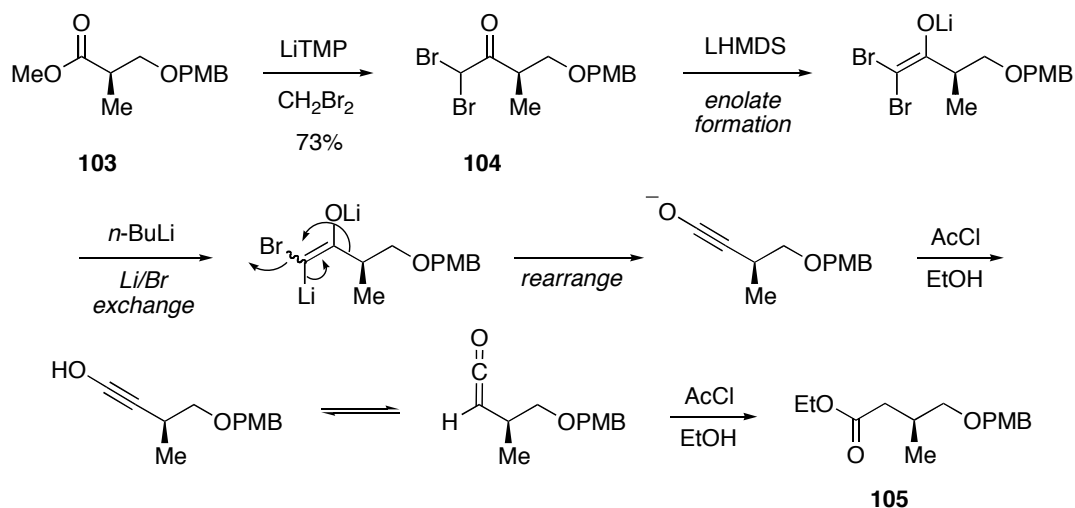
Figure 19. Mechanism of the Kowalski rearrangment.

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**.[47] 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).

(16)
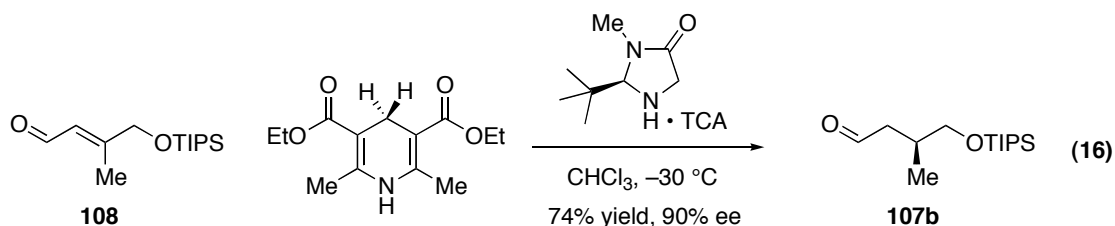
[47] Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32.

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.
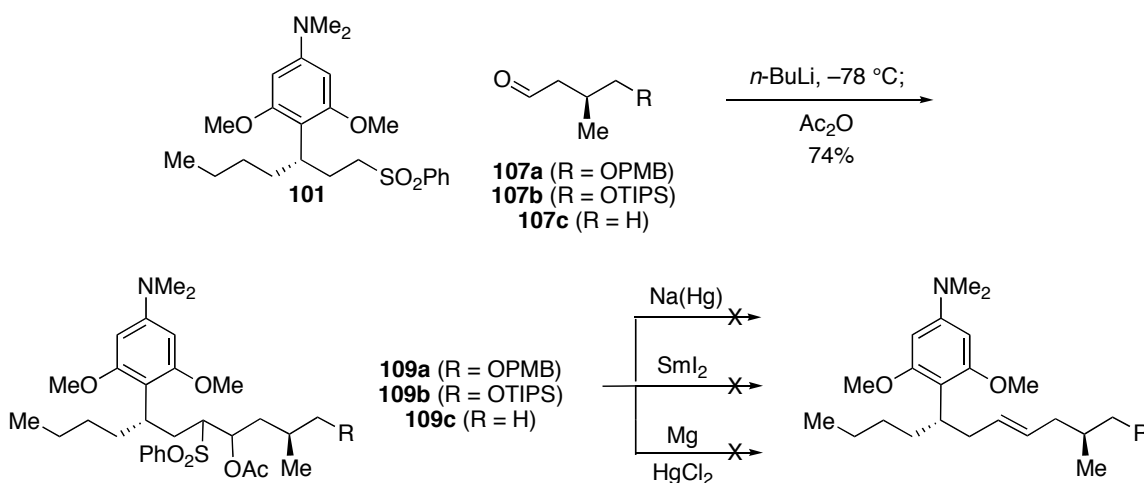
[48] (a) Lythgoe, B.; Waterhouse, I. *Tetrahedron Lett.* **1977**, *48*, 4223. (b) Bremmer, J.; Julia, M.; Launay, M.; Stacino, J. P. *Tetrahedron Lett.* **1982**, *53*, 3265.

[49] Kende, A. S.; Mendoza, J. S. *Tetrahedron Lett.* **1990**, *31*, 7105.

[50] Evans, D. A.; Carter, P. H.; Carreira, E. M.; Charette, A. B.; Prunet, J. A.; Lautens, M. *J. Am. Chem. Soc.* **1999**, *121*, 7540.

The proposed mechanism involves a one electron transfer from the Na(Hg) or SmI$_2$ to reduce the vinyl sulfone to the vinyl radical, which is further reduced to the vinyl carbanion (Fig. 20).[44]
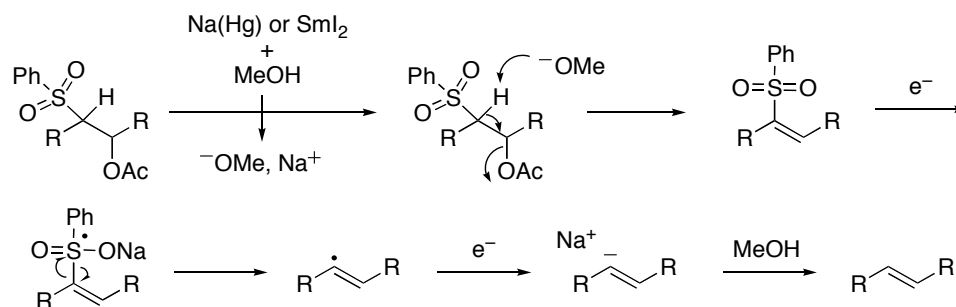
Figure 20. Proposed mechanism for cleavage of acetoxy sulfones.

It is plausible that the dimethoxyaniline moiety accepts the electrons being donated to the system by the Na(Hg) amalgam or SmI$_2$, 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.
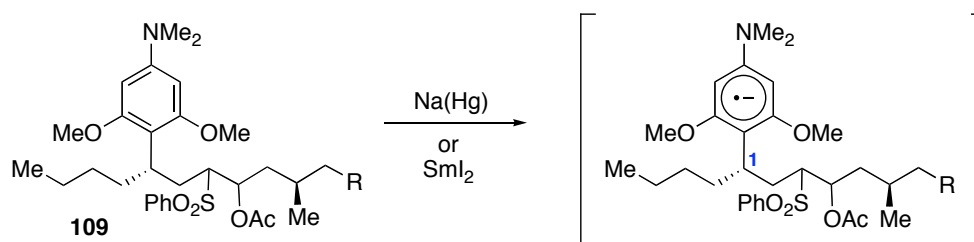
Figure 21. An unreactive intermediate under one electron reducing conditions.

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).
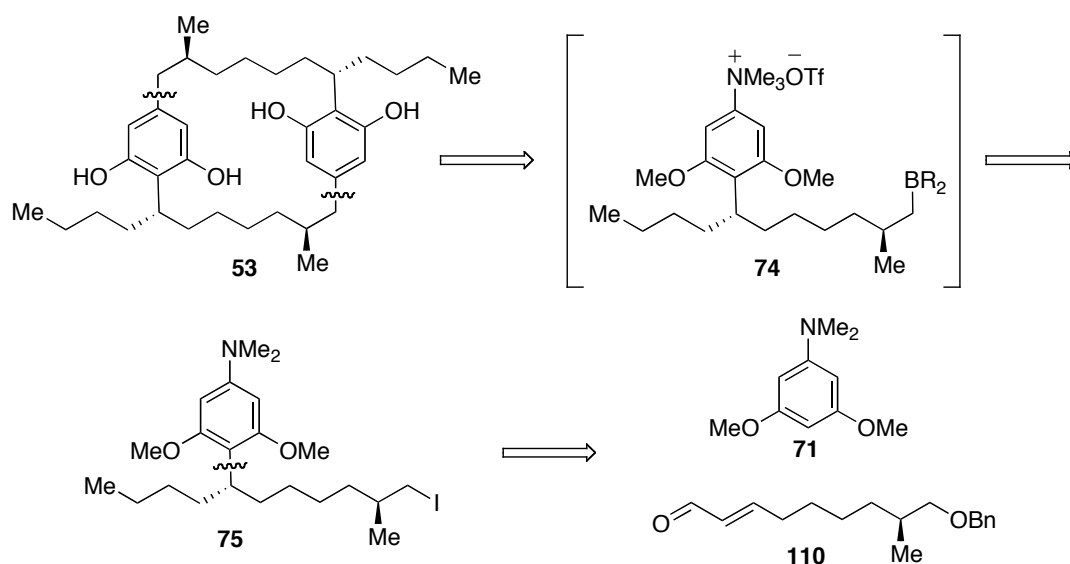
Figure 22. Alternate retrosynthetic strategy.

Scheme 21. Successful synthesis of the dimerization precursor.
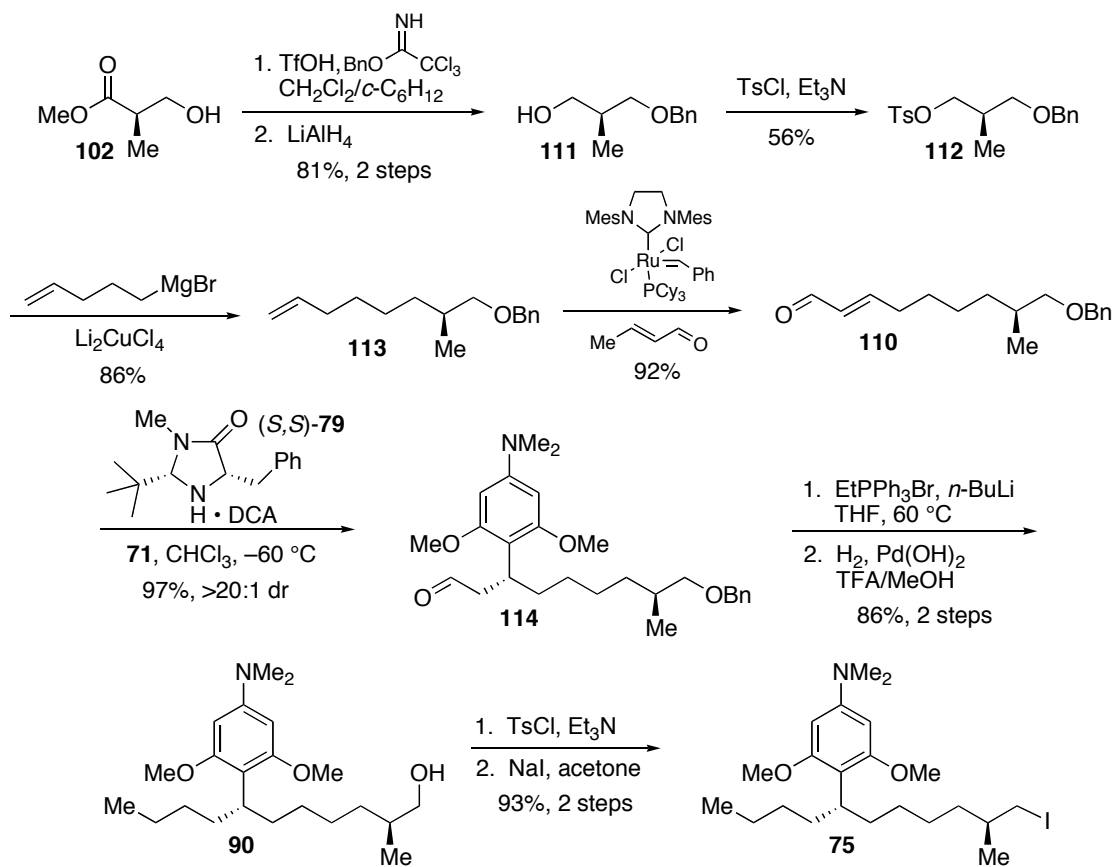
Starting with the commercially available (*R*)-Roche ester **102**, homologation to

α,β-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-

[51] (a) Paquette, L. A.; Guevel, R.; Sakamoto, S.; Kim, I. H.; Crawford, J. *J. Org. Chem.* **2003**, *68*, 6096. (b) White, J. D.; Kawasaki, M. *J. Org. Chem.* **1992**, *57*, 5292.

[52] (a) Mori, Y.; Makamura, M.; Wakabayashi, T.; Mori, K.; Kobayashi, S. *Synlett* **2002**, *4*, 601. (b) Kosikowski, A. P.; Ghosh, A. K. *J. Org. Chem.* **1084**, *49*, 2762.

pentenylmagnesium bromide gave olefin **113**.[53] Cross-metathesis[54] of **113** with crotonaldehyde using the second-generation Grubbs metathesis catalyst gave an excellent yield of *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.

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.

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[53] (a) Bates, R. W.; Fernandez-Megia, E.; Ley, S. V.; Ruck-Braun, K.; Tilbrook, D. M. G. *J. Chem. Soc., Perkins Trans. I* **1999**, 1917. (b) Boons, G.-J.; Lennon, I. C.; Ley, S. V.; Owen, E. S. E.; Staunton, J.; Wadsworth, D. J. *Tetrahedron Lett.* **1994**, *35*, 323.

[54] For a review, see: Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

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.
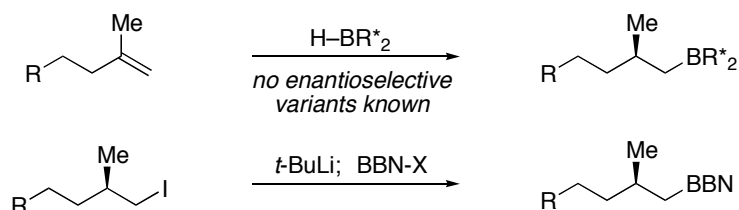
Figure 23. Access to β-stereogenicity on the alkyl borane.

This approach to generate β-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]

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55 For a review on asymmetric hydroboration, see: Crudden, C. M.; Edwards, D. *Eur. J. Org. Chem.* **2003**, *24*, 4695.

56 Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885.

57 Yuan, Y.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 14720.
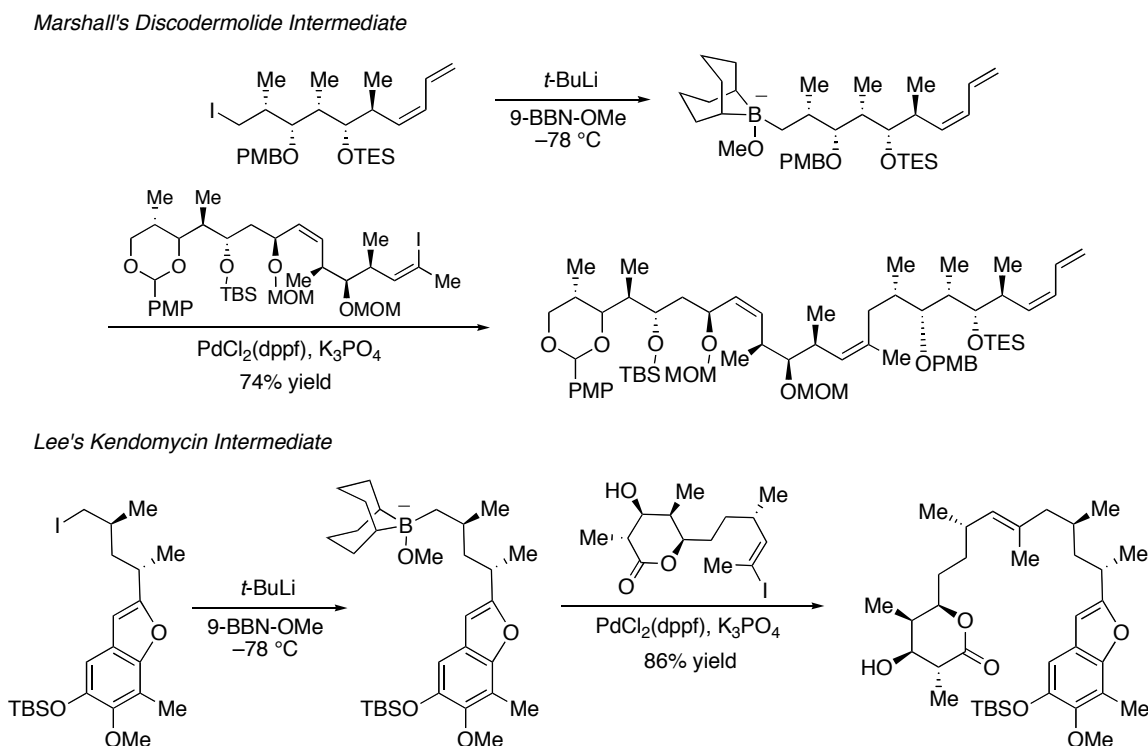
Figure 24. Lithiation/transmetalation preparation of alkyl boranes in natural product synthesis.

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.
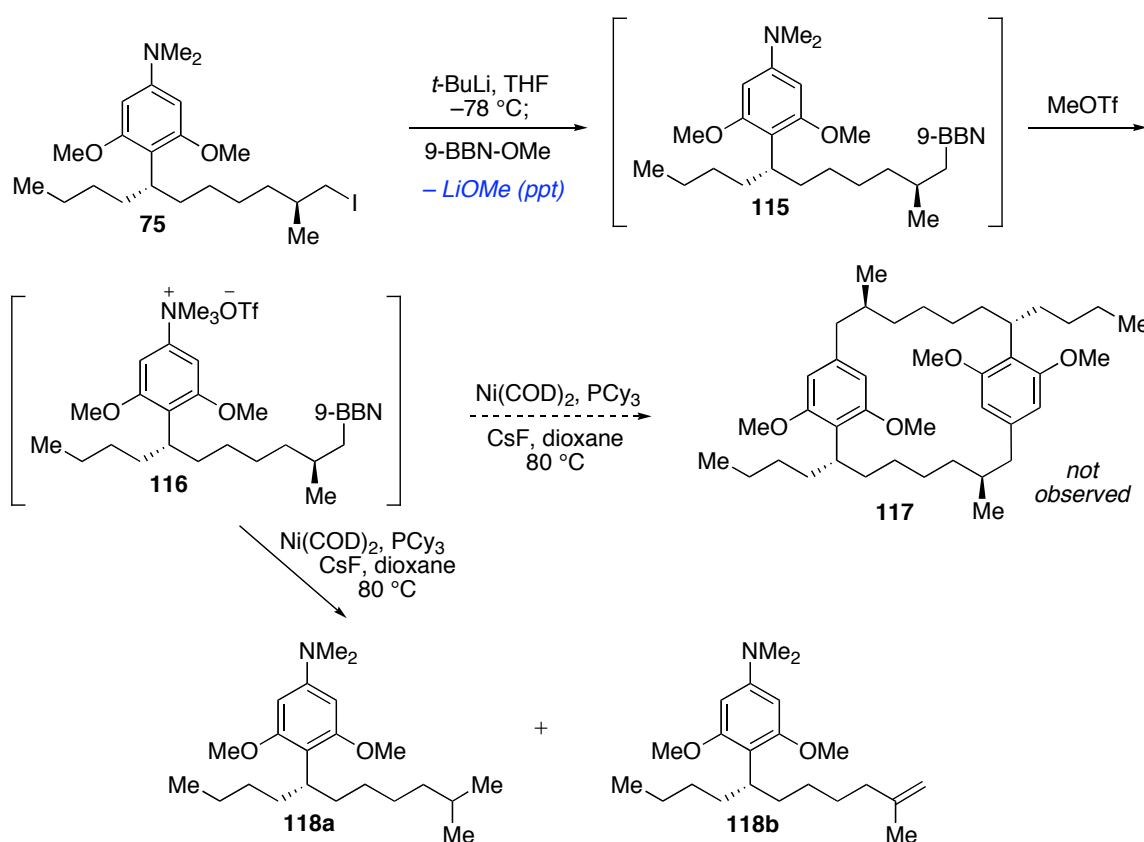
The most notable difference between this system and the model system previously explored was the preparation of the alkyl borane. The model system was generated via hydroboration whereas the real system utilized a lithiation/transmetalation procedure that generated an equivalent of lithium methoxide 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.
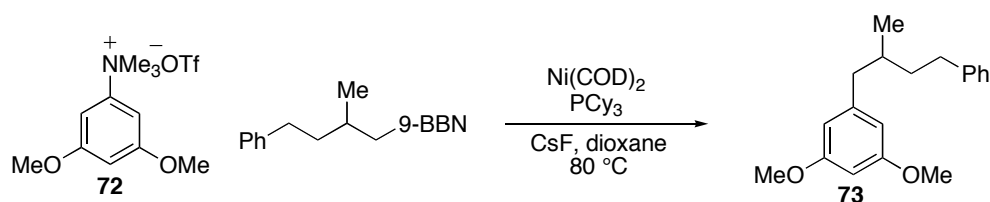
Entry	alkyl borane prep	additives	yield
1	**A**	none	25%
2	**B**	none	no reaction
3	**A**	LiOMe (1 equiv)	no reaction
4	**C**	none	no reaction

A: *hydroboration*
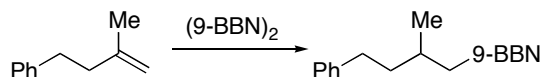
B: *lithiation/transmetalation onto 9-BBN-OMe*
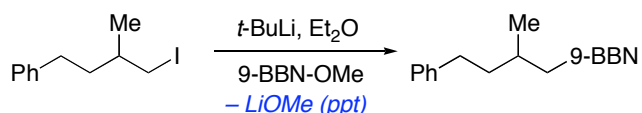
C: *lithiation/transmetalation onto 9-BBN-OTf*
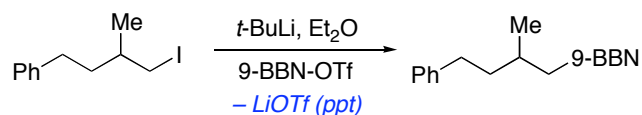
The lack of reactivity seen for the procedure in table 6, entry 4 was unexpected and prompted a boron NMR study in order to ascertain the exact nature of the different boron intermediates. Figure 25 shows boron NMR shifts that will be of importance in this study.[58]

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58 Cole, T. "¹¹B NMR Chemical Shifts." Retrieved June 2, 2006, from San Diego State University: www.chemistry.sdsu.edu/research/BNMR/#summary
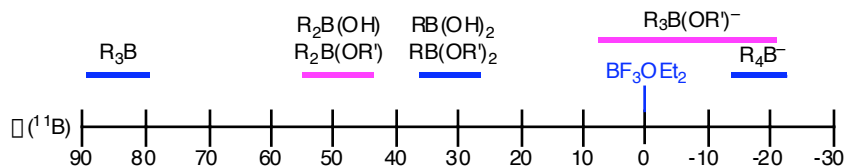
Figure 25. Boron NMR chemical shifts.

Literature precedent suggested that the nucleophilic addition of an alkyl lithium into 9-BBN-OMe leads to the formation of the boron "ate" complex,[56,57] which would be expected to have an ^{11}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.
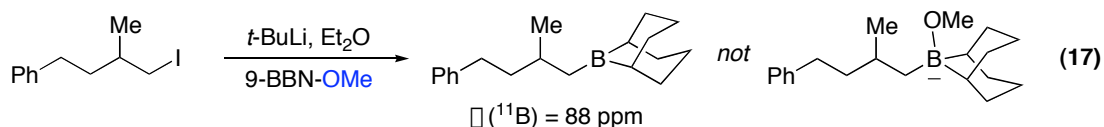
Interestingly, the addition of the same alkyl lithium species into 9-BBN-OTf did not produce a signal for the trialkylborane (80–90 ppm) or the boron "ate" (<0 ppm). Instead, a chemical shift of 56 ppm was observed, which is indicative of a dialkylborate species. Rearrangements of trialkylboron "ate" complexes have been reported,[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.

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[59] (a) Colberg, J. C.; Rane, A.; Vaquer, J.; Soderquist, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 6065. (b) Soderquist, J. A.; Najafi, M. R. *J. Org. Chem.* **1986**, *51*, 1330.

$$\delta\ (^{11}\text{B}) = 56\ \text{ppm} \tag{18}$$
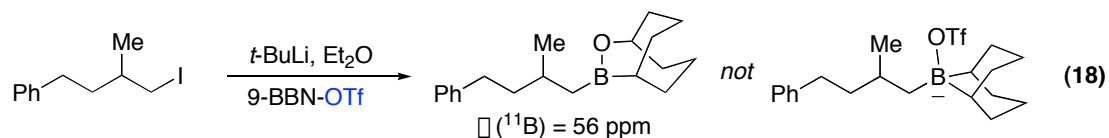
It was presented in this chapter that substrates less reactive than trialkylboranes were not compatible as transmetalating partners in the nickel(0)-catalyzed cross-coupling reaction with trimethylanilinium salts. Even though the triflate counterion should be inert to the reaction conditions, the less 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 α,β-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.[60] 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.[61] 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 (δ 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$_2$ (δ = 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

[60]Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals, 3rd ed.*; Pergamon Press, Oxford, 1988.

[61]Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978,** *43*, 2923.

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 β-DM (30 m x 0.25 mm) column or a Chiraldex Γ-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.
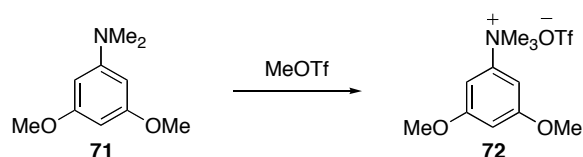
3,5-Dimethoxy-*N*,*N*,*N*-trimethylanilinium triflate (72). To a 0.5 M solution of 3,5-dimethoxy-*N*,*N*-dimethylaniline **71** (1.81g, 10 mmol) in dichloromethane (20 mL) was added trifluoromethanesulfonate via syringe (1.08 mL, 10.5 mmol). The reaction was stirred at room temperature for 15 minutes, 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, Ar**H**), 6.53 (t, 1H, *J* = 1.8 Hz, Ar**H**), 3.86 (s, 6H, OC**H$_3$**), 3.69 (s, 9H, NC**H$_3$**) . ^{13}C NMR (125 MHz, CDCl$_3$) δ 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.
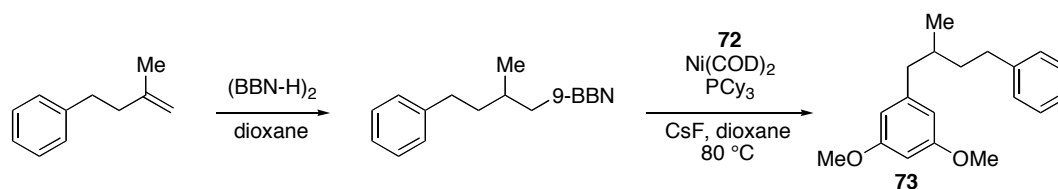
1,3-Dimethoxy-5-(2-methyl-4-phenylbutyl)benzene (73). The reagents and glassware in this reaction were thoroughly dried prior to use. Dioxane was prepared by freeze-pump thaw deoxygenation. A 0.6M stock solution of the alkyl BBN derivative was prepared as follows: To a flame-dried flask charged with 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 μL 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

[62] Lebel, H.; Guay, D.; Paquet, V.; Huard, K. *Org. Lett.* **2004**, *6*, 3047.

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$_3$) 7.14-7.32 (m, 5H, Ph**H**), 6.53 (d, 2H, J = 1.8 Hz, Ar**H**), 6.36 (t, 1H, J = 1.8 Hz, Ar**H**), 3.77 (s, 6H, OC**H$_3$**), 2.56-2.78 (m, 2H, ArC**HH**C**H**), 2.37 (dd, 1H, J = 9.0, 12.6 Hz, ArC**HH**), 1.35–1.94 (m, 4H, PhC**H$_2$**C**H$_2$**), 0.95 (d, 3H, J = 7.2 Hz, CHC**H$_3$**).
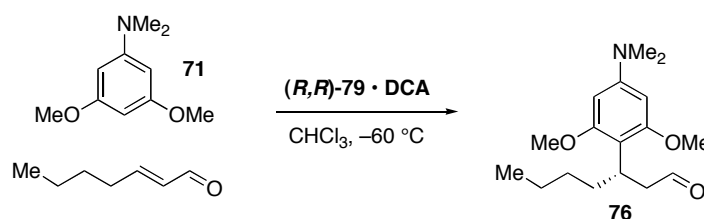
(S)-3-(4-(Dimethylamino)-2,6-dimethoxyphenyl)heptanal (76).   A solution of 3,5-dimethoxy-*N,N*-dimethylaniline[63] (1.81g, 10 mmol), imidazolidinone DCA salt (*R,R*)-**79•DCA** (668 mg, 2 mmol) in chloroform (20 mL, 0.5M) was cooled to –60 °C. (*E*)-2-Heptenal (4 mL, 30 mmol) was added via syringe. 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, 1255, 1207, 1129, 1007, 797, 638 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.59 (t, 1H, J = 3.0 Hz, **CH**O); 5.91 (s, 2H, Ar**H**); 3.78 (s, 6H, OC**H$_3$**); 3.77 (m, 1H, ArC**H**); 2.95 (s, 6H, NC**H$_3$**); 2.81 (ddd, 1H, J = 3.0, 9.0, 16.5 Hz, C**H**HCHO); 2.66 (ddd, 1H, J = 3.0, 6.6, 16.2 Hz. CH**H**CHO); 1.76–1.92 (m, 1H, C**H**HEt); 1.50–1.62 (m, 1H, CH**H**Et); 1.04–1.3 (m, 4H, C**H$_2$**C**H$_2$**CH$_3$); 0.82 (t, 3H, J = 7.2 Hz, CH$_2$C**H$_3$**); ^{13}C

63 Arevalo, F.; Castedo, L.; Fernandez, B. R.; Mourino, A.; Sarandese, L. *Chem. Lett.* **1998**, *5*, 745.

NMR (125 MHz, CDCl$_3$) 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•]$^+$ (C$_{18}$H$_{26}$O$_4$) requires m/z 293.1991, found m/z 293.1994; [α]$_D$= –5.37 (c = 0.95, CHCl$_3$). 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 t$_r$= 24.7 min, *(R)* isomer t$_r$= 21.7 min.
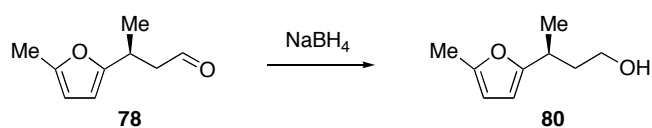
(*S*)-3-(5-Methylfuran-2-yl)butan-1-ol (80). Sodium borohydride (4.16 g, 110 mmol) was added to a solution of furan adduct **78**[43] (15.2 g, 100 mmol) in 200 mL of CH$_2$Cl$_2$/EtOH (3:1 v:v) at 0 °C. The reaction was stirred for 90 minutes before it was *carefully* quenched with saturated NaHCO$_3$ at 0 °C. The biphasic mixture was warmed to ambient temperature and extracted with CH$_2$Cl$_2$ (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}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.84 (m, 2H, Ar**H**), 3.65 (m, 2H, **CH$_2$**OH), 2.93 (app sex, 1H, J = 7.2 Hz, C**H**CH$_3$), 2.24 (s, 3H, C**H$_3$**furan), 1.85 (m, 1H, C**H**HCH$_2$OH), 1.76 (m, 1H, CH**H**CH$_2$OH), 1.25 (d, 3H, J = 6.6 Hz, CHC**H$_3$**). ^{13}C NMR (125 MHz, CDCl$_3$) 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•]$^+$ (C$_9$H$_{14}$O$_2$) requires m/z 154.0994, found m/z 154.0991. [α]$_D$= +21.6 (c = 1.2, CHCl$_3$).
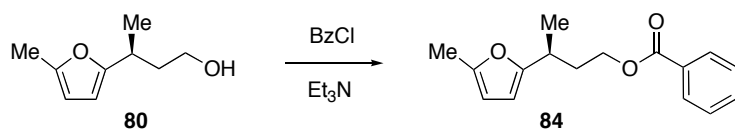
(*S*)-3-(5-Methylfuran-2-yl)butyl benzoate (84). Triethylamine (11.7 mL, 84.2 mmol) and catalytic DMAP was added to a solution of alcohol **80** (12.4 g, 80.2 mmol) in 160 mL CH_2Cl_2 at 0 °C under an argon atmosphere. Benzoyl chloride (9.8 mL, 84.2 mmol) was added and the reaction was slowly warmed 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 $NaHCO_3$, 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}; ^{1}H NMR (300 MHz, CDCl$_3$) 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, Ar**H**), 4.34 (m, 2H, C**H**$_2$OBz), 3.00 (app sex, 1H, *J* = 7.2 Hz, C**H**CH$_3$), 2.22 (s, 3H, C**H**$_3$furan), 2.13 (ddt, 1H, *J* = 6.6, 7.8, 13.8 Hz, C**H**HCH$_2$OH), 1.98 (ddt, 1H, *J* = 6.6, 7.2, 13.8 Hz, CH**H**CH$_2$OH), 1.25 (d, 3H, *J* = 6.6 Hz, CHC**H**$_3$). ^{13}C NMR (125 MHz, CDCl$_3$) 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•]$^+$ ($C_{16}H_{18}O_3$) requires *m/z* 258.1256, found *m/z* 258.1262. [α]$_D$= +39.7 (c = 1.14, CHCl$_3$).
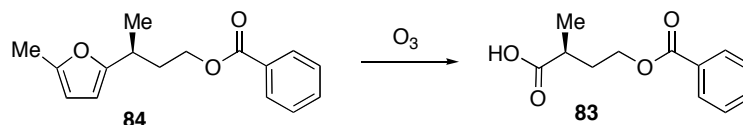
(*S*)-2-Methyl-4-(phenylcarbonyloxy)butanoic acid (83). A solution of benzoyl ether

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}; ^{1}H NMR (300

MHz, CDCl$_3$) 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, **CH$_2$**OBz), 2.67 (app sex, 1H, *J* = 7.2 Hz,

C**H**CH$_3$), 2.18 (m, 1H, *J* = C**H**HCH$_2$OBz), 1.88 (m, 1H, CH**H**CH$_2$OBz), 1.24 (d, 3H, *J* =

7.2 Hz, CHC**H$_3$**). ^{13}C NMR (125 MHz, CDCl$_3$) 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]$^+$ (C$_{12}$H$_{15}$O$_4$)

requires *m/z* 223.0970, found *m/z* 223.0964. [α]$_D$= +18.8 (c = 1.0, CHCl$_3$).
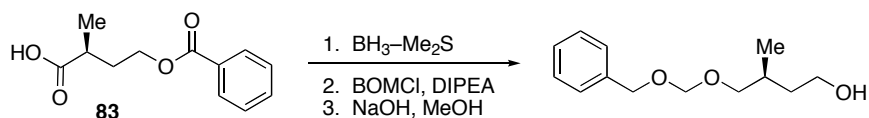
(*S*)-4-(Benzyloxymethoxy)-3-methylbutan-1-ol.   Carboxylic acid **83** (12.3 g, 55.4 mmol) was taken up in 110 mL diethyl ether and cooled to 0 °C under a nitrogen atmosphere.   Borane-dimethyl sulfide adduct (42 mL, 83.1 mmol) was added to the solution at 0 °C and the mixture was allowed to warm to 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 CH$_2$Cl$_2$ and di*iso*-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$_3$) δ 7.34 (m, 5H, Ar**H**), 4.77 (s, 2H, OC**H$_2$**O), 4.61 (s, 2H, PhC**H$_2$**O), 3.69 (m, 2H, C**H$_2$**OH), 3.48 (dd, 1H, J = 6.3, 12.0 Hz, BOMOC**H**H), 3.44 (dd. 1H, J = 6.3, 12.0 Hz, BOMOCH**H**), 2.11 (bs, 1H, O**H**), 1.91 (app sex, 1H, J = 6.3 Hz, C**H**CH$_3$), 1.66 (m, 1H, C**H**HCH$_2$OH), 1.50 (m, 1H, CH**H**CH$_2$OH), 0.97 (d, 3H, J = 6.9 Hz, CHC**H$_3$**). ^{13}C NMR (125 MHz, CDCl$_3$) δ 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. [α]$_D$= −3.87 (c = 1.0, CHCl$_3$).
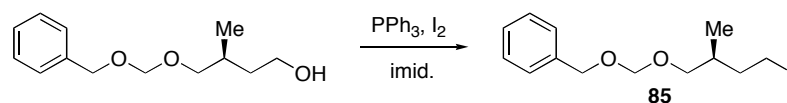
(*S*)-((((4-Iodo-2-methylbutoxy)methoxy)methyl)benzene (85). 4-(Benzyloxymethoxy)-3-methylbutan-1-ol (224 mg, 1.0 mmol), triphenylphosphine (275 mg, 1.05 mmol), and imidazole (72 mg, 1.05 mmol) were dissolved in 2 mL Et$_2$O and 0.6 mL acetonitrile at room temperature. Once the mixture turned homogenous, 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$_3$) δ 7.42 m, 5H, Ar**H**), 4.80 (s, 2H, OC**H$_2$**O), 4.65 (s, 2H, PhC**H$_2$**O), 3.48 (m, 2H, BOMOC**H$_2$**), 3.28 (m, 2H, C**H$_2$**I), 2.08 (m. 1H, C**H**HCH$_2$I), 1.94 (app sex, 1H, J = 6.3 Hz, C**H**CH$_3$), 1.75 (m, 1H, CH**H**CH$_2$I), 0.99 (d, 3H, J = 6.6 Hz, CHC**H$_3$**). ^{13}C NMR (125 MHz, CDCl$_3$) δ 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 $[MH]^+$ ($C_{13}H_{18}O_2I$) requires m/z 333.0352, found m/z 333.0359. $[\alpha]_D = -6.66$ (c = 1.1, CHCl$_3$).
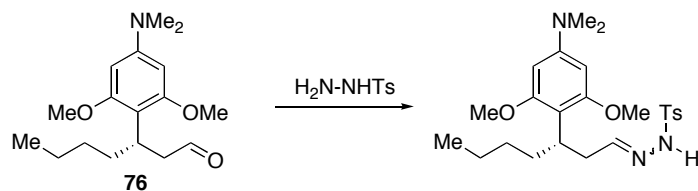
(S)-N'-(3-(4-(Dimethylamino)-2,6-dimethoxyphenyl)heptylidene)-4-methylbenzene-sulfonohydrazide.[64] *p*-Toluenesulfonyl hydrazone (768 mg, 4.12 mmol) was added to a solution of aldehyde **76** (1.1 g, 3.75 mmol) in THF (18.75 mL, 0.2M). A catalytic amount of *p*-toluenesulfonic acid was added. The reaction 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^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.87 (bs, 1H, N**H**), *7.73* (d, 2H, *J* = 8.4 Hz, Ar**H**); 7.63 (d, 2H, *J* = 8.4 Hz, Ar**H**); *7.26* (d, 2H, *J* = 8.1 Hz, Ar**H**); 7.19 (d, 2H, *J* = 8.1 Hz, Ar**H**); *6.97* (dd, 1H, *J* = 5.4, 6.3 Hz, C**H**=N); 6.68 (dd, 1H, *J* = 5.1, 7.2 Hz, C**H**=N); *5.85* (s, 2H, Ar**H**); 5.83 (s, 2H, Ar**H**); 3.74 (s, 6H, OC**H**$_3$); *3.69* (s, 6H, OC**H**$_3$); 3.35 (m, 1H, ArC**H**); 2.93 (s, 6H, NC**H**$_3$); *2.92* (s, 6H, NC**H**$_3$); 2.73 (m, 1H, C**H**HC=N); 2.56 (m, 1H, CH**H**C=N); *2.40* (s, 3H, C$_6$H$_4$C**H**$_3$); 2.37 (s, 3H, C$_6$H$_4$C**H**$_3$); 2.28 (dt, 1H, *J* = 5.4, 12.0 Hz, CHC**H**HCH$_2$); 1.64-1.85 (m, 1H, CHCH**H**CH$_2$); 0.92-1.5 (m, 4H, C**H**$_2$C**H**$_2$CH$_3$); 0.79 (t, 3H, *J* = 7.2 Hz, CH$_2$C**H**$_3$); *0.76* (t, 3H, *J* = 7.2Hz, CH$_2$C**H**$_3$); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.8, 159.1,

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[64] 5:4 rotamer ratio complicated interpretation of the spectra. Minor peaks noted in *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]$^+$ (C$_{24}$H$_{36}$N$_3$O$_4$S) requires *m/z* 462.2427, found *m/z* 462.2411.
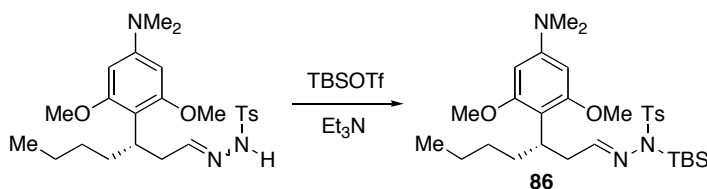
(*S*,*E*)-*N*-(*tert*-Butyldimethylsilyl)-*N*'-(3-(4-(dimethylamino)-2,6-dimethoxyphenyl)-heptylidene)-4-methylbenzenesulfonohydrazide (86). Triethylamine (0.50 mL, 3.59 mmol) was added to a solution of tosyl hydrazone (1.11 g, 2.76 mmol) in 13.8 mL THF at –78 °C under argon. *tert*-Butyldimethylsilyl 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 NaHCO$_3$ 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}; ^{1}H NMR (300 MHz, CDCl3) δ 7.62 (m[65], 2H, ArH); 7.25 (m[65], 2H, ArH); 5.87 (s, 2H, Ar**H**); 3.73 (s, 6H, OC**H$_3$**); 3.43 (m, 1H, ArC**H**); 2.93 (s, 6H, NC**H$_3$**); 2.80 (m, 1H, C**H**HC=N); 2.61 (m, 1H, CH**H**C=N); 2.38 (s, 3H, C$_6$H$_4$C**H$_3$**); 1.68-1.82 (m, 1H, CHC**H**HCH$_2$); 1.42-1.54 (m, 1H, CHCH**H**CH$_2$); 1.01-1.33

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[65] Rotomers around the imine bond caused proton NMR to be an indecipherable mixture at some chemical shifts.

(m, 4H, **CH$_2$CH$_2$CH$_3$**); 0.89 (s, 9H, SiMe$_2$(**CH$_3$**)$_3$); 0.79 (t, 3H, J = 7.2 Hz, CH$_2$**CH$_3$**);

0.20 (d, 3H, J = 12.0 Hz, Si**CH$_3$**); 0.12 (d, 3H, J = 12.0 Hz, Si**CH$_3$**). ^{13}C NMR (125 MHz,

CDCl$_3$) δ 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]$^+$ (C$_{30}$H$_{50}$N$_3$O$_4$SiS) requires m/z 576.3291, found m/z

576.3315.
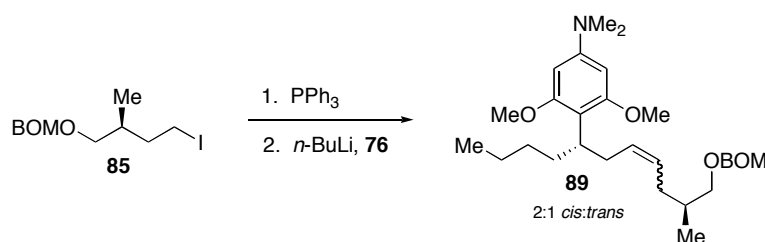
4-((5S,10S)-11-(Benzyloxymethoxy)-10-methylundec-7-en-5-yl)-3,5-dimethoxy-N,N-dimethylaniline (89).[66] Triphenylphosphine (40 mg, 0.15 mmol) was added to a solution

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 μL, 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,

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[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 °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$_3$) δ 7.34 (m, 5H, Ph**H**), 5.96 (s, 2H, Ar**H**), 5.34 (m, 2H, **CH**=**CH**), 4.79 *4.75* (s, 2H, OC**H$_2$**O), 4.64 *4.62* (s, 2H, PhC**H$_2$**O), *3.83* 3.80 (s, 6H, OC**H$_3$**), 3.50 (dd, 2H, J = 6.0, 9.6 Hz, BOMOC**HH**), 3.40 (dd, 2H, J = 6.9, 9.3 Hz, BOMOCH**H**), 3.24 (m, 1H, ArC**H**), *2.98* 2.97 (s, 6H, NC**H$_3$**), 2.45 (m, 2H, CHC**H$_2$**), 2.16 (m. 1H, =CHC**H**H), 1.92 (m, 1H, =CHCH**H**), 1.52-1.85 (m, 2H, C**H**(alkyl)), 1.75 (m, 3H, C**H**(alkyl)), 0.94 (d, 3H, J = 6.6 Hz, CHC**H$_3$**), 0.85 (t, 3H, J = 7.2 Hz, CH$_2$C**H$_3$**). ^{13}C NMR (125 MHz, CDCl$_3$) δ 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. [α]$_D$= – 1.95 (c = 1.0, CHCl$_3$).
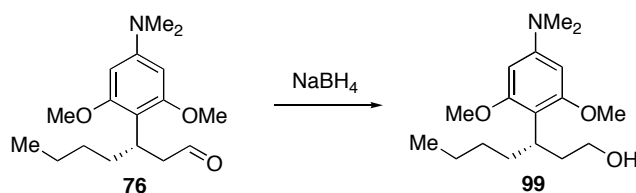

(*S*)-3-(4-(Dimethylamino)-2,6-dimethoxyphenyl)heptan-1-ol (99). Aldehyde **76** (2.65 g, 9.1 mmol) was taken up in 5 mL EtOH and 20 mL CH$_2$Cl$_2$. Sodium borohydride (1.8g, 45.5 mmol) was added in portions and stirred for 2 h at ambient temperature. The reaction was quenched with saturated NaHCO$_3$. 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}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.93 (s, 2H, Ar**H**); 3.78 (s, 6H, OC**H**$_3$); 3.47 (m, 1H, ArC**H**); 3.31 (m, 2H, C**H**$_2$OH); 2.95 (s, 6H, NC**H**$_3$); 2.04 (bs, 1H, O**H**); 1.87 (m, 1H, CH**H**CHC**H**$_2$); 1.58 (m, 1H, C**H**HCHCH$_2$); 1.04-1.3 (m, 4H, C**H**$_2$C**H**$_2$CH$_3$); 0.83 (t, 3H, J = 7.2 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (125 MHz, CDCl$_3$) 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]$^+$ (C$_{17}$H$_{29}$NO$_3$) requires m/z 295.2147, found m/z 295.2143; [α]$_D$= −5.57 (c = 1.0, EtOH).
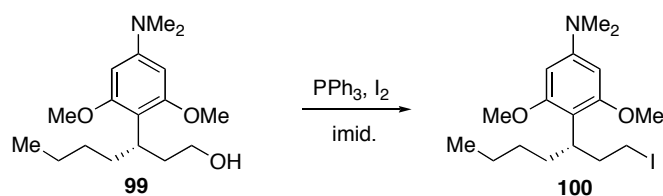
(*S*)-4-(1-Iodoheptan-3-yl)-3,5-dimethoxy-*N,N*-dimethylaniline (100). Iodine (2.42g, 9.55 mmol) was added to a mixture of triphenylphosphine (2.71g, 10.3 mmol) and imidazole (694 mg, 10.3 mmol) in 80 mL CH$_2$Cl$_2$ at 0 °C. Alcohol **99** (2.35g, 7.96 mmol) was added dropwise. The reaction was stirred at 0 °C for 30 min. and warmed to 23 °C for 1 h. The reaction was quenched with 150 mL saturated NH$_4$Cl, which was then extracted with CH$_2$Cl$_2$ (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% Et$_2$O/pentanes, silica pretreated with Et$_3$N) 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$_6$) δ 5.84 (s, 2H, Ar**H**); 3.62 (tt, 1H, J = 5.4, 9.9 Hz, ArC**H**); 3.41 (broad s, 6H, OC**H$_3$**); 3.00-3.14 (m, 2H, C**H$_2$**I); 2.71 (m, 1H, CH**H**CHCH$_2$); 2.59 (s, 6H, NC**H$_3$**); 2.28 (m, 1H, C**H**HCHCH$_2$); 2.08 (m, 1H, CH$_2$CHC**H**H); 1.70 (m, 1H, CH$_2$CHCH**H**); 1.24-1.44 (m, 4H, C**H$_2$**C**H$_2$**CH$_3$); 0.86 (t, 3H, J = 7.2 Hz, CH$_2$C**H$_3$**); ^{13}C NMR (125 MHz, C$_6$D$_6$) δ 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$_{228}$INO$_2$) requires m/z 405.1165, found m/z 405.1156; [α]$_D$= +29.1 (c = 1.0, EtOH).
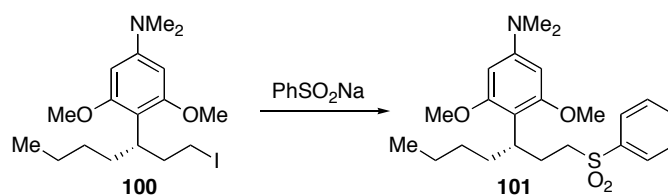
(S)-3,5-Dimethoxy-N,N-dimethyl-4-(1-(phenylsulfonyl)heptan-3-yl)aniline (101). The sodium salt of benzene sulfinic acid (PhSO$_2$Na, 446 mg, 2.72 mmol) dried under vacuum at 50 °C for 2h. It was then added to a solution of iodide **100** (1 g, 2.27 mmol) in DMF (15 mL, 0.16 M) at room temperature and 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$_3$) δ 7.84 (m, 2H, Ph**H**), 7.62 (m, 1H, Ph**H**), 7.52 (m, 2H, Ph**H**), 5.83 (s, 2H,

ArH); 3.64 (broad s, 6H, OCH$_3$); 3.14 (m, 1H, ArCH); 2.94 (m, 1H, CHHS); 2.93 (s, 6H,

NCH$_3$); 2.82 (ddd, 1H, J = 4.8, 12.6, 14.1 Hz, CHHS), 2.17 (m, 1H, CHHCHCH$_2$); 1.87

(m, 1H, CHHCHCH$_2$); 1.72 (m, 2H, CH$_2$CHCHH); 1.45 (m, 1H, CH$_2$CHCHH); 0.96-

1.32 (m, 5H, CH$_2$CHCHH and CH$_2$CH$_2$CH$_3$); 0.78 (t, 3H, J = 7.2 Hz, CH$_2$CH$_3$); ^{13}C

NMR (125 MHz, CDCl$_3$) 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]$^+$

(C$_{23}$H$_{33}$NO$_4$S) requires m/z 419.2130, found m/z 419.2131; [α]$_D$= –7.78 (c = 1.0, EtOH).
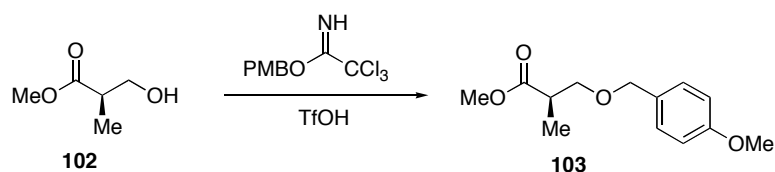
(*R*)-Methyl 3-(4-methoxybenzyloxy)-2-methylpropanoate (103). PMBO-trichloroacetimidate was prepared by the following sequence: *p*-Methoxybenzyl alcohol (5.8 mL, 46.55 mmol) was slowly added to a slurry of sodium hydride (60%, 373 mg, 9.31 mmol) in 12 mL diethyl ether at 0 °C. Trichloroacetonitrile (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 µL 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$_3$) δ 7.25 (m, 2H, Ar**H**), 6.88 (m, 2H, Ar**H**), 4.46 (s, 2H, C**H$_2$**OPMB), 3.81 (s, 3H, OC**H$_3$**), 3.70 (s, 3H, OC**H$_3$**), 3.64 (dd, 1H, J = 7.5, 9.3 Hz, C**H**HOPMB), 3.47 (dd, 1H, J = 6.0, 9.3 Hz, CH**H**OPMB), 2.78 (ddq, 1H, J = 6.0, 7.2, 7.5 Hz, C**H**CH$_3$), 1.18 (d, 3H, J = 7.2 Hz, CHC**H$_3$**). ^{13}C NMR (125 MHz, CDCl$_3$) δ 175.3, 159.1, 130.2, 129.1, 113.7, 72.7, 71.6, 55.2, 51.6, 40.1, 13.9; HRMS (EI+) exact mass calculated for [M•]$^+$ (C$_{13}$H$_{18}$O$_4$) requires m/z 238.1205, found m/z 238.1196. [α]$_D$= –8.23 (c = 1.0, CHCl$_3$).
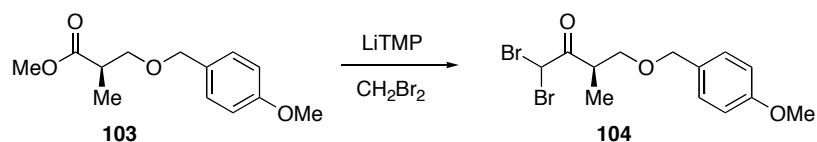
(R)-1,1-Dibromo-4-(4-methoxybenzyloxy)-3-methylbutan-2-one (104). LiTMP was generated in a flame-dried round bottom flask at 0 °C under argon by the addition of *n*-BuLi (2.5M, 4 mL, 10.0 mmol) to a solution of tetramethylpiperidine (1.85 mL, 11.0 mmol) in 15 mL THF. The LiTMP was transferred via cannula 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 °C. The reaction was stirred at 0 °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 α-

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$_3$) δ 7.21

(m, 2H, Ar**H**), 6.88 (m, 2H, Ar**H**), 6.09 (s, 1H, C**H**Br$_2$), 4.40 (s, 2H, C**H$_2$**OPMB), 3.81 (s,

3H, OC**H$_3$**), 3.70 (s, 3H, OC**H$_3$**), 3.48 (m, 3H, C**H$_2$**OPMB and C**H**CH$_3$), 1.21 (d, 3H, J =

6.3 Hz, CHC**H$_3$**). ^{13}C NMR (125 MHz, CDCl$_3$) δ 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. [α]$_D$= −129.6 (c = 1.0, CHCl$_3$).
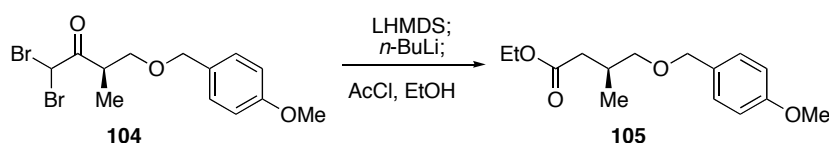
(*S*)-Ethyl 4-(4-methoxybenzyloxy)-3-methylbutanoate (105). LiHMDS was freshly

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 Et$_2$O/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}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.25 (d, 2H, J = 6.0 Hz, Ar**H**), 6.87 (d, 2H, J = 5.7 Hz, Ar**H**), 4.42 (s, 2H, C**H$_2$**OPMB), 4.10 (q, 2H, J = 7.2 Hz, OC**H$_2$**CH$_3$), 3.80 (s, 3H, OC**H$_3$**), 3.70 (s, 3H, OC**H$_3$**), 3.34 (dd, 1H, J = 5.4, 9.3 Hz, C**H**HOPMB), 3.26 (dd, 1H, J = 6.9, 9.3 Hz, CH**H**OPMB), 2.47 (dd, 2H, J = 5.7, 15.0 Hz, C**H**HCO$_2$Et), 2.29 (m, 1H, C**H**CH$_2$), 2.13 (dd, 2H, J = 8.1, 15.0 Hz, CH**H**CO$_2$Et), 1.23 (t, 3H, J = 7.2 Hz, OCH$_2$C**H$_3$**), 0.96 (d, 3H, J = 6.3 Hz, CHC**H$_3$**). ^{13}C NMR (125 MHz, CDCl$_3$) δ 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•]$^+$ (C$_{15}$H$_{22}$O$_4$) requires m/z 266.1518, found m/z 266.1508. [α]$_D$= –3.34 (c = 1.0, CHCl$_3$).
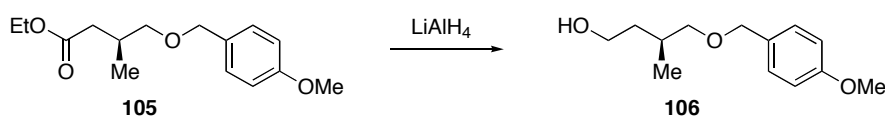
(**S**)-4-(4-Methoxybenzyloxy)-3-methylbutan-1-ol (106). Lithium aluminum hydride (154 mg, 4.06 mmol) was added to a solution of ester **105** (721 mg, 2.71 mmol) in 13.6 mL diethyl ether at 0 °C. The reaction was stirred for 1 h. A saturated aqueous Na/K tartrate solution was added and the biphasic mixture was stirred at ambient temperature until all solids were dissolved. The aqueous layer was separated and exracted 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}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.25 (d, 2H, J = 5.7 Hz, Ar**H**), 6.87 (d, 2H, J = 5.7 Hz, Ar**H**), 4.44 (s, 2H, C**H$_2$**OPMB), 3.79 (s, 3H, OC**H$_3$**), 3.62 (m, 2H, C**H$_2$**OH), 3.34 (dd, 1H, J = 4.8, 9.0 Hz, C**H**HOPMB), 3.27 (dd, 1H, J = 7.5, 9.3 Hz, CH**H**OPMB), 2.55 (bs, 1H, O**H**), 1.90 (m, 1H, C**H**CH$_3$), 1.57 (m, 2H, C**H$_2$**CH$_2$OH), 0.93 (d, 3H, J = 6.9 Hz, CHC**H$_3$**). ^{13}C NMR (125 MHz, CDCl$_3$) δ 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•]$^+$ (C$_{13}$H$_{20}$O$_3$) requires m/z 224.1413, found m/z 224.1421. [α]$_D$= –4.48 (c = 1.0, CHCl$_3$).
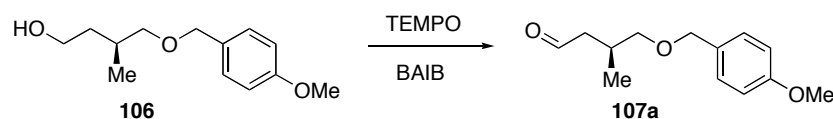
(*S*)-4-(4-Methoxybenzyloxy)-3-methylbutanal (107a). Bisacetoxyiodosobenzene (95 mg, 0.295 mmol) was added to a solution of alcohol **106** (60 mg, 0.269 mmol) in 0.54 mL CH$_2$Cl$_2$. TEMPO (6 mg, 0.0384 mmol) was added and the reaction was stirred for 3 h at room temperature. The reaction was quenched with 3 mL saturated Na$_2$S$_2$O$_3$. 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% Et$_2$O/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}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.76 (t, 1H, J = 2.1 Hz, C**H**O), 7.25 (d, 2H, J = 8.4 Hz, Ar**H**), 6.89 (d, 2H, J = 8.4 Hz, Ar**H**), 4.43 (s, 2H, C**H$_2$**OPMB), 3.81 (s, 3H, OC**H$_3$**), 3.40 (dd, 1H, J = 5.4, 9.3 Hz, C**H**HOPMB), 3.23 (dd,

1H, J = 7.5, 9.0 Hz, C**H**HOPMB), 2.54 (ddd, 1H, J = 2.1, 6.0, 15.6 Hz, C**H**HCHO), 2.41

(m, 1H, C**H**CH$_2$), 2.28 (ddd, 1H, J = 2.1, 6.9, 15.9 Hz, CH**H**CHO), 0.99 (d, 3H, J = 6.6

Hz, CHC**H$_3$**). ^{13}C NMR (125 MHz, CDCl$_3$) δ 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. [α]$_D$= –13.4 (c = 1.0, CHCl$_3$).
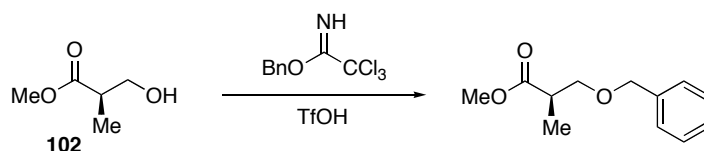
(R)-Methyl 3-(benzyloxy)-2-methylpropanoate. To a solution of the (R)-Roche ester

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$_3$). δ 7.33 (m, 5H, Ar**H**);

4.52 (s, 2H, C**H$_2$**OBn); 3.70 (s, 3H, CO$_2$C**H$_3$**); 3.70 (s, 3H, CO$_2$C**H$_3$**); 3.66 (dd, 1H, J =

7.2, 9.0 Hz, C**H**HOBn); 3.49 (dd, 1H, J = 6.0, 9.0 Hz, CH**H**OBn); 2.78 (m, 1H, C**H**CH$_3$);

1.18 (d, 3H, J = 6.9 Hz, CHC**H$_3$**); ^{13}C NMR (75 MHz, CDCl$_3$). δ175.3, 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, CHCl$_3$).
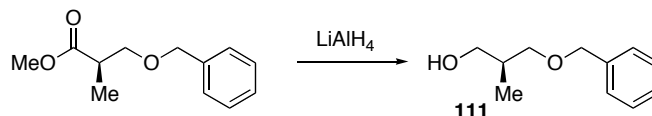

(*S*)-3-(Benzyloxy)-2-methylpropan-1-ol (111). Lithium aluminum hydride (3.86 g, 101.7 mmol) was suspended in 68 mL of ether at 0 °C. (*R*)-methyl 3-(benzyloxy)-2-methylpropanoate (14.16g, 67.8 mmol) was added dropwise via addition funnel as a solution in 68 mL of ether. When the addition was complete, the reaction was warmed to room temperature at which point the reaction was judged complete by TLC analysis. 2.5 mL H$_2$O, 5.5 mL 2N NaOH, and then 12.5 mL H$_2$O 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 (9.25g, 77% yield). IR (film). 3393 (broad), 3026, 2686, 1452, 1363, 1095, 1040, 752, 734 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$). δ 7.33 (m, 5H, Ar**H**); 4.52 (s, 2H, C**H$_2$**OBn); 3.61 (m, 2H, C**H2**OBn); 3.54 (dd, 1H, *J* = 4.5, 9.0 Hz, C**H**HOH); 3.43 (dd, 1H, *J* = 8.1, 9.0 Hz, CH**H**OH); 2.64 (app q, H, *J* = 9.0 Hz, OH); 2.0 (m, 1H, C**H**CH$_3$); 0.89 (d, 3H, *J* = 7.5 Hz, CHC**H$_3$**); ^{13}C NMR (75 MHz, CDCl$_3$). 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$_{16}$Br$_2$O$_3$) requires *m/z* 180.1150, found *m/z* 180.1144; [α]$_D$ = −16.09 (c = 1.36, CHCl$_3$).

(*R*)-3-(benzyloxy)-2-methylpropyl 4-methylbenzenesulfonate (112). *p*-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 CuSO$_4$ 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}. ^{1}H NMR (300 MHz, CDCl$_3$). δ 7.87 (m, 2H, Ar**H**); 7.30 (m, 2H, Ar**H**); **7**.22-7.36 (m, 5H, C**H**$_2$**Ph**); 6.87 (m, 2H, Ar**H**); 4.40 (s, 2H, C**H**$_2$OBn); 4.05 (dd, 1H, *J* = 5.4, 9.3 Hz, C**H**HOTs); 3.99 (dd, 1H, *J* = 5.7, 9.3 Hz, CH**H**OTs); 3.34 (ddd, 2H, *J* = 5.4, 9.6, 12.9 Hz, C**H**$_2$OBn); 2.42 (s, 2H, , ArC**H**$_3$); 2.11 (m, 1H, C**H**CH$_3$); 2.12 (dd, 1H, *J* = 8.1, 15.0Hz, CH**H**CO$_2$Et); 0.94 (d, 3H, *J* = 6.6 Hz, CHC**H**$_3$); ^{13}C NMR (75 Mhz, CDCl$_3$). 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•]$^+$ (C$_{15}$H$_{22}$O$_4$) requires *m/z* 334.1239, found *m/z* 334.1231; [α]$_D$ = –6.42 (c = 1.06, CHCl$_3$).
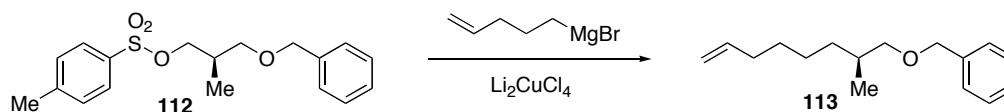
(S)-((2-Methyloct-7-enyloxy)methyl)benzene (113). 5-Bromopentene (2.2 mL, 18.7

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_2CuCl_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_4Cl (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_2O/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, $CDCl_3$) δ 7.21-7.38 (m, 5H, Ar**H**); 5.82 (ddt, 1H, J = 3.0,

3.6, 6.6 Hz, CH_2C**H**=CH_2); 4.97 (m, 2H, J = CH_2CH=C**H$_2$**); 4.51 (s, 2H, **CH$_2$**OBn); 3.34

(dd, 1H, J = 6.0, 9.0 Hz, C**H**HOBn); 3.25 (dd, 1H, J = 6.6, 9.0, CH**H**OBn); 2.06 (dt, 2H,

J = 6.3, 7.2 Hz, CH$_2$=CHC**H$_2$**); 1.77 (m, 1H, J = 5.7 Hz, C**H**Me); 1.23-1.50 (m, 5H,

C**H**(alkyl)); 1.09-1.19 (m, 1H, C**H**(alkyl)); 0.94 (d, 3H, J = 6.9 Hz, CHC**H$_3$**); ^{13}C NMR

(125 MHz, CDCl$_3$) δ 139.1, 138.8, 128.3(x2), 127.5(x2), 127.4, 114.2, 76.0, 72.9, 33.8,

33.5, 33.4, 29.2, 26.4, 17.1; HRMS (EI+) exact mass calculated for [M•]$^+$ (C$_{18}$H$_{26}$O$_4$)

requires m/z 232.1827, found m/z 232.1822; [α]$_D$= –0.31 (c = 1.50, CHCl$_3$).
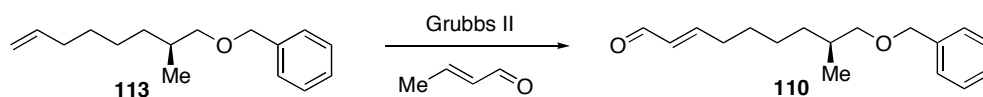
(S,E)-9-(Benzyloxy)-8-methylnon-2-enal (110). The second-generation Grubbs catalyst

(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 α,β-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, 974, 737 cm^{-1}; ^{1}H

NMR (300 MHz, CDCl$_3$) δ 9.50 (d, 1H, J = 7.5 Hz, C**H**O); 7.25-7.35 (m, 5H, Ar**H**); 6.84

(dt, 1H, J = 6.8, 15.6 Hz, CHOCH=C**H**); 6.11 (ddt, 1H, J = 1.5, 7.2, 15.6 Hz,

CHOC**H**=CH); 4.50 (s, 2H, C**H$_2$**OBn); 3.31 (dd, 1H, J = 6.0, 9.0 Hz, C**H**HOBn); 3.25

(dd, 1H, J = 5.7, 9.0, CH**H**OBn); 2.33 (dt, 2H, J = 6.3, 7.2 Hz, CH$_2$=CHC**H$_2$**); 1.75 (m,

1H, C**H**Me); 1.26-1.56 (m, 5H, C**H**$_{(alkyl)}$); 1.09-1.19 (m, 1H, C**H**$_{(alkyl)}$); 0.92 (d, 3H, J = 6.6

Hz, CHC**H$_3$**); ^{13}C NMR (125 MHz, CDCl$_3$) δ 194.1, 158.8, 138.7, 133.0, 128.3(x2),

127.5(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•]⁺ ($C_{18}H_{26}O_4$) requires *m/z* 260.1776, found *m/z* 260.1781; $[\alpha]_D$= –2.50

(c = 1.21, $CHCl_3$).
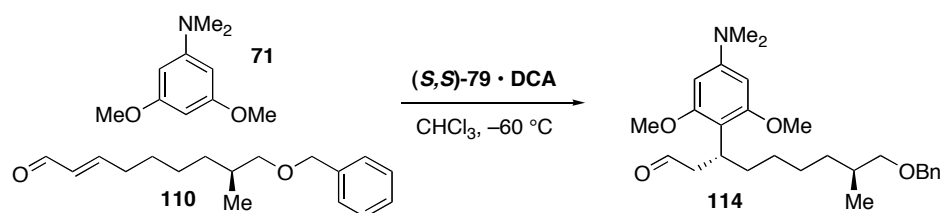
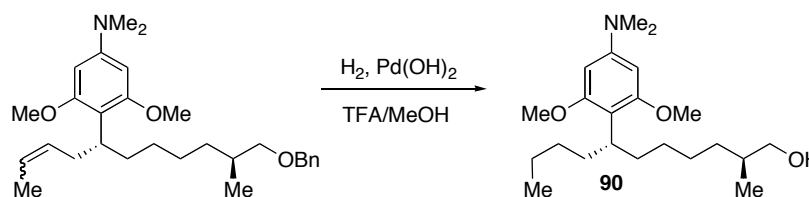**(3R,8S)-9-(Benzyloxy)-3-(4-(dimethylamino)-2,6-dimethoxyphenyl)-8-methyl-**

nonanal (114). 3,5-Dimethoxy-*N,N*-dimethylaniline (181 mg, 1m mmol) was added to a

solution of imidazolidinone **(S,S)-79 • DCA** (75 mg, 0.2 mmol) in 4 mL $CHCl_3$. The

reaction was cooled to –60 °C, at which point α,β-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, $CDCl_3$) δ 9.59 (t, 1H, *J* = 5.7 Hz,

CHO); 7.25-7.33 (m, 5H, Ar**H**); 5.89 (s, 2H, Ar**H**); 4.48 (s, 2H, **CH₂**OBn); 3.77 (s, 6H,

O**CH₃**); 3.76 (m, 1H, ArC**H**); 3.30 (dd, 1H, *J* = 6.0, 9.0 Hz, C**H**HOBn); 3.19 (dd, 1H, *J* =

7.2, 9.0, CH**H**OBn); 2.94 (s, 6H, N**CH₃**); 2.80 (ddd, 1H, *J* = 2.4, 7.5, 15.9 Hz,

C**H**HCHO); 2.65 (ddd, 1H, *J* = 3.0, 6.6, 15.9 Hz, CH**H**CHO); 1.82 (m, 1H, C**H**Me); 1.70

(m, 1H); 1.56 (m, 1H); 1.01-1.40 (m, 6H, C**H**(alkyl)); 0.89 (d, 3H, *J* = 6.6 Hz, CHC**H₃**);

¹³C NMR (125 MHz, $CDCl_3$) δ204.9, 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]$^+$ (C$_{27}$H$_{37}$NO$_4$) requires m/z 441.868, found m/z 441.2879; [α]$_D$= –2.50 (c = 1.21, CHCl$_3$). 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 t$_r$= 18.36 min, (R) isomer t$_r$= 16.17 min.
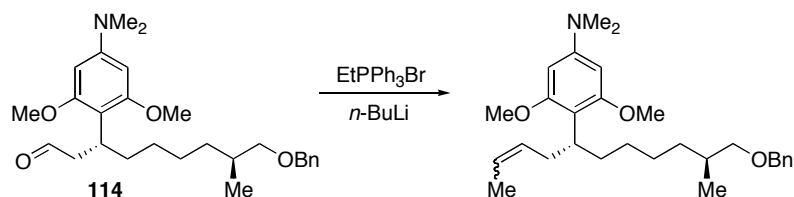
4-((5R,10S)-11-(Benzyloxy)-10-methylundec-2-en-5-yl)-3,5-dimethoxy-N,N-dimethylaniline. (Minor chemical shifts of (E)-olefin are in parentheses.) n-BuLi (4.52 mL, 11.32 mmol) was added to a heterogeneous mixture of ethyl triphenylphosphonium bromide (4.2 g, 11.32 mmol) in 45 mL THF at 0 °C under an argon 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}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.25-7.33 (m, 5H, Ar**H**); 5.92 (s, 2H, Ar**H**); 5.33 (m, 2H, **CH**=**CH**), 4.48 (s, 2H, **CH$_2$**OBn); 3.77 (s, 6H, O**CH$_3$**); 3.30 (dd, 1H, *J* = 5.7, 9.0 Hz, C**H**HOBn); 3.23 (m, 1H, Ar**CH**); 3.19 (dd, 1H, *J* = 6.0, 9.0, CH**H**OBn); 2.94 (s, 6H, N**CH$_3$**); 2.3-2.5 (m, 2H, **CH$_2$**CH=CH); 1.65-1.85 (m, 2H, **CH**Me and **CH**(alkyl)); 1.56(1.58) (d, 3H, *J* = 7.2 Hz, **CH$_3$**CH=CH); 1.01-1.40 (m, 6H, **CH**(alkyl)); 0.89 (d, 3H, *J* = 6.6 Hz, CH**CH$_3$**); ^{13}C NMR (125 MHz, CDCl$_3$) δ 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]$^+$ (C$_{29}$H$_{44}$NO$_3$) 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-(Benzyloxy)-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$_3$) δ 5.96 (s, 2H, Ar**H**); 3.77 (s, 6H, OC**H$_3$**); 3.47 (dd, 1H, J = 6.0, 7.5 Hz,

C**H**HOH); 3.37 (dd, 1H, J = 6.6, 7.5 Hz, C**H**HOH); 3.14 (ddt, 1H, J = 6.0, 9.3, 11.7 Hz,

ArC**H**); 2.95 (s, 6H, NC**H$_3$**); 1.69-1.83 (m, 3H, C**H**(alkyl)); 1.47-1.60 (m, 3H, O**H** and

C**H**(alkyl)); 1.01-1.40 (m, 10H, C**H**(alkyl)); 0.89 (d, 3H, J = 6.6 Hz, CHC**H$_3$**); 0.82 (t,

3H, J = 7.2 Hz, CH$_2$C**H$_3$**); ^{13}C NMR (125 MHz, CDCl$_3$) δ 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.
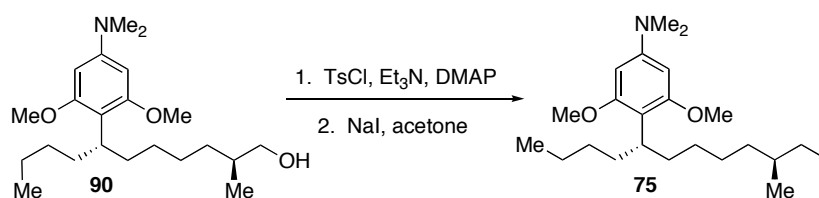
4-((5S,10S)-11-Iodo-10-methylundecan-5-yl)-3,5-dimethoxy-N,N-dimethylaniline

(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 µL, 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_2Cl_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_3N) provided the product **75** as an oil (241mg, 93% yield). ^1H NMR (300 MHz, C_6D_6) δ 5.93 (s, 2H, Ar**H**), 3.65 (tt, 1H, *J* = 5.1, 9.3 Hz, ArC**H**), 3.52 (s, 6H, OC**H₃**), 2.83 (dd, 1H, *J* = 5.1, 9.9 Hz, C**H**HI), 2.72 (dd, 1H, *J* = 5.7, 9.3 Hz, CH**H**I), 2.62 (s, 6H NC**H₃**), 2.24 (m, 2H, CHC**H₂**), 1.85 (m, 2H, C**H₂**CH), 0.9-1.56 (m, 11H, C**H**(alkyl)), 0.92 (t, 3H, *J* = 7.2 Hz, CH₂C**H₃**), 0.75 (d, 3H, *J* = 6.0 Hz, C**H₃**CH). ^{13}C NMR (125 MHz, CD_6D_6) δ 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.
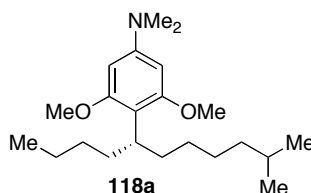
(*S*)-3,5-Dimethoxy-*N*,*N*-dimethyl-4-(10-methylundecan-5-yl)aniline (118a). ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.97 (s, 2H, Ar**H**), 3.80 (s, 6H, OC**H**$_3$), 3.17 (m, 1H, ArC**H**), 2.98 (s, 6H NC**H**$_3$), 1.77 (m, 3H, C**H**(alkyl)), 1.52 (m, 1H, C**H**(alkyl)), 1.04-1.32 (m, 11H, C**H**(alkyl)), 0.86 (d, 6H, *J* = 6.3 Hz, (C**H**$_3$)$_2$CH), 0.85 (t, 3H, *J* = 7.2 Hz, CH$_2$C**H**$_3$).