APPLICATION OF IMINIUM ACTIVATION TECHNOLOGIES TO NATURAL PRODUCT SYNTHESIS:

Total Syntheses of the Spiculisporic Acids, Progress Towards the Total Synthesis of Cylindrocyclophane F, and Formal Synthesis of Cylindrocyclophane A.

Thesis by

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I would like to thank my family for being there for the past five years. Just knowing that I could call for anything was truly a gift. Dad always listens to my chemistry and gives me advice on working in the real world, and Jamie has patiently taken my phone calls when I think I am ailing of something. My "little" brothers are adorable and I know they will always be there to protect me. I am so proud of you guys! I would like to acknowledge my Nana and my late Grumps for allowing me a spare room in their house in Ventura whenever I wanted – I wish I got to use it more often! They live life they way we should all aspire to: travel the world, do everything first class, and end the day with a glass of champagne!

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ABSTRACT

The first enantioselective, catalytic vinylogous Mukaiyama-Michael reaction of siloxyfurans with simple α,β-unsaturated aldehydes has been reported using chiral imidazolidinones. This methodology provides access to enantioenriched γ-butenolides, a privileged motif in organic synthesis. The utility of this organocatalytic Mukaiyama-Michael reaction was highlighted by the total syntheses of (–)-spiculisporic acid and (–)-5-*epi*-spiculisporic acid.

Investigations into the total syntheses of cylindrocyclophanes A and F necessitated the development of a novel *B*-alkyl Suzuki cross-coupling of trimethylanilinium salts using a nickel(0) catalyst and bulky phosphine ligand. This methodology study revealed a very competitive nickel-catalyzed demethylation pathway, which produced dimethylaniline byproducts. A possible explanation for this side reaction is discussed. This technology was applied to a dimerization strategy for the C_2-symmetric cylindrocyclophane F. Synthesis of a dimerization precursor included an enantioselective organocatalytic 1,4-addition of 3,5-dimethoxy-*N,N*-dimethylaniline into an α,β-unsaturated aldehyde. However, the *B*-alkyl Suzuki cross-coupling was unsuccessful in promoting a dimerization.

Next, the synthesis of cylindrocyclophane A was explored using an alternative ring-closing metathesis dimerization strategy. A dimerization precursor was to be assembled via the cross-coupling of trimethylanilinium salts with potassium (vinyl)trifluoroborate salts, whose syntheses featured an organocatalytic 1,4-conjugate reduction of a α,β-disubstituted enal. This cross-coupling strategy revealed olefin isomerization as a major

side-reaction in the nickel-catalyzed Suzuki dimerization, making this route a non-productive approach to the natural product.

Lastly, formal synthesis of cylindrocyclophane A was accomplished using (i) a nickel-catalyzed Stille cross-coupling of an activated vinyl stannane with a judiciously chosen trimethylanilinium salt and (ii) an asymmetric palladium-catalyzed allylic alkylation of an acyclic ketone. The latter represents the first example of application of the $Pd_2(dba)_3$/*t*-Bu-PHOX catalyst system to effect an asymmetric allylic alkylation on an acyclic system with good stereoselectivity. This route constituted a formal synthesis of cyclindrocyclophane A in eight linear steps, making it more efficient than the published route to the same advanced intermediate reported by Smith, which was synthesized in eleven steps.

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ABBREVIATIONS

acac	acetylacetonate
Ac_2O	acetic anhydride
AcCl	acetyl chloride
AcOH	acetic acid
AIBN	azabisisobutyronitrile
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	*tert*-butyl carbamate
BOM	benzyloxymethyl
BOM-Cl	benzyloxymethyl chloride
Bpin	pinacolatoboron
BPS	*tert*-butyldiphenylsilyl
Bz	benzoyl
Bu	butyl
COD	cyclooctadiene
Cp*	pentamethylcyclopentadiene
dba	dibenzylideneacetone
DCA	dichloroacetic acid
DEAD	diethyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIP-Cl	*B*-chlorodiisopinocampheylborane
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DNBA	2,4-dinitrobenzoic acid

dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphine)propane
EtOAc	ethyl acetate
GC	gas chromatography
Glu	glucosyl
h	hour
HOMO	highest occupied molecular orbital
HPLC	high pressure liquid chromatography
IC_{50}	concentration necessary for 50% inhibition
IMes • HCl	1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride
imid	imidazole
$IpcBH_2$	isopinocamphenylborane
IPr • HCl	1,3-bis(2,6-diisopropylphenyl)imidazolium chloride
LA	Lewis acid
LDA	lithium diisopropylamine
LiHMDS	lithium hexamethyldisilamide
LiTMP	lithium 2,2,6,6-tetramethylpiperidine amide
LUMO	lowest unoccupied molecular orbital
MCA	monochloroacetic acid
MeOH	methanol
MeOTf	methyl trifluoromethanesulfonate
min	minutes
MOM	methoxymethyl
NADH	nicotinamide adenine dinucleotide
NBA	2-nitrobenzoic acid
NMO	*N*-methylmorpholine-4-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect

Nu	nucleophile
OBBD	10-bora-9-oxabicyclo[3.3.2]decane
PCy_3	tricyclohexylphosphine
PHOX	phosphinooxazoline
Piv	trimethylacetyl
PMB	*para*-methoxybenzyl
ppm	parts per million
PT	5-phenyltetrazole
***p*-TSA**	*para*-toluenesulfonic acid
Pyr	pyridine
R_L	R_{LARGE}
R_S	R_{SMALL}
RAMP	(*R*)-1-amino-2-methoxymethylpyrrolidine
RCM	ring-closing metathesis
SAEP	(*S*)-1-amino-2-(1-ethyl-1-ethoxypropyl)pyrrolidine
SAMP	(*S*)-1-amino-2-methoxymethylpyrrolidine
SAPP	(*S*)-1-amino-2-(1-propyl-1-ethoxypropyl)pyrrolidine
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium triphenyldifluorosilicate
TBDPS	*tert*-butyldiphenylsilyl
TBDPSCl	*tert*-butylchlorodiphenylsilane
TBS	*tert*-butyldimethylsilyl
TBSCl	*tert*-butylchlorodimethylsilane
TBSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
TCA	trichloroacetic acid
TES	triethylsilyl
TESCl	chlorotriethylsilane
TFA	trifluoroacetic acid

TFE	2,2,2-trifluoroethanol
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TIPSOTf	triisopropylsilyl trifluoromethanesulfonate
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSCl	chlorotrimethylsilane
TPAP	tetrapropylammonium perruthenate
$\mathbf{X_C}$	chiral auxiliary

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Enantioselective LUMO-Lowering Organocatalysis.

I. Introduction.

The presentation of the Nobel Prize in 2001 to William S. Knowles, Ryoji Noyori, and K. Barry Sharpless recognized the influence and power of asymmetric catalysis in organic synthesis.[1] These laureates demonstrated that chiral ligands bound to metals imparted high levels of selectivity and catalytic activity to a diverse range of organic transformations and industrial processes.[2] Building on their seminal work, the area of asymmetric catalysis using chiral Lewis acids has expanded to a variety of metal-mediated, catalytic enantioselective reactions and now covers a range of reaction mechanisms and conditions.[3]

In contrast to the vast literature on Lewis-acid and metal-catalyzed processes, there are fewer asymmetric transformations catalyzed by organic molecules. This is surprising because chiral organometallic Lewis acids require enantiopure ligands, which generally require a multi-step synthesis from organic building blocks. The metals employed often are expensive and require inert atmospheres for preparation and storage.

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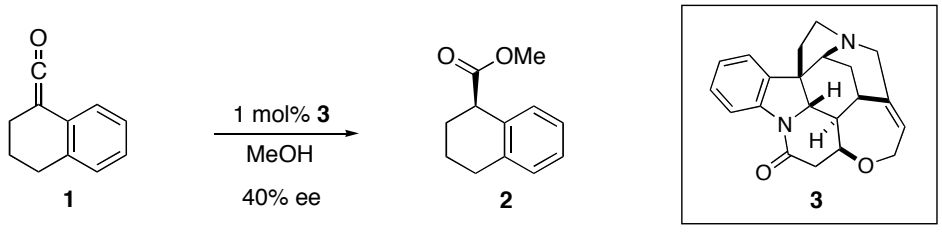
[1] (a) Knowles, W. S. *Angew. Chem. Int. Ed. Engl.* **2001**, *41*, 1998. (b) Noyori, R. *Angew. Chem. Int. Ed. Engl.* **2001**, *41*, 2008. (c) Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **2001**, *41*, 2024.

[2] For an example of industrial process, see L-DOPA synthesis: Knowles, W. S.; Sabacky, M. J. *Chem. Commun.* **1968**, 1445.

[3] (a) *Asymmetric Catalysis in Organic Synthesis*; Noyori, R., Ed.; Wiley: New York, 1994. (b) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Heidelberg, 1999.

Organocatalysts, on the other hand, are insensitive to air and moisture, thus making them more practical for use in synthetic laboratory procedures. Moreover, nature provides us with an array of enantiopure organic compounds from which to develop organic catalysts. These include α-amino acids, α-hydroxy acids, nucleic acids, and carbohydrates.

There are some reports of organocatalyzed reactions that date back almost a century. In 1912, Bredig and Fiske reported the use of alkaloids to catalyze the syntheses of cyanohydrins, noting that the opposite enantiomers were generated in the presence of quinine and quinidine.[4] Almost 50 years later, Pracejus demonstrated the use of strychnine (**3**) to catalyze the asymmetric methanolysis of a ketene **1** to provide an enantioenriched methyl ester **2** (eq. 1).[5]



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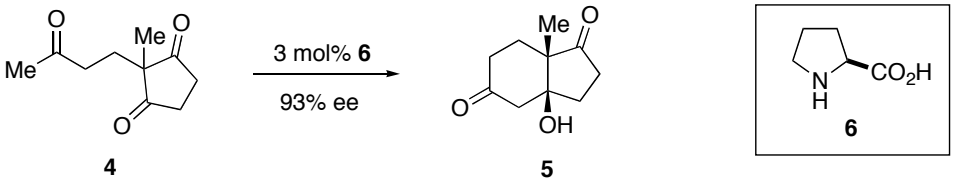


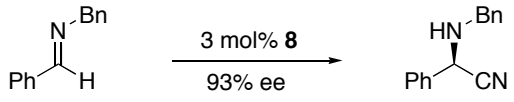
(2)

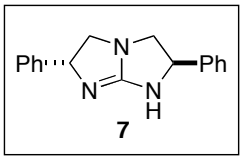
[4] Bredig, G.; Fiske, P. S. *Bichem. Z.* **1912**, *46*, 7.

[5] (a) Pracejus, H. *Annalen Der Chemie-Justus Liebig* **1960**, *634*, 9. (b) Pracejus, H. *ibid.* **1960**, *634*, 23.

Weichert,[6] and Hajos and Parrish[7] separately reported what is perhaps the most well-known example of an organocatalyzed reaction. Sub-stoichiometric quantities of proline (**6**) were able to effect the highly enantioselective Robinson annulation of triketone **4** to provide the Wieland-Mieschler ketone **5** (eq. 2).

Over the next 25 years, there were limited reports of the use of organic molecules to catalyze synthetic transformations. Corey and Jacobsen reported the use of imidazole-type catalysts **7** to effect the hydrocyanation of imines (eq. 3).[8,9] Shi, Yang, and Denmark demonstrated that the asymmetric epoxidation of styrenes can be affected in a highly stereoselective manner using fructose-derived ketone **8** (eq. 4).[10] The quaternary cinchonidine-derived alkaloid **9** was employed initially by O'Donnell as well as Corey to do enantioselective alkylations under phase transfer conditions (eq. 5).[11,12]





(3)

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[6] Eder, U.; Sauer, G.; Weichert, R. *Angew. Chem. Int. Ed.* **1971**, *10*, 496.

[7] Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.

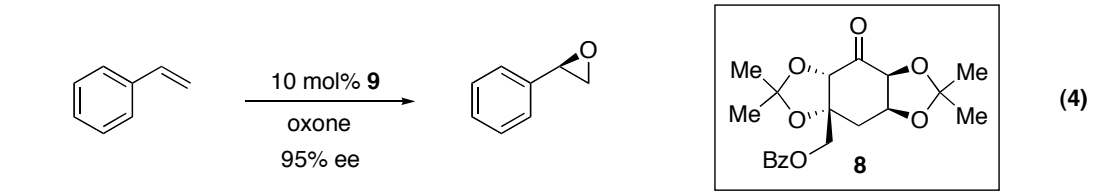
[8] Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157.

[9] (a) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2000**, *39*, 1279. (b) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867.

[10] (a) Tu, Y.; Wang, Z. X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (b) Tian, H. Q.; She, X. G.; Shu, L.-H.; Yu, H. W.; Shi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11551. (c) Yang, D.; Wong, M. K.; Wang, X. C.; Tang, Y. C. *J. Am. Chem. Soc.* **1998**, *120*, 6611. (d) Denmark, S. E.; Wu, Z. C. *Synlett.* **1999**, 847.

[11] O'Donnell, M. J.; Bennett, W. D.; Wu, S. D. *J. Am. Chem. Soc.* **1989**, *111*, 2353.

[12] Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414.



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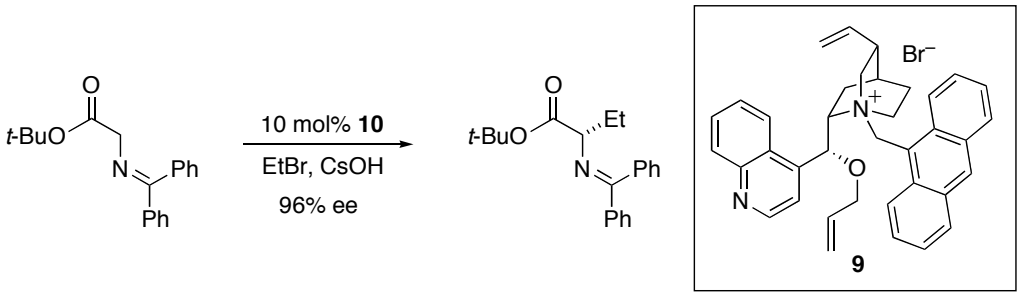
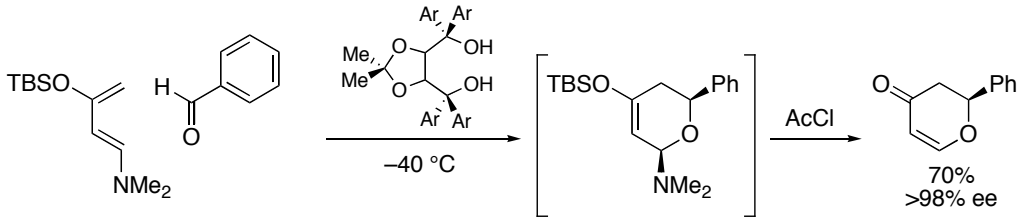


(5)

More recently, chiral diols and phosphoric acids have opened a new field of organocatalysis. Rawal and Huang showed that TADDOL derivatives can act as enantioselective hydrogen bonding catalysts to effect a highly selective hetero-Diels-Alder reaction (eq. 6).



(6)

While each of these examples has been a major contribution to synthetic chemistry, each of the organocatalysts shown above only affects a single transformation. The MacMillan group became interested in rediscovering the field of organocatalysis by developing a novel organocatalytic platform that would be effective for a broad range of transformations.

II. A General Approach to Enantioselective LUMO-lowering Catalysis.

Lewis acids have long been used to activate various π-systems towards nucleophilic attack. As depicted in figure 1, the mechanism of Lewis acid activation occurs via reversible binding of the Lewis acid to an electrophilic substrate, which lowers the energetic potential of the lowest unoccupied molecular orbital (LUMO). This electronic redistribution, in turn, decreases the energy gap between the LUMO of the electrophile and the HOMO of the nucleophile, thus facilitating the reaction between the two reacting partners. After bond formation occurs, the Lewis acid can then dissociate from the product to allow for catalyst turnover.

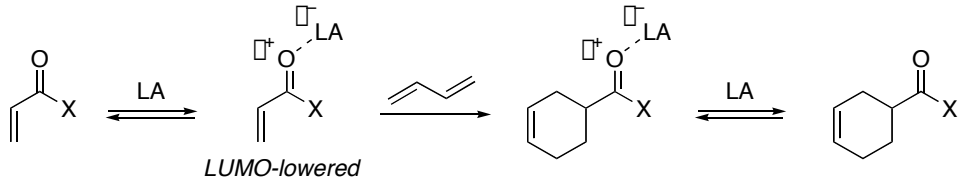


Figure 1. Lewis-acid catalysis of the Diels-Alder reaction.

Our group recognized that this type of Lewis acid LUMO-lowering activation could be emulated by secondary amines (Fig. 2). The reversible condensation of a secondary amine with an α,β-unsaturated aldehyde to form an iminium ion achieves the LUMO-lowered π-system that would have enhanced susceptibility to nucleophilic attack. A variety of chiral secondary amines are readily available, thus providing a new platform for enantioselective catalysis.

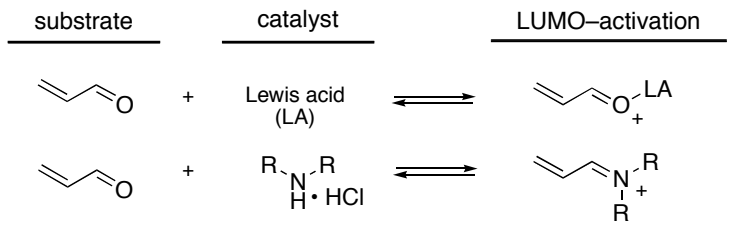


Figure 2. Complementary modes of LUMO-lowering catalysis.

i. *Chiral imidazolidinones as privileged organocatalysts.*

In order to achieve enantiocontrol in the nucleophilic attack onto activated iminium systems, there are a few requirements that must be met. First, the catalyst must be able to control iminium ion geometry. As shown in figure 3, the larger group (R_L) of the amine will partition the iminium to be oriented on the same side as the smaller group (R_S) in order to avoid non-bonding interactions with the β-proton of the iminium.

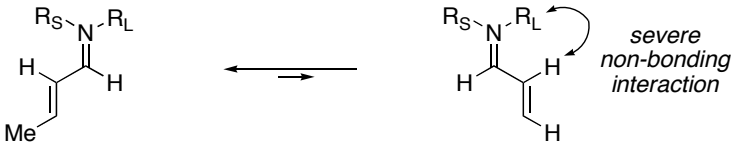


Figure 3. Iminium geometry control with imidazolidinones.

Second, the catalyst must be able to provide enantiofacial discrimination of the *Re* and *Si* faces of the π-system by protecting one face from nucleophilic attack. A variety of amines were tested for these requirements, and chiral imidazolidinones emerged as the

most successful catalyst framework. Using (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (Fig. 4), the larger *tert*-butyl and benzyl groups of the catalyst framework shield the *Si* face effectively to leave the *Re* face exposed for nucleophilic attack.

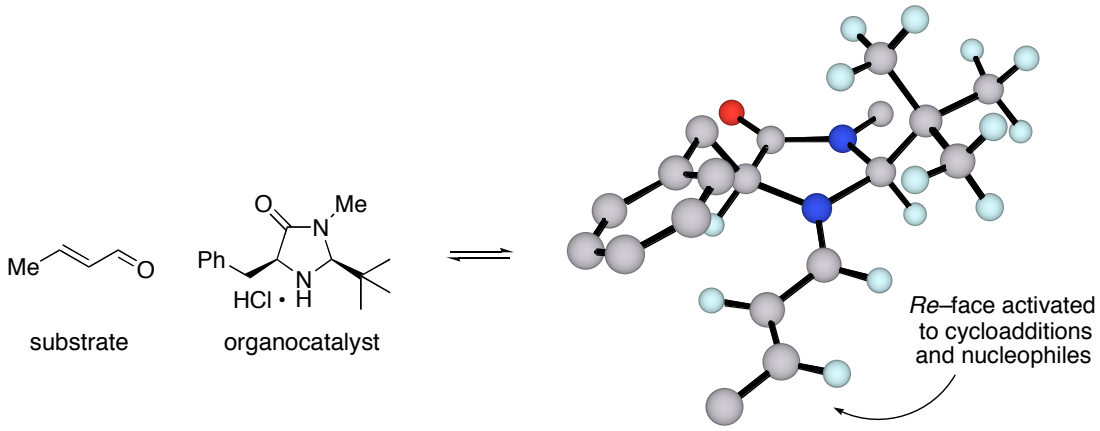


Figure 4. Enantiofacial discrimination of chiral imidazolidinones.

In 2004, Houk reported a thorough computational study to explain the observed enantioselectivities in the organocatalytic conjugate additions of pyrroles and indoles.[13] The calculated preferred conformations of the iminium intermediates are similar to the structure presented in figure 4. The most stable conformers **(*E*)-11a** and **(*E*)-11b** constitute 92% of all the existing species in the gas phase at 25 °C (Fig. 5). This work complements the proposed reasons for the high levels of stereoselectivity typically observed in these organocatalytic reactions.

[13] Gordillo, R.; Carter, J.; Houk, K. N. *Adv. Synth. Cat.* **2004**, *346*, 1175.

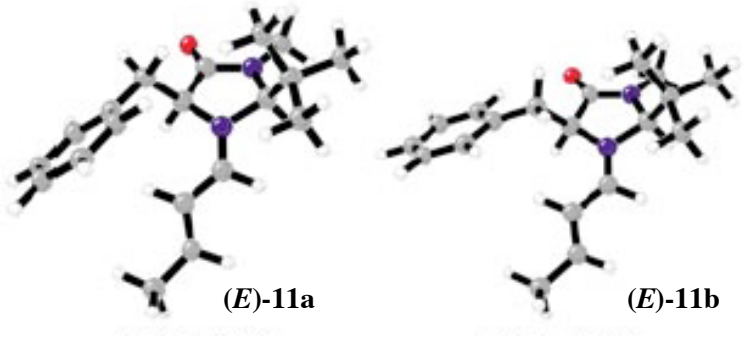


Figure 5. Calculated minimized structures for the iminium in figure 4.

Unlike the chiral ligands often employed in Lewis acid catalysis, preparation of chiral imidazolidinones does not require a lengthy synthetic sequence. In fact, they are available in two steps from readily-available amino acids (Fig. 6). Preparation of the amide derived from phenylalanine is accomplished via the acid chloride. Iron trichloride-mediated condensation of pivaldehyde onto the amine and subsequent cyclization of the amide gives a mixture of *cis* and *trans* isomers of imidazolidinone **11**, which are easily separable by silica gel chromatography.

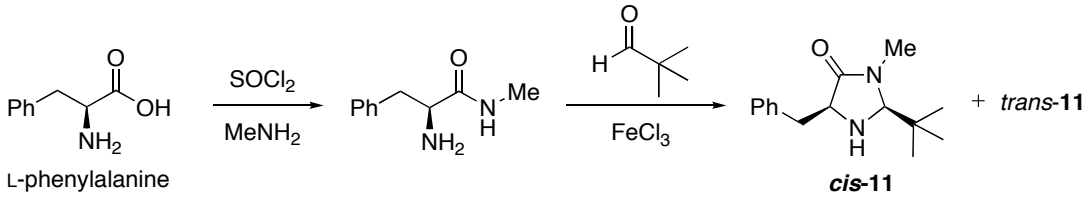


Figure 6. Easy access to imidazolidinones.

Over the past six years, different variations of this catalyst framework (Fig. 7) have been shown to be widely effective for a broad range of transformation. Initial investigations into the Diels-Alder and nitrone cycloadditions as well as limited use in

1,4-conjugate additions of electron-rich heteroaromatic π-nucleophiles commenced with *gem*-dimethyl imidazolidinone **10**.[14] When the research described in this thesis began, the MacMillan group had already developed *tert*-butyl imidazolidinone **11**,[15] and it is this catalyst that appears throughout much of this work. The imidazolidinone framework has been adjusted for different reactions. For example, catalyst **12** was developed for the asymmetric ketone Diels-Alder cycloadditions[16] and catalyst **13** was developed for 1,4-conjugate hydride reduction[17] – a reaction that will appear in Chapter 4 of this work.

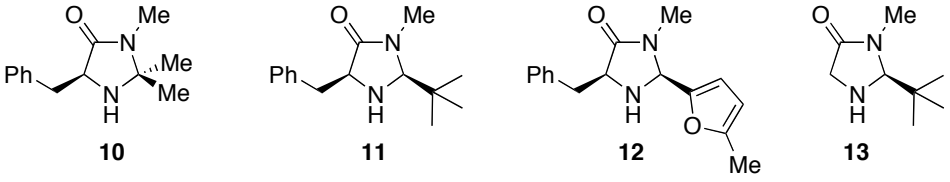


Figure 7. Imidazolidinones developed and used within the MacMillan group.

The organocatalytic, enantioselective transformations developed in our labs display a wide scope of aldehydes and nucleophiles with superior enantio- and diastereoselectivity. However, to test the true utility and generality of these transformations, they must be utilized in the total synthesis of natural products where substrates are more complicated than those used in methodology studies.

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[14] (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. (b) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874. (c) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370.

[15] (a) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172. (b) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894.

[16] Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458.

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

III. Summary of Thesis Research.

The following chapters describe the application of iminium activation technologies towards the total syntheses of natural products. The development of the first organocatalytic vinylogous Mukaiyama-Michael reaction is presented in Chapter 2. This methodology, which generates highly stereoselective butenolide architectures, is then applied to the total syntheses of spiculisporic acid and 5-*epi*-spiculisporic acid. The remainder of the research in this thesis has been devoted to investigations towards the cylindrocyclophanes. Chapter 3 introduces the *B*-alkyl nickel(0)-catalyzed cross-coupling of trimethylanilinium salts and its application towards the total synthesis of cylindrocyclophane F. Chapters 4 and 5 feature two different trimethylanilinium cross-coupling strategies towards cylindrocyclophane A: a Suzuki cross coupling with a vinyl potassium trifluoroborate and a Stille cross-coupling with an activated vinyl stannane, respectively. The latter chapter culminates with a formal synthesis of cylindrocyclophane A.

C h a p t e r 2

Total Syntheses of the Spiculisporic Acids: Exploitation of the Organocatalytic Vinylogous Mukaiyama-Michael Addition.*

I. Introduction.

i. *The γ-Butanolide Architecture.*

The γ-butanolide architecture is a privileged motif in organic synthesis and can be found in over 13,000 natural products, some of which are shown in figure 1.[1] Kallolide is a diterpenoid and a member of the rare pseudopterane family.[2] Members of this family possess significant biological activity, and kallolide is an anti-inflammatory agent with activity comparable to that of indomethacin. Merrilactone A has received considerable attention in the past few years because of its role as a neurotropic agent. It is implicated in the treatment of Alzheimer's and Parkinson's diseases due to its ability to affect the maintenance and growth of neurons as well as its ability to prevent neurological death. Spiculisporic acid is a commercial surfactant that will be discussed in more detail (*vide infra*).

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* A preliminary communication of this work has been published: Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am Chem. Soc.* **2003**, *125*, 1192.

[1] The Beilstein database reports >200 natural isolates that incorporate γ-butanolide structure.

[2] Look, S. A.; Burch, M. T.; Fenical, W.; Zhen, Q.-T.; Clardy, J. *J. Org. Chem.* **1995**, *50*, 5741.

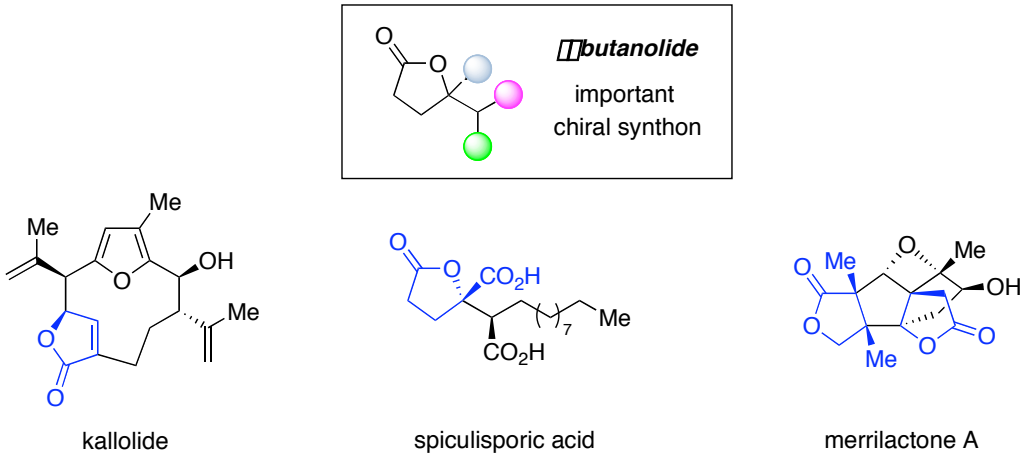


Figure 1. Butanolides in natural products.

Despite their prevalence in natural products, there are only a few methods in which γ-butanolides are commonly synthesized.[3] The two most common ways are (i) lactonization of a γ-alcohol onto a carboxylic moiety (Fig. 2**A**) and (ii) oxidation of a siloxyfuran (Fig. 2**B**). An alternative strategy is the metal-catalyzed trapping of a pendant carboxylic acid onto an alkene or alkyne (Fig. 2C). The latter route is not amenable to varying functionality on the γ-system, as there are few examples of this reaction with a tetrasubstituted olefin as shown in figure 2. Within the realms of these three methods, the biggest challenge is setting the stereochemistry about the fully-substituted γ-carbon.

[3] For reviews on synthesis of butenolides, see: (a) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Recent Res. Dev. Syn. Org. Chem.* **2000**, 65. (b) Negishi, E.-I.; Kotora, M. *Tetrahedron* **1997**, *53*, 6707. (c) Knight, D. W. *Contemporary Org. Synth.* **1994**, *1*, 287.

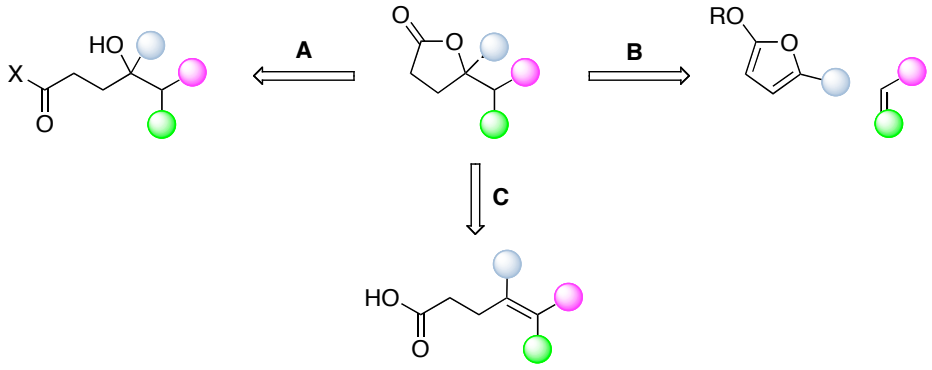
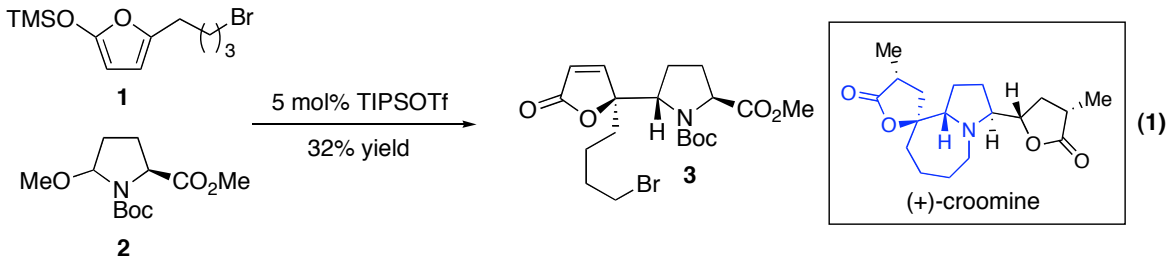


Figure 2. Syntheses of the butanolide architecture.

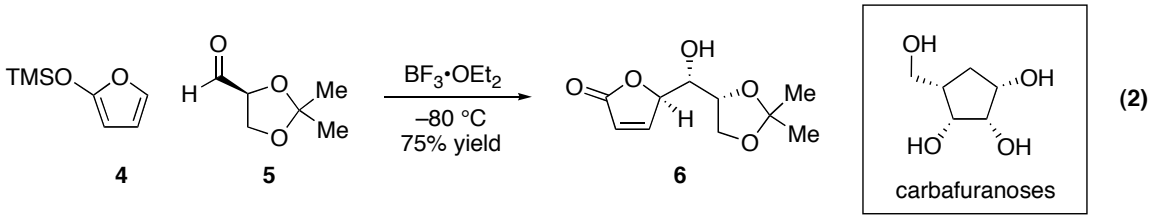
A variety of diastereoselective methods have been developed for the stereoselective formation of □-butanolides. In the synthesis of (+)-croomine, Martin and co-workers reported that the addition of functionalized siloxyfuran **1** to chiral □-methoxyamine **2** under Lewis acidic conditions affects a diastereoselective Mannich reaction to form butenolide **3** (eq. 1).[4] Analogously, the diastereoselective Aldol reaction in the presence of $BF_3 \bullet OEt_2$ produces a single diastereomer of butenolide **6**, which is an intermediate in the syntheses of a variety of furanose derivatives (eq. 2).[5]



(1)

[4] (a) Martin, S. F.; Barr, K. J.; Smith, D. W.; Bur, S. K. *J. Am. Chem. Soc.* **1999**, *121*, 6990. (b) Martin, S. F.; Barr, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 3299.

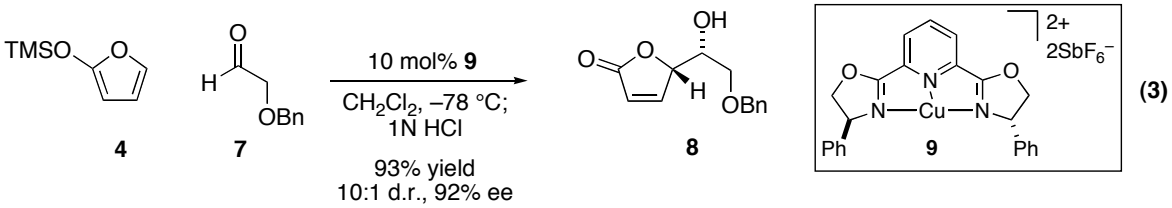
[5] Rassu, G.; Auzzas, L.; Pinna, L.; Zambrano, V.; Battistini, L.; Zanardi, F.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J. Org. Chem.* **2001**, *66*, 8070.



(2)

The catalytic coupling of siloxyfurans and aldehydes and a,b-unsaturated system using chiral Lewis acids has emerged as a preeminent strategy to generate enantioenriched butenolide structures. These are termed the Mukaiyama-Aldol and Mukaiyama-Michael reaction, respectively.

In 1999, the Evans group reported that utilization of chiral copper complex **9** catalyzed the addition of siloxyfuran **4** to □-oxyacetaldehydes **7** to furnish the enantioenriched vinylogous Mukaiyama-Aldol product **8** in excellent yield (eq. 3). [6] While the Mukaiyama-Aldol transformation has received considerable attention within the synthetic community,[7] the enantioselective 1,4-addition of silyl enol ethers to electron-deficient olefins was not as well studied.



(3)

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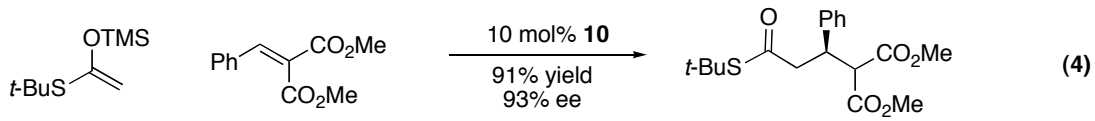
[6] (a) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669. (b) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686.

[7] For reviews that incorporate this topic, see: (a) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357. (b) Carreira, E. M. In *Catalytic Asymmetric Synthesis*, *2nd ed.*; Ojima, I., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 8B2. (c) Carreira, E. M. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim 2000; Chapter 8.

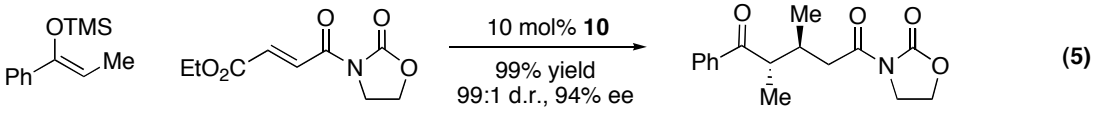
ii. *The Mukaiyama-Michael Reaction.*

Since its discovery by Mukaiyama in 1974,[8] the Mukaiyama-Michael reaction of silyl enol ethers with α,β-unsaturated carbonyl compounds has become a powerful technique for the stereoselective formation of carbon-carbon bonds under mild reaction conditions.

Prior to this research, only electrophiles that were capable of bidentate chelation to a chiral Lewis acid complex were suitable electrophiles for the Mukaiyama-Michael addition. For example, the Evans group used copper(II) bisoxazoline **10** to catalyze the enantioselective addition of silyl enol ethers to alkylidene malonates[9] (eq. 4) or unsaturated acyl oxazolidinones[10] (eq. 5). In separate reports, Katsuki[11] and Desimoni[12] employed chiral Lewis acids **10** and **11** to catalyze the Mukaiyama-Michael addition of siloxyfuran **4** to acyl oxazolidinones (eq. 6 and 7).



(4)



(5)

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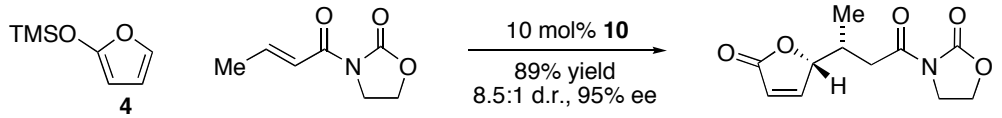
[8] (a) Narasaki, K.; Soai, K.; Mukaiyama, T. *Chem. Lett.* **1974**, 1223.

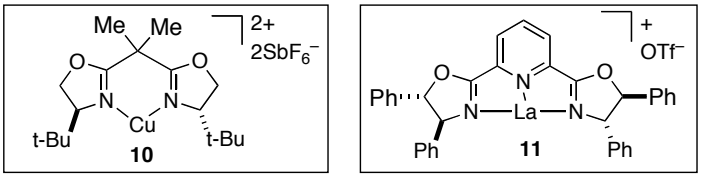
[9] Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, C. W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134.

[10] Evans, D. A.; Scheidt, K. A.; Johnston, J. N.; Willis, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480.

[11] (a) Kitajima, H.; Ito, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 17015. (b) Kitajima, H.; Katsuki, T. *Synlett* **1997**, 568.

[12] Desimoni, G.; Faita, G.; Filippone, S.; Mella, M.; Zampori, M. G.; Zema, M. *Tetrahedron* **2001**, *53*, 10203.





iii. *Mukaiyama-Aldol versus Mukaiyama-Michael Addition.*

The deficiency in enantioselective Mukaiyama-Michael reactions may be due to the propensity of Lewis acids to promote 1,2-addition to the carbonyl in preference to 1,4-addition to the □,□-unsaturated system (Fig. 3).[13] In fact, it is documented that metal-mediated siloxyfuran additions to enals proceed in a highly selective fashion to give the Mukaiyama-Aldol product.[14]

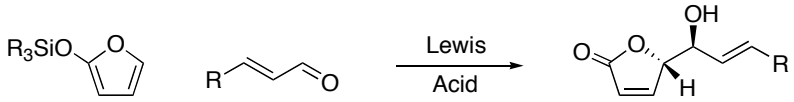


Figure 3. Lewis acids promote a Mukaiyama-Aldol addition.

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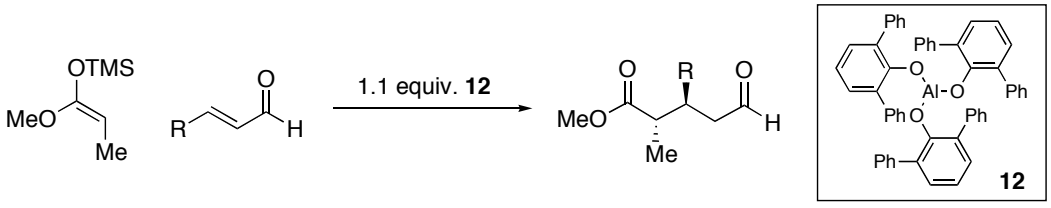
[13] (a) Rodriguez, A. D.; Shi, J. G.; Huang, S. P. D. *J. Org. Chem.* **1998**, *63*, 4425.

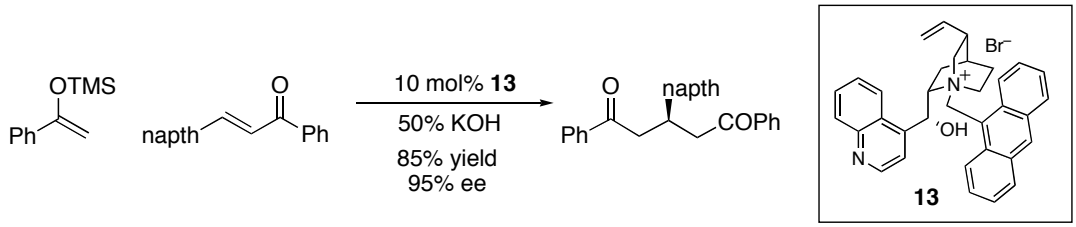
[14] (a) von der Ohe, F.; Bruckner, R. *Tetrahedron Lett.* **1998**, *39*, 1909. (b) von der Ohe, F.; Bruckner, R. *New. J. Chem.* **2000**, *24*, 659.

To date, the only example of a metal-mediated Mukaiyama-Michael addition has been reported by the Yamamoto group, who utilized the sterically demanding aluminum acid complex **12** to promote the 1,4-addition of silyl enol ethers to enals (eq. 8).[15] It is hypothesized that the steric demand imposed by the aluminum promoter partitions the reaction away from addition to the carbonyl to give the Mukaiyama-Michael product.



(8)

While metal-catalyzed reactions are mostly ineffective in this synthetic transformation, several organocatalytic approaches to the enantioselective Michael reaction have been reported. The first report was in 1975 when quinine was used to catalyze the 1,4-addition of 1,3-dicarbonyls to enones.[16] Twenty-five years later, Corey demonstrated that cinchona alkaloid derivative **13** could catalyze the Mukaiyama-Michael addition of silyl enol ethers to enones with high levels of enantioselectivity (eq. 9).[17]



(9)

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[15] Maruoka, K.; Imoto, H.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 4131.

[16] Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, *14*, 4057.

[17] (a) Zhang, F. Y.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1097. (b) Zhang, F. Y.; Corey, E. J. *Org. Lett.* **2001**, *3*, 639.

II. Organocatalytic Vinylogous Mukaiyama-Michael Reaction.

During our group's studies on LUMO-lowering organocatalysis (*vide* Chapter 1), α,β-unsaturated aldehydes had been shown to be quite useful substrates in a broad range of transformations.[18] It was expected that organocatalysis with chiral imidazolidinones would render the α,β-unsaturated aldehyde inert to 1,2-addition by the siloxyfuran, thus overcoming the limitations to the construction of γ-butenolides imposed by Lewis acid catalysis (Fig. 3). α,β-Unsaturated iminium ions arising from chiral imidazolidinone **14** should favor 1,4-addition because of the steric constraints imposed by the catalyst framework (Fig. 4).

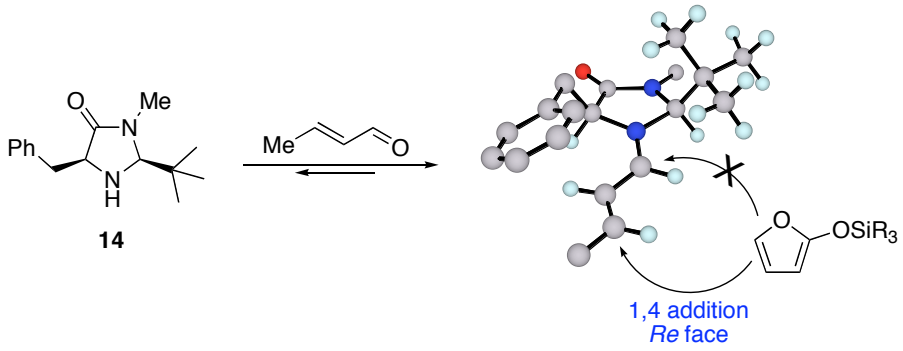

Figure 4. 1,2-addition versus 1,4-addition in the presence of chiral amines.

Additionally, the catalyst framework should enforce high levels of diastereo- and enantioselectivity in the carbon-carbon bond-forming event by shielding the *Si* face and exposing only the *Re* face towards the attack of π-nucleophiles.

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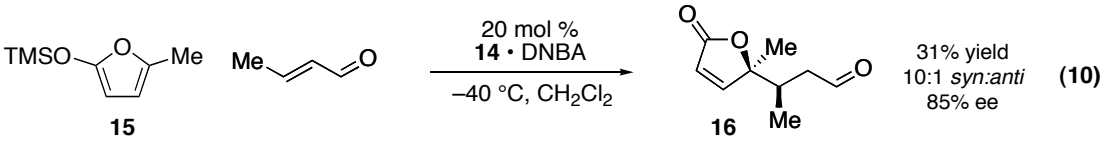
[18] (a) Ahrendt, K.A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. (b) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874. (c) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370. (d) Austin, J. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172. (e) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894.

i. *Initial Investigations into the Organocatalytic Mukaiyama-Michael.*

The enantioselective organocatalytic synthesis of butenolides was first examined using siloxyfuran **15**, crotonaldehyde, and imidazolidinone **14**.[19] Preliminary results demonstrated that the proposed 1,4-addition was possible with good levels of diastereo- and enantioselectivity; however, the efficiency of the reaction was poor (eq. 10).



It was believed that the catalytic cycle was being arrested by the consumption of water due to desilylation of the silyl cation intermediate **17** (Fig. 5). Therefore, there was no hydrolysis of the iminium adduct **18** and thus no turnover of catalyst.

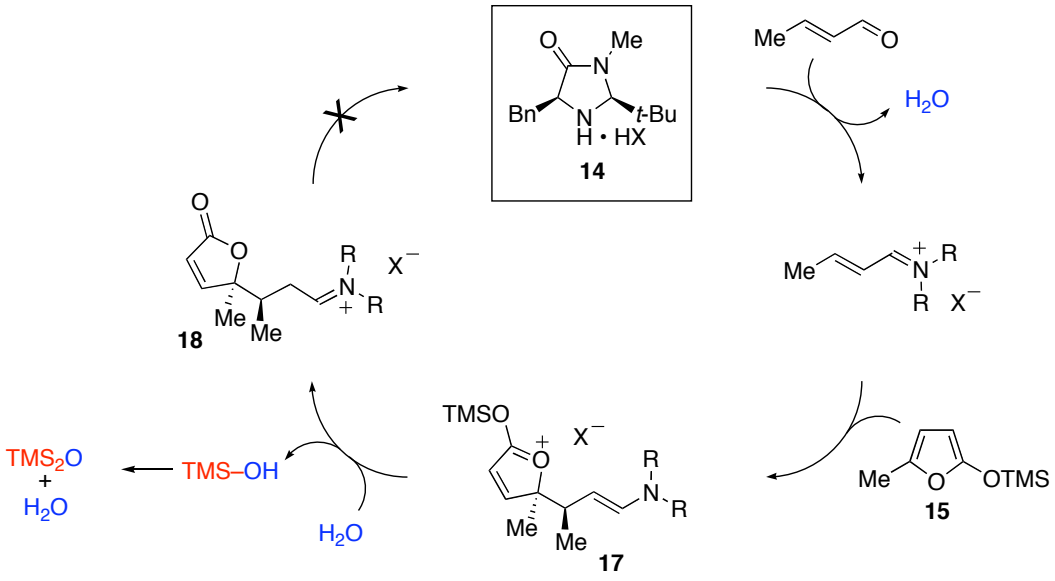


Figure 5. Consumption of water in the catalytic cycle.

[19] Initial investigations were conducted by Sean P. Brown. See: Brown, S. P. Ph.D. thesis. California Institute of Technology, 2005.

It was hypothesized that the addition of a protic nucleophile to facilitate the desilylation of intermediate **17** would allow for hydrolysis of iminium **18** and complete the catalytic cycle to release desired product **16** (Fig. 6)

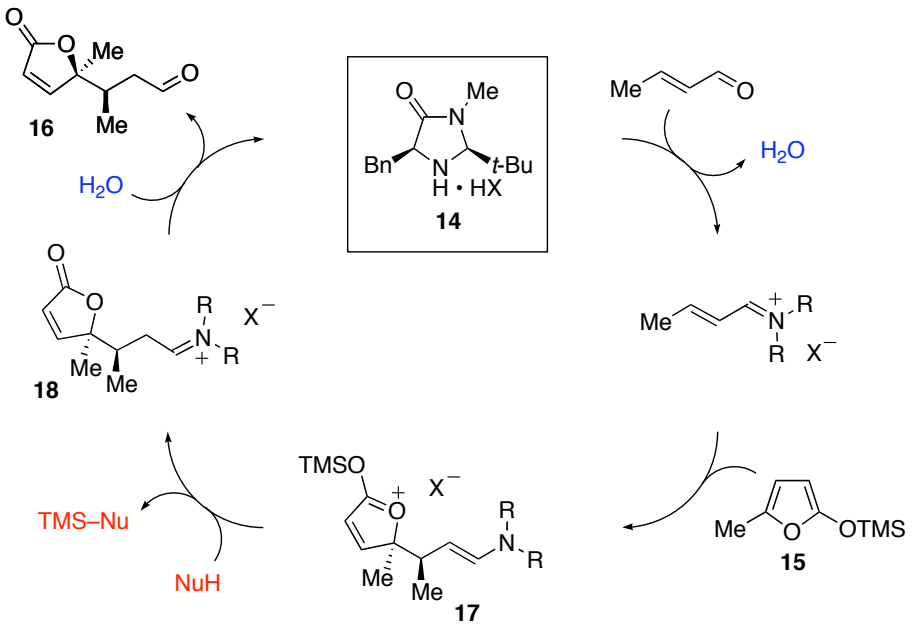
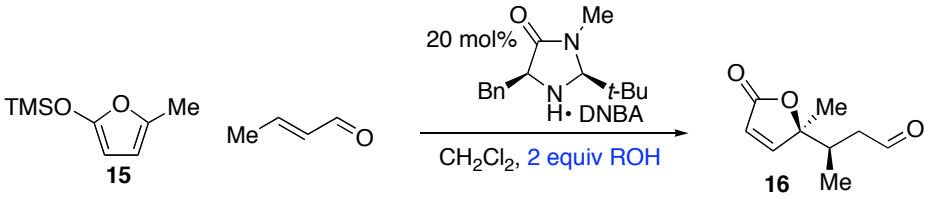


Figure 6. Restoration of the catalytic cycle by protic nucleophiles.

While a variety of protic nucleophiles were effective in scavenging the putative silyl cation intermediate (Table 1, entries 2–5), the addition of excess water provided optimal reaction efficiency (entries 5 and 6) with superior levels of diastereoselectivity and enantioselectivities greater than 90%.

Table 1. The effect of protic sources in the organocatalytic Mukaiyama-Michael.



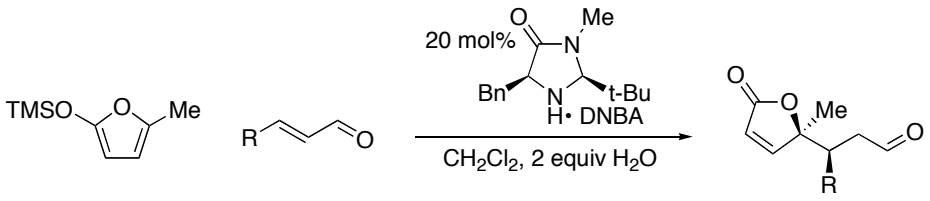
Entry	ROH	temp (°C)	time (h)	% yield	syn:anti	% ee[a,b]
1	none	–40	10	31	10:1	85
2	*i*-PrOH	–40	10	83	16:1	84
3	$(CF_3)_2CHOH$	–40	10	42	10:1	83
4	phenol	–40	10	58	11:1	82
5	H_2O	–40	10	93	16:1	85
6	H_2O	–70	11	84	22:1	92

[a] Stereoselectivities determined by chiral GLC analysis. [b] Absolute and relative configuration assigned by X-ray or nOe analysis.

ii. *Scope of the organocatalytic Mukaiyama-Michael reaction.*

The reaction conditions developed (*vide supra*) proved to be applicable to a wide range of steric demands on the □-olefin substituent of the enal (Table 2, entries 1–4) to produce 5-(1-alkyl)-5-methylfuranones (7:1 to 31:1 *syn*:*anti*, 84–99% ee). Variation in the electronic nature of the enal has little influence on the sense of enantioinduction. For example, optimal levels of selectivity can be achieved with enals that do not readily participate in iminium formation (entry 6, 84% yield, 99% ee), as well as aldehydes that provide stable iminium intermediates (entry 4, 77% yield, 99% ee).

Table 2. Organocatalyzed addition of siloxyfuran into α,β-unsaturated aldehydes.

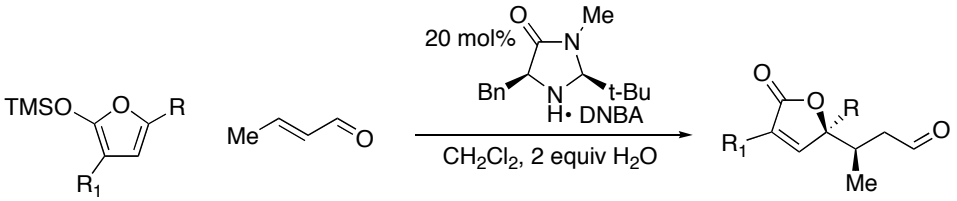


Entry	R	temp (°C)	time (h)	% yield	syn:anti	% ee[a,b]
1	Me	–70	11	81	22:1	92
2	*n*-Pr	–50	20	87	31:1	84
3	*i*-Pr	–20	30	80	7:1	98
4	Ph	–40	30	77	1:6	99
5	CH_2OBz	–70	24	86	20:1	90
6	CO_2Me	–60	22	84	11:1	99

[a] Stereoselectivities determined by chiral GLC analysis. [b] Absolute and relative configuration assigned by X-ray or nOe analysis.

Significant structural variation in the siloxyfuran system can be tolerated (Table 3). The reaction appears to be quite tolerant to substitution at the 5-position of the furan (entries 1–4, 90–92% ee). While high levels of *syn* stereogenicity are available in the construction of g-butenolides (entries 1–4, 6), access to the *anti* diastereomer can also be realized with the appropriate choice of co-catalyst and solvent in systems that bear an electron-withdrawing substituent on the furan (entry 5, 1:7 *syn*:*anti*, 98% ee, 83% yield). Moreover, introduction of alkyl substituents at C(3) of the furan moiety can be accommodated without loss in stereocontrol (entry 6, 24:1 *syn*:*anti*, 98% ee, 73% yield).

Table 3. Organocatalyzed addition of siloxyfurans into crotonaldehyde.



Entry	R	R_1	temp (°C)	time (h)	% yield	syn:anti	% ee[a,b]
1	H	H	–50	7	87	8:1	90
2	Me	H	–70	11	80	22:1	92
3	Et	H	–70	11	83	16:1	90
4	CO_2Me	H	–10	44	86	6:1	98[c]
5	CO_2Me	H	–10	96	83	1:7	98[d]
6	Me	Me	–65	23	73	24:1	90

[a] Stereoselectivities determined by chiral GLC analysis. [b] Absolute and relative configuration assigned by X-ray or nOe analysis. [c] With 20 mol% catalyst•TFA in THF. [d] With 20 mol% catalyst•TfOH in $CHCl_3$

III. Total Syntheses of the Spiculisporic Acids.

A demonstration of the utility of this organocatalytic vinylogous Mukaiyama-Michael methodology was its use in the total synthesis of spiculisporic acid and its epimer, 5-*epi*-spiculisporic acid.

i. *Background.*

Spiculisporic acid **19** is a fermentation adduct isolated from the recrystallization of the precipitate formed on acidification of the culture broth of *Penicillium spiculisporum* Lehman and other *P.* species.[20] It is believed that the active metabolite is

[20] (a) Clutterbuck, P. W.; Raistrick, H.; Rintoul, M. L. *Philos. Trans. R. Soc. London, Ser. B.* **1931**, *220*, 301. (b) Birkinshaw, J. H.; Raistrick, H. *Biochem. J.* **1934**, *228*, 828. (c) Asano, M.; Kameda, S. *J. Pharm. Soc. Jpn.* **1941**, *61*, 81.

not the lactone **19** but the hydrolyzed tricarboxylic acid **19a**, secospiculisporic acid (Fig. 7).[21]

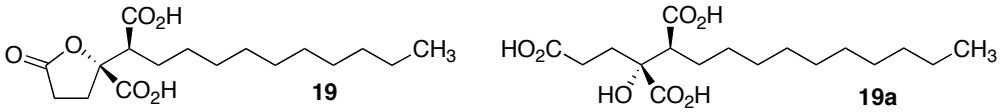


Figure 7. Spiculisporic acid and secospiculisporic acid.

Spiculisporic acid has found commercial application (i) as a biosurfactant for metal decontamination processes to remove hard, large metal cations from water[22] and (ii) in fine polymer production.[23] Furthermore, it was shown that the (*n*-hexylamine) salt of spiculisporic acids **19** and **19a** change their state of molecular aggregation depending on the environmental pH: vesicles form at pH of about 6.0, lipid particles at pH of 6.3–6.6, and micelles at pH above 6.8 (Fig 8).[24] Because of these physiological properties, these materials have potential use as new controlled release carriers of active chemicals in the cosmetic, pharmaceutical, agricultural, and biotechnology industries.

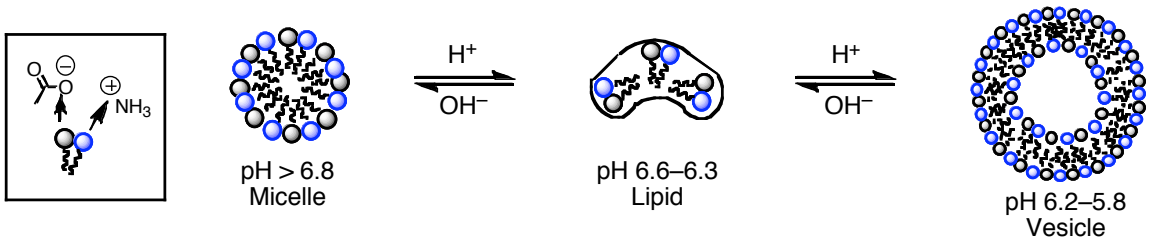


Figure 8. pH-Dependent molecular aggregation of the amine salts of spiculisporic acid.

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[21] Tabuchi, T.; Nakamura, I.; Kobayashi, T. *J. Ferment. Technol.* **1977**, *55*, 37.

[22] Pekdemir, T.; Tokunaga, S.; Ishigami, Y.; Hong, H.-J. *J. Surfactants Detergents* **2000**, *3*, 43.

[23] Yamazaki, S.; Suzuki, H.; Ishigami, Y. *Kagaku Gijutsu Hokoku* **1988**, *83*, 125.

[24] (a) Ishigami, Y.; Zhang, Y.; Ji, F. *Chiimica Oggi* **2000**, 32.; (b) Ishigami, Y.; Gama, Y.; Yamazaki, S. *J. Jpn. Oil Chem. Soc.* **1987**, *36*, 490.

To date, the only other reported enantioselective synthesis was complete by Brandænge and co-workers in 1984.[25] The elaboration from D-glucose was accomplished in 22 steps and utilized none of glucose's resident stereocenters (Fig. 9)

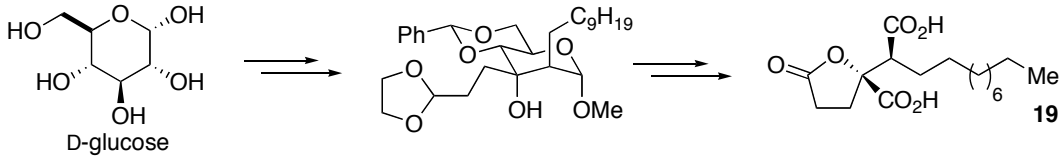


Figure 9. Brandænge's synthesis of spiculisporic acid.

ii. *Investigation of key organocatalytic Mukaiyama-Michael reaction.*

As shown in figure 10, it was envisioned that the stereochemical core **20** of the natural product **19** could be constructed in one step from the organocatalytic Mukaiyama-Michael addition of siloxyfuran **21** into methyl 4-oxobutenoate (**22**).

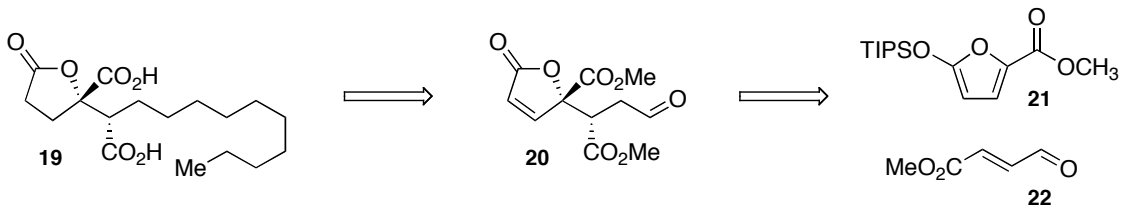


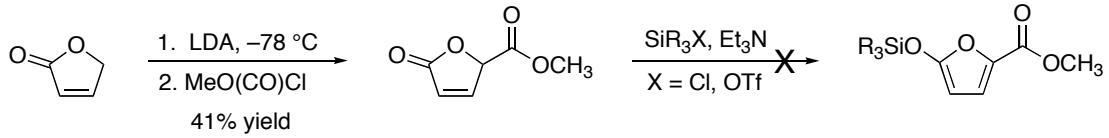
Figure 10. Retrosynthetic analysis of spiculisporic acid.

In accordance with known methodology to prepare 5-alkyl-2-siloxyfurans, alkylation at the 5-position was attempted by simple vinylogous enolate addition of 2-

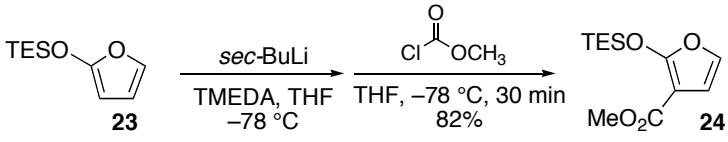
[25] Brandaenge, S.; Dahlman, O.; Lindqvist, B.; Maahlen, A.; Moerch, L. *Acta Chem. Scand. Ser. B* **1984**, *10*, 837.

(5*H)*-furanone to carboxylic acid derivatives (Scheme 1). Alkylation directly to the carboxylic acid with CO_2 was unsuccessful. However, analogous alkylation with methyl chloroformate proceeded with a 41% yield. Attempts to deprotonate the alkylated lactone and silylate to form the siloxyfuran were unsuccessful.

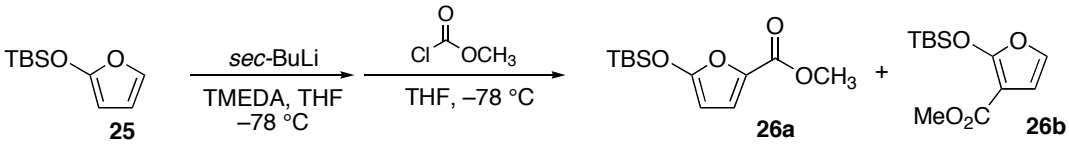
Scheme 1. Preparation of 5-carboxyl-2-siloxyfurans.



Due to the stability of the TIPS group relative to other silyl protecting groups, we were concerned about the desilylation step in the catalytic cycle. Therefore more readily desilylated furan derivatives were made. However, triethylsiloxyfuran **23** alkylated exclusively in the 3-position to afford **24** (eq. 11). Under the same conditions, *tert*-butyldimethylsiloxyfuran **8** produced with a 1:1 mixture of alkylation in the 3-position **26a** and the 5-position **26b** (eq. 12). Other alkylating reagents, such as benzyl and ethyl chloroformate, led to decomposition of the starting material.



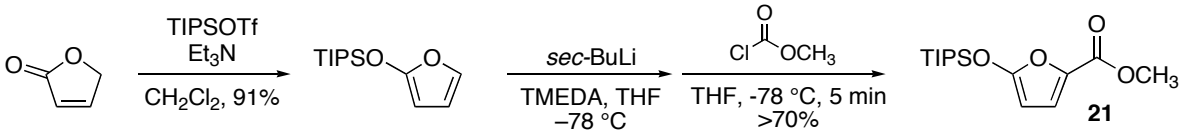
(11)



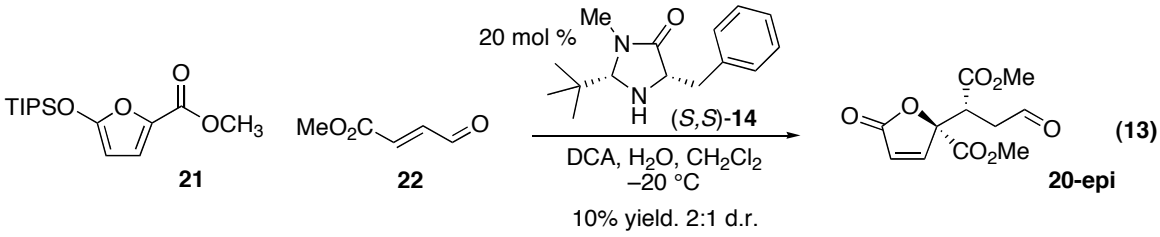
(12)

A report by Martin and co-workers in 1999 demonstrated that the 5-position of triisopropylsilylfurans could be alkylated with aryl halides.[26] The TIPS group sterically protects the 3-position of the furan thus exposing only the 5-position for deprotonation and subsequent alkylation. Using methyl chloroformate as the electrophile, this reaction proceeded cleanly with yields consistently above 70% (Scheme 2).

Scheme 2. Preparation of siloxyfuran 21.



With the siloxyfuran **21** in hand, the organocatalystic step was attempted using enal **22**. Using 5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one [(*S*,*S*)-**14**], the reaction was conducted at –20°C with dichloroacetic acid (DCA) as the co-catalyst. A diastereoselectivity of 2:1 was observed in the proton NMR with about a 10% isolated yield of the product **20-epi** (eq. 13).[27]

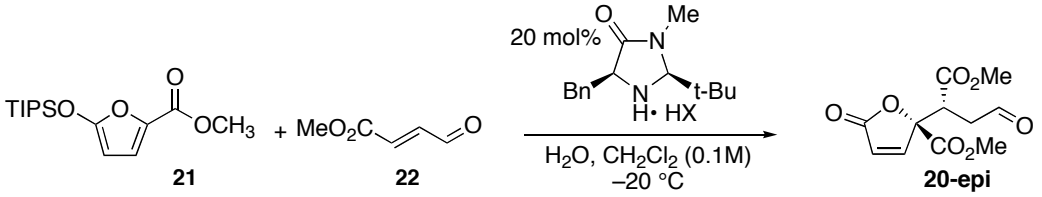


[26] Martin, S. F.; Barr, K. J.; Smith, D. W.; Bur, S. K. *J. Am. Chem. Soc.* **1999**, *121*, 6990.

[27] At the start of this synthesis, the relative stereochemistry was unknown. Once the synthesis was completed, it was determined by correlation to the natural product that the original optimization series was furnishing the epimer of the desired natural product.

The limited reactivity of this system showed that the desired reaction was operative, but further optimization was still needed. Examination of the acid co-catalyst, solvent, and concentration quickly produced a more efficient and more stereoselective reaction. Stronger acid co-catalysts produced conversions over 60%, diastereoselectivities greater than 4 to 1, and enantioselectivtities greater than 85% (Table 4, entries 1 and 2). Further studies were conducted with triflic acid as the co-catalyst.

Table 4. Examination of acid co-catalyst.

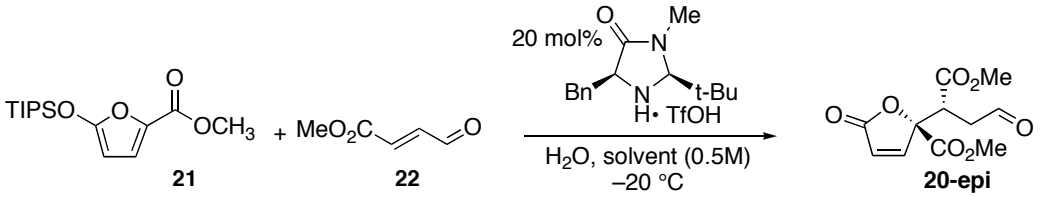


Entry	HX	pKa	conversion (%)	*syn*:*anti*	% ee[a,b]
1	TfOH	–14	63	5.9:1	85
2	HCl	–8	63	4.3:1	86
3	TFA	–0.25	44	2.5:1	80
4	DCA	1.29	49	1:1.2	58
5	DBA	1.48	48	1:1.1	66
6	2,4-DNBA	1.86	48	1:1.3	59
7	2-NBA	2.21	35	1:1.6	34
8	MCA	2.87	29	1:1.3	32

[a] Stereoselectivities determined by chiral GLC analysis. [b] Absolute and relative configuration assigned by correlation to the natural product.

A survey of a variety of solvents revealed that non-polar solvents complimented the use of more acidic co-catalysts, now producing a highly diastereoselective and enantioselective reacton (Table 5, entries 2–4).

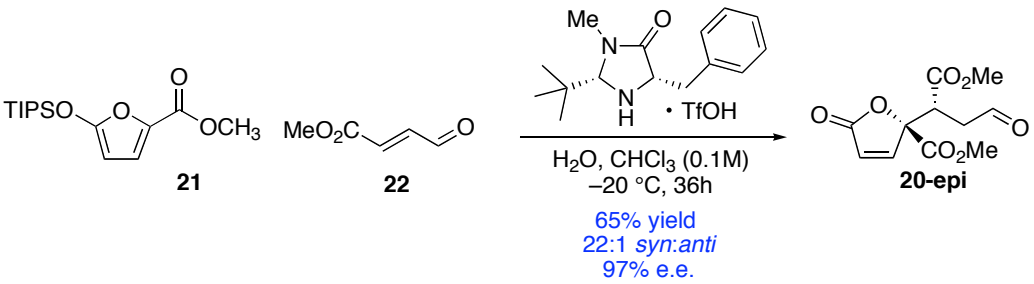
Table 5. Examination of solvent with triflic acid as the co-catalyst.



Entry	Solvent	conversion (%)	*syn*:*anti*	% ee[a,b]
1	CH_2Cl_2	69	5.2:1	86
2	$CHCl_3$	63	12.3:1	92
3	CCl_4	29	19.6:1	92
4	toluene	51	19.8:1	92
5	hexanes	24	5.1:1	78
6	pentanes	17	4.3:1	76
7	cyclohexane	20	8.3:1	81
8	THF	56	6.7:1	92
9	dioxane	64	14.5:1	92

[a] Stereoselectivities determined by chiral GLC analysis. [b] Absolute and relative configuration assigned by correlation to the natural product.

The optimal reaction parameters for the addition of furan **21** into methyl ester aldehyde **21** employ trifluoromethanesulfonic acid (TfOH) as the co-catalyst in chloroform. When the concentration of the system was decreased from 0.5M to 0.1M at –20 °C, the diastereoselectivity and enantioselectivity increased. These conditions ultimately provided an efficient reaction with superior levels of diastereo- and enantioselectivity (eq. 14).



(14)

iii. *Completion of 5-epi-spiculisporic acid.*

After the successful enantioselective synthesis of the vinylogous Michael adduct **20-epi**, completion of the synthesis required olefination of the aldehyde, hydrogenation of the olefins, and deprotection of the methyl esters to afford the natural product. Although the olefination seemed to be a straightforward proposal, initial studies showed that the olefination product was quite elusive. It appears that the aldehyde is in a sterically protected environment, as larger reagents like Wittig reagents (octyl or methyl) and Julia-Kocienski phenyl-sulfone reagents[28] were unsuccessful (Fig. 11).

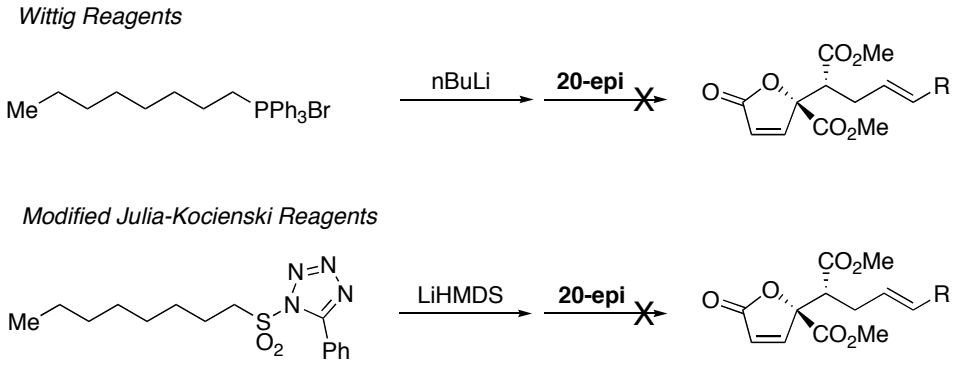


Figure 11. Unsuccessful strategies for olefination.

Takai and co-workers reported an olefination using 1,1-diiodoalkanes in the presence of chromium(II) to effect alkene formation.[29] 1,1-diiodooctane (**27**) was synthesized by literature procedure.[1] Takai olefination under standard conditions[30] gave desired product **28**, although the reaction was inefficient giving no more than 30% yields.

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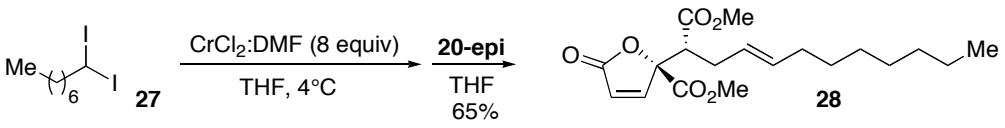
[28] Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett.* **1998**, 26.

[29] Okazoe, T.; Takai, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 953.

[30] (a) Martinez, A. G.; Alvarez, R. M.; Fraile, A. G.; Subramanian, L. R.; Hanack, M. *Synthesis* **1987**, 49. (b) Martinez, A. G.; Alvarez, R. M.; Gonzalez, S. M.; Subramanian, L. R.; Conrad, M. *Tetrahedron Lett.* **1992**, *33*, 2043.

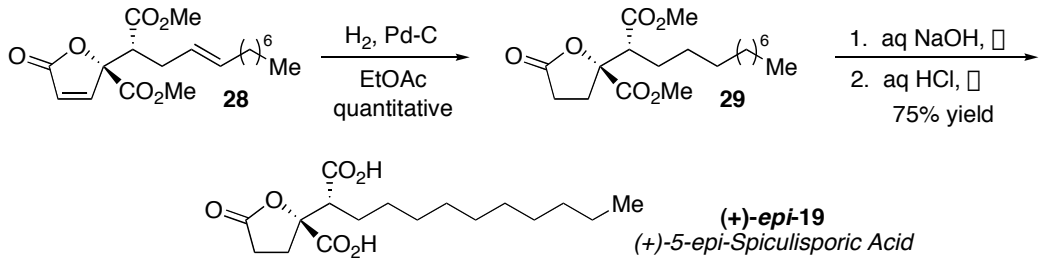
An increase in temperature and equivalents of chromium quickly revealed a more efficient system to afford the olefinated product **28** in a 65% isolated yield (eq. 15).



(15)

Completion of the synthesis is outlined in scheme 3. Hydrogenation of both olefins of butenolide **28** proceeded smoothly in ethyl acetate at room temperature to afford butanolide **29**. Finally, saponification of the esters in the system (including the butanolide) followed by selective reclosure of the butanolide under acidic conditions provided good yield of the product. However, the final product was determined to be (+)-5-*epi*-spiculisporic acid [***(+)-epi*-19**], as all of the characterization data was similar to the natural product, but significant differences in the chemical shifts in the ^{1}H and ^{13}C NMRs were observed.

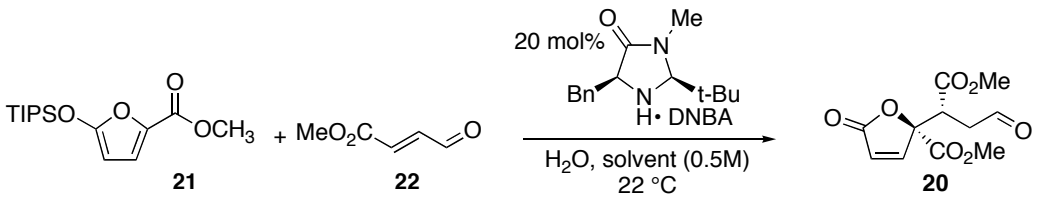
Scheme 3. Completion of (+)-5-*epi*-spiculisporic acid.



iv. *Reassessment of the Organocatalytic Step.*

In the initial synthesis of **20-epi**, it was demonstrated that the effect of the solvent on the diastereoselectivity of the reaction was critical (Table 6).

Table 6. Examination of solvents in the presence of weaker acidic co-catalysts.



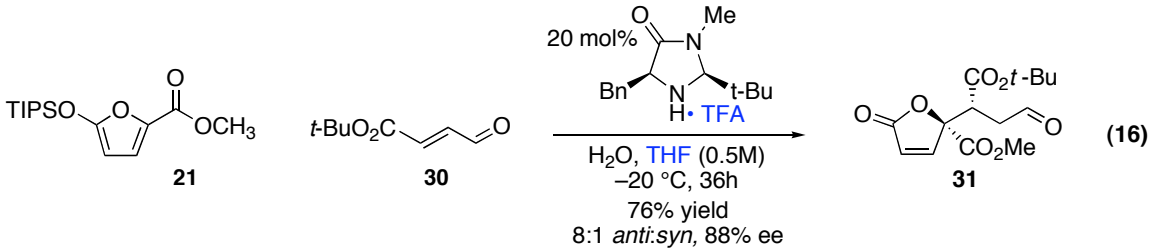
Entry	Solvent	conversion (%)	*anti*:*syn*	% ee[a,b]
1	CH_2Cl_2	30	1:1.3	33
2	$CHCl_3$	14	1:1.1	12
3	CCl_4	10	1:2.0	15
4	toluene	16	1:1.2	34
5	hexanes	4	1:1.4	41
6	pentanes	2	1:2.0	44
7	THF	31	2.0:1	28
8	dioxane	43	3.0:1	–3.2
9	CH_3CN	30	1.1:1	20
10	Et_2O	30	2.4:1	33
11	DMF	24	1:1.3	–11
12	MeOH	27	1.4:1	49
13	DMSO	15	1.5:1	–2.3
14	CH_3NO_2	41	1:1.3	53

[a] Stereoselectivities determined by chiral GLC analysis. [b] Absolute and relative configuration assigned by correlation to the natural product.

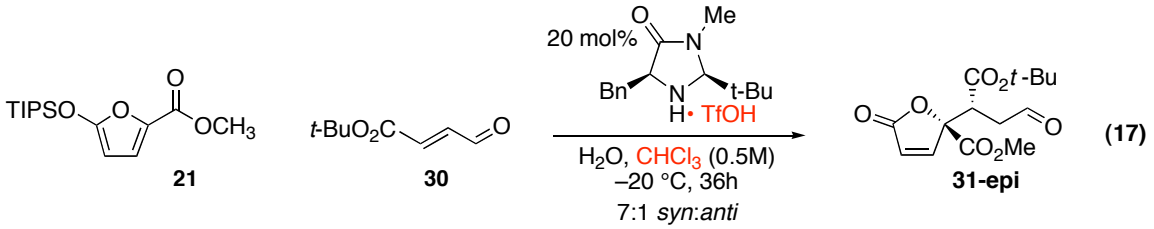
The opposite sense of diastereoinduction was obtained with reasonable enantioselectivities in the presense of weaker acids (Table 4, entries 4–8). After reexamining weaker acid co-catalysts under a variety of conditions, the diastereoselectivity in the *anti* direction remained poor. More polar solvents, however,

increased the bias toward the *anti* diastereomer while maintaining a noticeable level of enantioselectivity (Table 6, entries 7, 10, and 12, 2:1 to 3:1 *anti*:*syn*).

To test the effect of the steric contribution of the enal on the incoming trajectory of the nucleophile, the Michael acceptor was then changed from the methyl ester aldehyde **22** to the *tert*-butyl ester aldehyde **30**. The first reaction with enal **30** in THF with TFA as the co-catalyst gave the highest preference for the *anti* diastereomer seen thus far (eq. 16, 8:1 d.r.). Interestingly, under the previous optimal conditions, a 7:1 ratio of *syn* to *anti* was still observed (eq. 17). A postulated explanation of this is provided in section III of this chapter.



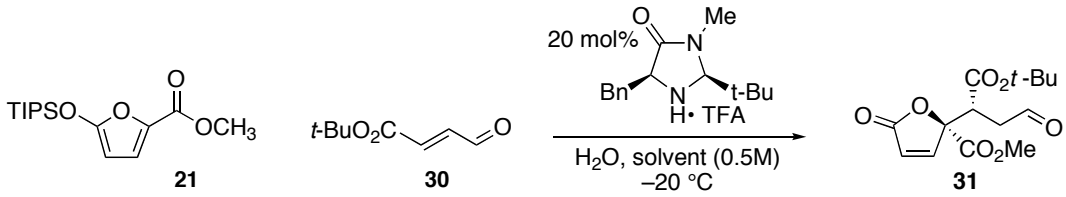
(16)



(17)

A solvent screen with enal **30** showed that while chlorinated solvents provided selectivity for the *syn* product (Table 7, entries 1 and 2), more polar solvents like THF and ether imparted high levels of *anti* selectivity (Table 7, entries 3 and 5).

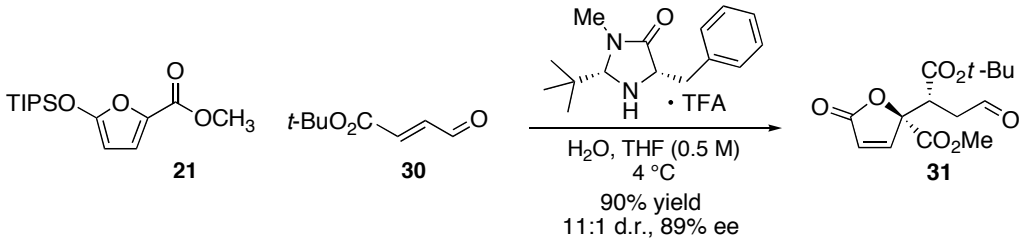
Table 7. Effect of polar solvents on diastereoselectivity of adduct 31.



Entry	Solvent	conversion (%)	*anti*:*syn*	% ee[a,b]
1	$CHCl_3$	34	1:2.5	35
2	CH_2Cl_2	49	1:1.1	40
3	**THF**	**50**	**9.4:1**	**86**
4	dioxane	23	5.7:1	87
5	Et_2O	43	8.2:1	83
6	CH_3CN	70	3.1:1	78
7	MeOH	44	4.5:1	84
8	EtOH	70	5.3:1	85
9	DMSO	29	3.3:1	65
10	H_2O	19	1.9:1	77

[a] Stereoselectivities determined by chiral GLC analysis. [b] Absolute and relative configuration assigned by correlation to the natural product.

The optimal conditions for the *anti* selective vinylogous Mukaiyama-Michael addition of siloxyfuran **21** are given in equation 18. After increasing the temperature and concentration of the reaction, the *anti* adduct **31** was isolated in a 90% yield with good levels of diastereo- and enantioselectivity (11:1 d.r., 89% ee).



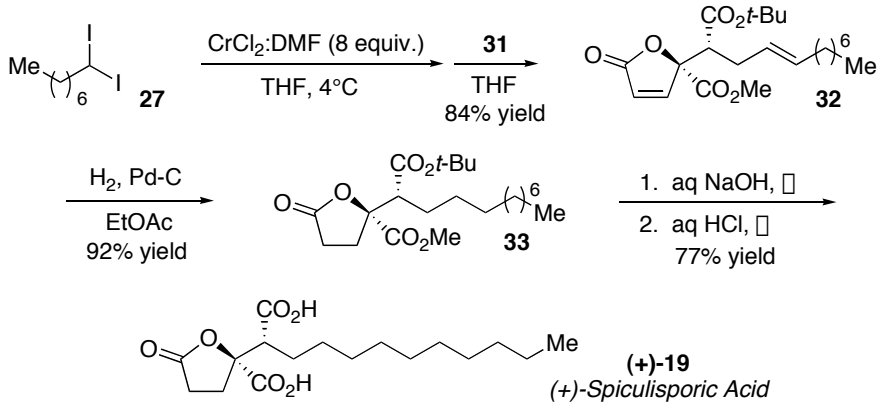
(18)

v. *Completion of spiculisporic acid.*

The remainder of the synthesis of spiculisporic acid was completed as described

above (*vide infra*). Takai olefination and hydrogenation was followed by saponification and acid-assisted reclosure of the butanolide to furnish the correct diastereomer of the natural product **(+)-19** (Scheme 4), with 54% overall yield for the five-step linear sequence. However, the optical rotation of the synthetic material was opposite to that observed for the natural product. Thus, the same sequence reported here was repeated with the opposite enantiomer of the imidazolidinone catalyst to prepare the matching enantiomeric series of (–)-spiculisporic acid.[31]

Scheme 4. Completion of (+)-spiculisporic acid.



IV. Proposed Explanation for the Change in Diastereoselectivity.

As shown in equations 14 and 18, by altering the conditions of the organocatalytic Mukaiyama-Michael reaction of siloxyfuran **21** into α,β-unsaturated aldehydes, the sense of diastereoinduction can be completely turned over to favor either the *anti* or *syn*

[31] The Supporting Information reports the enantiomeric series for (–)-spiculisporic acid (–)-5-*epi*-spiculisporic acid using (*S*,*S*)-*tert*-butyl benzyl imidazolidinone catalyst (*S*,*S*)-**14.**

diastereomer with high levels of enantioselectivity using a single enantiomer of the imidazolidinone catalyst **14**. It is impossible to aver the exact reason; however, a look at the different possible transition states may give insight for this diastereodivergence.

i. *Approach of the nucleophile onto the iminium system.*

It has been proposed in the literature that Mukaiyama-Michael additions onto an α,β-unsaturated system can occur through an open transition state, preferably through an antiperiplanar approach of the nucleophile.[2] As shown in figure 12, there are six possible approaches of siloxyfuran **21** onto the iminium system.

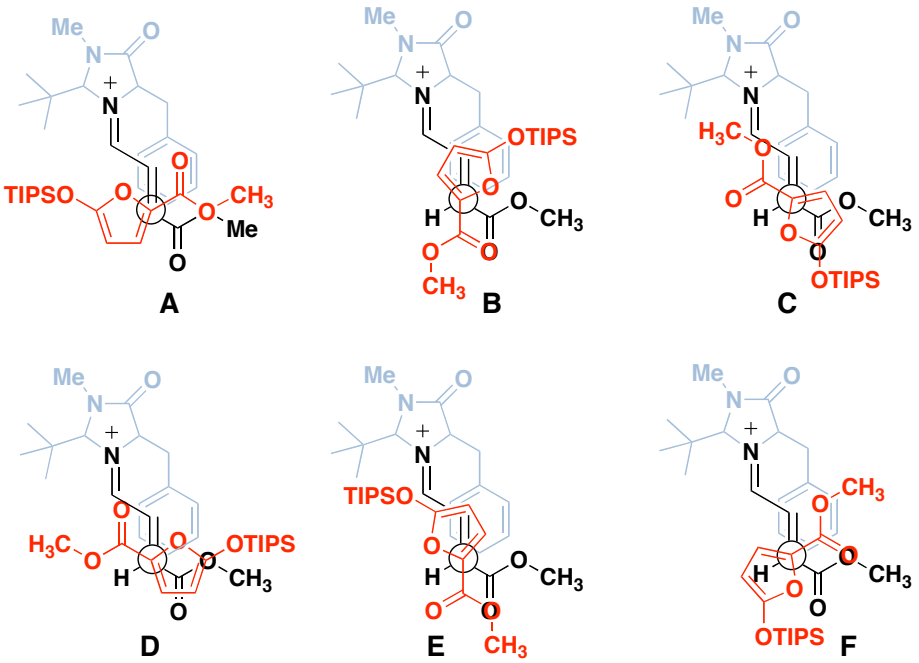
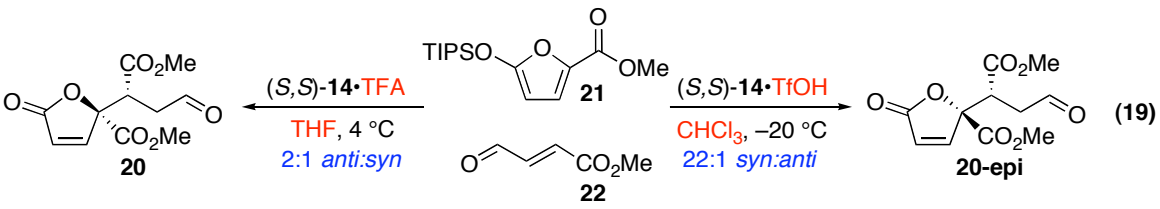


Figure 12. Possible transition states for organocatalytic Mukaiyama-Michael.

Transition states **A**–**C** will provide the *syn* diastereomer of the butenolide adduct while **D**–**F** provide the *anti* diastereomer. The furan moiety may prefer to be oriented over the hydrogen of the enal in order to avoid a steric interaction in the transition state. This would suggest that transition states **A** and **F** could be contributing to the preferred orientation. For the following analyses of each reaction under both sets of optimized conditions (TfOH/$CHCl_3$ or TFA/THF), only transition states like **A** and **F** will be presented.

ii. *Mukaiyama-Michael into methyl-4-oxobutenoate (22).*



As shown in equation 19, the addition of siloxyfuran **21** proceeded with excellent levels of diastereocontrol to favor the *syn* product **20-epi B** (22:1 *syn*:*anti*). When a less acidic co-catalyst was employed in combination with a more polar solvent, the *anti* diastereomer **20** was slightly favored (2:1 *anti*:*syn*).

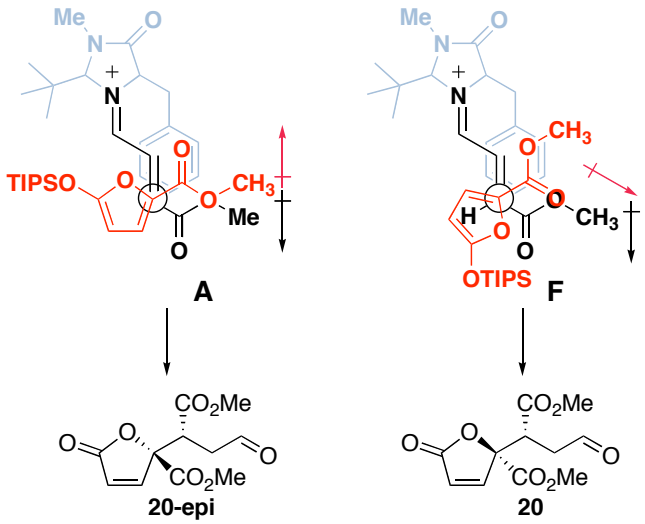
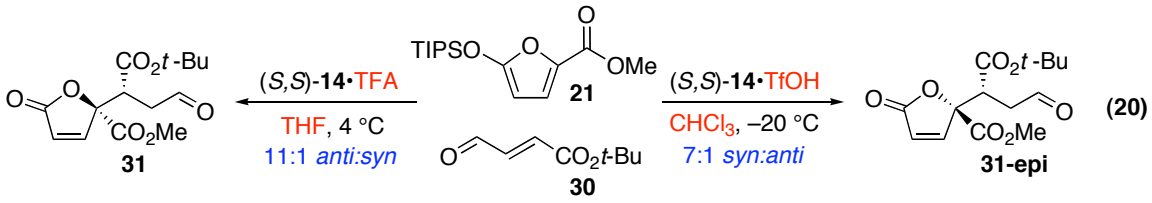


Figure 13. Dipole interactions in the transition state.

Transition state **A** (Fig. 13) may be preferred because it (i) minimizes steric interactions, (ii) has the nucleophile arranged in an antiperiplanar fashion onto the iminium, and (iii) minimizes the net dipole of the siloxyfuran (Fig. 12, red dipole arrow) and the iminium (Fig. 12, black dipole arrow). A non-polar solvent should reinforce this propensity to minimize the dipoles, whereas a more polar solvent should be more accommodating to a net charge. It is hypothesized that the non-polar solvent $CHCl_3$ favors transition state **A**, thus explaining the formation of the *syn* product **20-epi** with high diastereoinduction (eq. 19). A more polar solvent like THF, meanwhile, could provide stabilization for transition state **F**, thus resulting in a slight preference for the *anti* product **20** that is observed.

iii. *Mukaiyama-Michael into tert-butyl-4-oxobutenoate (30).*



(20)

As shown in equation 20, the addition of siloxyfuran **21** to *tert*-butyl enal **30** proceeded with moderate levels of diastereocontrol to deliver the *syn* product **31-epi** when a TfOH/$CHCl_3$ co-catalyst/solvent combination was used (7:1 *syn*:*anti*). The same conditions with the methyl ester enal **22** provided a much larger preference for the *syn* product (eq. 19, 22:1 *syn*:*anti*). Conversely, when a less acidic co-catalyst was employed with a more polar solvent, the *anti* diastereomer **20** was now favored with good levels of diastereoselectivity (eq. 20, 11 to 1 *anti*:*syn*).

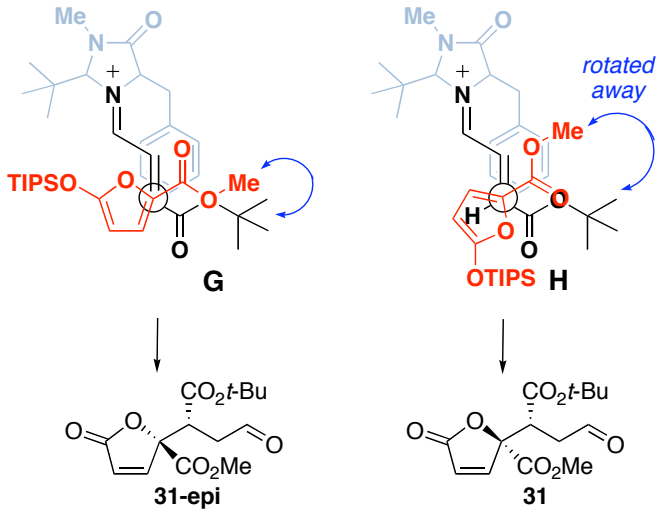
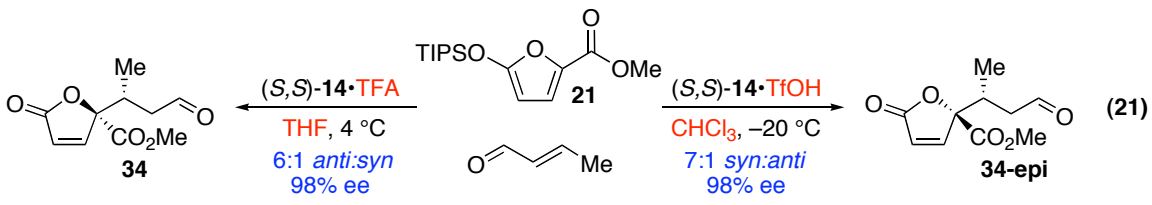


Figure 14. Transition state with *tert*-butyl-4-oxobutenoate (30).

While transition state **G** in figure 14 positions the furan over the empty quadrant of the iminium ion in an antiperiplanar orientation, the increased steric bulk of the *tert*-butyl group of the ester of the enal **30** may introduce an unfavorable interaction with the methyl ester of siloxyfuran **21**. This interaction could alter the nucleophile to approach via transition state **H** in order to minimize steric interaction between the methyl and *tert*-butyl ester groups.

iv. *Mukaiyama-Michael into crotonaldehyde.*

In order to test the hypothesis that the transition state for the Mukaiyama-Michael addition of this specific siloxyfuran **21** is influenced by the dipole interactions of the reaction partners, the 1,4-vinylogous Mukaiyama-Michael addition of nucleophile **21** into crotonaldehyde was performed (eq. 21).



The developed conditions provided offer access to both diastereomers of the butenolide products (**34** and **34-epi**, 6:1 and 1:7 *anti*:*syn*).

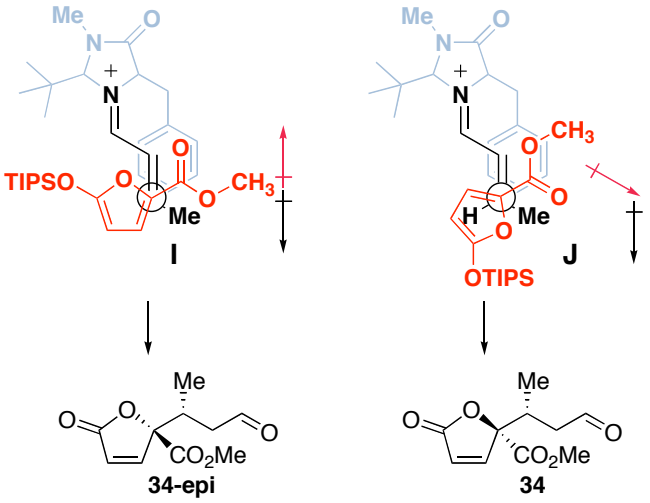


Figure 15. Electronic contributions to the transition state.

Transition state **I** (Fig. 15) could be favored in a non-polar solvent like $CHCl_3$ in order to minimize the dipole interactions of the transition state. THF may proceed through transition state **J** because it can accommodate this net charge, thus giving the *anti* product. Because these two reactions in equation 21 do not differ with respect to the steric demands of the enal, this may suggest that electronic contributions to the Mukaiyama-Michael reaction may help to control the diastereoselection of the reaction.

Interestingly, when the methyl ester group on the furan was replaced with a methyl group and subjected to the optimized $TfOH/CHCl_3$ or TFA/THF conditions, the reaction offered no sense of diastereocontrol (Fig. 16). This makes the 5-methyl ester siloxyfuran **21**a unique substrate for the organocatalytic Mukaiyama-Michael addition

due to its ability to provide access to either the *anti* or *syn* butenolide products with excellent levels of diastereo- and enantioselectivity using a single catalyst.

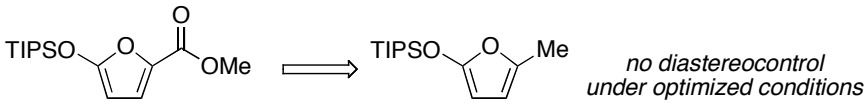


Figure 16. 5-Methyl ester versus 5-methyl siloxyfuran.

v. *Another transition state consideration.*

In a recent study, Houk and co-workers calculated the relative energies of the transition structures for the organocatalytic conjugate additions of pyrroles and indoles into an α,β-unsaturated iminium system.[32] When pyrrole was employed as a β-donor, it preferably reacted through a closed Diels-Alder-like transition state with an *endo* or *exo* orientation; these two transition structures had a small energetic difference of 0.3 kcal/mol.

It is possible that a Diels-Alder-like geometry may be operative in the organocatalytic vinylogous Mukaiyama-Michael reaction. The analogous transitions states for the conjugate addition of siloxyfuran **21** are illustrated in figure 17. The *endo* orientation leads to **34-epi**, which was observed when the TfOH/$CHCl_3$ co-catalyst/solvent combination was used, and the *exo* orientation leads to **34**, which was

[32] Gordillo, R.; Carter, J.; Houk, K. N. *Adv. Synth. Cat.* **2004**, *346*, 1175.

observed under the TFA/THF conditions. The reason for co-catalyst/solvent-mediation of either transitions state structure is indeterminable.

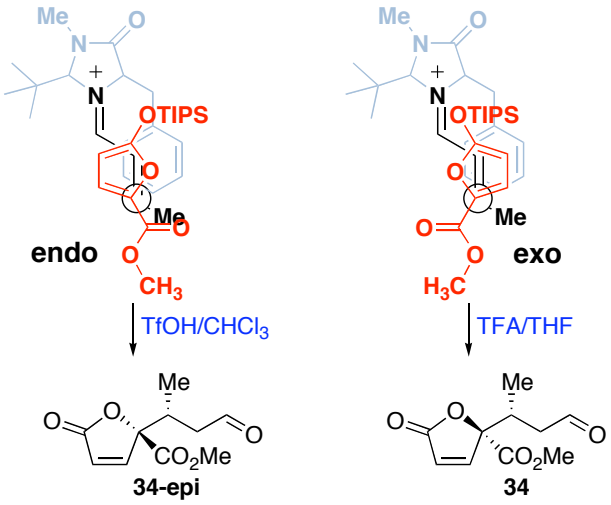


Figure 17. Possible endo and exo transition states.

Conclusion

In summary, this work further demonstrates the value of iminium catalysis in asymmetric synthesis. The first enantioselective organocatalytic vinylogous Mukaiyama-Michael addition using simple a,b-unsaturated aldehydes is presented herein. This novel methodology was highlighted with the total syntheses of spiculisporic acid (**19**) and its diastereomer 5-*epi*-spiculisporic acid (**19-epi**). While the natural *anti* diastereomer **19** is abundant in nature, its epimer **19-epi** is a butanolide that is not readily available via fermentation protocols or derivatization of the naturally occurring metabolite. The use of organocatalysis to access both diastereomers of the natural procuct in a rapid manner makes this the most efficient enantioselective syntheses of these natural products to date.

Supporting Information.

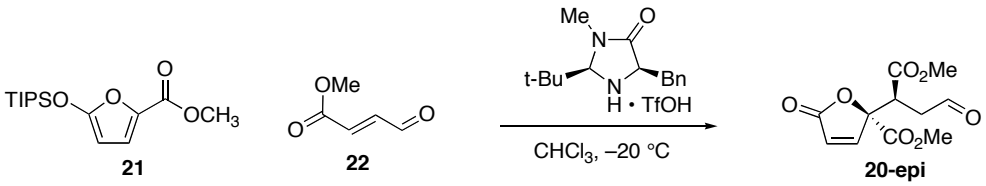
General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[33] Non-aqueous reagents were transferred under nitrogen via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method of Still.[34] 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 $KMnO_4$ stain.

^1H 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_6D_6 = 7.16 ppm, D_6-acetone = 2.05 ppm). Data for ^1H NMR are reported as follows: chemical shift (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. 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 chromatography (GC) was performed on Hewlett-Packard 6850 and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detector using a Bodman Chiraldex -DM

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

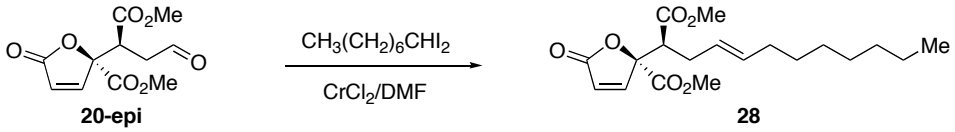
[34]Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978,** *43*, 2923.

(30 m x 0.25 mm) column. High pressure liquid chromatography (HPLC) was performed on Hewlett-Packard 1100 Series chromatographs using either a Chiralcel OD-H column (25 cm) and OD guard (5 cm) or a Chiralcel AD column (25 cm) and AD 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.



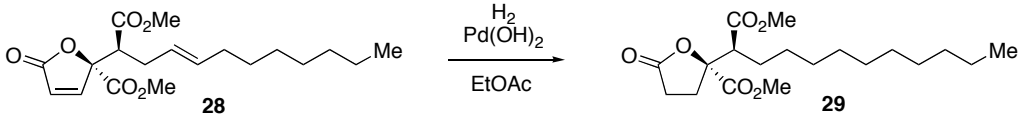
(*2R,1'R*)-2-(1'-Methoxycarbonyl-3'-oxo-propyl)-5-oxo-2,5-dihydrofuran-2-carboxylic acid methyl ester (20-epi). 4-Oxobut-2-enoic acid methyl ester (**22**) (574 mg, 5.03 mmol) was added to a stirring solution of (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one [**(*S,S*)-14**] (82.6 mg, 0.335 mmol), trifluoromethanesulfonic acid (30 μL, 0.335 mmol), and distilled water (60 μL, 3.35 mmol) in $CHCl_3$ (16.8 mL, 0.1 M) at room temperature. The reaction mixture was cooled to –20 ˚C. 5-Triisopropylsilanyloxy-furan-2-carboxylic acid methyl ester (**21**) (500 mg, 1.68 mmol) was added in 1 mL $CHCl_3$. The reaction mixture was stirred for 40 h, filtered over a silica plug, and concentrated. After silica gel chromatography, aldehyde **20-epi** was isolated as a pale yellow solid after reconcentration from hexanes (278 mg, 65% yield, 22:1 d.r., 97% e.e.). IR (film): 3103, 2956, 2849, 1783, 1739, 1603, 1437, 1247, 1189, 1086, 1031, 917.8, 820.2 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (s, 1H, C**H**O), 7.48 (d, *J* = 5.4 Hz, 1H, CH=C**H**), 6.20 (d, *J* = 5.4 Hz, 1H, C**H**=CH), 3.94 (dd, *J* = 7.2, 4.8 Hz, 1H, C**H**CO_2CH_3), 3.80 (s, 3H, $CO_2C\mathbf{H_3}$), 3.73 (s, 3H, $CO_2C\mathbf{H_3}$), 3.11 (dd, *J* = 19.2, 7.5

Hz, 1H, CH**H**-CHO), 2.55 (dd, *J* = 18.6, 4.8 Hz, 1H, C**H**H-CHO); ^{13}C NMR (75 MHz, $CDCl_3$) □ 198.1, 170.5, 169.4, 166.9, 153.8, 122.9, 88.9, 53.8, 53.3, 43.5, 39.9; HRMS (EI+) exact mass calculated for ($C_{11}H_{12}O_7$) requires *m/z* 256.0583, found *m/z* 256.0576. [□]$_D$ = –124.0 (c = 0.97, $CHCl_3$). The enantiomeric ratio was determined by GLC analysis of the aldehyde using a Bodman Chiraldex □-TA (155 ˚C, 1.0 mL/min); *(2R,1'R)* isomer t_r = 62.8 min, *(2S,1'S)* isomer t_r = 58.4 min, minor *(2S,1'R)* and *(2R, 1'S)* isomers t_r = 53.4, 55.0 min.



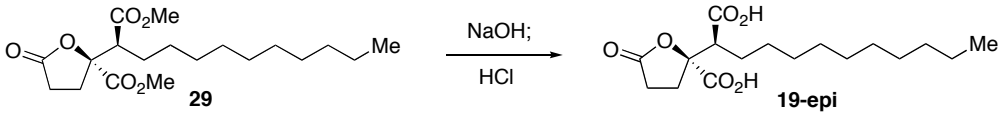
(*2R,1'R*)-2-(1'-Methoxycarbonyl-undec-3'-enyl)-5-oxo-2,5-dihydrofuran-2-carboxylic acid methyl ester (28). Chromous chloride (383 mg, 3.12 mmol) and *N,N*-dimethyl formamide (243 □L, 3.12 mmol) were stirred in anhydrous THF (7.8 mL) under an N_2 atmosphere at room temperature for 1 h to generate the $CrCl_2$:DMF complex. 1,1-Diiodooctane (287 mg, 0.780 mmol) and aldehyde **20-epi** (100 mg, 0.390 mmol) were added in 1.3 mL of anhydrous THF . TLC analysis showed consumption of the aldehyde after 3.5 h. The reaction was quenched with H_2O and the aqueous layer was extracted three times with pentanes. The pentane layers were dried (Na_2SO_4) and concentrated. Undecenyl methyl ester **28** was afforded as a white solid after silica gel chromatography (77 mg, 65% yield). IR (film): 2956, 2922, 2852, 1777, 1742, 1724, 1439, 1260, 1186, 1101, 968.8, 916.5, 833.0 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.25 (d, *J* = 5.4 Hz, 1H, C**H**=CH), 6.00 (d, *J* = 5.4 Hz, 1H, CH=C**H**), 5.22 (dt, *J* = 15.3, 6.6 Hz, 1H, CH_2C**H**=CHCH_2), 5.09 (dt, *J* = 15.3, 6.6 Hz, 1H, CH_2CH=C**H**CH_2), 3.58 (s, 3H,

CO_2CH_3), 3.50 (s, 3H, CO_2CH_3), 3.12 (dd, *J* = 8.1, 4.8 Hz, 1H, $CHCO_2CH_3$), 2.18 (m, 1H, $CHHCH{=}CH$), 2.03 (m, 1H, $CHHCH{=}CH$), 1.73 (dt, *J* = 6.9, 6.0 Hz, 2H, $CH{=}CHCH_2$), 1.03 (m, 10H, $(CH_2)_5$), 0.66 (t, 3H, *J* = 6.6 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) □ 170.8, 170.2, 167.4, 153.3, 134.5, 125.3, 122.8, 89.6, 53.7, 52.5, 50.1, 32.7, 32.0, 29.5, 29.4, 29.3, 29.3, 22.9, 14.3; HRMS (EI/CH_4) exact mass calculated for ($C_{19}H_{28}O_6$) requires *m/z* 352.1886, found *m/z* 352.1881. $[\square]_D$ = –70.0 (c = 1.0, $CHCl_3$).

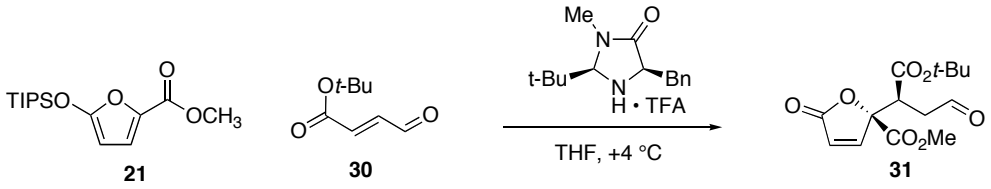


(*2R,1'R*)-2-(1'-Methoxycarbonyl-undecyl)-5-oxo-tetrahydrofuran-2-carboxylic acid methyl ester (29). A 25 mL round bottom flask equipped with a magnetic stir bar and containing undecenyl methyl ester **28** (100 mg, 0.284 mmol) and activated palladium on carbon (10 mg) was charged with EtOAc (2.8 mL, 0.1 M). The system was evacuated and purged with H_2 gas three times. The reaction was stirred at ambient temperature under a hydrogen atmosphere until TLC analysis showed the reaction complete after 4.5 h, at which point the reaction mixture was filtered over a pad of Celite and a pad of silica gel with EtOAc to afford (–)-epi-spiculisporic acid methyl ester **29** as a clear oil after concentration (101 mg, quantative yield). IR (film): 2955, 2926, 2855, 1796, 1740, 1456, 1436, 1269, 1230, 1165, 1060, 985.5, 896.9 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) □ 3.79 (s, 3H, CO_2CH_3), 3.70 (s, 3H, CO_2CH_3), 3.11 (dd, *J* = 10.8, 3.3 Hz, 1H, $CHCO_2CH_3$), 2.60 (m, 4H, $CH_2CH_2CO_2$), 1.77 (m, 1H, $CHCHH(CH_2)_8$), 1.56 (m, 1H, $CHCHH(CH_2)_8$), 1.25 (m, 16H, $(CH_2)_8$), 0.87 (t, 3H, *J* = 6.6 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) □ 175.3, 172.2, 170.6, 86.5, 60.7, 53.5, 52.3, 50.4, 32.1, 29.8, 29.8, 29.6,

29.6, 28.2, 28.1, 27.5, 27.3, 23.0, 14.4; HRMS (EI/CH_4) exact mass calculated for $(C_{19}H_{33}O_6)^+$ requires *m/z* 357.2277, found *m/z* 357.2273. $[\alpha]_D$ = +10.3 (c = 1.0, $CHCl_3$).

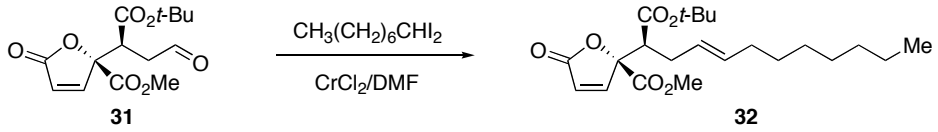


(–)-Epi-spiculisporic acid (19-epi). Dimethyl ester **29** (28.7 mg, 0.0805 mmol) was taken up in 0.5 mL THF and 1 mL of 4N aqueous NaOH. The biphasic mixture was refluxed at 100 ˚C for 5.5 h and then cooled to room temperature. The reaction mixture was acidified with 1N aqueous HCl to pH=1. The aqueous layer was extracted four times with EtOAc. The organic layers were concentrated to a white solid. The hydrolyzed intermediate was dissolved in a small amount of THF and 2 mL of 1N aqueous HCl was added. The reaction mixture was refluxed at 100 ˚C for 3.5 h, after which it was cooled to room temperature and extracted four times with EtOAc. The organic layers were dried (Na_2SO_4) and recrystallized from hot water to yield (–)-epi-spiculisporic acid **19-epi** as a white solid (20 mg, 76% yield). IR (film): 2917, 2850, 1801, 1709, 1466, 1420, 1182, 1133, 1055, 953.8 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 3.03 (dd, *J* = 9.3, 4.2 Hz, 1H, C**H**CO_2H), 2.57 (m, 4H, C$\mathbf{H_2}$C$\mathbf{H_2}$$CO_2$C), 1.66 (m, 2H, CHC$\mathbf{H_2}$$(CH_2)_8$), 1.30 (m, 16H, $(C\mathbf{H_2})_\mathbf{8}$), 0.90 (t, *J* = 6.6 Hz, 3H, $CH_2C\mathbf{H_3}$); ^{13}C NMR (75 MHz, CD_3OD) δ 178.4, 175.4, 173.8, 88.0, 51.9, 33.3, 30.9, 30.9, 30.7, 30.7, 30.7, 29.5, 29.1, 29.0, 28.3, 24.0, 14.7; HRMS (FAB+) exact mass calculated for $(C_{17}H_{29}O_6)^+$ requires *m/z* 329.1964, found *m/z* 329.1962. $[\alpha]_D$ = –6.3(c = 0.75, EtOH).



(*2S,1'R*)-2-(1'-*tert*-Butoxycarbonyl-3'-oxo-propyl)-5-oxo-2,5-dihydrofuran-2-carboxylic acid methyl ester (31). 4-Oxobut-2-enoic acid *tert*-butyl ester (**30**) (469 mg, 3.00 mmol) was added to a stirring solution of the (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one TFA salt [**(*S,S*)-14**] (72.3 mg, 0.200 mmol), and distilled water (36 μL, 2.00 mmol) in THF (8 mL) at room temperature. The reaction mixture was cooled to 4 ˚C. 5-Triisopropylsilanyloxy-furan-2-carboxylic acid methyl ester (**21**) (300 mg, 1.01 mmol) was added in 2 mL of THF. The reaction mixture was stirred at 4 ˚C for 43 h, filtered over a pad of silica gel, and concentrated. After silica gel chromatography, aldehyde **31** was isolated as a yellow solid after reconcentration from hexanes (268 mg, 90% yield, 11:1 d.r., 89% e.e.). IR (film): 2918, 2852, 1775, 1733, 1720, 1458, 1366, 1239, 1145, 1108, 1021, 828.8 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.69 (s, 1H, C**H**O), 7.60 (d, *J* = 5.7 Hz, 1H, CH=C**H**), 6.17 (d, *J* = 6.3 Hz, 1H, C**H**=CH), 3.81 (dd, *J* = 9.9, 4.5 Hz, 1H, C**H**$CO_2C(CH_3)_3$), 3.79 (s, 3H, $CO_2C\mathbf{H_3}$), 2.92 (dd, *J* = 18.0, 9.3 Hz, 1H, CH**H**-CHO), 2.58 (dd, *J* = 18.6, 3.9 Hz, 1H, C**H**H-CHO), 1.39 (s, 9H, $C(C\mathbf{H_3})_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 170.5, 168.0, 166.8, 153.9, 122.3, 88.6, 83.4, 54.0, 45.0, 40.8, 28.0 (3); HRMS (CI) exact mass calculated for ($C_{14}H_{19}O_7$) requires *m/z* 299.1131, found *m/z* 299.1121. $[\alpha]_D$ = +9.9 (c = 0.95, $CHCl_3$). The diastereomeric ratio was determined by GLC analysis of the aldehyde using a Bodman Chiraldex Γ-TA (170 ˚C,

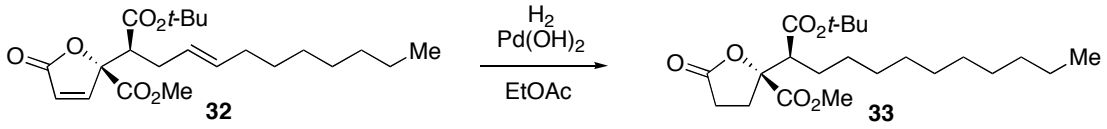
1.0 mL/min); *(2S,1'R)/(2R,1'S)* isomers t_r= 28.2 min, *(2S,1'S)/(2R,1'R)* isomers t_r=30.3 min. The enantiomeric ratio was determined by HPLC analysis of the 2,2-dimethylpropane acetal, obtained by acetal formation of the aldehyde with 2,2-dimethylpropane diol and paratoluenesulfonic acid, using a Chiralcel OD-H and OD-H guard column (1.5% ethanol/hexanes, 214 nm, 1.0 mL/min); *(2S,1'R)* isomer t_r = 19.6 min, *(2R,1'S)* isomer t_r = 16.6 min.



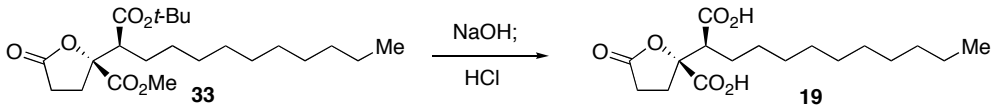
31 **32**

(*2S,1'R*)-2-(1'-*tert*-Butoxycarbonyl-undec-3'-enyl)-5-oxo-2,5-dihydrofuran-2-carboxylic acid methyl ester (32). Chromous chloride (383 mg, 3.12 mmol) and *N,N*-dimethyl formamide (243 μL, 3.12 mmol) were stirred in anhydrous THF (7.8 mL) under an N_2 atmosphere at room temperature for 1 h to generate the $CrCl_2$:DMF complex. 1,1-Diiodooctane (287 mg, 0.780 mmol) and aldehyde **31** (100 mg, 0.390 mmol) were added in 1.3 mL of anhydrous THF. TLC analysis showed consumption of the aldehyde after 3.5 h. The reaction was quenched with H_2O and the aqueous layer was extracted three times with pentanes. The pentane layers were dried (Na_2SO_4) and concentrated. Undecenyl methyl ester **32** was afforded as a white solid after silica gel chromatography (77 mg, 65% yield). IR (film): 2956, 2928, 2856, 1783, 1740, 1723, 1457, 1437, 1369, 1256, 1156, 1099 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 5.4 Hz, 1H, C**H**=CH), 6.18 (d, *J* = 5.4 Hz, 1H, CH=C**H**), 5.46 (dt, *J* = 15.3, 6.6 Hz, 1H, CH_2C**H**=$CHCH_2$), 5.25 (dt, *J* = 15.6, 6.6 Hz, 1H, CH_2CH=C**H**CH_2), 3.77 (s, 3H, CO_2C**H**$_3$), 3.21 (dd, *J* = 9.6, 4.8 Hz, 1H, C**H**$CO_2C(CH_3)_3$), 2.20 (m, 2HC**H**$_2$CH=CH), 1.94 (dt, *J* =6.6, 6.0 Hz, 2H,

CH=CHC**H**$_2$), 1.41 (s, 9H, $CO_2C(C\mathbf{H}_3)_3$), 1.24 (m, 10H, $(C\mathbf{H}_2)_5$), 0.87 (t, J = 6.6 Hz, 3H, $CH_2C\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 169.7, 167.2, 153.7, 134.5, 124.9, 122.7, 89.4, 82.3, 53.7, 51.2, 32.8, 32.1, 30.7, 29.5, 29.4, 28.2 (3), 23.0, 14.4; HRMS (CI) exact mass calculated for $(C_{22}H_{35}O_6)^+$ requires m/z 395.2433, found m/z 395.2428. $[\alpha]_D$ = –3.9 (c = 0.98, $CHCl_3$).



(*2S,1'R*)-2-(1'-*tert*-Butoxycarbonyl-undecyl)-5-oxo-tetrahydrofuran-2-carboxylic acid methyl ester (33). A 25 mL round bottom flask equipped with a magnetic stir bar and containing undecenyl *tert*-butyl ester **32** (100 mg, 0.284 mmol) and activated palladium on carbon (10 mg) was charged with EtOAc (2.8 mL, 0.1M). The system was evacuated and purged with H_2 gas three times. TLC analysis showed the reaction complete after 4.5 h, at which point the reaction mixture was filtered over a pad of Celite and a pad of silica gel with EtOAc to afford (–)-epi-spiculisporic acid methyl ester **33** as a clear oil after concentration (94.0 mg, 92% yield). IR (film): 2957, 2927, 2855, 1797, 1744, 1731, 1460, 1369, 1249, 1169, 1132, 1055 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 3H, $CO_2C\mathbf{H}_3$), 2.94 (dd, J = 10.8, 3.0 Hz, 1H, $C\mathbf{H}CO_2C(CH_3)_3$), 2.50 (m, 4H, $C\mathbf{H}_2C\mathbf{H}_2CO_2C$), 1.73 (m, 1H, $CHC\mathbf{H}H(CH_2)_8$), 1.47 (m, 1H, $CHCH\mathbf{H}(CH_2)_8$), 1.43 (s, 9H, $CO_2C(C\mathbf{H}_3)_3$), 1.23 (m, 16H, $(C\mathbf{H}_2)_8$), 0.85 (t, J = 6.6 Hz, 3H, $CH_2C\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 171.1, 170.8, 86.7, 81.9, 53.2, 51.9, 32.1, 29.8, 29.8, 29.6, 29.6, 29.5, 28.4, 28.3, 28.2 (3), 22.9, 14.4; HRMS (CI) exact mass calculated for $(C_{22}H_{39}O_6)^+$ requires m/z 399.2746, found m/z 399.2736. $[\alpha]_D$ = –21.4 (c = 1.1, $CHCl_3$).



(–)-Spiculisporic acid (19). *tert*-Butyl ester **33** (28.7 mg, 0.0805 mmol) was taken up in 0.5 mL THF and 1 mL of 4N aqueous NaOH. The biphasic mixture was refluxed at 100 ˚C for 5.5 h and then cooled to room temperature. The reaction mixture was acidified with 1N aqueous HCl to pH=1. The aqueous layer was extracted four times with EtOAc. The organic layers were concentrated to a white solid. The hydrolyzed intermediate was dissolved in a small amount of THF and 2 mL of 1N aqueous HCl was added. The reaction mixture was refluxed at 100 ˚C for 3.5 h, after which it was cooled to room temperature and extracted four times with EtOAc. The organic layers were dried (Na_2SO_4) and recrystallized from hot water to yield the title compound **19** as white crystals (20 mg, 76% yield). IR (film): 2919, 2850, 1793, 1778, 1716, 1654, 1559, 1540, 1510, 1458, 1419, 1290, 1182, 927.3 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) □ 3.01 (dd, *J* = 10.8, 2.7 Hz, 11H, C**H**CO_2H), 2.53 (m, 4H, C$\mathbf{H_2}$C$\mathbf{H_2}$$CO_2$C), 1.85 (m, 1H, CHC**H**H$(CH_2)_8$), 1.52 (m, 1H, CHCH**H**$(CH_2)_8$), 1.29 (m, 16H, (C$\mathbf{H_2}$)$_\mathbf{8}$), 0.90 (t, *J* = 6.6 Hz, 3H, CH_2C$\mathbf{H_3}$); ^{13}C NMR (75 MHz, CD_3OD_3) □ 178.3, 175.3, 173.9, 88.1, 52.5, 33.3, 30.9, 30.8, 30.8, 30.7, 30.6, 30.5, 29.2, 29.0, 29.0, 23.9, 14.7; HRMS (FAB+) exact mass calculated for $(C_{17}H_{29}O_6)^+$ requires *m/z* 329.1964, found *m/z* 329.1965. $[□]_D$ = -10.9 (c = 0.43, EtOH). Commercial (–)-spiculisporic acid: $[□]_D$ = –10.2 (c = 1.0, EtOH). ^{1}H, ^{13}C, and IR spectra of synthetic **19** were identical to the natural spiculisporic acid.

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 □g/mL). In fact, all of the cyclophanes have an IC_{50} between 0.5–5.0 □g/mL but they are not selective for human solid tumor cell lines in the Corbett assay.[2] The structurally similar chlorinated nostocyclophanes[3] were found to be the major cytotoxic component of *Nostoclickia* (Fig. 1).

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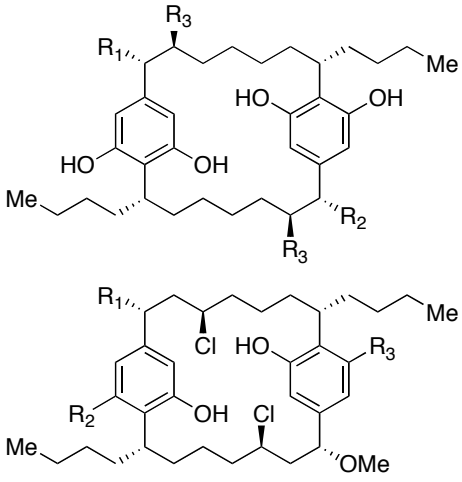
[1] Moore, B. S.; Chen, J.-L.; Patterson, G. M.; Moore, R. M.; Brinen, L. S.; Kato, Y.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 4061.

[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.



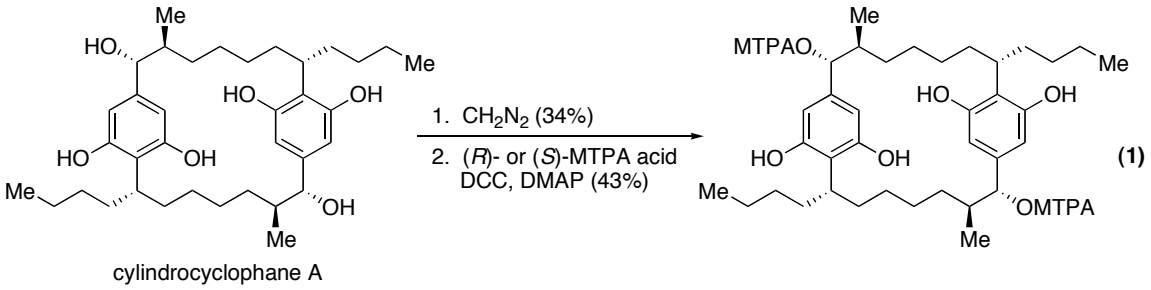
		R_1	R_2	R_3
Cylindrocyclophanes	**A**	OH	OH	Me
	B	OH	OAc	Me
	C	OH	H	Me
	D	OAc	OAc	Me
	E	OAc	H	Me
	F	H	H	Me

Nostocyclophane	**A**	OMe	□-D-glu	□-D-glu
	B	OMe	OH	□-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.

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



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]

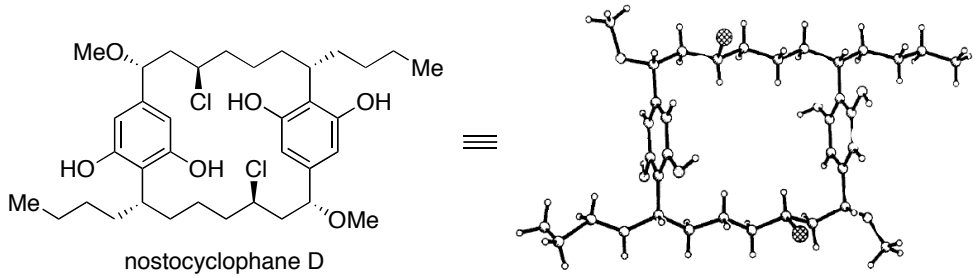


Figure 2. X-ray structure of nostocyclophane D.

ii. *Proposed biosynthesis of the cylindrocyclophanes*

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

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[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.

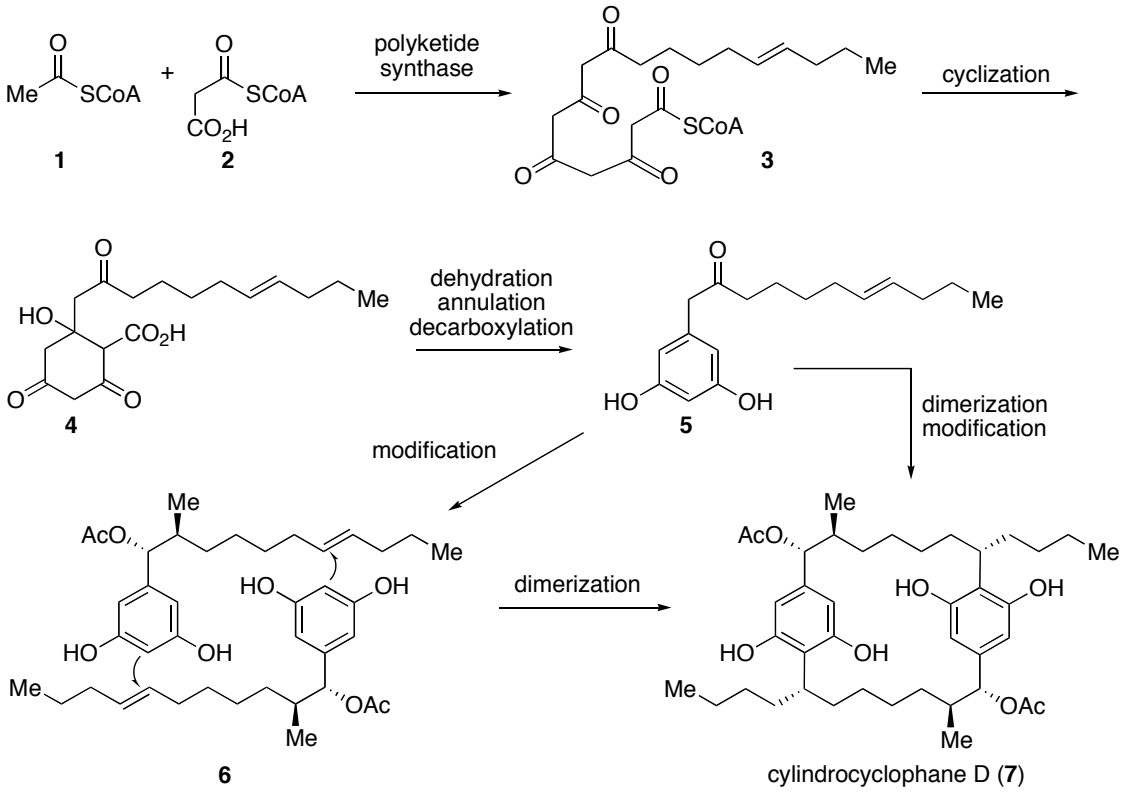

Figure 3. Proposed biosynthetic pathway.

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

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[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.

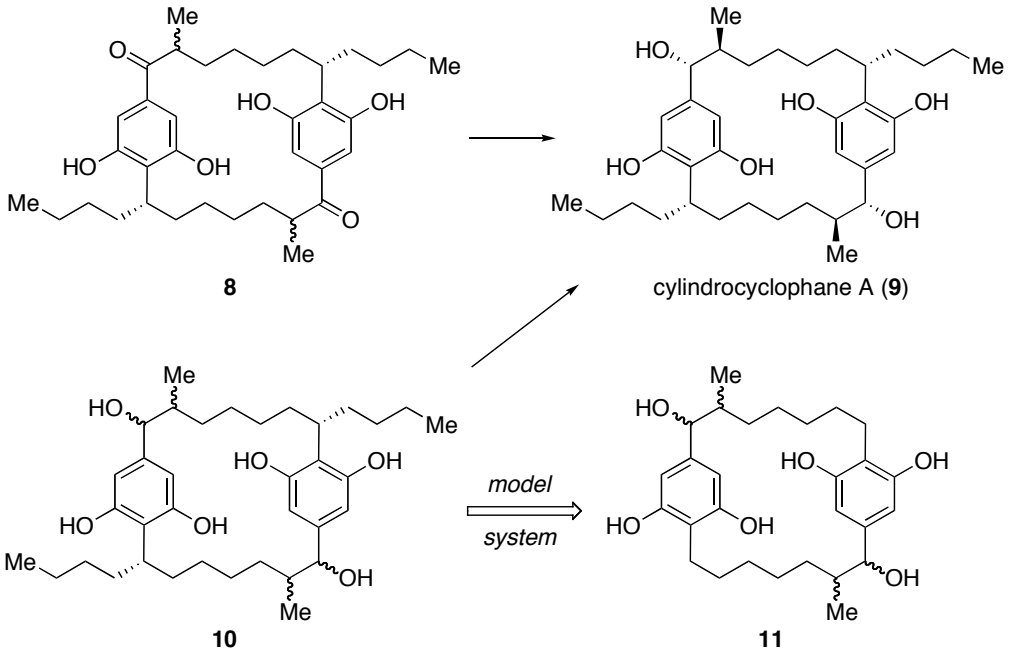


Figure 4. Albizati's equilibration hypothesis for the cylindrocyclophanes.

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**.

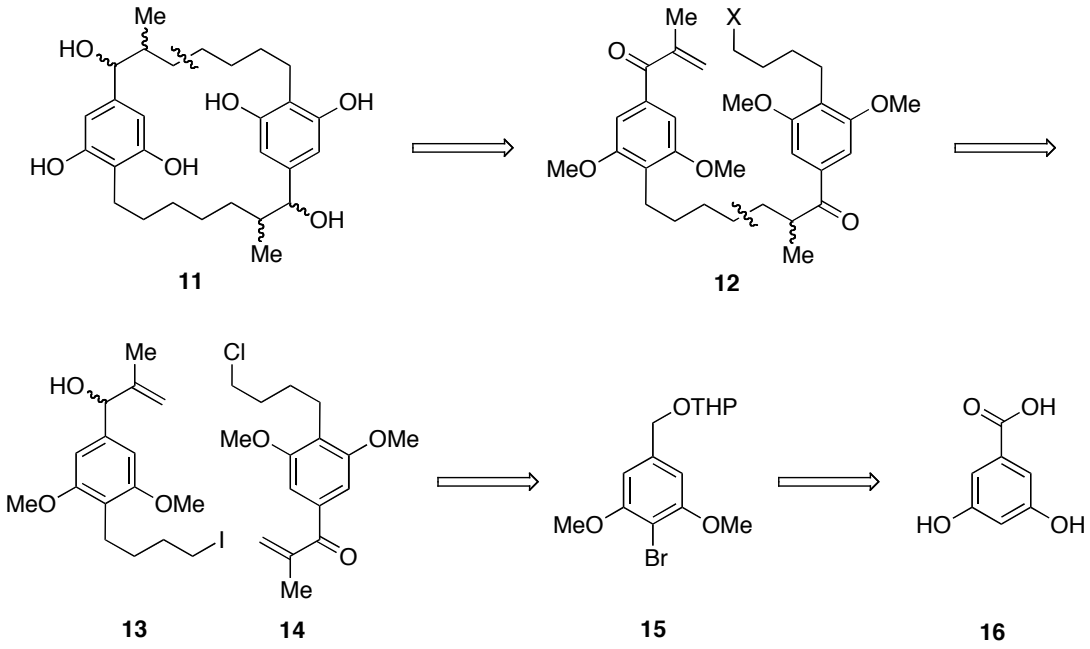
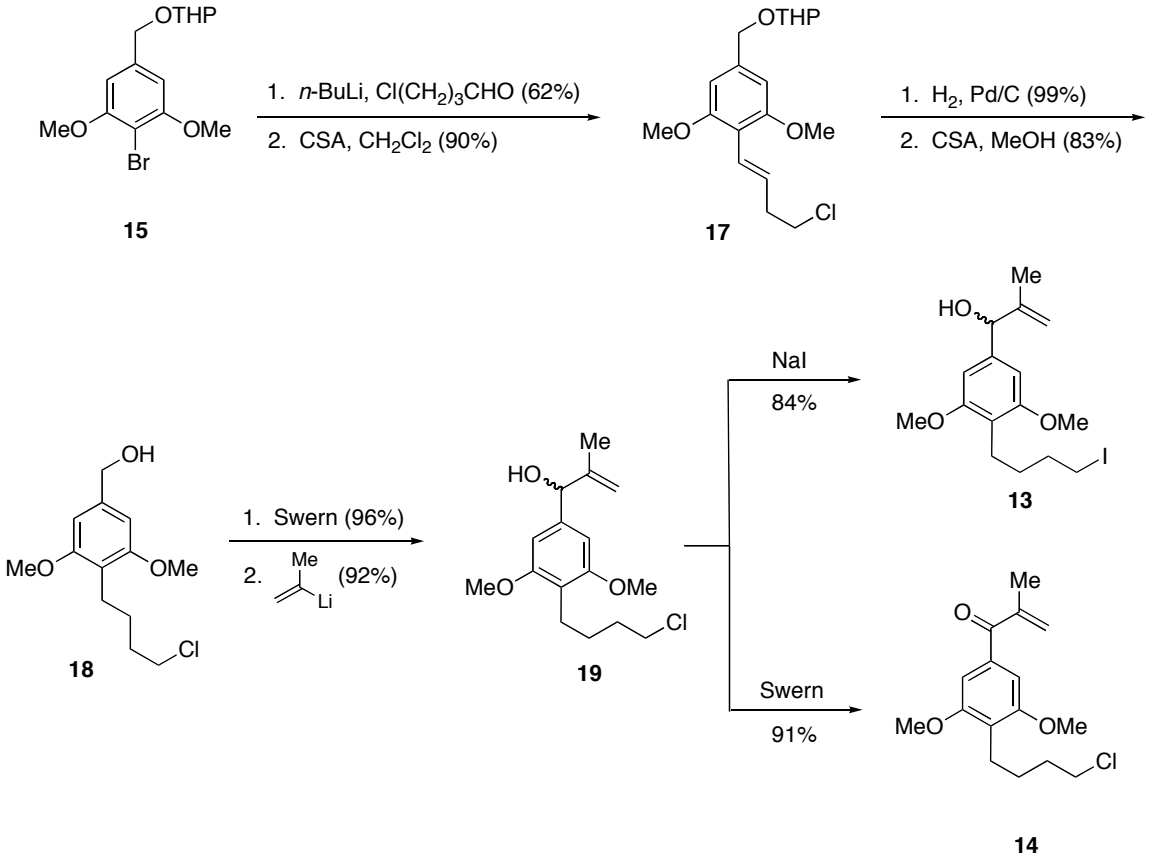


Figure 5. Albizati's retrosynthetic analysis of the model system.

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**.

[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.

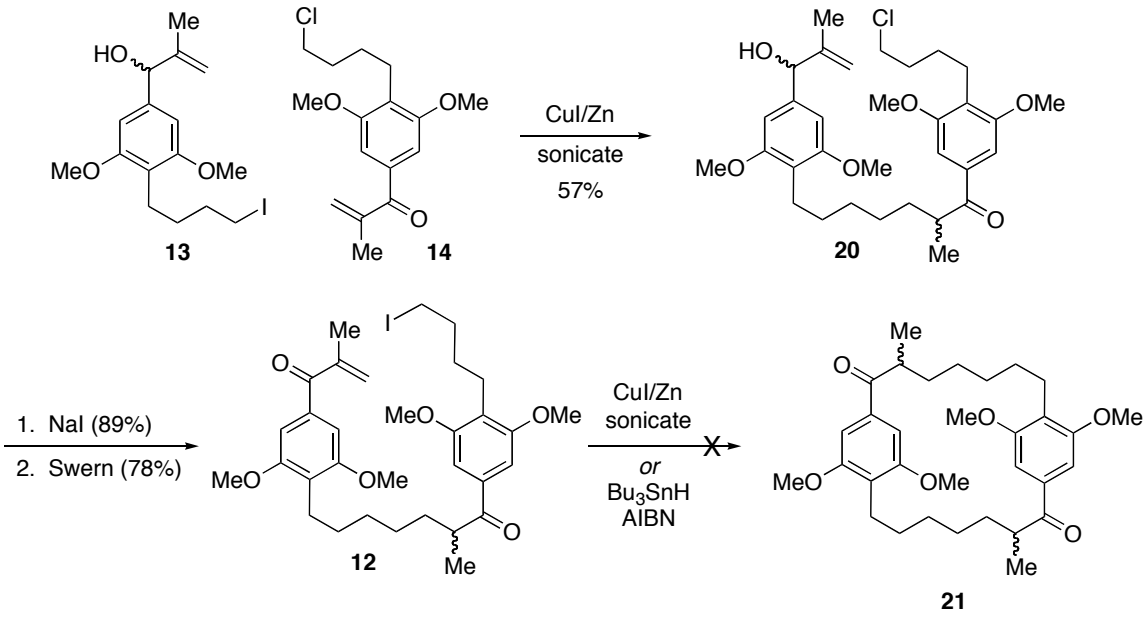


The intermolecular coupling of iodide **13** and enone **14** was effected by using conditions developed by Luche[10] (Scheme 2). Excess iodide **13** was added to a solution of enone **14** and activated zinc/copper couple under sonication to provide the coupled product **20** in good yields. After iodination and subsequent oxidation, the same free radical-mediated intramolecular coupling was attempted. The previously successful Luche conditions and the more standard Bu_3SnH/AIBN conditions failed to afford the

[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

[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**.

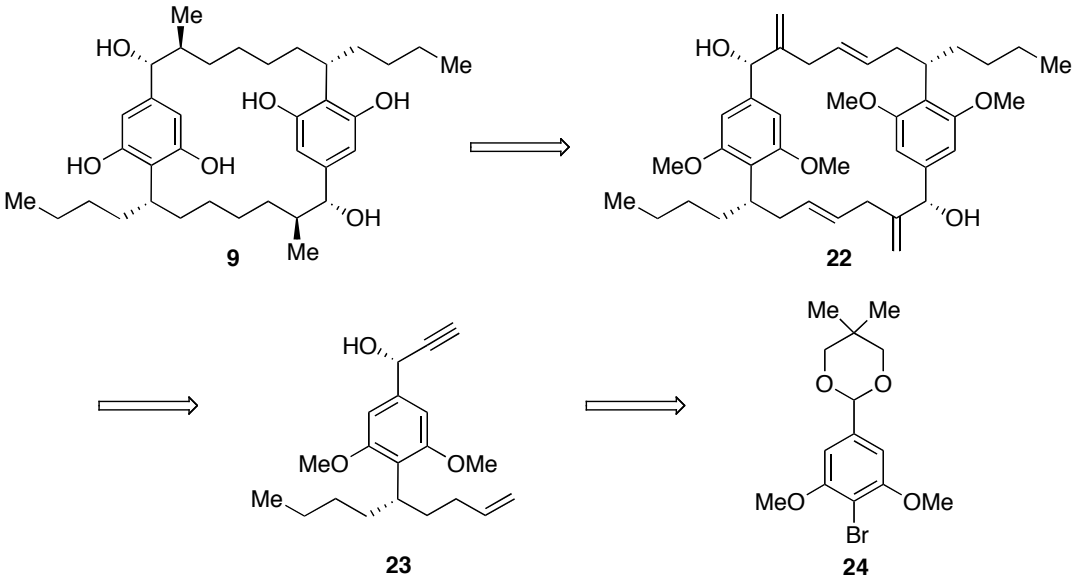


Figure 6. Trost's retrosynthetic analysis of cylindrocyclophane A.

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.

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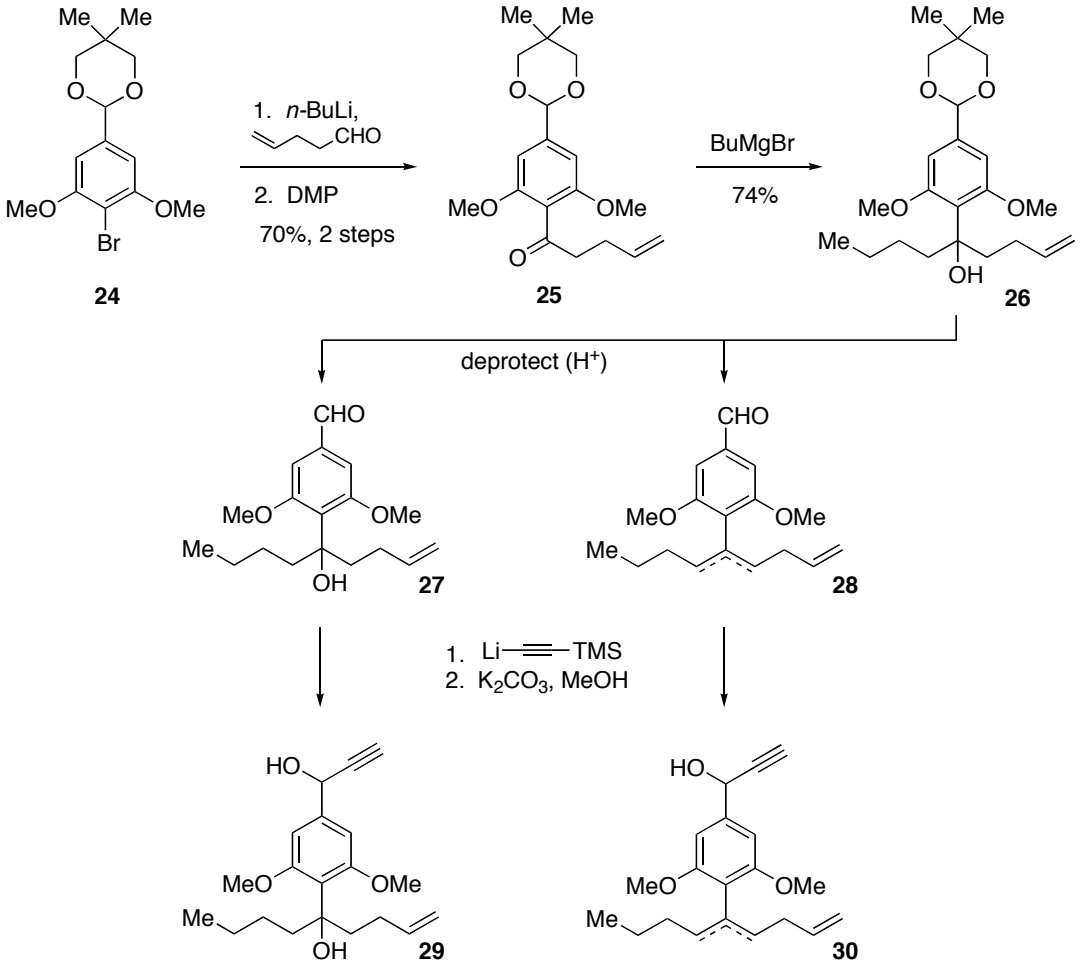
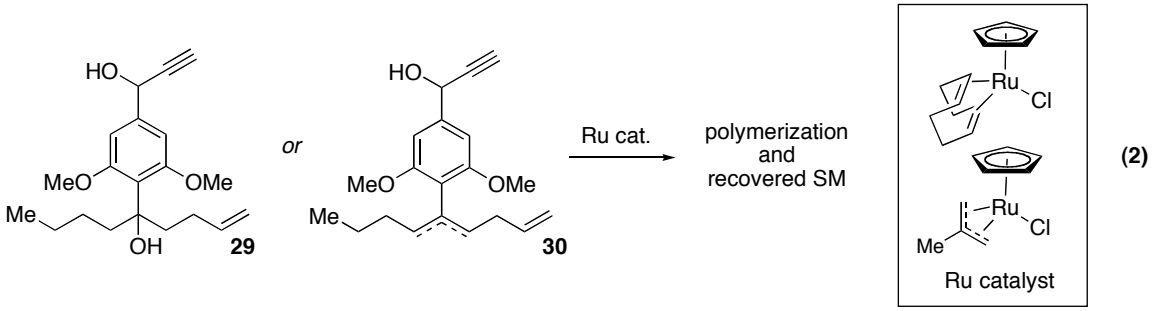
[12] For reviews on the Alder-ene reaction, see: (a) Hoffmann, H. M. R. *Angew. Chem. Int. Ed.* **1969**, *8*, 556. (b) Oppolzer, W.; Snieckus, V. *Angew. Chem. Int. Ed.* **1978**, *17*, 476. (c) Snider, B. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon 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.



(2)

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**).

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[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.

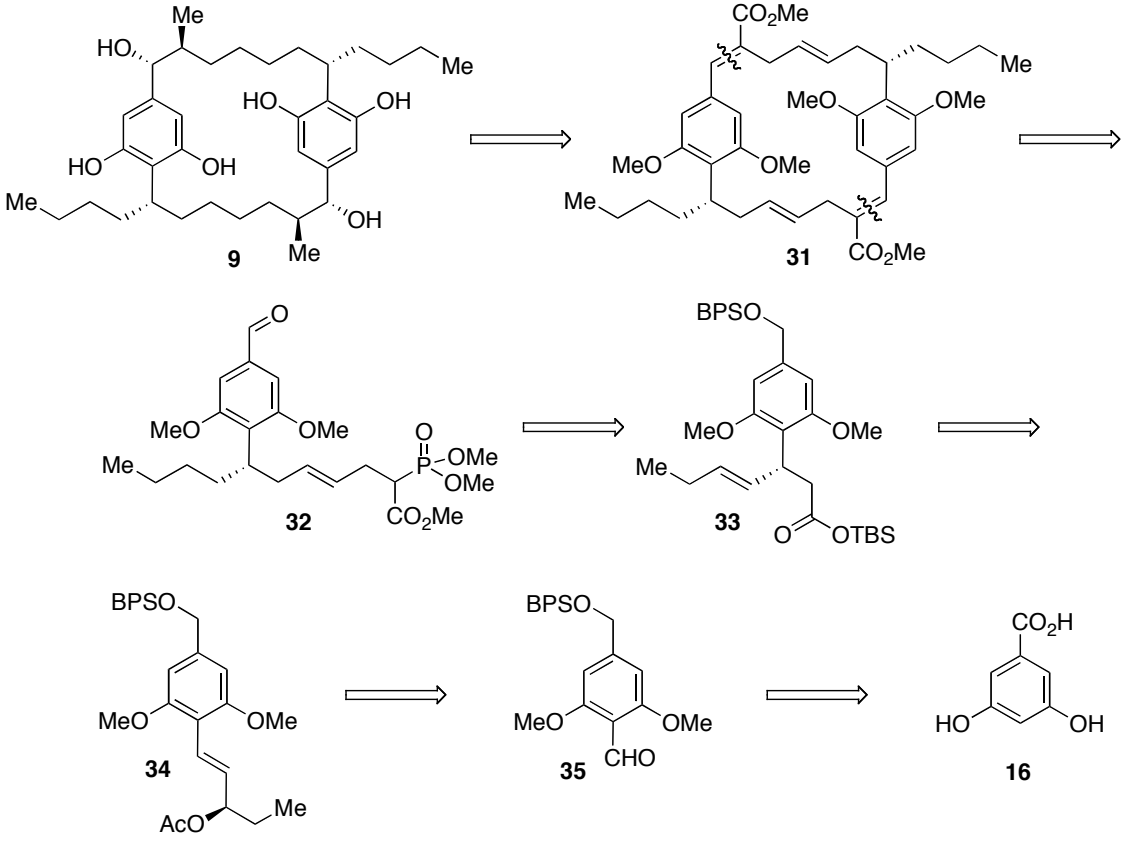

Figure 7. Hoye's retrosynthetic analysis of cylindrocyclophane A.

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**.

[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.

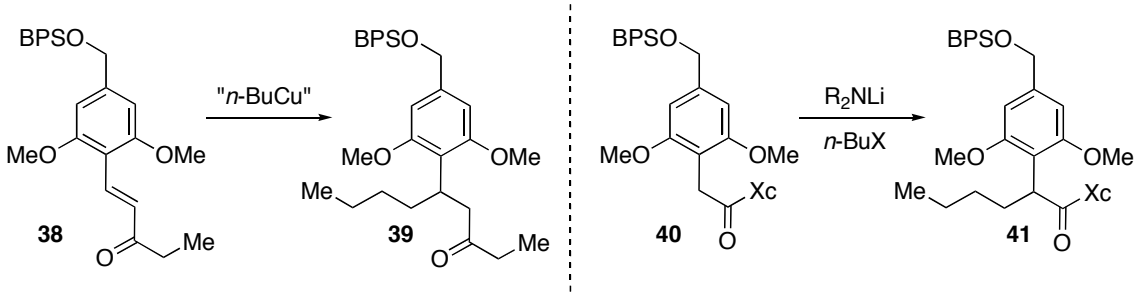

Figure 8. Unsuccessful incorporation of the butyl group.

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.

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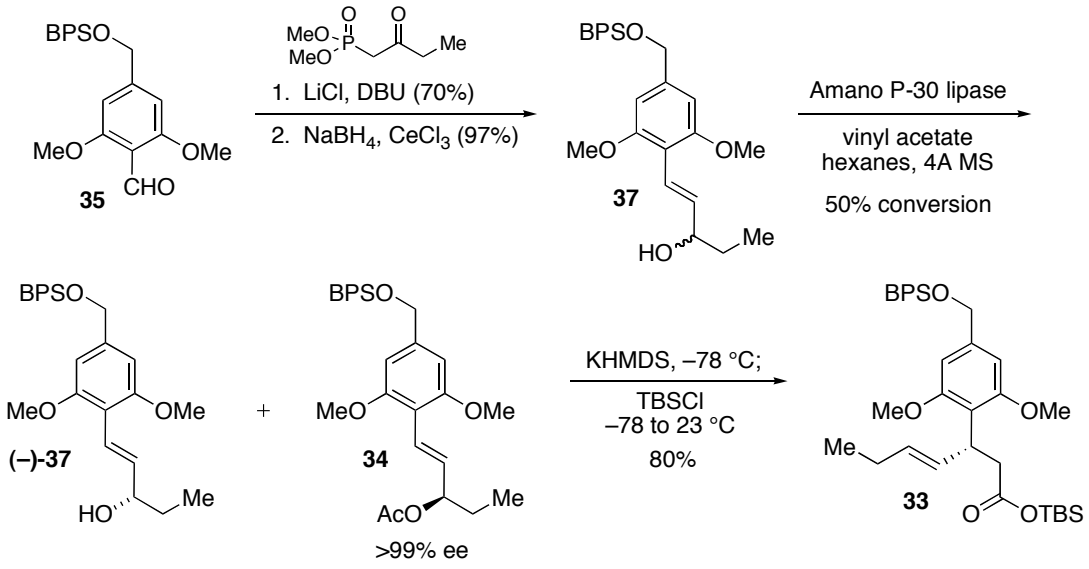
[17] Humpal, P. E. Ph.D. thesis. University of Minnesota, 1996.

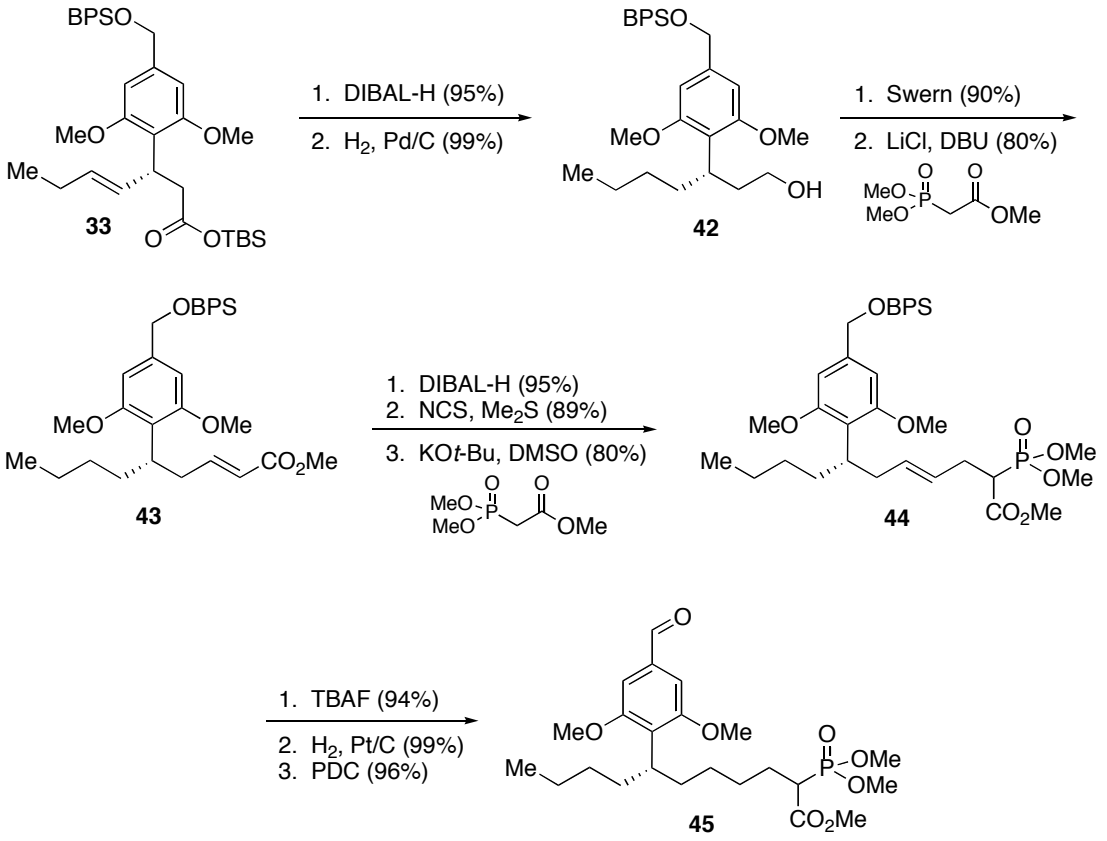
[18] (a) Burgess, K.; Jennings, L. D.; *J. Am. Chem. Soc.* **1991**, *113*, 6129. (b) Johnson, C. R.; Golebiowski, A.; McGill, T. K.; Steensma, D. H.; *Tetrahedron Lett.* **1991**, *32*, 2597. (c) Boland, W.; Frobl, C.; Lorenz, M. *Synthesis* **1991**, *12*, 1049. (d) Kazlauskas, R. L.; Weissfloch, A. 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 □,□-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**.

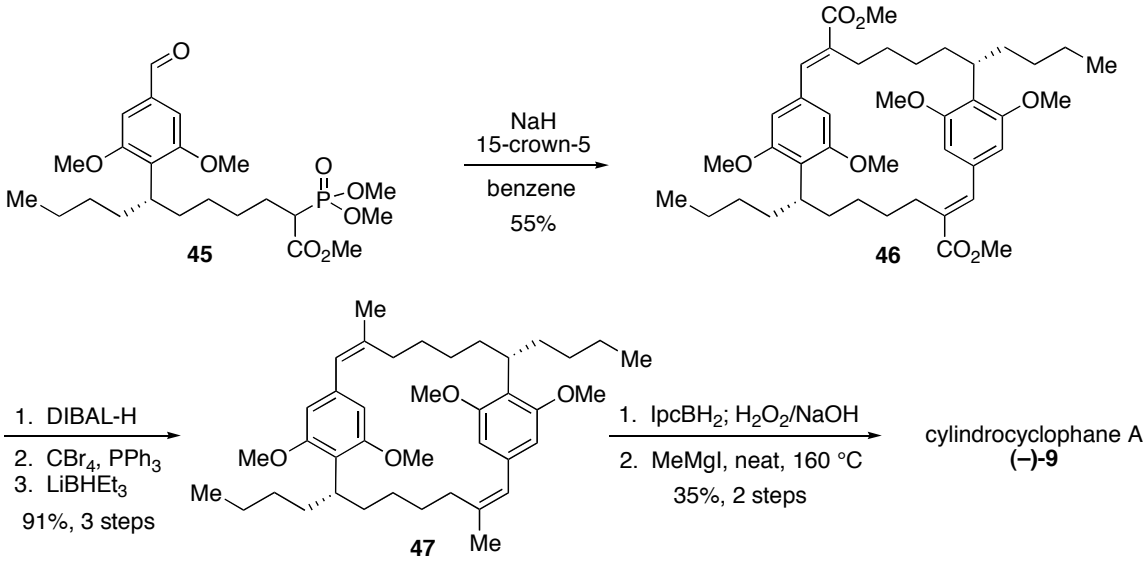
Scheme 5. Synthesis of saturated phosphonate ester 45.



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.

[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

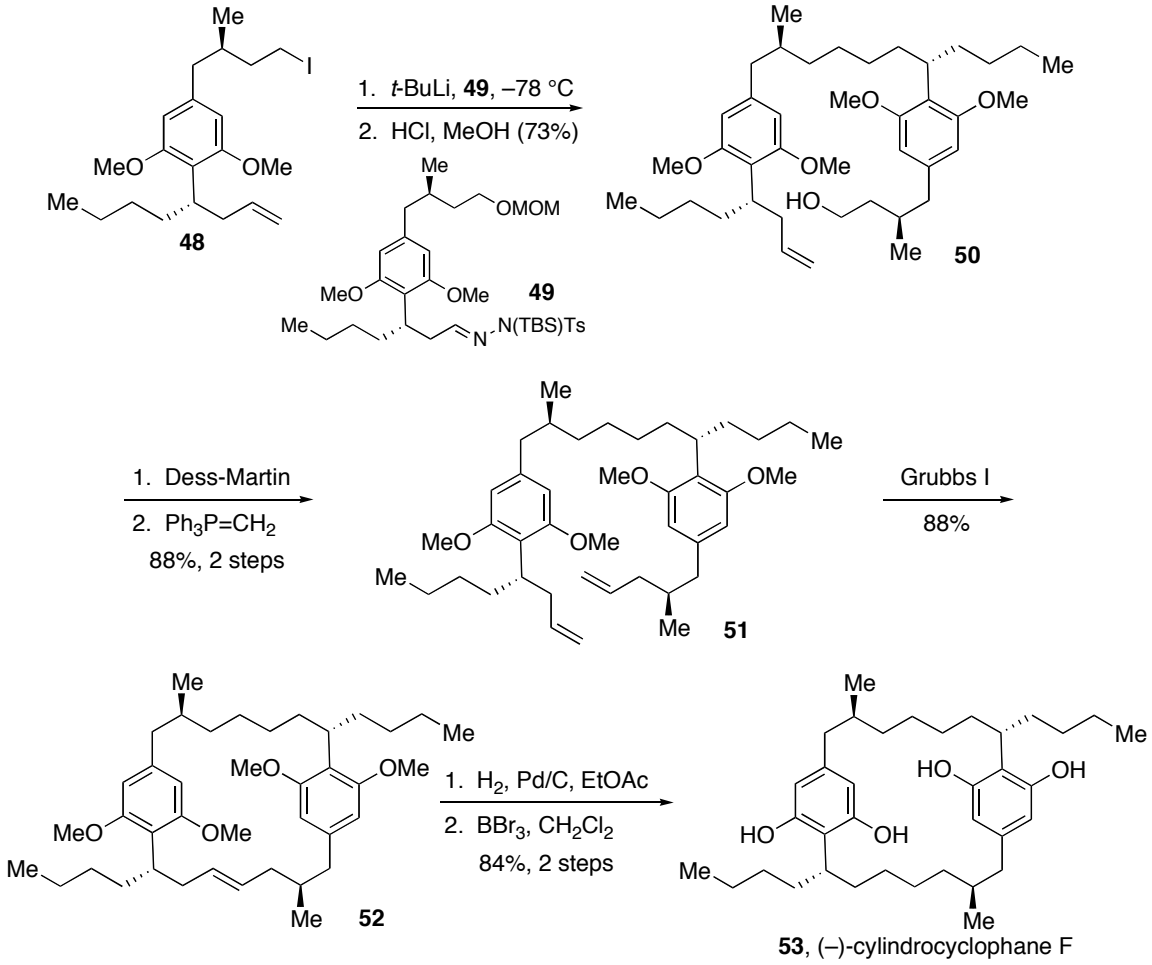
[20] Smith, A. B. III.; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **1999**, *121*, 7423.

[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**.

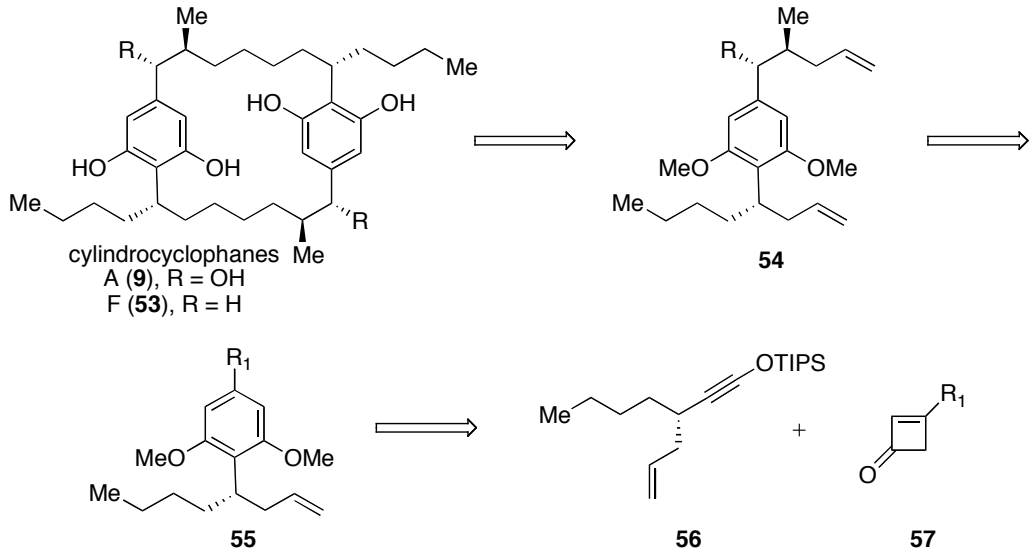
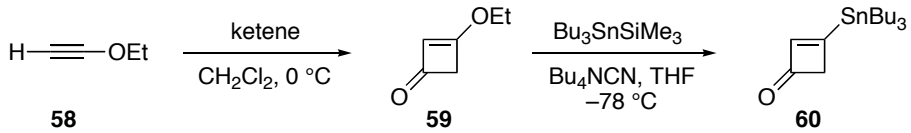


Figure 9. Smith's retrosynthetic plan for cylindrocyclophanes A and F.

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.



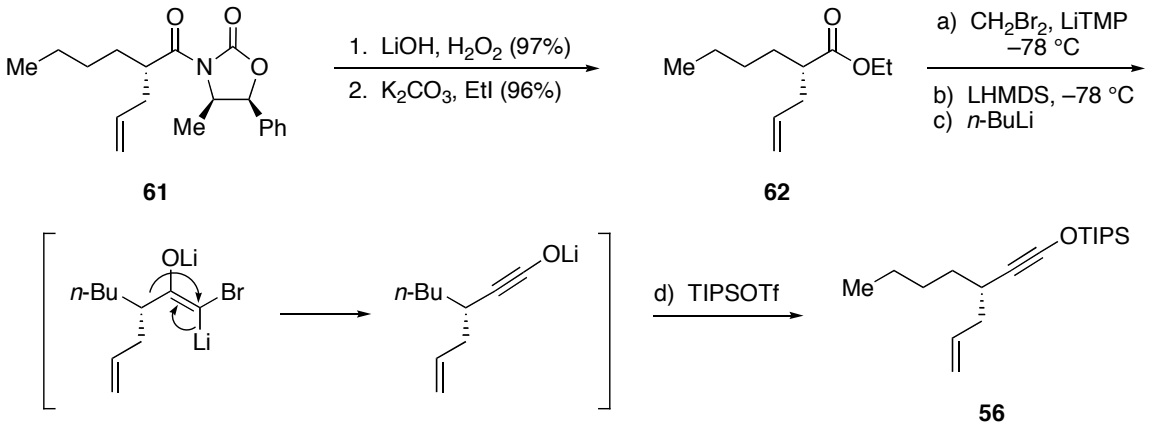
[23] Smith, A. B. III; Kozmin, S. A.; Adams, C. M.; Paone, D. V. *J. Am. Chem. Soc.* **2000**, *122*, 4984.

[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

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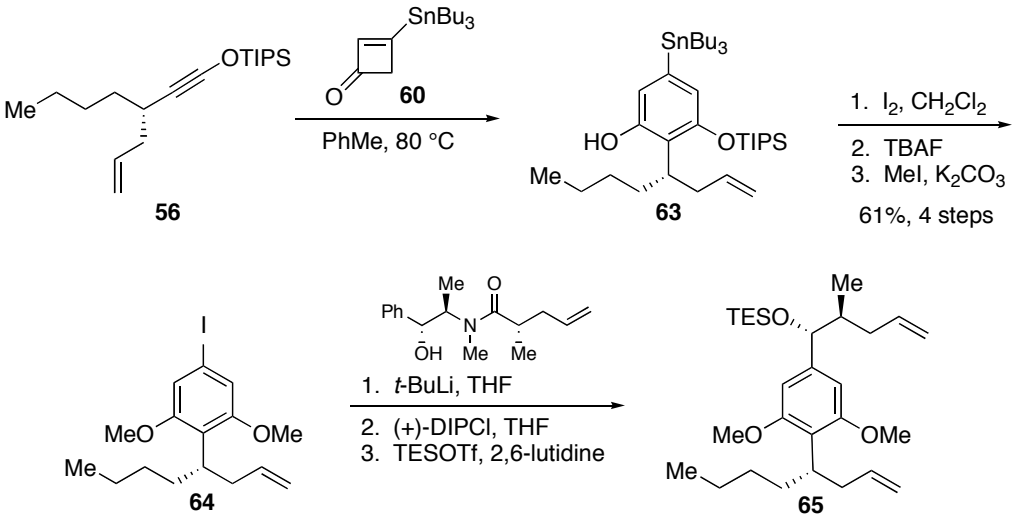
[26] Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506.

[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.

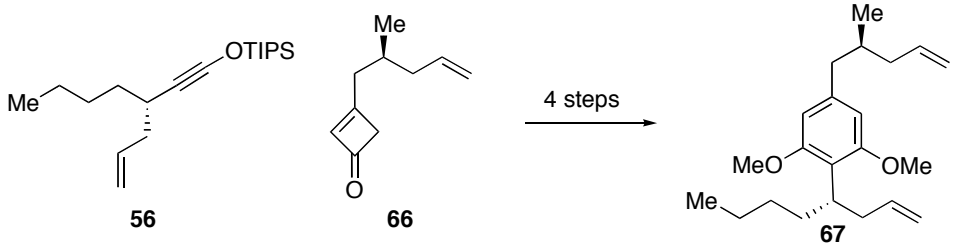
[28] Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.

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).



(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]

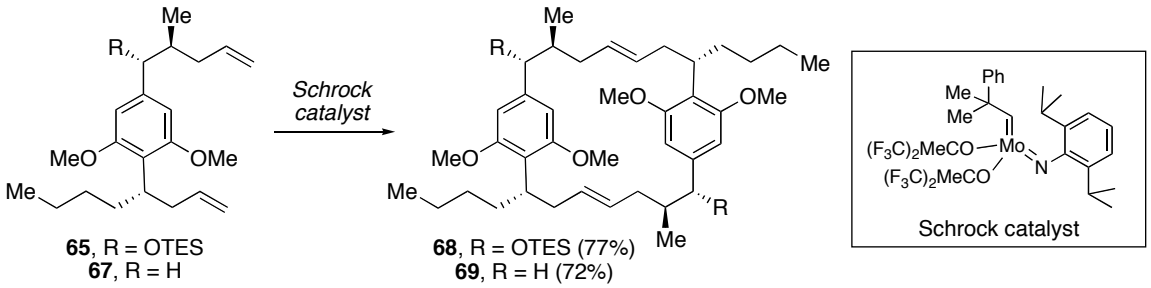
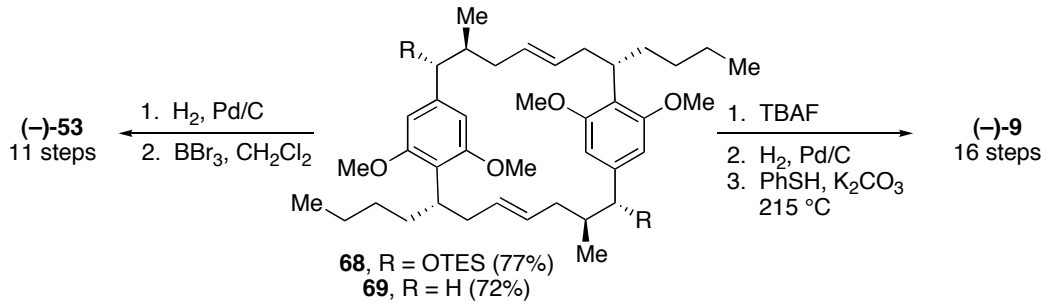


Figure 10. RCM dimerization to form the cylindrocyclophane macrocycle.

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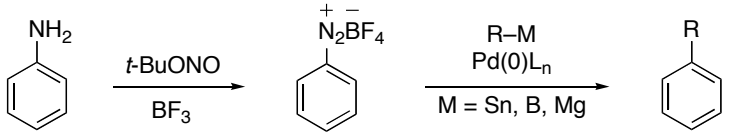
[30] Blakey, S. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 6046.

[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.

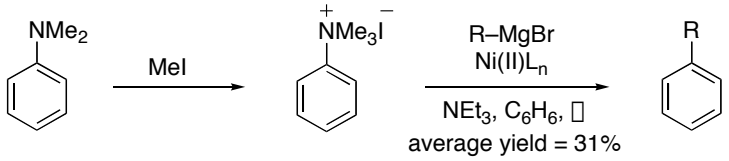
their application as -nucleophiles in a variety of synthetic transformations. One such example of insertion into an aryl-nitrogen bond is the cross-coupling of aryl diazonium salts, which requires derivitization of the primary aryl amine to the diazotized compound (eq. 4).[32]

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.

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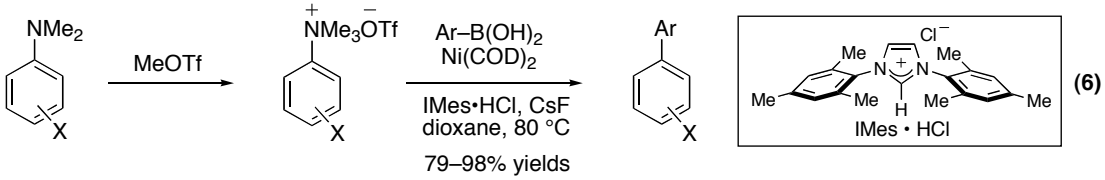
[32] (a) Willis, D. M.; Strongin, R. M. *Tetrahedron Lett.* **2000**, *41*, 6271. (b) Sengupta, S.; Bhattacharyya, S. *J. Org. Chem.* **1997**, *62*, 3405. (c) Darses. S.; Jeffrey, J. P.; Genet, J. P.; Brayer, J. L.; Demoute, J. P. *Tetrahedron Lett.* **1996**, *37*, 3857. (d) Kikukawa, K.; Kono, K.;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



(6)

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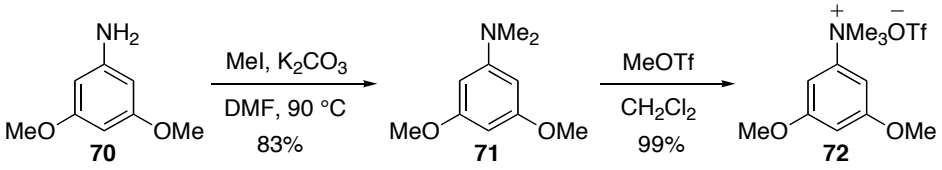
[34] For a review on *B*-alkyl Suzuki cross-couplings, see: Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 4544.

[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.

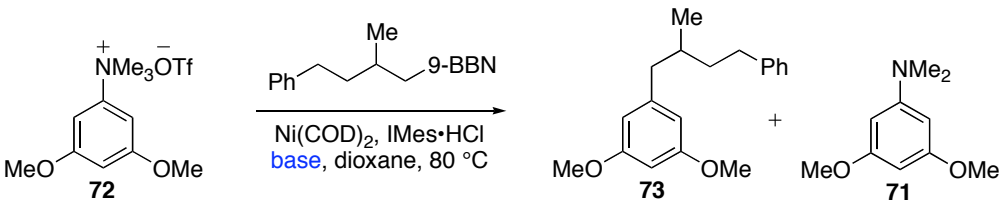
Scheme 12. Synthesis of trimethylanilinium salt.



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.



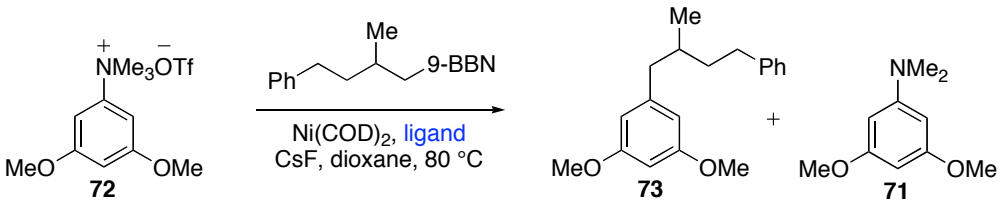
Entry	base	% conversion to **73**
1	CsF	~5
2	CsOH	0
3	KF	0
4	K_2CO_3	0
5	K_3PO_4	0
6	NaO*t*-Bu	trace
7	KOH	0
8	KOEt	0
9	NaOH	trace
10	NaOMe	0

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]

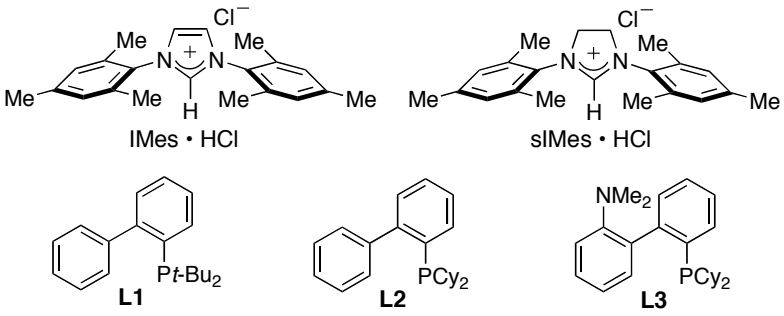
[36] For reviews on *N*-heterocyclic carbenes, see: (b) Herrmann, W. A.; Kocher, C. *Angew. Chem. Int. Ed.* **1997**, *36*, 2182. (c) Herrmann, W. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1290. (d) Jafarpour, L.; Nolan, S. P. *Adv Organomet. Chem.* **2001**, *46*, 181. (e) Arduengo, A. J. III. *Acc.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

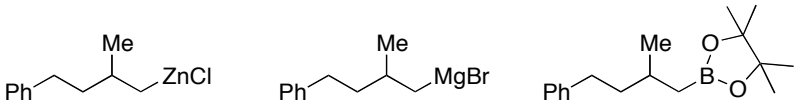
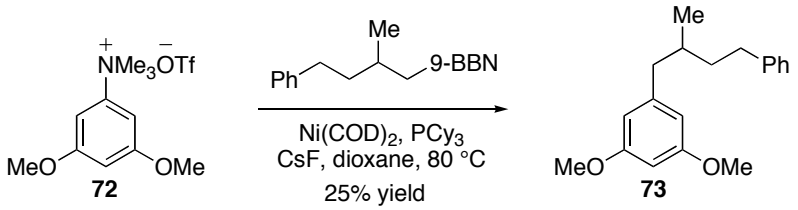


Figure 11. Ineffective transmetaling partners in the cross-coupling reaction.

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

[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).

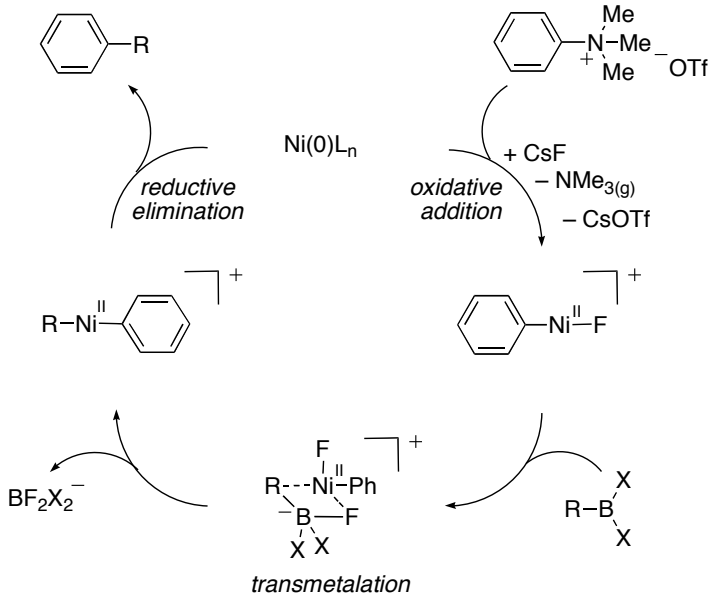


Figure 12. Proposed catalytic cycle for *B*-alkyl Suzuki cross-coupling.

[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.

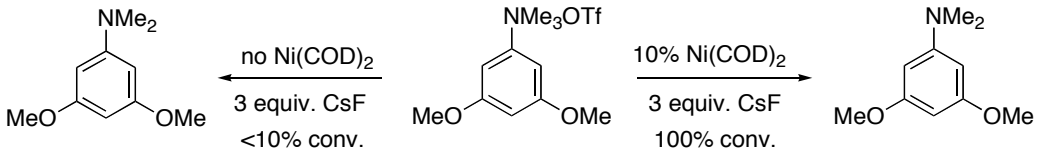


Figure 13. Nickel-catalyzed demethylation of trimethylanilinium salt.

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.

[41] Anslyn, E. V.; Dougherty, D. A. In *Modern Physical Organic Chemistry.* University Science Books: **2006**, p. 7.

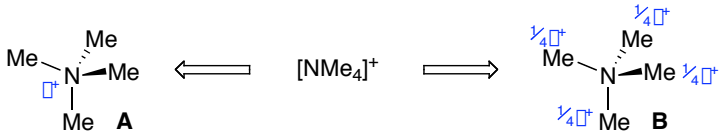


Figure 14. Charge distribution in the tetramethylammonium ion.

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.

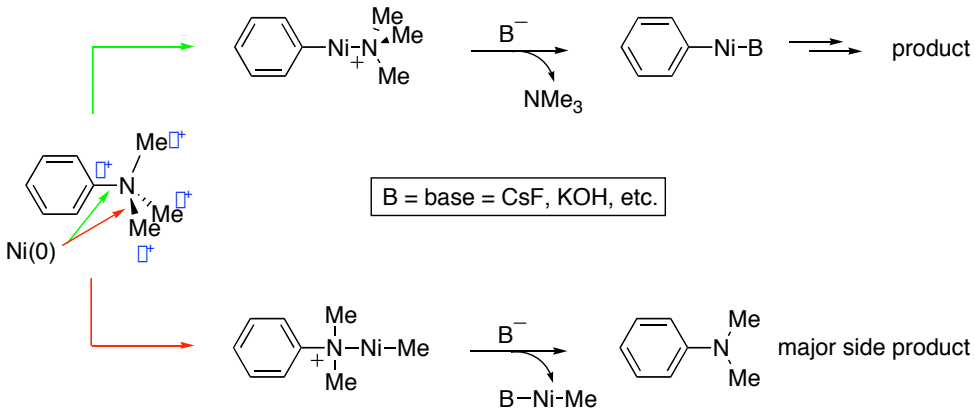


Figure 15. Competing oxidative addition pathways on trimethylanilinium salts.

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]

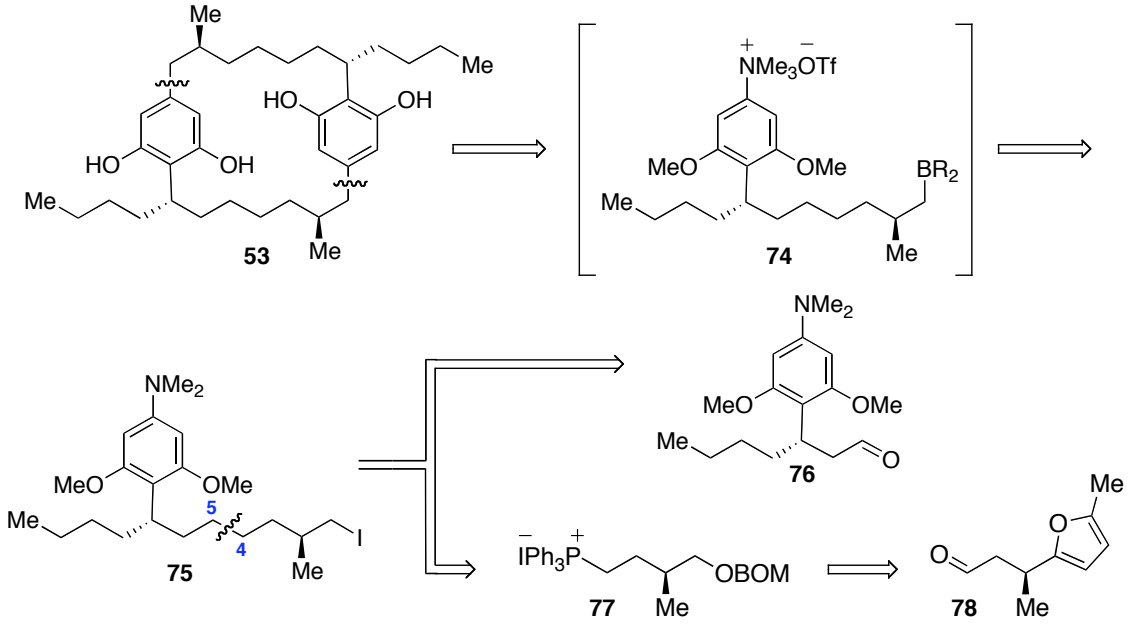


Figure 16. Retrosynthetic plan.

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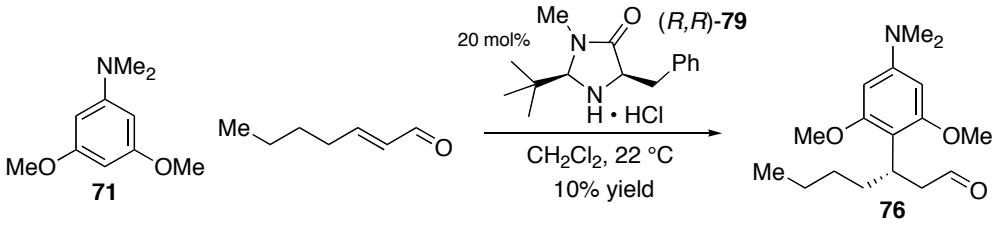
[42] Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894.

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

v. *Synthesis of a dimerization precursor.*

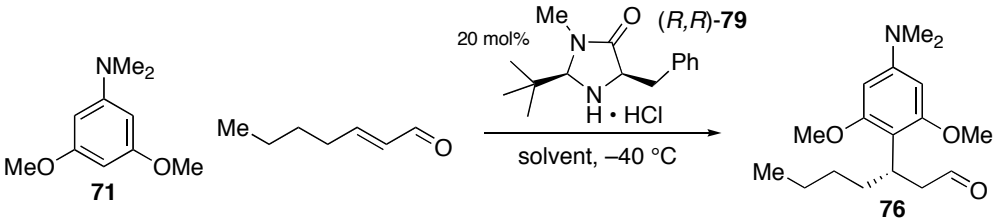
Following the retrosynthetic route outlined in figure 17, the first step forward was to access the two enantiopure fragments **76** and **78** by the organocatalytic 1,4-conjugation addition of □-nucleophiles into □,□-unsaturated aldehydes. In a forward sense, the addition of 3,5-dimethoxy-*N,N*-dimethylaniline (**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.

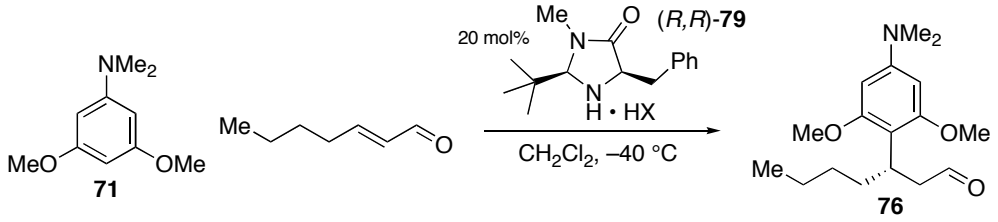


Entry	Solvent	conversion (%)	% ee[a]
1	CH_2Cl_2	74	74
2	$CHCl_3$	79	88
3	toluene	67	88
4	THF	79	80
5	DMF	75	46
6	CH_3CN	59	63
7	MeOH	59	41
8	Et_2O	74	49

[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).

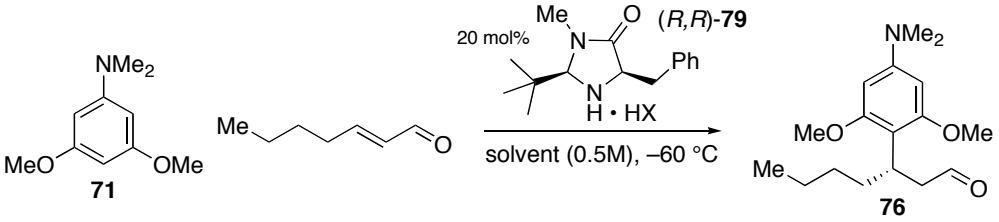
Table 4. Representative co-catalyst screen.



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

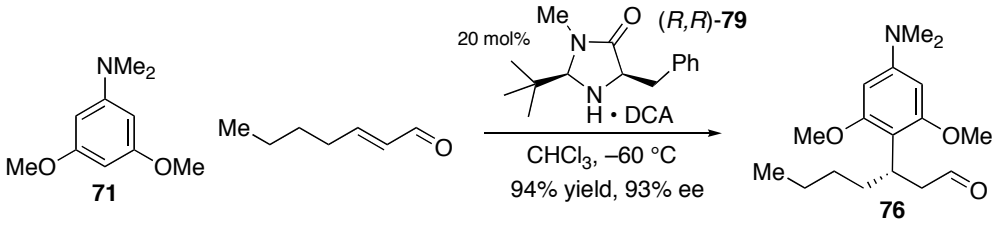
Table 5. Survey of a combination of co-catalyst and solvent conditions.



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).

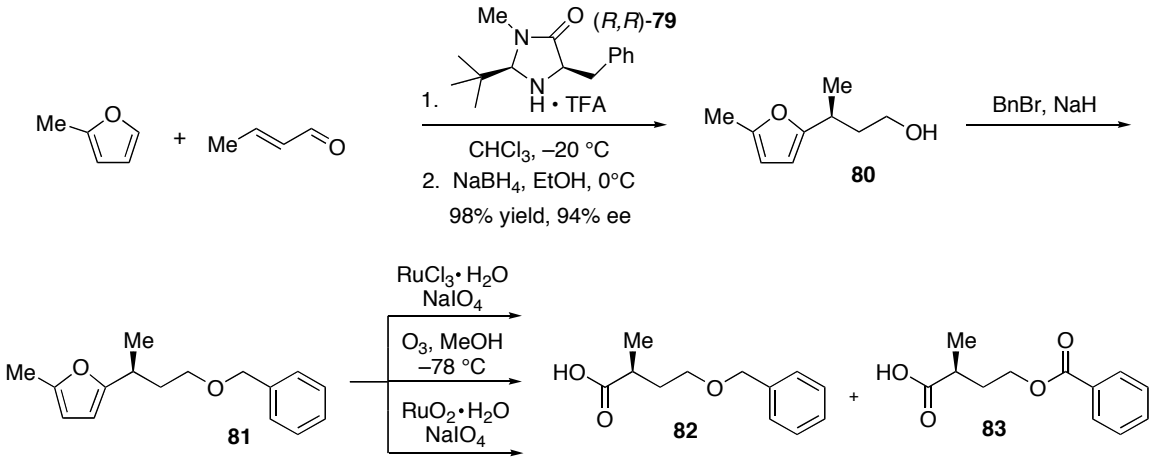


(9)

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

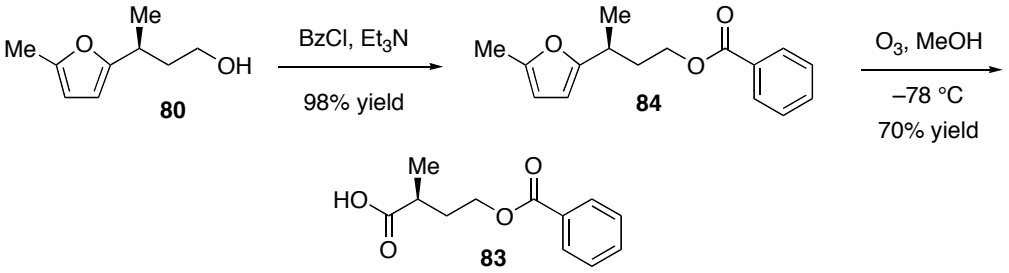
and 94% ee (Scheme 13). With alkylated furan **80** in hand, a suitable protecting group for the free hydroxyl was needed in order to withstand the subsequent oxidation of the furan ring.

Scheme 13. Undesired oxidation products of furan oxidation protocols.

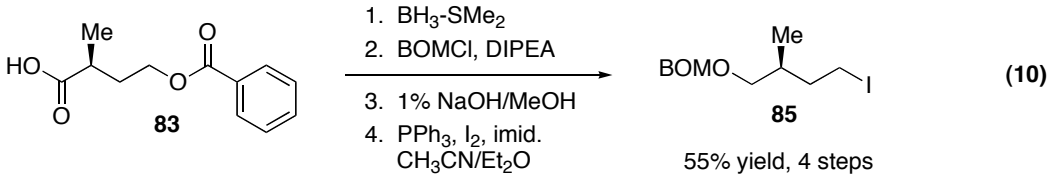


A benzyl protecting group was installed, and on a small scale the reaction proceeded to afford the benzylated product **81**. However, larger scale reactions (>50 mg) imparted a mixture of desired product **82** and overoxidized product **83**, all present in different mixtures depending on the oxidation 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.

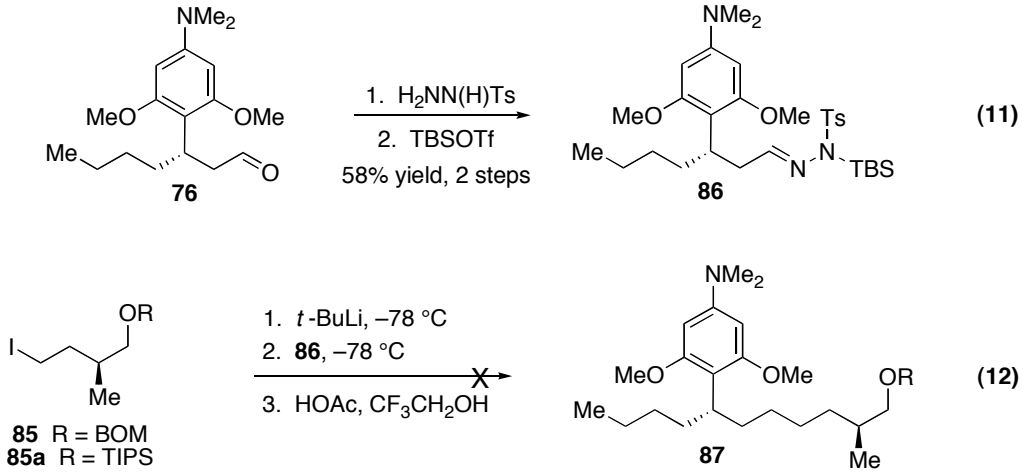


(10)

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.

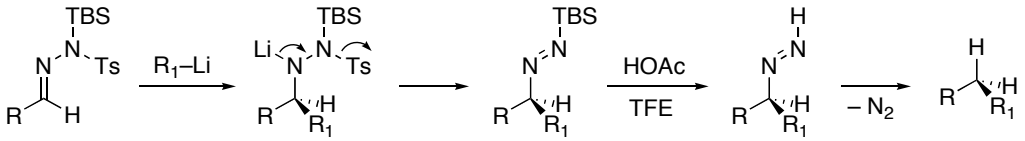
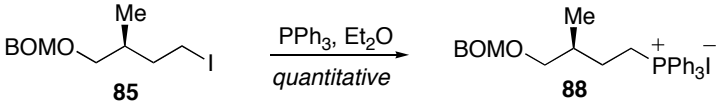


Figure 17. Myers' reductive alkylation mechanism.

vii. ***Wittig olefination strategy.***

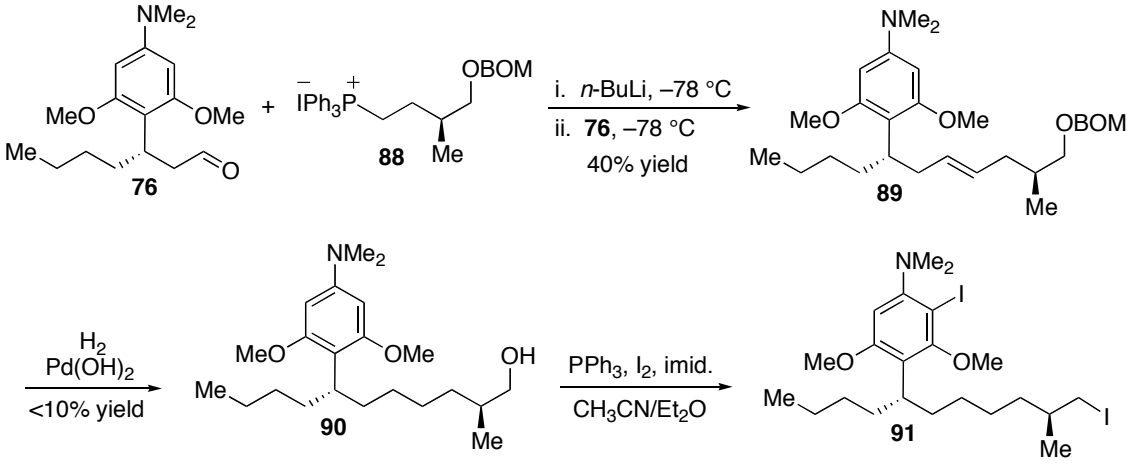
It was realized that installation of an olefin at C4–C5 would not change the number of chemical transformations in the synthesis so long as the protecting group was susceptible to hydrogenation conditions. The BOM protecting group was therefore targeted as the appropriate protecting group in the olefination 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.



(13)

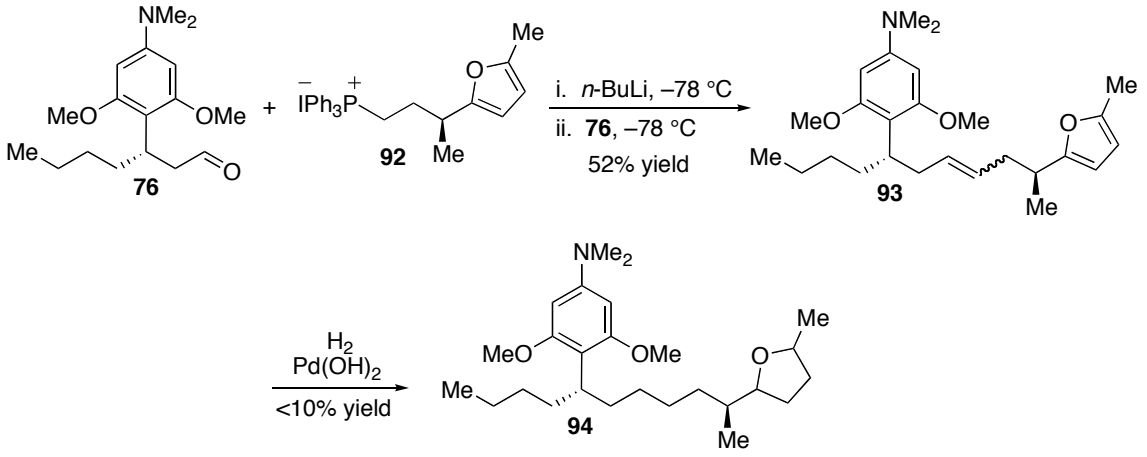
The intermolecular olefination (Scheme 15) was completed using the iodide Wittig salt **88** to give olefin **89** in low yield. If the temperature was kept at –78 °C throughout the reaction, completing decomposition pathways were suppressed and the yield improved to 40%. The bromide Wittig salt of **88** 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.

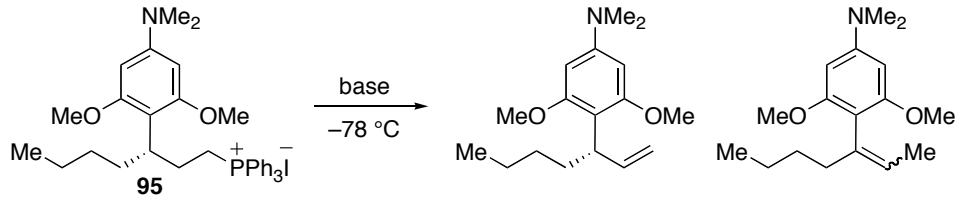


While the above protecting group strategy was being investigated, the same Wittig olefination sequence was performed bringing in the furan moiety as phosphonium salt **92** (Scheme 16). The olefination proved to be more efficient; however, the hydrogenation required elevated pressure, and reduction of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

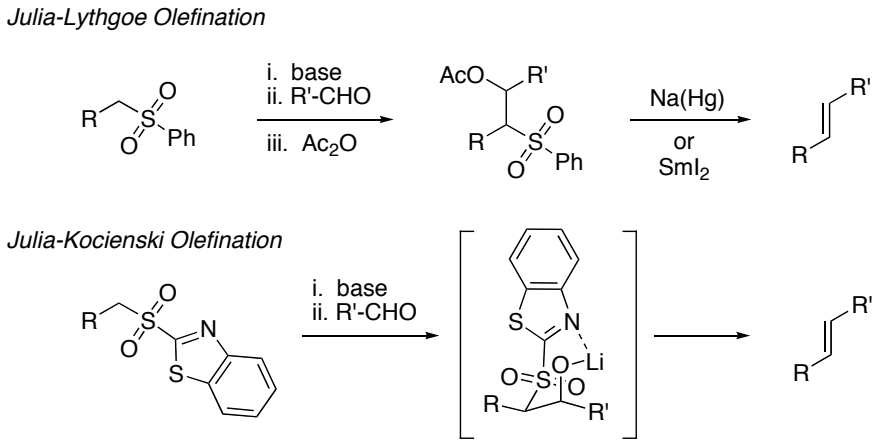


Figure 18. The Julia olefination.

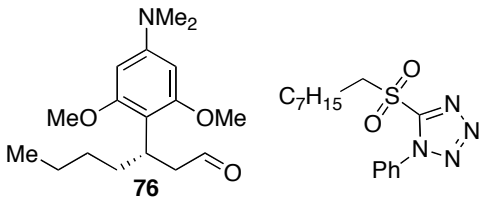
The modified Julia olefination, or the Julia-Kocienski olefination,[45] has been reported in order to avoid the second reducing step that is required to eliminate the aryl sulfone (Fig. 8). The phenyl groups of the sulfone were ingeniously replaced with heteroaromatic system, like the benzothiozyl shown 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).

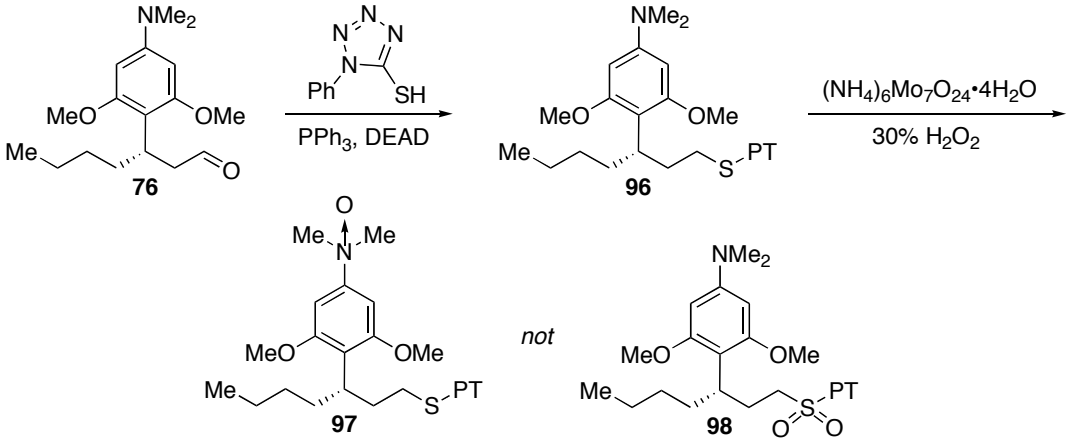


(15)

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**

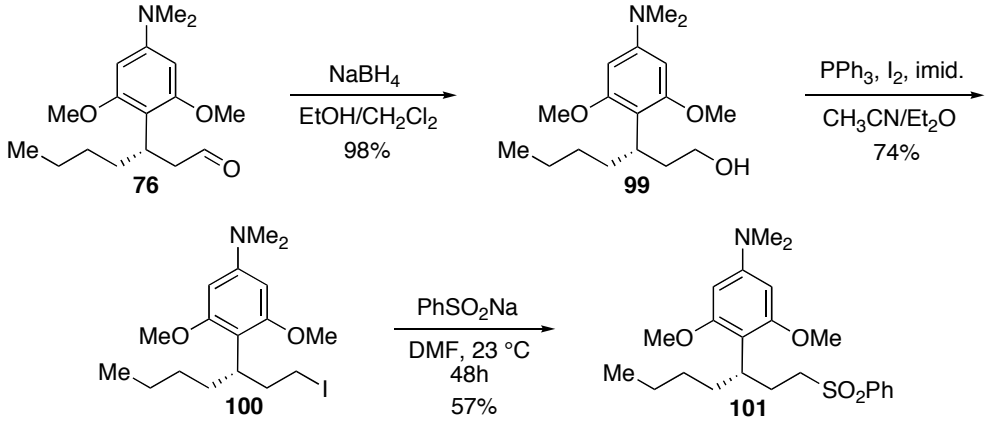
[46] McAlonan, H.; Potts, D.; Stevenson, P. J.; Thompson, N. *Tetrahedron Lett.* **2000**, *41*, 5411.

Scheme 17. Oxidation sequence forms *N*-oxide.



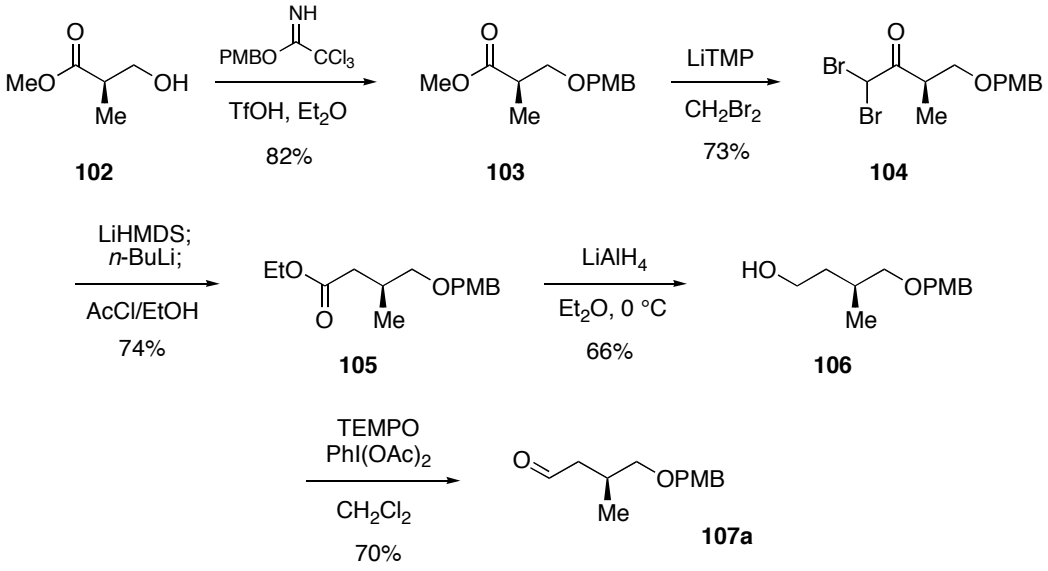
Because of the inability of this system to under selective thiol oxidation, the two-step Julia olefination sequence was attempted. Synthesis of phenylsulfone **101** was accomplished in three steps from aldehyde **76** (Scheme 18). Sodium borohydride reduction of the aldehyde gave alcohol **99** in excellent 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**.

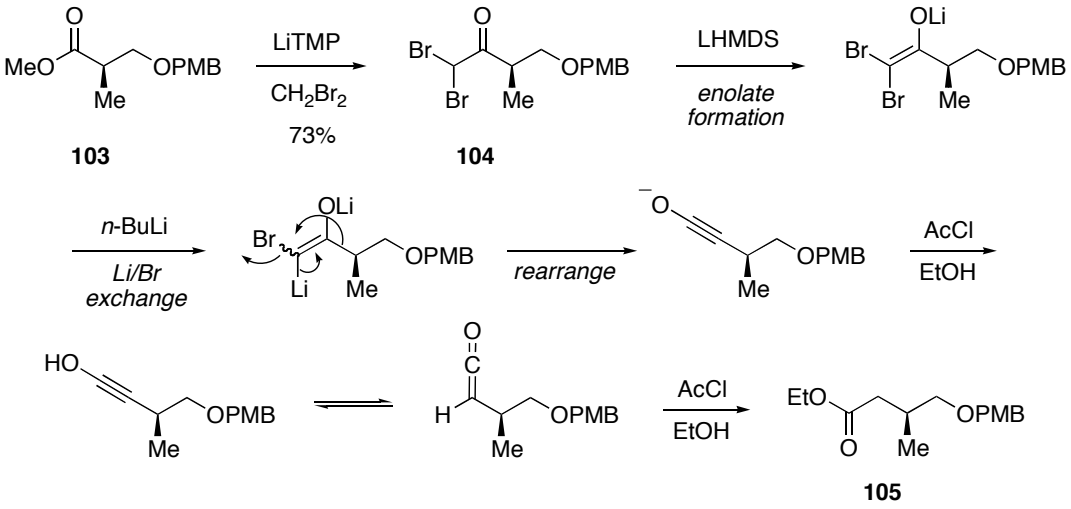
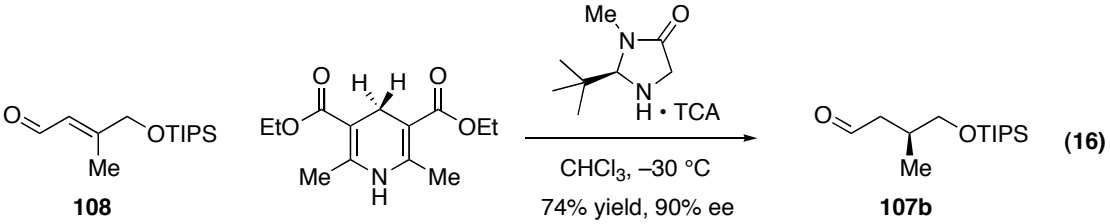


Figure 19. Mechanism of the Kowalski rearrangment.

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).

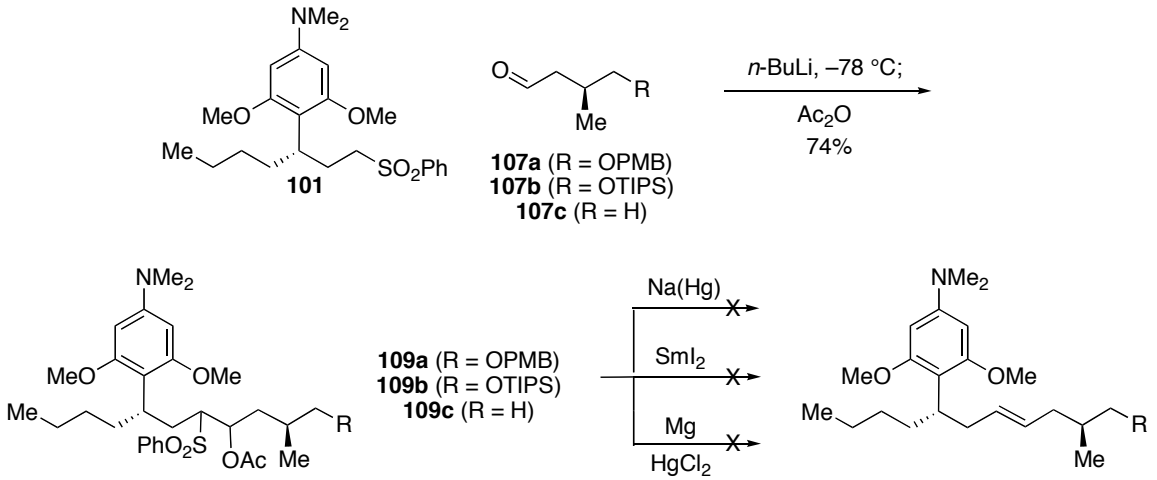


(16)

[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]

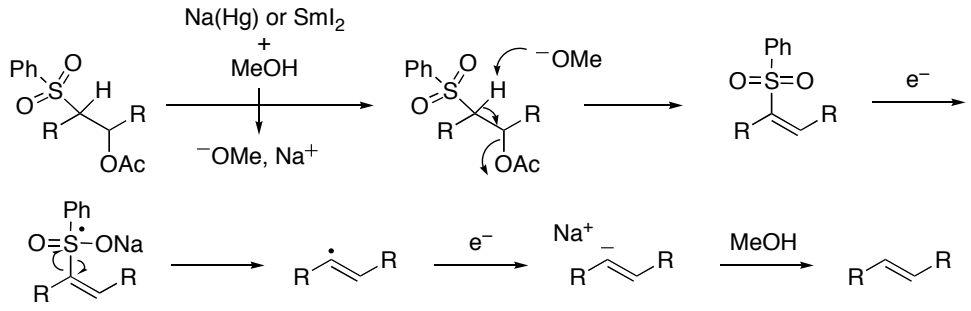


Figure 20. Proposed mechanism for cleavage of acetoxy sulfones.

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.

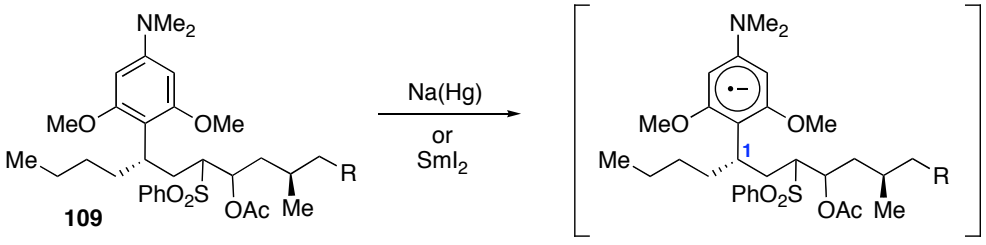


Figure 21. An unreactive intermediate under one electron reducing conditions.

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).

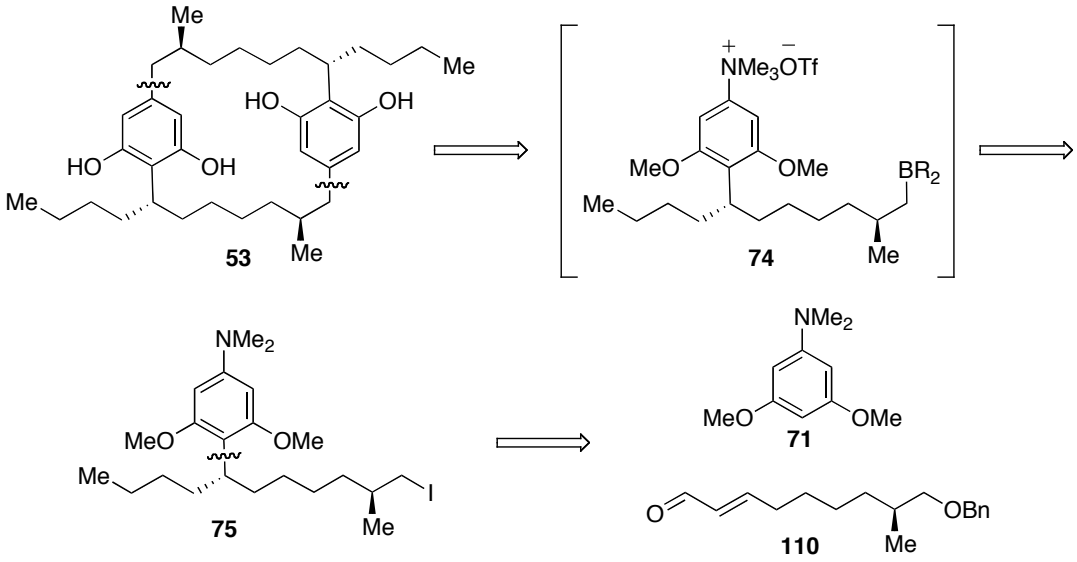
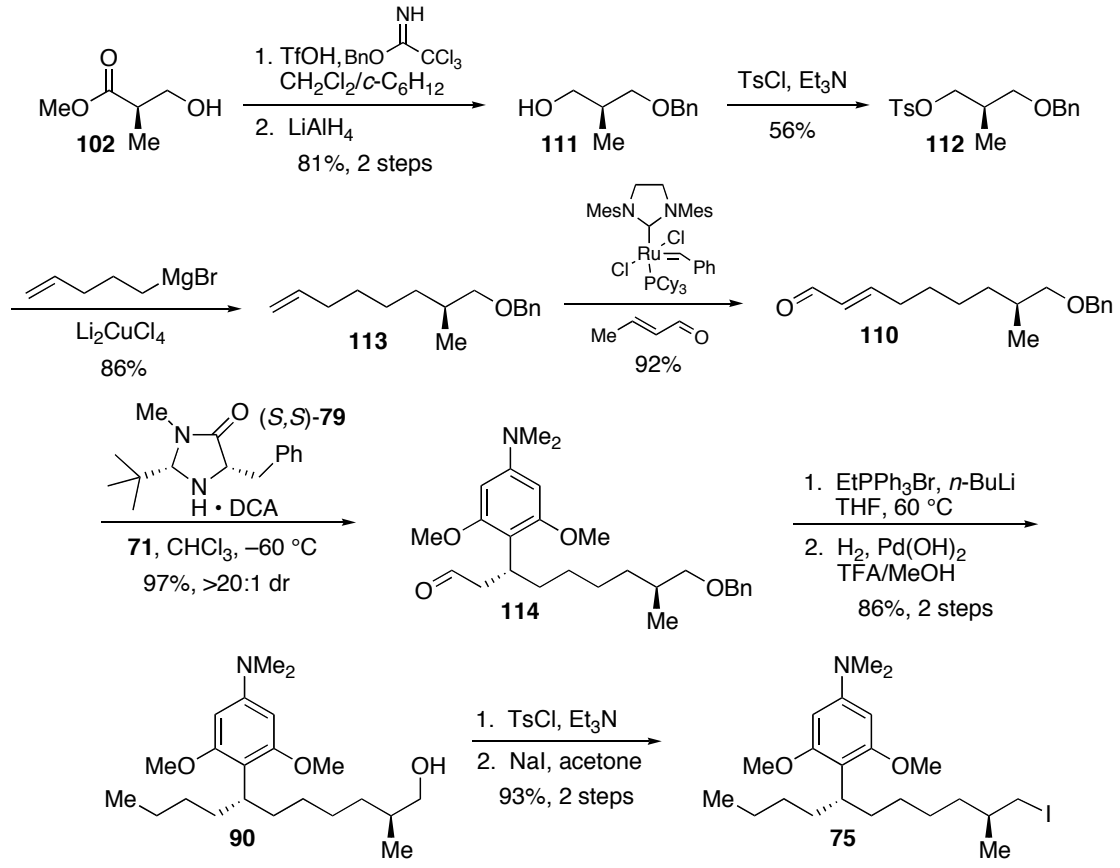


Figure 22. Alternate retrosynthetic strategy.

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.

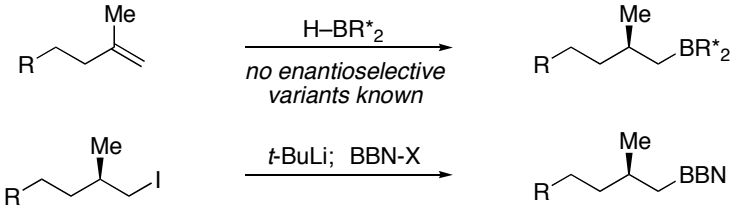


Figure 23. Access to α-stereogenicity on the alkyl borane.

This approach to generate α-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]

---

[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.

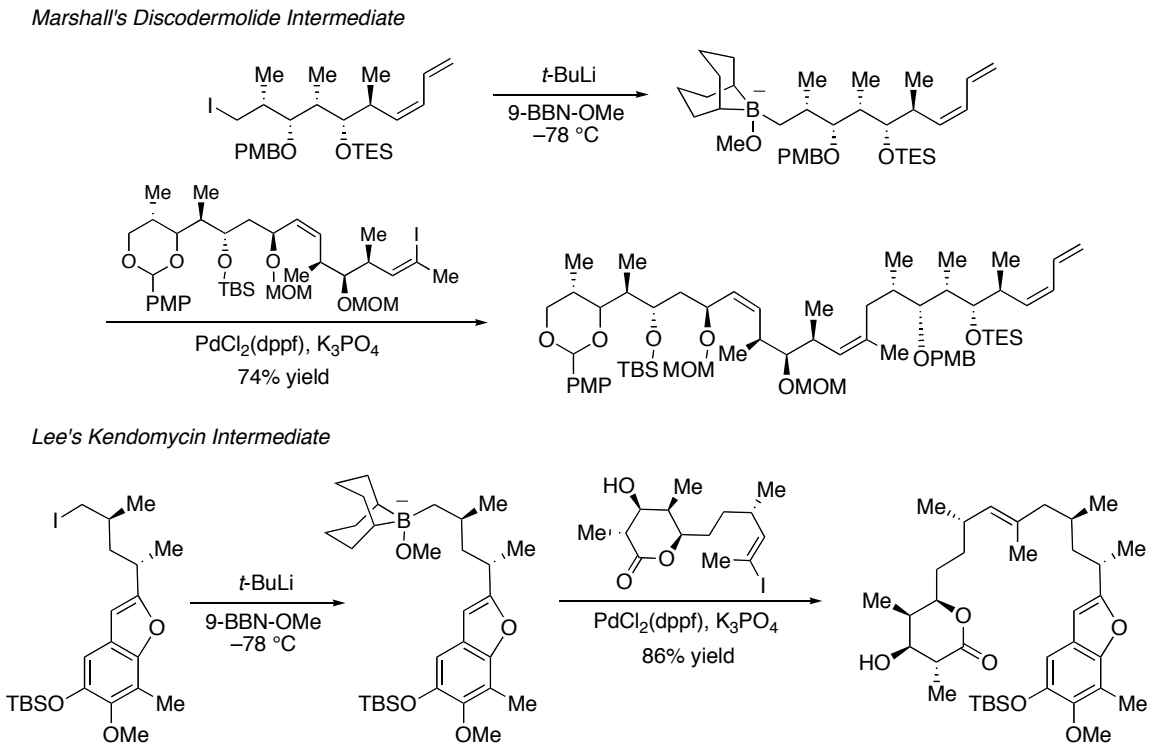
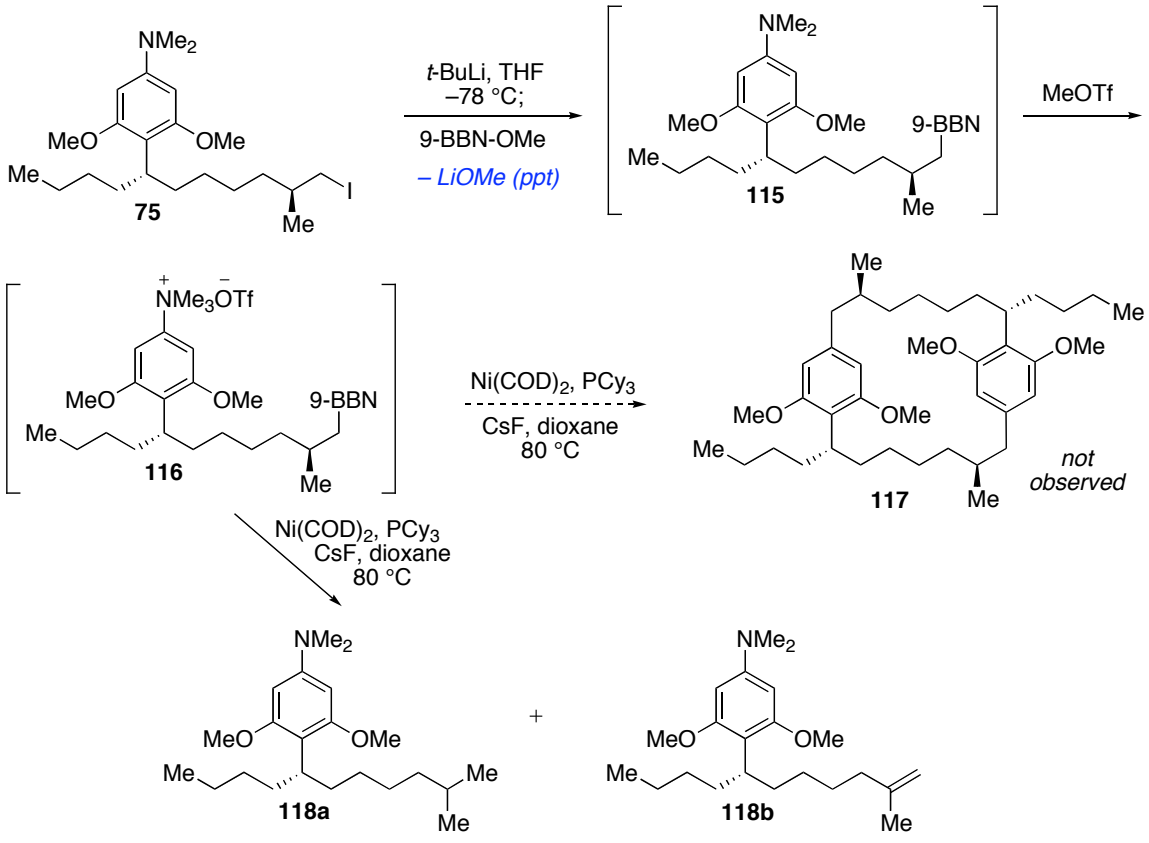


Figure 24. Lithiation/transmetalation preparation of alkyl boranes in natural product synthesis.

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.



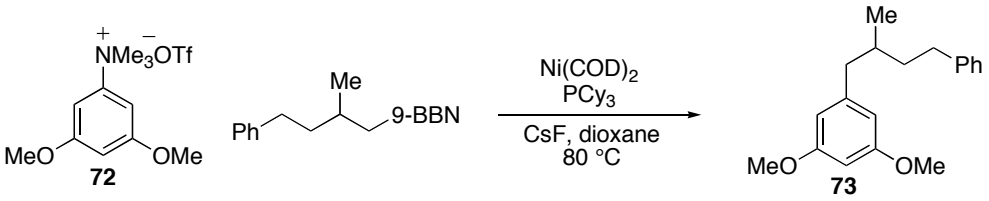
The most notable difference between this system and the model system previously explored was the preparation of the alkyl borane. The model system was generated via hydroboration whereas the real system utilized a lithiation/transmetalation procedure that generated an equivalent of lithium methoxide 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.*

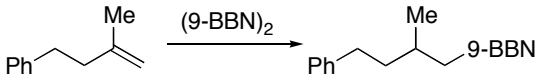
In order to test effects of the method in which the alkyl boranes were prepared, the initial model system was reinvestigated (Table 6). The alkyl 9-BBN-derivative prepared via hydroboration of the terminal olefin (prep **A**) gave the cross-coupled product **73** in 25% yield, the same result that was 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.

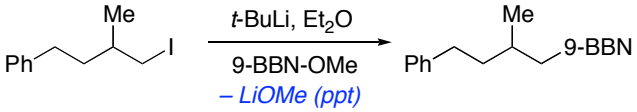


Entry	alkyl borane prep	additives	yield
1	**A**	none	25%
2	**B**	none	no reaction
3	**A**	LiOMe (1 equiv)	no reaction
4	**C**	none	no reaction

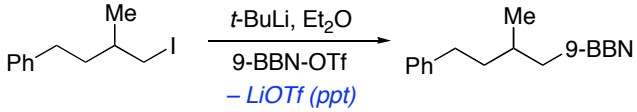
A: *hydroboration*



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]

[58] Cole, T. "^{11}B NMR Chemical Shifts." Retrieved June 2, 2006, from San Diego State University: www.chemistry.sdsu.edu/research/BNMR/#summary

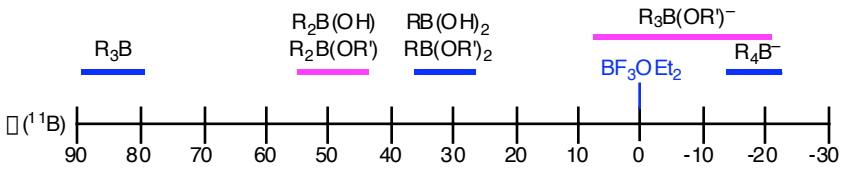
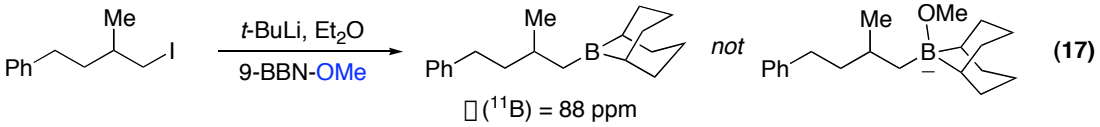


Figure 25. Boron NMR chemical shifts.

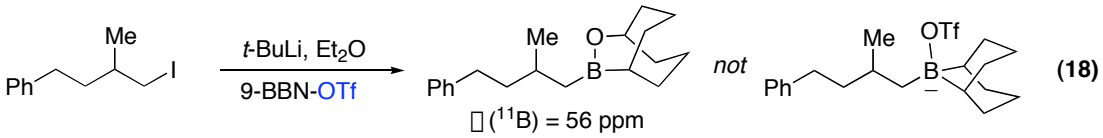
Literature precedent suggested that the nucleophilic addition of an alkyl lithium into 9-BBN-OMe leads to the formation of the boron "ate" complex,[56,57] which would be expected to have an ^{11}B NMR chemical shift equal to or less than zero. As shown in equation 17, it was discovered that the addition 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.



(17)

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.

[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.



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.

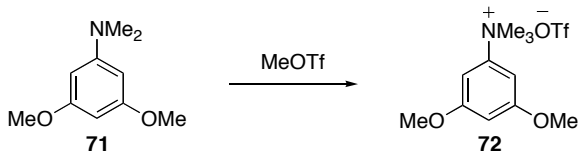
General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[60] Dimethylformamide was obtained from EM Science in a DriSolv™ container and used as supplied. Non-aqueous reagents were transferred under nitrogen via syringe or cannula. Organic solutions 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_6D_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_3OEt_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

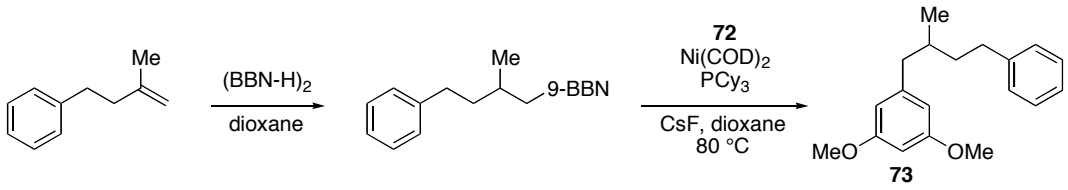
[60]Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals, 3rd ed.*; Pergamon Press, Oxford, 1988.

[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 Γ-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}; ^1H 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$\mathbf{H_3}$), 3.69 (s, 9H, NC$\mathbf{H_3}$) . ^{13}C NMR (125 MHz, $CDCl_3$) Γ 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.

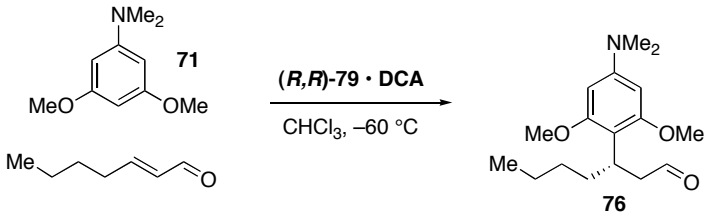


1,3-Dimethoxy-5-(2-methyl-4-phenylbutyl)benzene (73). The reagents and glassware in this reaction were thoroughly dried prior to use. Dioxane was prepared by freeze-pump thaw deoxygenation. A 0.6M stock solution of the alkyl BBN derivative was prepared as follows: To a flame-dried flask charged with 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.

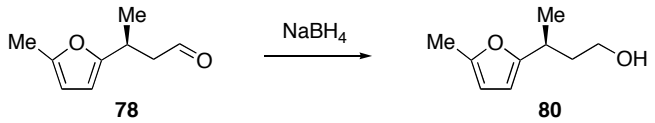
component in a mixture of other side products. Silica gel chromatography was done a second time to afford the title compound **73** as an oil with about 80% purity (10 mg, approx. 25% yield) ^{1}H NMR (300 MHz, $CDCl_3$) 7.14-7.32 (m, 5H, Ph**H**), 6.53 (d, 2H, *J* = 1.8 Hz, Ar**H**), 6.36 (t, 1H, *J* = 1.8 Hz, Ar**H**), 3.77 (s, 6H, OC**H**$_3$), 2.56-2.78 (m, 2H, ArC**H**HC**H**), 2.37 (dd, 1H, *J* = 9.0, 12.6 Hz, ArCH**H**), 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, $CDCl_3$) 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, CH**H**Et); 1.50–1.62 (m, 1H, **CH**HEt); 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

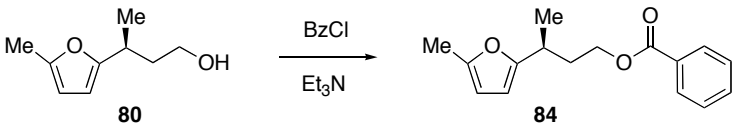
[63] Arevalo, F.; Castedo, L.; Fernandez, B. R.; Mourino, A.; Sarandese, L. *Chem. Lett.* **1998**, *5*, 745.

NMR (125 MHz, $CDCl_3$) □ 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; $[□]_D$= –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.



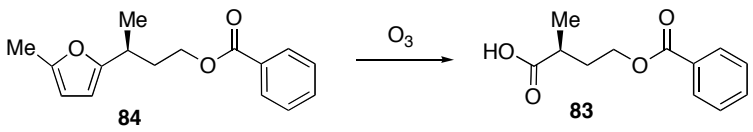
78 80

(*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_2Cl_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_2Cl_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, $CDCl_3$) □ 5.84 (m, 2H, Ar**H**), 3.65 (m, 2H, C**H$_2$**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_2OH), 1.76 (m, 1H, CH**H**CH_2OH), 1.25 (d, 3H, *J* = 6.6 Hz, CHC**H$_3$**). ^{13}C NMR (125 MHz, $CDCl_3$) □ 158.1, 150.2, 105.6, 104.2, 60.8, 38.7, 29.8, 19.3, 13.4; HRMS (EI+) exact mass calculated for $[M•]^+$ ($C_9H_{14}O_2$) requires *m/z* 154.0994, found *m/z* 154.0991. $[□]_D$= +21.6 (c = 1.2, $CHCl_3$).

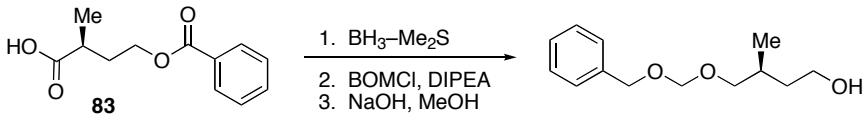


80 84

(*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}; ^1H NMR (300 MHz, $CDCl_3$) 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_2OH), 1.98 (ddt, 1H, *J* = 6.6, 7.2, 13.8 Hz, CH**H**CH_2OH), 1.25 (d, 3H, *J* = 6.6 Hz, CHC**H**$_3$). ^{13}C NMR (125 MHz, $CDCl_3$) 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 $[M\bullet]^+$ ($C_{16}H_{18}O_3$) requires *m/z* 258.1256, found *m/z* 258.1262. $[]_D$= +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}; ^1H NMR (300 MHz, $CDCl_3$) 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, C**H**$_2$OBz), 2.67 (app sex, 1H, *J* = 7.2 Hz, C**H**CH_3), 2.18 (m, 1H, *J* = C**H**HCH_2OBz), 1.88 (m, 1H, CH**H**CH_2OBz), 1.24 (d, 3H, *J* = 7.2 Hz, CHC**H**$_3$). ^{13}C NMR (125 MHz, $CDCl_3$) 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. $[]_D$= +18.8 (c = 1.0, $CHCl_3$).

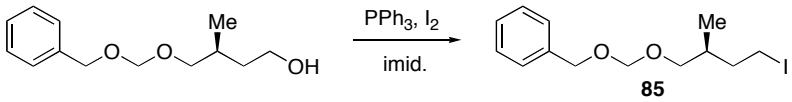


(*S*)-4-(Benzyloxymethoxy)-3-methylbutan-1-ol. Carboxylic acid **83** (12.3 g, 55.4 mmol) was taken up in 110 mL diethyl ether and cooled to 0 °C under a nitrogen atmosphere. Borane-dimethyl sulfide adduct (42 mL, 83.1 mmol) was added to the solution at 0 °C and the mixture was allowed to warm to ambient temperature for 2 h. The reaction was quenched with saturated $NaHCO_3$. 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_2Cl_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,

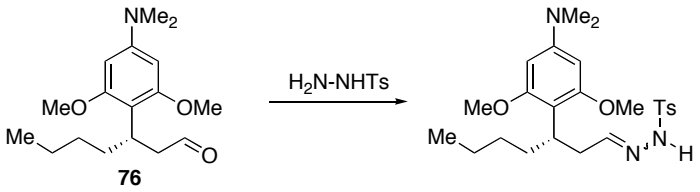
1047, 738, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.34 (m, 5H, Ar**H**), 4.77 (s, 2H, OC**H**$_2$O), 4.61 (s, 2H, PhC**H**$_2$O), 3.69 (m, 2H, C**H**$_2$OH), 3.48 (dd, 1H, *J* = 6.3, 12.0 Hz, BOMOC**H**H), 3.44 (dd. 1H, *J* = 6.3, 12.0 Hz, BOMOCH**H**), 2.11 (bs, 1H, O**H**), 1.91 (app sex, 1H, *J* = 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, $CDCl_3$) 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. $[]_D$= –3.87 (c = 1.0, $CHCl_3$).



85

(*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_2O 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}; ^1H NMR (300 MHz, $CDCl_3$) 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, CH**H**CH$_2$I), 1.94 (app sex, 1H, *J* = 6.3 Hz, C**H**CH$_3$), 1.75 (m, 1H, C**H**HCH$_2$I), 0.99 (d, 3H, *J* = 6.6 Hz, CHC**H**$_3$). ^{13}C NMR (125 MHz, $CDCl_3$) 137.8, 128.3, 127.8, 127.6, 94.7, 72.2, 69.3,

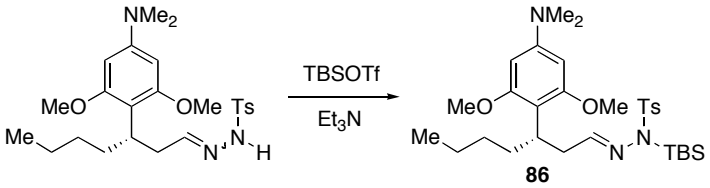
37.6, 34.4, 16.2, 4.6; HRMS (FAB+) exact mass calculated for $[MH]^+$ ($C_{13}H_{18}O_2I$) requires *m/z* 333.0352, found *m/z* 333.0359. $[\alpha]_D = -6.66$ (c = 1.1, $CHCl_3$).



(*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}; ^1H 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$\mathbf{H_3}$); *3.69* (s, 6H, OC$\mathbf{H_3}$); 3.35 (m, 1H, ArC**H**); 2.93 (s, 6H, NC$\mathbf{H_3}$); *2.92* (s, 6H, NC$\mathbf{H_3}$); 2.73 (m, 1H, C**H**HC=N); 2.56 (m, 1H, CH**H**C=N); *2.40* (s, 3H, $C_6H_4C\mathbf{H_3}$); 2.37 (s, 3H, $C_6H_4C\mathbf{H_3}$); 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, $C\mathbf{H_2}C\mathbf{H_2}CH_3$); 0.79 (t, 3H, *J* = 7.2 Hz, $CH_2C\mathbf{H_3}$); *0.76* (t, 3H, *J* = 7.2Hz, $CH_2C\mathbf{H_3}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 159.1,

[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 $[MH]^+$ ($C_{24}H_{36}N_3O_4S$) requires *m/z* 462.2427, found *m/z* 462.2411.

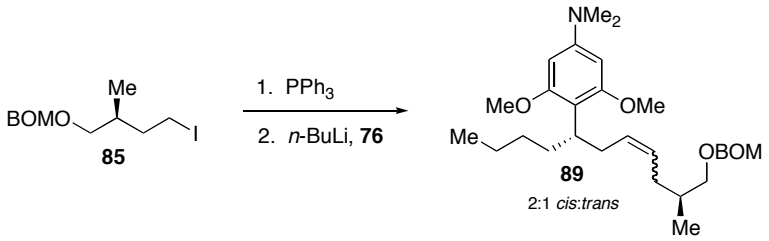


86

(*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}; ^1H NMR (300 MHz, CDCl3) □ 7.62 (m[65], 2H, ArH); 7.25 (m[65], 2H, ArH); 5.87 (s, 2H, Ar**H**); 3.73 (s, 6H, OC$\mathbf{H_3}$); 3.43 (m, 1H, ArC**H**); 2.93 (s, 6H, NC$\mathbf{H_3}$); 2.80 (m, 1H, C**H**HC=N); 2.61 (m, 1H, CH**H**C=N); 2.38 (s, 3H, $C_6H_4C\mathbf{H_3}$); 1.68-1.82 (m, 1H, CHC**H**HCH_2); 1.42-1.54 (m, 1H, CHCH**H**CH_2); 1.01-1.33

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

(m, 4H, C**H**$_2$C**H**$_2$CH$_3$); 0.89 (s, 9H, SiMe$_2$(C**H**$_3$)$_3$); 0.79 (t, 3H, *J* = 7.2 Hz, CH$_2$C**H**$_3$); 0.20 (d, 3H, *J* = 12.0 Hz, SiC**H**$_3$); 0.12 (d, 3H, *J* = 12.0 Hz, SiC**H**$_3$). ^{13}C NMR (125 MHz, $CDCl_3$) □ 173.8, 159.8, 150.7, 142.7, 129.3, 127.6, 126.2, 108.2, 90.1, 55.5, 53.7, 41.1, 37.9, 33.8, 32.2, 30.4, 27.1, 26.0, 25.9, 23.0, 21.8, 19.6, 14.4, -3.3, -4.2 ; HRMS (FAB+) exact mass calculated for [MH]$^+$ ($C_{30}H_{50}N_3O_4SiS$) requires *m/z* 576.3291, found *m/z* 576.3315.

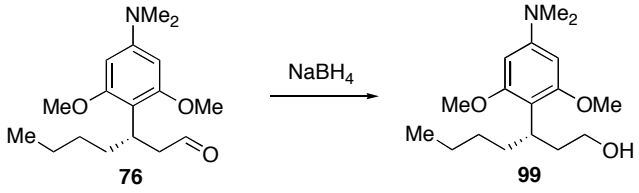


4-((5*S*,10*S*)-11-(Benzyloxymethoxy)-10-methylundec-7-en-5-yl)-3,5-dimethoxy-*N*,*N*-dimethylaniline (89).[66] Triphenylphosphine (40 mg, 0.15 mmol) was added to a solution of iodide **85** (50 mg, 0.15 mmol) in dry acetonitrile (0.38 mL, 0.4 M). The reaction was heated to reflux in a sealed vial for 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 □L, 0.145 mmol) was added, resulting in a reddish orange solution that was stirred for an hour at –78 °C. Aldehyde **76** (15 mg, 0.05 mmol) was added via syringe at –78 °C and it was stirred as this temperature for three hours,

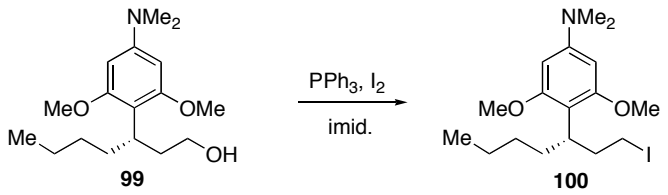
[66] Chemical shifts of minor *trans* isomer noted in *italics*.

during which time the solution turned yellow then brownish orange. The reaction was then warmed to –20 °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}; ^1H NMR (300 MHz, $CDCl_3$) □ 7.34 (m, 5H, Ph**H**), 5.96 (s, 2H, Ar**H**), 5.34 (m, 2H, C**H**=C**H**), 4.79 *4.75* (s, 2H, OC$\mathbf{H_2}$O), 4.64 *4.62* (s, 2H, PhC$\mathbf{H_2}$O), *3.83* 3.80 (s, 6H, OC$\mathbf{H_3}$), 3.50 (dd, 2H, *J* = 6.0, 9.6 Hz, BOMOC**H**H), 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$\mathbf{H_3}$), 2.45 (m, 2H, CHC$\mathbf{H_2}$), 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$\mathbf{H_3}$), 0.85 (t, 3H, *J* = 7.2 Hz, $CH_2C\mathbf{H_3}$). ^{13}C NMR (125 MHz, $CDCl_3$) □ 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 $[MH]^+$ ($C_{30}H_{46}O_4N$) requires *m/z* 484.3427, found *m/z* 484.23423. [□]$_D$= –1.95 (c = 1.0, $CHCl_3$).



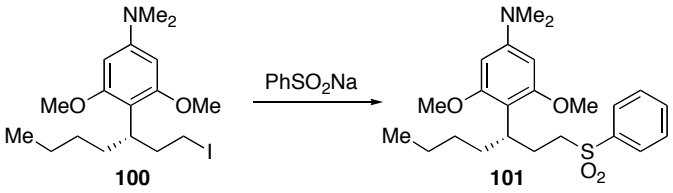
(*S*)-3-(4-(Dimethylamino)-2,6-dimethoxyphenyl)heptan-1-ol (99). Aldehyde **76** (2.65 g, 9.1 mmol) was taken up in 5 mL EtOH and 20 mL CH_2Cl_2. Sodium borohydride (1.8g, 45.5 mmol) was added in portions and stirred for 2 h at ambient temperature. The reaction was quenched with saturated $NaHCO_3$. The aqueous layer was separated and

extracted with EtOAc (2 x 50 mL). The organic layers were dried with sodium sulfate and the solvent was removed in vacuo. Flash chromatography (gradient elution: 10 to 40% EtOAc/hexanes) provided the primary alcohol **99** as a yellow oil (2.67 g, quantitative). IR (film) 3420 (bs), 2954, 2931, 2857, 1613, 1568, 1506, 1465, 1253, 1207, 1127, 1107, 798 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 5.93 (s, 2H, Ar**H**); 3.78 (s, 6H, OC**H**$_3$); 3.47 (m, 1H, Ar**CH**); 3.31 (m, 2H, C**H**$_2$OH); 2.95 (s, 6H, NC**H**$_3$); 2.04 (bs, 1H, OH); 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, $CDCl_3$) □ 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; $[□]_D$= –5.57 (c = 1.0, EtOH).



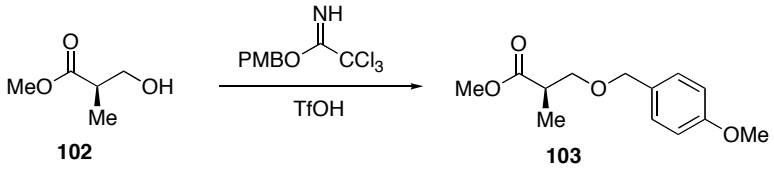
(*S*)-4-(1-Iodoheptan-3-yl)-3,5-dimethoxy-*N*,*N*-dimethylaniline (100). Iodine (2.42g, 9.55 mmol) was added to a mixture of triphenylphosphine (2.71g, 10.3 mmol) and imidazole (694 mg, 10.3 mmol) in 80 mL CH_2Cl_2 at 0 °C. Alcohol **99** (2.35g, 7.96 mmol) was added dropwise. The reaction was stirred at 0 °C for 30 min. and warmed to 23 °C for 1 h. The reaction was quenched with 150 mL saturated NH_4Cl, which was then extracted with CH_2Cl_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_2O/pentanes, silica pretreated with Et_3N) 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}; ^1H NMR (300 MHz, C_6D_6) □ 5.84 (s, 2H, Ar**H**); 3.62 (tt, 1H, *J* = 5.4, 9.9 Hz, ArC**H**); 3.41 (broad s, 6H, OC$\mathbf{H_3}$); 3.00-3.14 (m, 2H, C$\mathbf{H_2}$I); 2.71 (m, 1H, CH**H**CHCH_2); 2.59 (s, 6H, NC$\mathbf{H_3}$); 2.28 (m, 1H, C**H**HCHCH_2); 2.08 (m, 1H, CH_2CHC**H**H); 1.70 (m, 1H, CH_2CHCH**H**); 1.24-1.44 (m, 4H, C$\mathbf{H_2}$C$\mathbf{H_2}$CH_3); 0.86 (t, 3H, *J* = 7.2 Hz, CH_2C$\mathbf{H_3}$); ^{13}C NMR (125 MHz, C_6D_6) □ 160.2, 150.8, 108.1, 90.4, 55.1, 40.4, 39.3, 36.3, 34.0, 30..8, 23.3, 14.4, 6.6; HRMS (FAB+) exact mass calculated for $[MH]^+$ ($C_{17}H_{228}INO_2$) requires *m/z* 405.1165, found *m/z* 405.1156; $[□]_D$= +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 ($PhSO_2Na$, 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}; ^1H NMR (300 MHz, $CDCl_3$) □ 7.84 (m, 2H, Ph**H**), 7.62 (m, 1H, Ph**H**), 7.52 (m, 2H, Ph**H**), 5.83 (s, 2H,

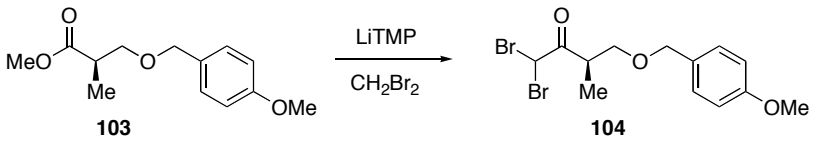
Ar**H**); 3.64 (broad s, 6H, OC**H**$_3$); 3.14 (m, 1H, ArC**H**); 2.94 (m, 1H, C**H**HS); 2.93 (s, 6H, NC**H**$_3$); 2.82 (ddd, 1H, *J* = 4.8, 12.6, 14.1 Hz, CH**H**S), 2.17 (m, 1H, CH**H**CHCH$_2$); 1.87 (m, 1H, C**H**HCHCH$_2$); 1.72 (m, 2H, CH$_2$CHC**H**H); 1.45 (m, 1H, CH$_2$CHCH**H**); 0.96-1.32 (m, 5H, CH$_2$CHCH**H** and C**H**$_2$C**H**$_2$CH$_3$); 0.78 (t, 3H, *J* = 7.2 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) □ 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 $[MH]^+$ ($C_{23}H_{33}NO_4S$) requires *m/z* 419.2130, found *m/z* 419.2131; $[\square]_D$= –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 □L, 0.168 mmol) was added via syringe. The reaction was warmed to ambient temperature

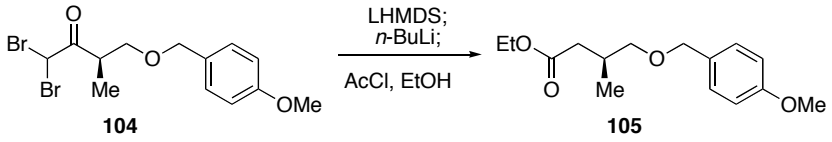
and stirred for 12 h. Additional portions of 30 μL triflic acid were added every 2 h until the reaction stopped progressing, as indicated by TLC analysis. The reaction was quenched with 150-200 mL saturated $NaHCO_3$. The aqueous layer was separated and extracted with pentanes (3 x 100 mL). The collected organic layers were washed with brine, dried with sodium sulfate and the solvents were removed in vacuo. Flash chromatography (15% Et_2O/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}; ^1H 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, C**H**HOPMB), 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. $[\alpha]_D$= –8.23 (c = 1.0, $CHCl_3$).



103 **104**

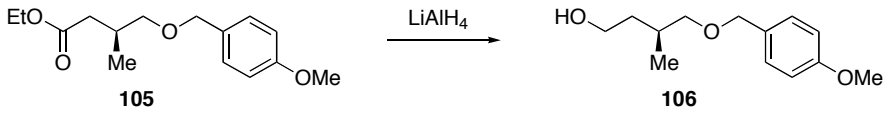
(*R*)-1,1-Dibromo-4-(4-methoxybenzyloxy)-3-methylbutan-2-one (104). LiTMP was generated in a flame-dried round bottom flask at 0 °C under argon by the addition of *n*-BuLi (2.5M, 4 mL, 10.0 mmol) to a solution of tetramethylpiperidine (1.85 mL, 11.0 mmol) in 15 mL THF. The LiTMP was transferred via cannula 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_2O/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}; ^1H 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 $[M\bullet]^+$ ($C_{13}H_{16}O_3Br_2$) requires m/z 379.9446, found m/z 379.9438. $[\alpha]_D$= –129.6 (c = 1.0, $CHCl_3$).



(*S*)-Ethyl 4-(4-methoxybenzyloxy)-3-methylbutanoate (105). LiHMDS was freshly generated by adding *n*-BuLi (1.6 mL, 4.00 mmol) to a solution of HMDS (0.87 mL, 4.18 mmol) in 18 mL THF at 0 °C under argon. This LHMDS solution was transferred via syringe to an addition funnel that was equipped to a flask already cooled to –78 °C and charged with dibromoketone **104** (1.395 g, 3.67 mmol) in 18 mL THF. LHMDS was slowly added dropwise over 20 minutes, and the reaction was stirred for an additional 20 minutes at –78 °C. 3.2 mL *n*-BuLi (8.07 mmol) was added and the reaction was stirred at –78 °C for 30 minutes. This reaction was transferred dropwise via cannula to an acidic solution of acetyl chloride (14 mL) in ethanol (72 mL). Upon completion of the addition

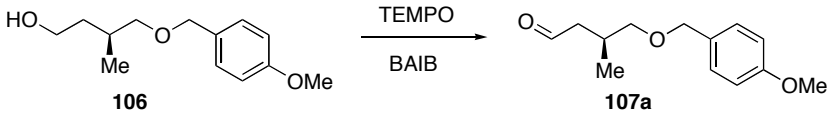
the reaction was quenched with water. The aqueous layer was separated and extracted with diethyl ether (3 x 50 mL). The organic extracts were washed with brine, dried with magnesium sulfate, and the solvents removed in vacuo. Flash chromatography (1:6.5 Et_2O/pentanes) provided the homologated ester **105** as a slightly yellow oil (721 mg, 74% yield). IR (film) 2960, 2859, 1732, 1613, 1514, 464, 1373, 1302, 1248, 1180, 1094, 1035, 820 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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, C**H**HOPMB), 2.47 (dd, 2H, *J* = 5.7, 15.0 Hz, C**H**HCO_2Et), 2.29 (m, 1H, $CHCH_2$), 2.13 (dd, 2H, *J* = 8.1, 15.0 Hz, C**H**HCO_2Et), 1.23 (t, 3H, *J* = 7.2 Hz, OCH_2C**H**$_3$), 0.96 (d, 3H, *J* = 6.3 Hz, CHC**H**$_3$). ^{13}C NMR (125 MHz, $CDCl_3$) 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 $[M\bullet]^+$ ($C_{15}H_{22}O_4$) requires *m/z* 266.1518, found *m/z* 266.1508. $[]_D$= –3.34 (c = 1.0, $CHCl_3$).



105 106

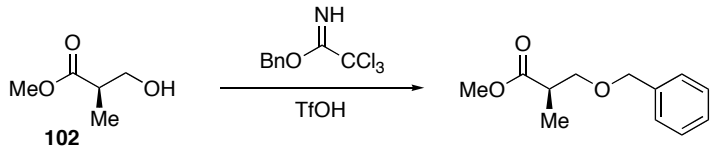
(*S*)-4-(4-Methoxybenzyloxy)-3-methylbutan-1-ol (106). Lithium aluminum hydride (154 mg, 4.06 mmol) was added to a solution of ester **105** (721 mg, 2.71 mmol) in 13.6 mL diethyl ether at 0 °C. The reaction was stirred for 1 h. A saturated aqueous Na/K tartrate solution was added and the biphasic mixture 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}; ^1H NMR (300 MHz, $CDCl_3$) 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, C**H**HOPMB), 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, $CDCl_3$) 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 $[M\bullet]^+$ ($C_{13}H_{20}O_3$) requires *m/z* 224.1413, found *m/z* 224.1421. $[]_D$= –4.48 (c = 1.0, $CHCl_3$).



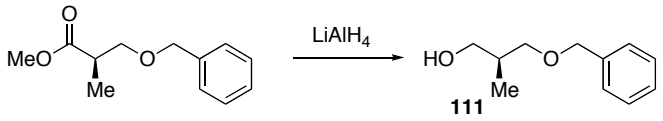
(*S*)-4-(4-Methoxybenzyloxy)-3-methylbutanal (107a). Bisacetoxyiodosobenzene (95 mg, 0.295 mmol) was added to a solution of alcohol **106** (60 mg, 0.269 mmol) in 0.54 mL CH_2Cl_2. TEMPO (6 mg, 0.0384 mmol) was added and the reaction was stirred for 3 h at room temperature. The reaction was quenched with 3 mL saturated $Na_2S_2O_3$. 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_2O/pentanes) provided the aldehyde as a clear oil (41 mg, 70% yield). IR (film) 3390 (broad), 2838, 1722, 1612, 1513, 1463, 1362, 1302, 1247, 1174, 1090, 1034, 820 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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$\mathbf{H_3}$). ^{13}C NMR (125 MHz, $CDCl_3$) 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 $[M\bullet]^+$ ($C_{13}H_{18}O_3$) requires *m/z* 222.1256, found *m/z* 222.1258. $[]_D = -13.4$ (c = 1.0, $CHCl_3$).



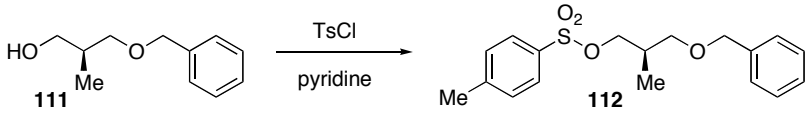
(*R*)-Methyl 3-(benzyloxy)-2-methylpropanoate. To a solution of the (*R)*-Roche ester **102** (5g, 42.3 mmol) and benzyl trichloroacetimidate (13.28g, 52.8 mmol) in cyclohexane/CH_2Cl_2 (160 mL, 2:1 v:v) at 23 °C under an argon atmosphere, triflic acid (0.38 mL, 4.23 mmol) was added via syringe. The reaction mixture was stirred for 17 h, during which time CCl_3CONH_2 precipitated out of solution. The heterogeneous reaction mixture was filtered and washed with cold CH_2Cl_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, $CDCl_3$). 7.33 (m, 5H, Ar**H**); 4.52 (s, 2H, C$\mathbf{H_2}$OBn); 3.70 (s, 3H, CO_2C$\mathbf{H_3}$); 3.70 (s, 3H, CO_2C$\mathbf{H_3}$); 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$\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$). 175.3, 138.1, 128.3(x2), 127.5(x2), 127.5, 73.1, 76.6, 51.7, 40.1, 14.0; HRMS (EI+) exact mass

calculated for $[M\bullet]^+$ ($C_{13}H_{18}O_4$) requires *m/z* 208.1100, found *m/z* 208.1095; $[\alpha]_D$ = –11.45 (c = 1.23, $CHCl_3$).

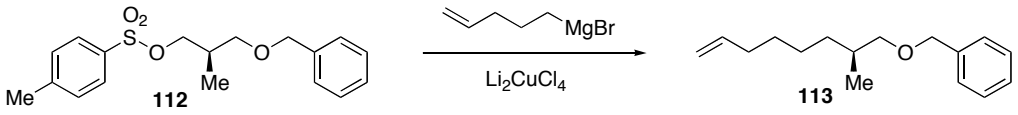


111

(*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_2O, 5.5 mL 2N NaOH, and then 12.5 mL H_2O 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}. ^1H 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 $[M\bullet]^+$ ($C_{13}H_{16}Br_2O_3$) requires *m/z* 180.1150, found *m/z* 180.1144; $[\alpha]_D$ = –16.09 (c = 1.36, $CHCl_3$).

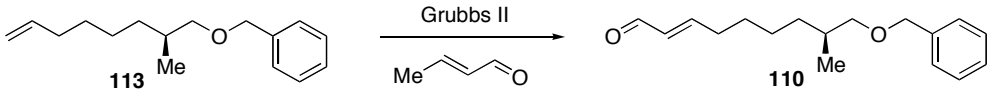


(*R*)-3-(benzyloxy)-2-methylpropyl 4-methylbenzenesulfonate (112). *p*-Toluenesulfonyl chloride (12.9 g, 67.5 mmol) was added to a solution of alcohol **111** (9.25 g, 51.9 mmol) in 200 mL pyridine at 0 °C. The reaction was stirred at room temperature for 13 h. The reaction was poured into ice-cooled 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}. ^1H NMR (300 MHz, $CDCl_3$). □ 7.87 (m, 2H, Ar**H**); 7.30 (m, 2H, Ar**H**); **7**.22-7.36 (m, 5H, CH_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_2Et); 0.94 (d, 3H, *J* = 6.6 Hz, CHC**H**$_3$); ^{13}C NMR (75 Mhz, $CDCl_3$). □ 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 $[M\bullet]^+$ ($C_{15}H_{22}O_4$) requires *m/z* 334.1239, found *m/z* 334.1231; $[□]_D = –6.42$ (c = 1.06, $CHCl_3$).



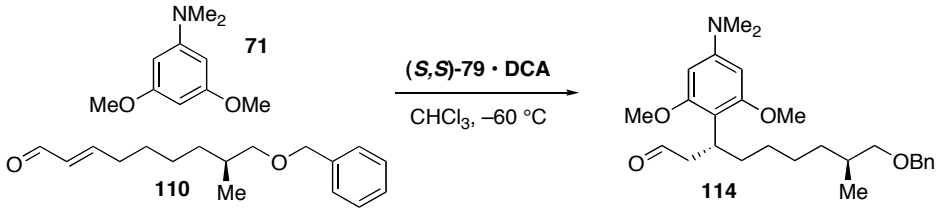
(*S*)-((2-Methyloct-7-enyloxy)methyl)benzene (113). 5-Bromopentene (2.2 mL, 18.7 mmol) was added to magnesium turnings (509 mg, 20.9 mmol) in 9.4 mL dry THF. A small crystal of iodine was added before the reaction was refluxed at 65 °C for 2 h. The reaction was cooled to ambient temperature to produce 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}; ^1H NMR (300 MHz, $CDCl_3$) □ 7.21-7.38 (m, 5H, Ar**H**); 5.82 (ddt, 1H, *J* = 3.0, 3.6, 6.6 Hz, $CH_2C\mathbf{H}=CH_2$); 4.97 (m, 2H, *J* = $CH_2CH=C\mathbf{H_2}$); 4.51 (s, 2H, $C\mathbf{H_2}OBn$); 3.34 (dd, 1H, *J* = 6.0, 9.0 Hz, C**H**HOBn); 3.25 (dd, 1H, *J* = 6.6, 9.0, C**H**HOBn); 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, $CDCl_3$) □ 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 $[M\bullet]^+$ ($C_{18}H_{26}O_4$) requires *m/z* 232.1827, found *m/z* 232.1822; $[\square]_D$= –0.31 (c = 1.50, $CHCl_3$).



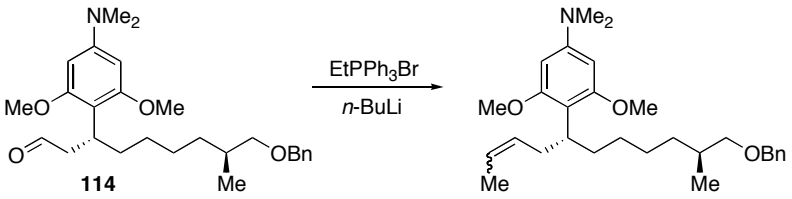
(*S*,*E*)-9-(Benzyloxy)-8-methylnon-2-enal (110). The second-generation Grubbs catalyst (268 mg, 0.317 mmol) was added to a solution of olefin **113** (1.47 g, 6.33 mmol) and crotonaldehyde (2.62 mL, 31.7 mmol) in CH_2Cl_2 (31 mL, 0.2M). The reaction was heated to 40 °C for 18 h. The crotonaldehyde and solvent were evaporated in vacuo. The crude reaction residue was subjected to silica gel flash chromatography (20% Et_2O/hexanes), which provided □,□-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, $CDCl_3$) □ 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, C**H**HOBn); 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, $CDCl_3$) □ 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 $[M\bullet]^+$ ($C_{18}H_{26}O_4$) requires *m/z* 260.1776, found *m/z* 260.1781; $[\alpha]_D$= –2.50 (c = 1.21, $CHCl_3$).



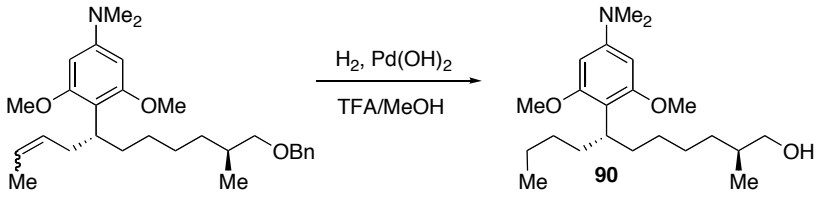
(3*R*,8*S*)-9-(Benzyloxy)-3-(4-(dimethylamino)-2,6-dimethoxyphenyl)-8-methyl-nonanal (114). 3,5-Dimethoxy-*N,N*-dimethylaniline (181 mg, 1m mmol) was added to a solution of imidazolidinone **(*S,S*)-79 • DCA** (75 mg, 0.2 mmol) in 4 mL $CHCl_3$. The reaction was cooled to –60 °C, at which point α,β-unsaturated 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, C**H**O); 7.25-7.33 (m, 5H, Ar**H**); 5.89 (s, 2H, Ar**H**); 4.48 (s, 2H, C$\mathbf{H_2}$OBn); 3.77 (s, 6H, OC$\mathbf{H_3}$); 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, C**H**HOBn); 2.94 (s, 6H, NC$\mathbf{H_3}$); 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$\mathbf{H_3}$); ^{13}C 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; $[\alpha]_D$= –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.



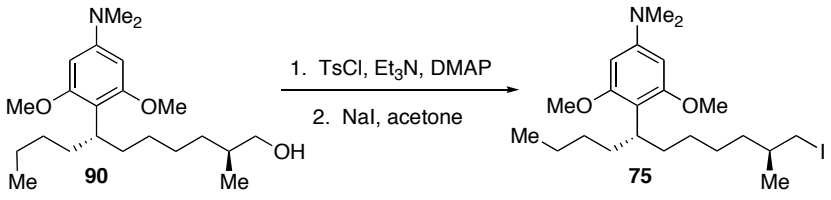
4-((5*R*,10*S*)-11-(Benzyloxy)-10-methylundec-2-en-5-yl)-3,5-dimethoxy-*N*,*N*-dimethylaniline. (Minor chemical shifts of (*E*)-olefin are in parentheses.) *n*-BuLi (4.52 mL, 11.32 mmol) was added to a heterogeneous mixture of ethyl triphenylphosphonium bromide (4.2 g, 11.32 mmol) in 45 mL THF at 0 °C 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-((5*R*,10*S*)-11-(benzyloxy)-10-methylundec-2-en-5-yl)-3,5-dimethoxy-*N*,*N*-dimethylaniline as a yellow oil as approximately a 2:1

mixture of *cis*:*trans* olefin isomers (1.53 g, 75% yield). IR (film) 2929, 2854, 1612, 1566, 1503, 1452, 1359, 1254, 1203, 1130, 1107, 1008, 797, 735, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.25-7.33 (m, 5H, Ar**H**); 5.92 (s, 2H, Ar**H**); 5.33 (m, 2H, C**H**=C**H**), 4.48 (s, 2H, C$\mathbf{H_2}$OBn); 3.77 (s, 6H, OC$\mathbf{H_3}$); 3.30 (dd, 1H, *J* = 5.7, 9.0 Hz, C**H**HOBn); 3.23 (m, 1H, ArC**H**); 3.19 (dd, 1H, *J* = 6.0, 9.0, C**H**HOBn); 2.94 (s, 6H, NC$\mathbf{H_3}$); 2.3-2.5 (m, 2H, C$\mathbf{H_2}$CH=CH); 1.65-1.85 (m, 2H, C**H**Me and C**H**(alkyl)); 1.56(1.58) (d, 3H, *J* = 7.2 Hz, C$\mathbf{H_3}$CH=CH); 1.01-1.40 (m, 6H, C**H**(alkyl)); 0.89 (d, 3H, *J* = 6.6 Hz, CHC$\mathbf{H_3}$); ^{13}C NMR (125 MHz, $CDCl_3$) 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



(2*S*,7*S*)-7-(4-(Dimethylamino)-2,6-dimethoxyphenyl)-2-methylundecan-1-ol (90). 4-((5*R*,10*S*)-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}; ^1H NMR (300 MHz, $CDCl_3$) □ 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_2C**H**$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) □ 149.8, 128.8, 111.1, 90.5, 68.4, 55.7, 40.8, 35.8, 34.5, 34.0, 33.8, 33.1, 30.6, 29.7, 28.5, 27.8, 27.0, 22.9, 16.6, 14.1; HRMS (FAB+) exact mass calculated for $[MH]^+$ ($C_{22}H_{39}NO_3$) requires *m/z* 365.2930, found *m/z* 365.2937.



4-((5*S*,10*S*)-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 □L, 3.28 mmol), and DMAP (194 mg, 0.602 mmol) in 5.5 mL CH_2Cl_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_2Cl_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). ^{1}H NMR (300 MHz, C_6D_6) 5.93 (s, 2H, Ar**H**), 3.65 (tt, 1H, *J* = 5.1, 9.3 Hz, ArC**H**), 3.52 (s, 6H, OC**H**$_3$), 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**H**$_3$), 2.24 (m, 2H, CHC**H**$_2$), 1.85 (m, 2H, C**H**$_2$CH), 0.9-1.56 (m, 11H, C**H**(alkyl)), 0.92 (t, 3H, *J* = 7.2 Hz, CH_2C**H**$_3$), 0.75 (d, 3H, *J* = 6.0 Hz, C**H**$_3$CH). ^{13}C NMR (125 MHz, CD_6D_6) 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.

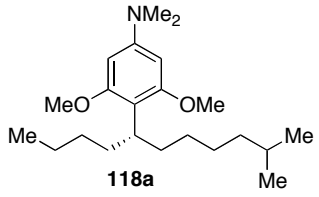
Reaction procedure for the cross-coupling Suzuki dimerization:

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.



118a

(*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_2C**H**$_3$).

C h a p t e r 4

Progress Towards the Total Synthesis of Cylindrocyclophane A: Cross-Coupling with an Alkenyl Potassium Trifluoroborate Salt.

I. A New Synthetic Target: Cylindrocyclophane A.

The ineffective *B*-alkyl Suzuki cross-coupling/dimerization strategy of the first-generation approach to cylindrocyclophane F prompted the investigation of alternative routes to assemble the 22-membered macrocycle. The *B*-alkyl Suzuki cross-coupling was abandoned in favor of a strategy that featured a transmetalation partner that was reactive but stable to isolation and purification prior to use. The advantage of the previous synthesis was the extraordinary control observed in the installation of both stereocenters using organocatalytic methods. These reactions were carried over into a new study directed towards the total synthesis of cylindrocyclophane A.

i. *Revisiting the cross-coupling of trimethylanilinium salts.*

In order to find a suitable cross-coupling transmetalation partner, a variety of organometallic reagents were tested for reactivity. These included alkenyl and alkynyl substrates that employed magnesium, tin, boronic acids, boronic esters, and potassium trifluoroborate salts (Fig. 1).

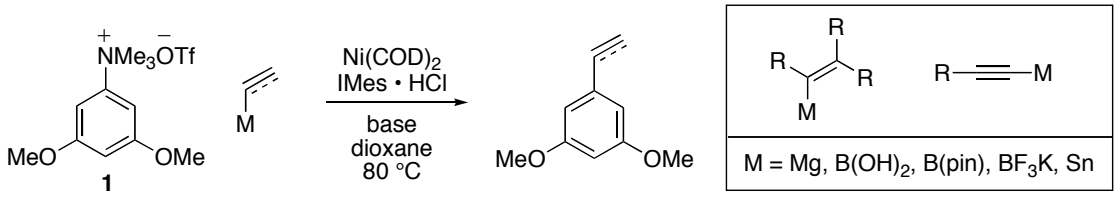
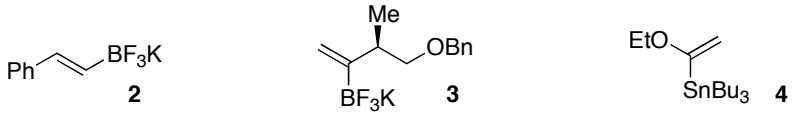


Figure 1. Transmetalation reagents operable with Ni(0) cross-coupling.

Of the reagents tested, three of them showed reactivity with the electron-rich model system **1**. Both 1,2- and 1,1-disubstituted potassium trifluoroborate salts (**2b** and **3**)[1] gave modest yields under the reaction conditions shown in figure 1 using potassium hydroxide as the base.[2] Activated α-ethoxytributylstannane **4** cross-coupled to produce a new carbon-carbon bond with the best yield seen thus far.



This presented two options to incorporate **4** as part of a convergent synthetic effort.[3] The first of these was to incorporate a species such as **5**, which would possess all the carbons necessary for dimerization of the molecule, for example, by the ring-closing metathesis dimerization strategy introduced in the Smith synthesis. However, both

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[1] **2** is commercially available. **3** was synthesized in six steps from the commercially available (*R*)-3-hydroxy-2-methylpropionic acid methyl ester (commonly referred to as (*R*)-Roche methyl ester). See supporting information for the procedure and characterization.

[2] Cesium fluoride also was an equally effective base. However, reactions utilizing the BF_3K salts were cleaner with KOH.

[3] (a) Smith, A. B., III; Kozmin, S. A.; Adams, C. M.; Paone, D. V. *J. Am. Chem. Soc.* **2000**, *122*, 4984. (b) Smith, A. B., III; Adams, C. M.; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 5925.

macrocycle **7** and monomer **6** lack any conformational bias that would be necessary to induce a diastereoselective alkylation (Fig. 2).

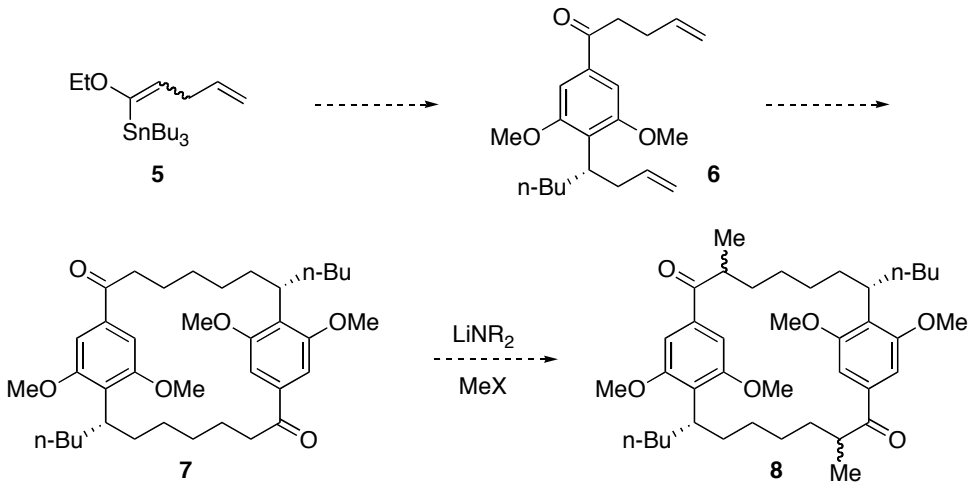


Figure 2. Lack of diastereocontrol in an alkylation of the macrocycle.

Potassium trifluoroborate salts have received considerable attention within the past decade as cross-coupling partners and other nucleophiles.[4] While more reactive than their boronic acid or ester counterparts, they are bench-stable salts that are capable of isolation. Because of these desirable properties, 1,1-disubstituted potassium trifluoroborate salt **4** was incorporated into a new retrosynthetic strategy.

ii. *Retrosynthetic strategy for cylindrocyclophane A.*

The retrosynthetic strategy for a second-generation approach to the cylindrocyclophanes targeted cylindrocyclophane A (**9**) (Fig. 3), which was expected to

[4] For recent reviews on potassium trifluoro(organo)borates, see: (a) Molander, G. A.; Figueroa, R. *Aldrichimica Acta* **2005**, *38*, 49. (b) Darses, S.; Genet, J. P. *Eur. J. Org. Chem.* **2003**,

arise from C_2-symmetric bisketone **10**. Formation of the macrocycle would be accomplished via ring-closing metathesis dimerization of triene **11**, which is the product of a nickel(0)-catalyzed cross-coupling of trimethylanilinium salt **13** and potassium trifluoroborate **12**. The 1,1-substitution of the methylene in **12** would be accessible from alkynyl aldehyde **14** in a few transformations. The lone stereocenter in **14** is the product of an enantioselective organocatalytic hydride reduction of alkynyl enal **16** using methodology recently developed in the MacMillan group. Trimethylanilinium salt **13** can be synthesized in a few steps from aldehyde **15**, which is a product of the enantioselective organocatalytic addition of electron-rich anilines into heptenal. This reaction was discussed in chapter 3 of this manuscript.

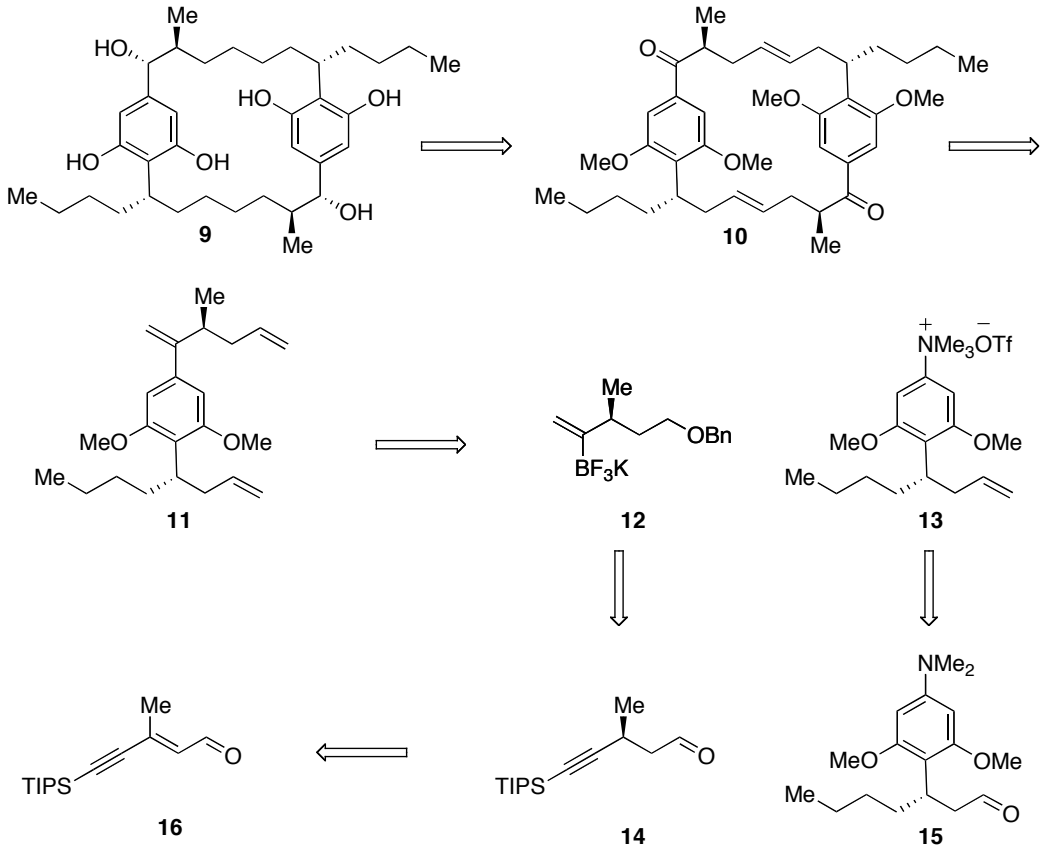
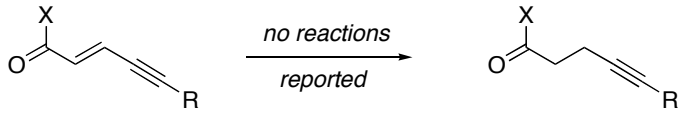


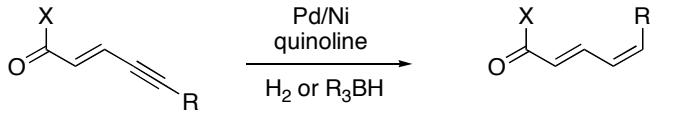
Figure 3. Retrosynthetic plan for cylindrocyclophane A.

II. Organocatalytic 1,4-Hydride Reduction of α,β-Unsaturated Aldehydes.

It is not an easy synthetic task to reduce an olefin in the presence of an alkyne, especially in an unsaturated system as shown in figure 3. In fact, a survey of the literature revealed that there are no reported instances of such a chemoselective transformation in which the α,β-unsaturated olefin is reduced before the β,γ-unsaturated alkyne (eq. 1). Traditional hydrogenation techniques will reduce the alkyne faster than the olefin in the same system (eq. 2).[5] However, it was hypothesized that a 1,4-nucleophilic addition into an activated α,β-unsaturated system might accomplish the reduction of the olefin in the presence of a neighboring alkyne.



(1)



(2)

In 2005, Ouellet, Tuttle, and MacMillan showed that chiral *tert*-butylimidazolidinone **17** was highly effective in catalyzing the 1,4-reduction of enals using the Hantzsch ester as a hydride source.[6] The Hantzsch ester is analogous to the biologically important reducing agent NADH (Fig. 4).[7]

---

[5] (a) Bayer, A.; Maier, M. E. *Tetrahedron.* **2004**, *60*, 6665. (b) Conde, J. J.; McGuire, M.; Wallace, M. *Tetrahedron Lett.* **2003**, *44*, 3081. (c) Kobayashi, S.; Shigekazu, M.; Mukaiyama, T. *Chem. Lett.* **1988**, *9*, 1491.

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

[7] For reviews on Hantzsch esters, see: (a) Eisner, U.; Kuthan, J. *Chem. Rev.* **1972**, *1*, 1. (b) Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223. (c) Lavilla, R. *J. Chem. Soc., Perkin Trans.* **2002**, *1*, 1141.

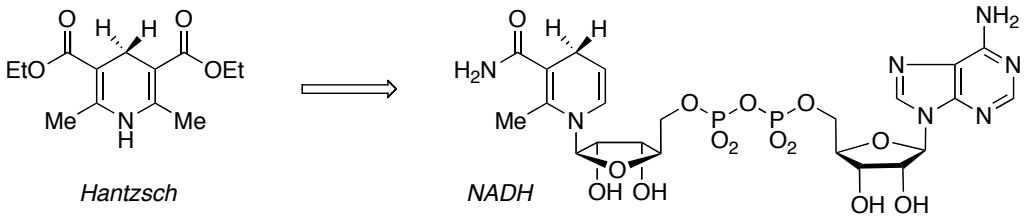
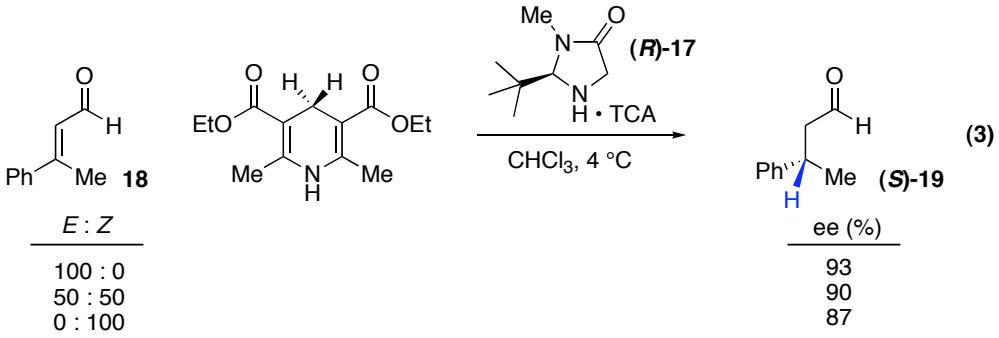


Figure 4. Hantzsch ester as a biological mimetic for NADH.

The scope of this reduction included a wide array of functional groups on the enal, including aryl, alkyl, and heteroatom moieties. Interestingly, it was shown that the olefin geometry did not affect the sense of enantioinduction in the reaction. For example, equation 3 shows that various (*E*) and (*Z*) olefin isomer mixtures of □-methylcinnamaldehyde (**18**) led to the same enantiomer of product **19**.



Hydride delivery is considered to be the irreversible rate-determining step; therefore the catalyst **17** and its co-catalyst are involved in pre-equilibrium isomerization of the enal starting material (Fig. 5). The steric bulk of the *tert*-butyl group on the catalyst framework experiences an unfavorable steric interaction with the larger phenyl group (R_L) in *cis*-**18**, thus making *trans*-**18** the reactive intermediate that undergoes reduction to give (*S*)-**19** as the favored product.

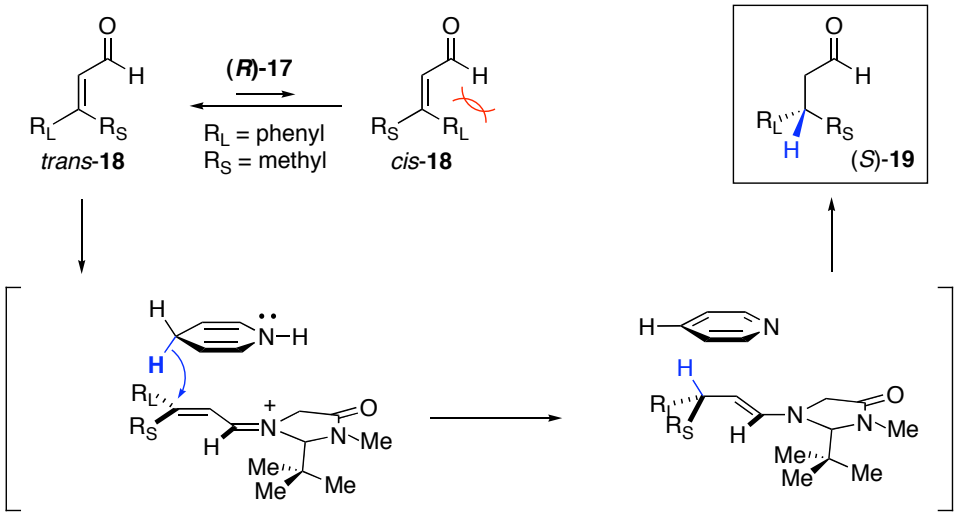
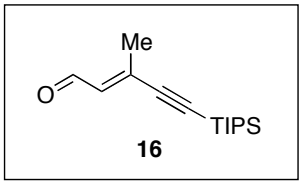


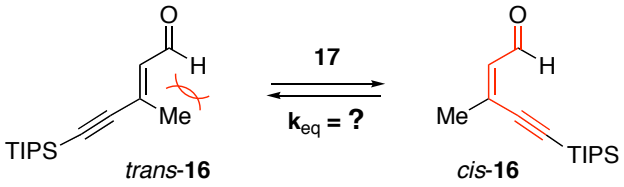
Figure 5. Catalyst-assisted isomerization of α,β-unsaturated aldehydes.



The approach to cylindrocyclophane A required the reduction of β-alkynylcrotonaldehyde **16**. This would require a closer look at the isomerization process. In the example in figure 4, the electronic preference of the phenyl group to be conjugated with the enal π-system favors *trans*-**18**. The steric requirement reinforces the electronic bias because phenyl is larger than methyl, thus the *trans* configuration should be favored as well.

However, with alkynylcrotonaldehyde **16**, the alkynyl group is *smaller* than the methyl group and thus, based on the steric argument, the methyl group would prefer to be *trans* to the aldehyde to favor *cis*-**16** (eq. 4). Yet electronically, the alkynyl group should prefer to be placed *trans* in order to remain in conjugation with the π-system as depicted

in *trans*-**16**. Thus the question of whether sterics or electronics dominates the isomerization process arose.



(4)

The olefin isomers *trans*-**16** and *cis*-**16** were synthesized separately (Scheme 1). The *trans* olefin geometry was set by Heck reaction of TIPS-acetylene onto the commercially available alkyne **20**, which is known to occur through a *syn*-addition of the alkynyl palladium species, to give isomerically pure enyne **21** in good yield.[8] Reduction of the ester followed by Dess-Martin oxidation afforded the desired *trans*-**16** as a single olefin isomer. Synthesis of the *cis* isomer began with (*Z*)-3-iodo-2-buten-1-ol (**22**), which was synthesized in a single transformation from the Red-Al reduction of 2-butenol followed by an iodine quench.[9] Sonogashira coupling of vinyl iodide 2**2** with TIPS-acetylene gave (*Z*)-allylic alcohol **23**.[10] Lastly, a Parikh-Doering oxidation[11] proceeded without any olefin isomerization to provide *cis*-**16** in excellent yield.

---

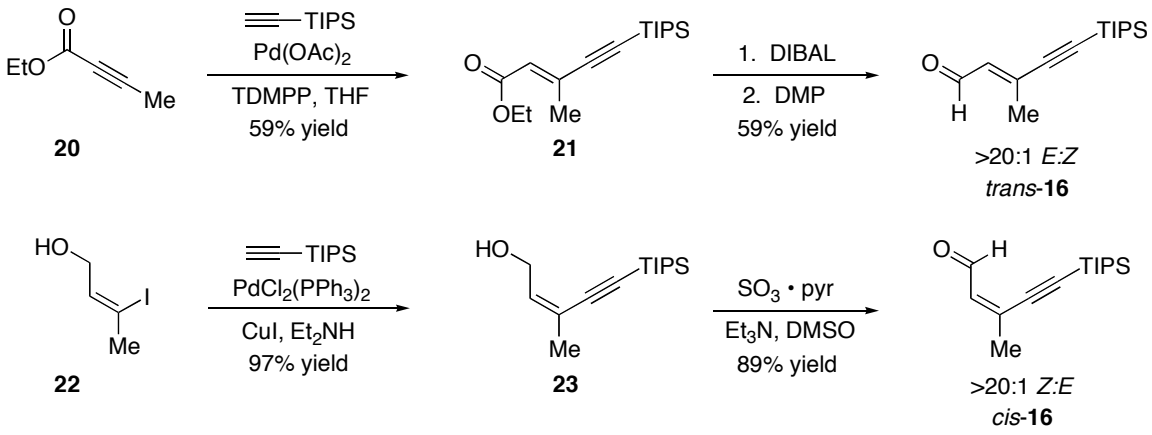
[8] Trost, B. M.; Sorum, M. T.; Chan, C.; Tuehter, G.. *J. Am. Chem. Soc.*. **1997**, *119*, 698.

[9] Dakoji, S.; Li, D.; Agnihotri, G.; Zhou, H.-Q.; Liu, H.-W. *J. Am. Chem. Soc.* **2001**, *123*, 9749.

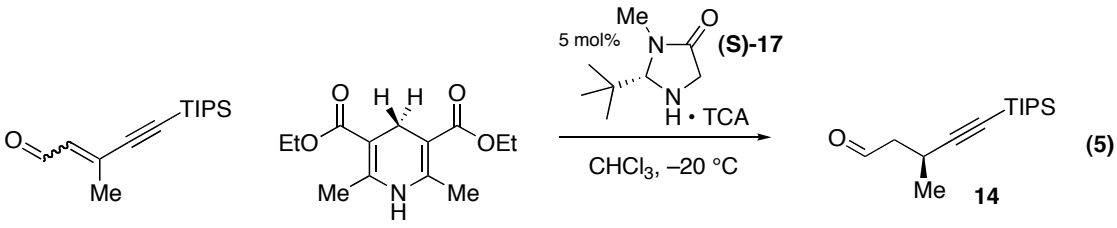
[10] Odedra, A.; Wu, C.-J.; Madhushaw, R. J.; Wang, S.-L.; Liu, R.-S. *J. Am. Chem. Soc.* **2003**, *125*, 9610.

[11] Parikh, J. P.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

Scheme 1. Synthesis of (*E*)- and (*Z*)-alkynyl enals.



When both isomers of enal **16** were subjected to catalytic (*S*)-*tert*-butylimidazolidinone **17** in the presence of 1.2 equivalents of the Hantzsch ester, a 1,4 reduction was observed without any reaction of the alkyne (eq. 5). Just as with the previous example, both isomers of enal **16** gave the same enantiomer of the product. Correlation to a known compound[12] proved that the desired (*S*)-enantiomer of product **14** was being produced.



(5)

substrate	*E* : *Z*	yield (%)	ee (%)
trans-**16**	>20 : 1	74	+90
cis-**16**	1 : >20	79	+92

[12] See supporting information of this chapter for the chemical correlation to a literature-reported compound.

In this example, sterics dominates over electronics in the imidazolidinone-catalyzed isomerization of the □,□-unsaturated aldehydes that occurs *before* the organocatalytic hydride reduction event. Figure 6 shows the two iminium conformations that are produced upon condensation of catalyst **17** with *cis* and *trans* alkynyl enal **16**. The iminium of *trans*-**16** may result in an unfavorable interaction between the catalyst framework and the methyl group, which is the larger substituent for this substrate. This would force the equilibrium towards the iminium of *cis*-**16** and force the alkynyl substituent out of conjugation in order to avoid the steric interaction.

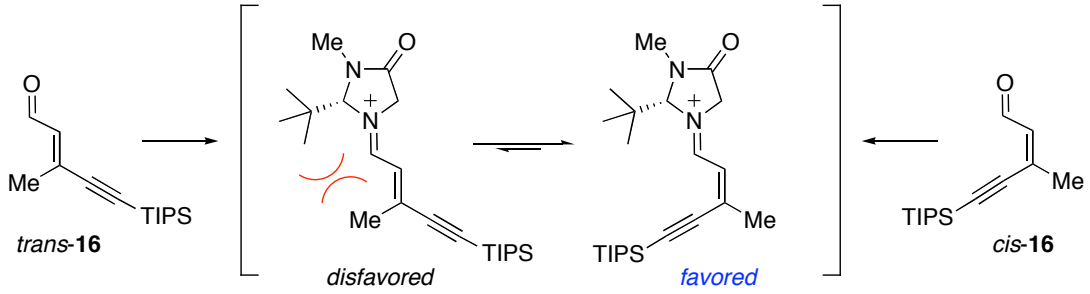
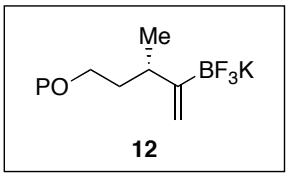


Figure 6. Sterics was the dominating factor in the iminium olefin isomerization.

III. Synthesis of Potassium Trifluoroborate Cross-Coupling Substrates.

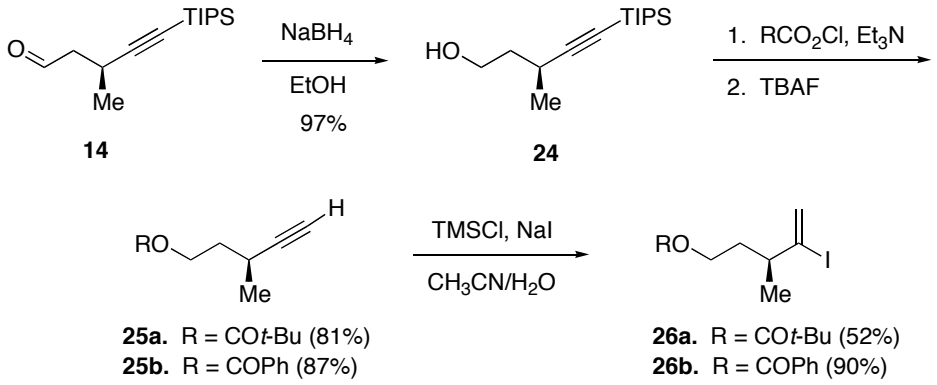
The choice of protecting group of potassium trifluoroborate salt **12** was crucial in the cross-coupling reaction with trimethylanilinium salt **13**. There were two considerations that were important: (i) the protecting group should withstand the basic conditions of refluxing KOH in dioxane and (ii) it should not interfere with the nickel source through chelation or any other mechanism that would render the nickel ineffective.



i. ***Electron-withdrawing protecting group strategy.***

The initial protecting groups that were chosen were benzoyl and pivaloyl because they had the greatest probability of being stable to the basic, yet anhydrous conditions of the cross-coupling. The electron-withdrawing natures of these protecting groups also render the ether linkage incapable of chelation to the nickel. Synthesis of these two compounds from enantioenriched organocatalytic adduct **14** was straightforward (Scheme 2).

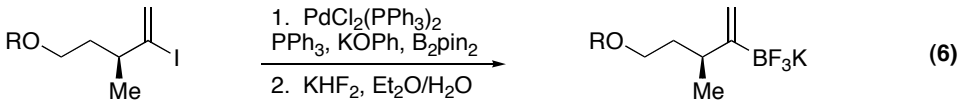
Scheme 2. Preparation of vinyl iodides with electron-withdrawing groups.



Sodium borohydride reduction of aldehyde **14** provided alcohol **24**, which was protected with the carboxyl protecting groups pivaloyl (R = CO*t*-Bu) and benzoyl (R = COPh). Fluoride-assisted removal of the TIPS group revealed unprotected alkynes **25a**

and **25b**. Hydroiodination of the terminal olefin using TMSCl and NaI, which forms "HI" in situ,[13] furnished vinyl iodides **26a** and **26b** in excellent yield.

Transformation to the necessary cross-coupling borate fragment **12a** and **12b** required a two-step procedure (eq. 6). Formation of the pinacol boronic ester was done under palladium-catalyzed cross-coupling conditions with bispinacolatodiboron and vinyl iodides **26a/b**.[14] Exposure to aqueous KHF_2 provided the desired borates **12a** and **12b**. However, unlike many reported potassium trifluoroborate salts, the potassium borate salts **12** employed in this chapter did not readily precipitate from the reaction medium. Because standard methods to isolate (vinyl)trifluoroborates via precipitation were ineffective, specialized workup conditions had to be developed for this substrate in order to separate pinacol from the product. An aqueous wash followed by extraction of the aqueous layer with 20% ether/pentanes extraction was the most effective workup to partition the more polar salt into the water layer while slowly pulling the pinacol into the organic wash. The low yields observed for these transformations should be attributed to the difficulty in purification of the BF_3K salt and not the palladium-catalyzed formation of the vinyl pinacolatoboron.



26a. R = CO*t*-Bu
26b. R = COPh

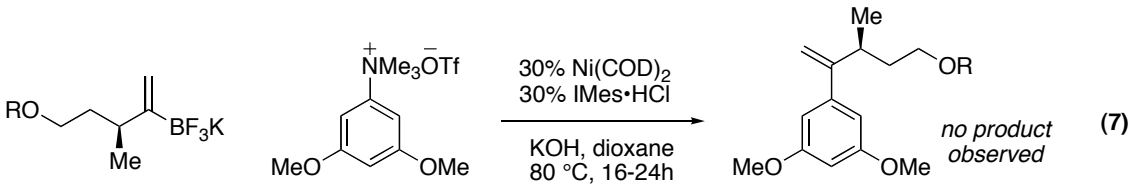
12a. R = CO*t*-Bu (30%)
12b. R = COPh (40%)

(6)

[13] Sugiyama, H.; Yokokawa, F.; Shioiri, T. *Tetrahedron* **2003**, *59*, 6579.

[14] Takagi, J.; Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 8001.

The functional compatibility of the protecting groups of **12a/b** was tested with the model 3,5-dimethoxy-*N,N,N*-trimethylanilinium triflate (**1**) under the optimized reaction conditions. However, these usually inert protecting groups were cleaved, presumably under the basic reaction conditions, leading to decomposition of the reactants (eq. 7). Changing the base in the cross-coupling from potassium hydroxide to cesium fluoride did not affect the desired reaction either. The only observable product was demethylation of anilinium salt **1** to give 3,5-dimethoxy-*N,N*-dimethylaniline.



12a. R = CO*t*-Bu
12b. R = COPh

1

27a. R = CO*t*-Bu
27b. R = COPh

(7)

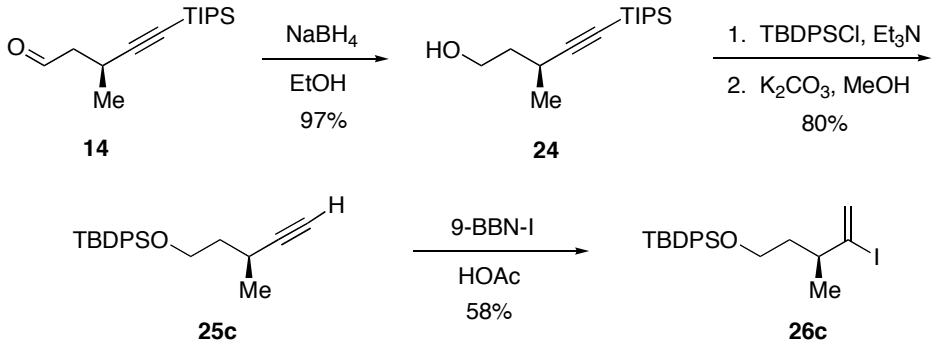
ii. ***A bulky silyl group as a choice of protecting group.***

A large silyl group was expected to be stable to anhydrous basic conditions[15] and incapable of adversely interfering with the nickel during the course of the cross-coupling reaction. The siloxy-protected BF_3K salt **12c** was synthesized in a similar manner as its carboxyl analogues **12a** and **12b** (Scheme 3). After reduction of aldehyde **14**, installation of the TBDPS group followed by selective removal of the alkynyl TIPS group with methanolic K_2CO_3 provided alkyne **25c**. Hydroiodination was accomplished by

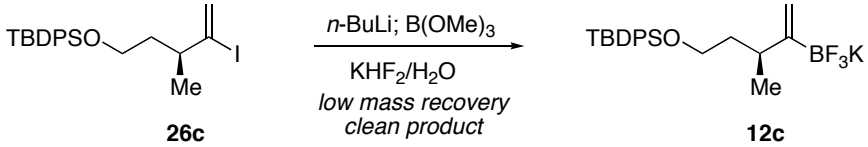
[15] Greene, T. W.; Wutts, P. G. M. In *Protective Groups in Organic Synthesis, 3td Ed.* Wiley: New York, 1999.

haloboration with 9-BBN-I followed by protodeborylation with acetic acid[16] to give vinyl iodide **26c** in good yield.

Scheme 3. Preparation of vinyl iodide with TBDPS protecting group.



Conversion of the iodide to the potassium trifluoroborate **12c** was accomplished in a three-step, one-pot sequence of (i) lithium/halogen exchange, (ii) formation of the alkenyl boronic acid, and (iii) transformation to the BF_3K salt by exposure to aqueous potassium hydrogen difluoride (eq. 8).[17] Once again, the isolated yield was low due to difficulty in purification of borate salt **12c**. Salt **12c** was more soluble in organic solvents expected. This was probably due to the added non-polar properties that were bestowed by the TBDPS moiety.

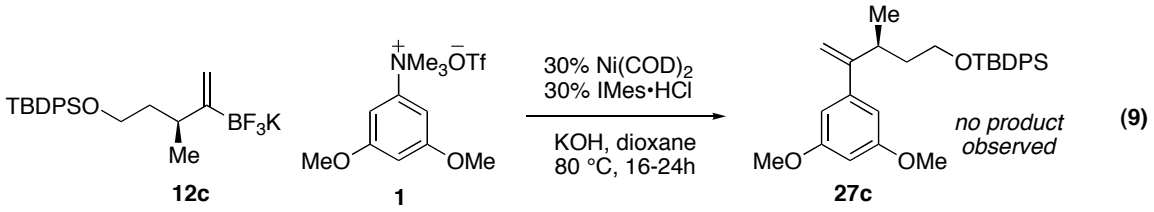


(8)

[16] (a) Hara, S.; Hidetaka, T.; Takinami, T.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731. (b) MacMillan, D. W. C.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2001**, *123*, 9033.

[17] Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R.. *J. Org. Chem.* **1995**, *60*, 3020.

Despite recovering a clean sample of the transmetalation partner **12c**, cross-coupling with model system **1** again did not provide any products of carbon-carbon bond formation (eq. 9). The larger TBDPS group was also cleaved under the reaction conditions as *tert*-butyldiphenylsilyl by-products were isolated along with the usual 3,5-dimethoxy-*N,N*-dimethylaniline. However, no identifiable remains of the BF_3K salt were isolated. The lack of success of the silyl and carboxyl protecting groups was attributed to the highly basic nature of the reaction conditions.

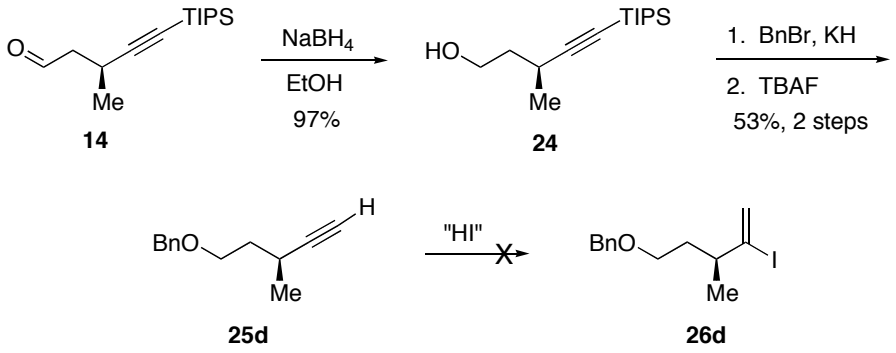


(9)

iii. *Ethers as base-stable protecting groups.*

The next protecting groups considered for this reaction were ethers because they are completely stable to basic conditions, though it was kept in mind that the ether oxygen might be capable of coordinating the nickel. Benzyl and methoxymethyl (MOM) ethers were chosen as suitable groups to investigate.

Scheme 4. Preparation of vinyl iodides with benzyl ether protecting group.



Synthesis of the vinyl iodide **26d** was similar to the synthetic routes shown in the previous sections. Outlined in scheme 4, reduction of aldehyde **14** followed by benzyl protection and TBAF deprotection provided quick access to alkyne **25d**. However, standard acidic iodination conditions were ineffective, resulting in only recovered starting material. In fact, other methods to functionalize the alkyne, including exposure to 9-BBN-I[16b] and to Trost's ruthenium-catalyzed hydrosilylation[18], were unsuccessful (Fig. 7). 9-BBN-I did perform the desired hydroiodination, however, the oxidation and concomitant cleavage of the benzyl group to form **28** outcompeted the hydroiodination. Attempts to reprotect alcohol **27** were unproductive, as all of these conditions immediately effected elimination of the vinyl iodide to alkyne **29**.

[18] (a) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2001**, *123*, 12726. (b) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2005**, *127*, 17644.

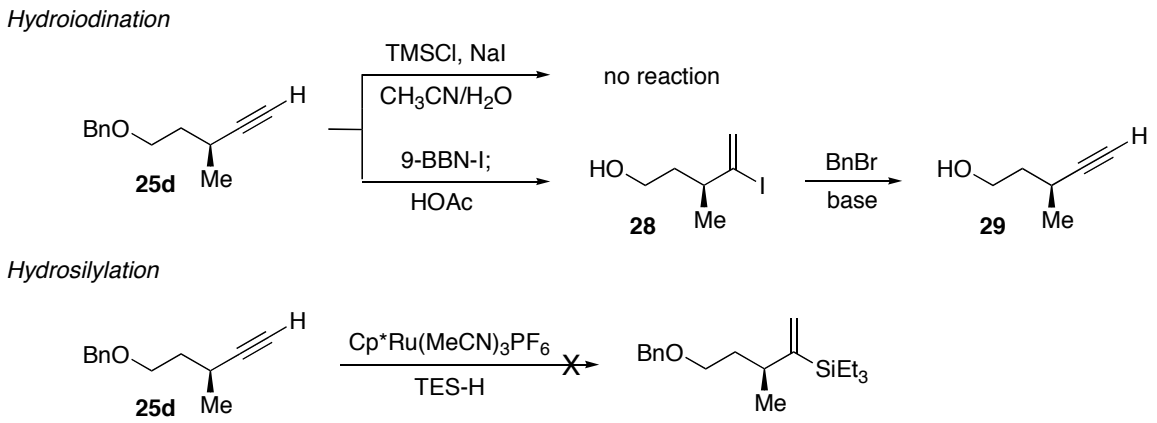


Figure 7. Unsuccessful attempts to functionalize the terminal alkyne.

A possible mechanism for this lack of reactivity was proposed (Fig. 8). While lack of reactivity for these types of reactions with bishomopropargylic alcohols has been noted in the literature, there has been no explanation. Under acidic conditions (HI, HBr, HOTf)[19] and metal-catalyzed conditions, either the acid or the metal effectively coordinates to the alkyne, pulling electron-density out of the system. The bishomopropargylic ether (or free alcohol) most likely closes down to form the 5-*exo*-dig cationic intermediate (purple, Fig. 8), or it traps as the 6-*endo*-dig cationic dihydropyran intermediate (blue, Fig. 8), though this latter option is less likely. Upon workup, both of these pathways would yield the starting material.

[19] For HI, see: Hiyama, T.; Wakas, N.; Ueda, T.; Kusumoto, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 640. For HBr, see: Marshall, J. A.; Sehon, C. A. *Org. Synth.* **1999**, *76*, 263. For HOTf, see: Takai, K.; Sakogawa, K.; Kataoka, Y.; Oshima, K.; Utimoto, K. *Org. Synth.* **1995**, *72*, 180.

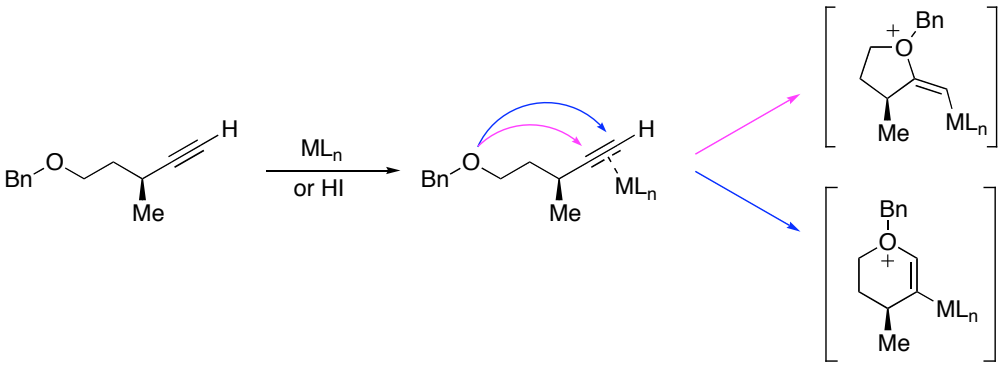
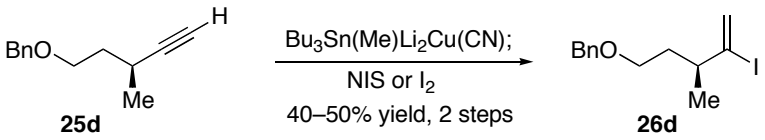


Figure 8. Intramolecular trap of ether oxygen onto the alkyne.

Instead of using a reagent that would pull electron-density out of the alkyne, a reagent that was known to act through a more concerted [2+2] addition would circumvent the issues described above. 9-BBN-I is a good example of such a reagent; however, it has already been shown to have a deleterious side-reaction that cleaves the benzyl group. In 1993, Fleming reported the use of stannylcuprates to do this kind of [2+2] addition across alkynes to furnish Markovnikov hydrostannylation products.[20] Gratifyingly, tributylmethylstannyl cuprate[21] gave an acceptable conversion to the vinyl stannane, which was subjected to electrophilic iodine (I_2 or *N*-iodosuccinimide) to provide access to the desired vinyl iodide product **26d** (eq. 10).



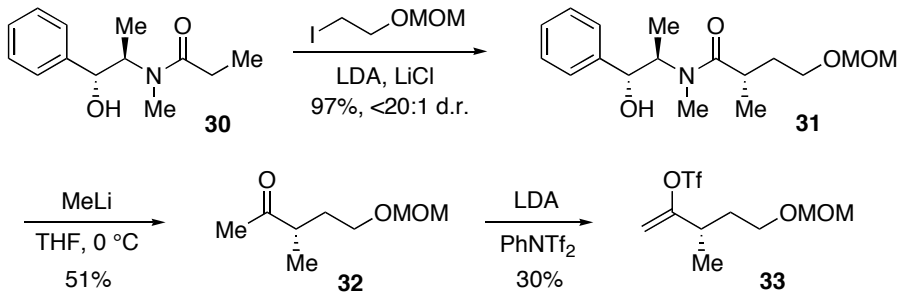
(10)

[20] Barbero, A.; Cuadrado, P.; Fleming, I.; Gonzalez, A. M.; Pulido, F. J.; Rubio, R. *J. Chem. Soc., Perkin 1.* **1993**, 1657.

[21] Still, W. C. *J. Am. Chem. Soc.* **1977**, *99*, 4836.

The synthesis of the analogous MOM-protected system was carried out using the pseudoephedrine chiral auxiliary technology developed by Myers.[22] Starting with (*S*)-pseudoephedrine propionate, its lithium enolate was alkylated with 1-iodo-2-(methoxymethoxy)ethane, prepared in a single step from commercially-available iodoethanol (Scheme 5). A single diastereomer **31** was produced in excellent yield, which was converted to the methyl ketone **32**. Enolization of the methyl ketone under kinetic control and trapping with *N*-triflamide formed vinyl triflate **33**.

Scheme 5. Alternative route to chiral BF_3K salts.



Formation of the potassium trifluoroborate salts of both the benzyl and MOM ether substrates was done under identical conditions as shown in equation 8. Palladium-catalyzed cross-coupling onto bispinacolatodiboron formed the vinyl boronic ester with good yield for iodide **26c** (eq. 11). However, vinyl triflate **33** was less reactive under these conditions, which is in agreement with the observations of Miyaura's report for similar cross-couplings of 1,1-disubstituted vinyl iodides and triflates.[14] Despite the lower yield, enough product was recovered in order to form the potassium borate salts **12d** and **12e** under conditions previously described.

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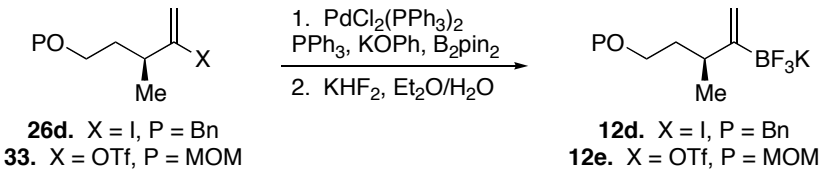
[22] Myers, A. G.; McKinstry, L. *J. Org. Chem.* **1996**, *61*, 2428.

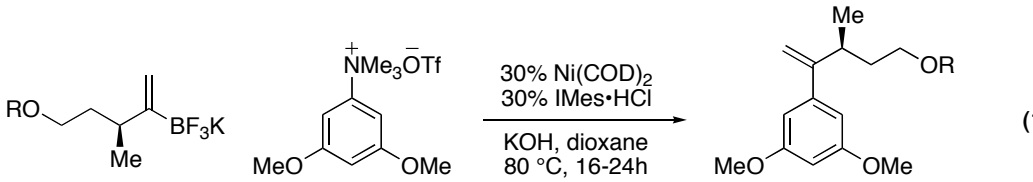


26d. X = I, P = Bn
33. X = OTf, P = MOM

12d. X = I, P = Bn
12e. X = OTf, P = MOM

(11)

Cross-coupling with the model system was run with the newly synthesized BF_3K salts **12d** and **12e** (eq. 12). MOM ether **12e** failed to perform the carbon-carbon bond formation and only 3,5-dimethoxy-*N,N*-dimethylaniline was recovered. However, benzyl ether **12d** did participate in the cross-coupling reaction to give 25% yield of exomethylene **27d**, providing the first instance of product formation seen thus far.



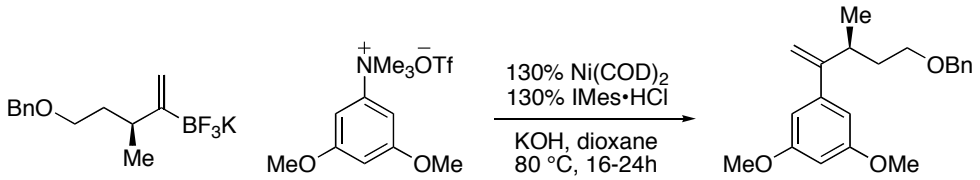
12d. R = Bn
12e. R = MOM

1

27d. R = Bn (25%)
27e. R = MOM (no product)

(12)

It was conceivable that the benzyl ether was consuming some of the nickel, thus resulting in the low yield. The cross-coupling reaction was not displaying any catalytic turnover with a 25% yield in the presence of 30 mol% catalyst. In order to increase the yield, the cross-coupling with model substrate **1** was performed with stoichiometric nickel and ligand (eq. 13). However, the reaction was significantly less efficient than before and multiple aromatic side-products were seen.



12d. R = Bn

1

27d. R = Bn (<10%)

(13)

iv. ***Isoprenyl functionality in the cross-coupling.***

Encouraged by the product formation observed with a benzyl group on the vinyl potassium trifluoroborate, it was thought that installing an isoprene moiety would be the ideal functionality at this position. Perhaps a reversible coordination of the isoprene unit to any of the nickel intermediates would facilitate a transmetalation event and thus facilitate overall product formation (Fig. 9).[23]

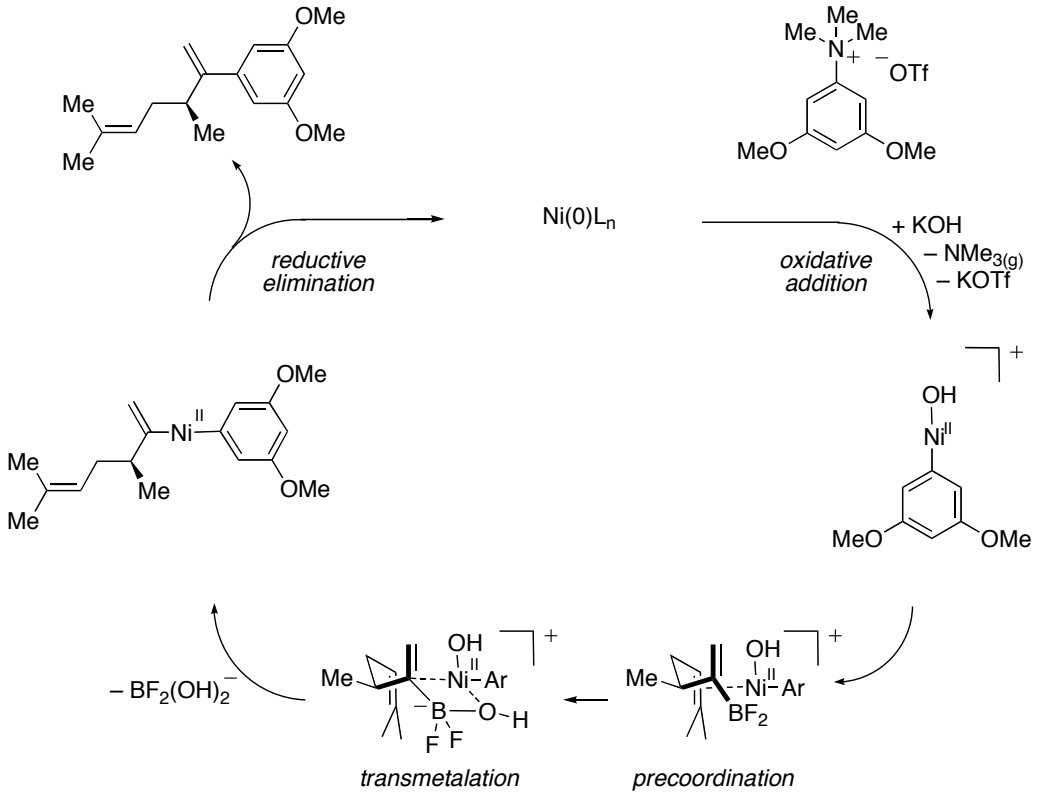
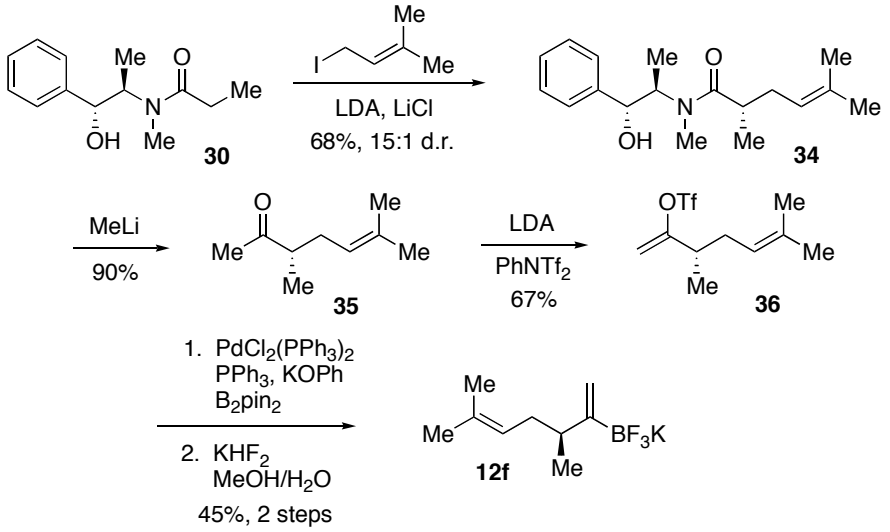


Figure 9. Facilitation of a transmetalation event with a pendant isoprenyl group.

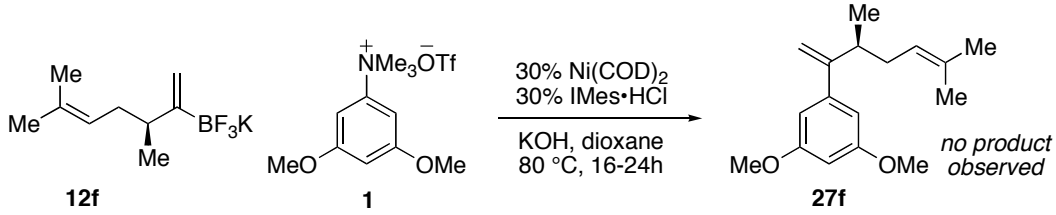
[23] For a discussion on the transmetalation of potassium organotrifluoroborates, see: Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461.

Using the conditions developed previously in scheme 5, the six step synthetic sequence starting again with the alkylation of (*S*)-pseudoephedrine propionate with 1-iodo-3-methylbut-2-ene provided rapid access to the chiral BF_3K salt **36** (Scheme 6).

Scheme 6. Synthesis of isoprenyl vinyl iodide via chiral auxiliary.



Unfortunately, when the trifluoroborate salt **12f** was subjected to catalytic or stoichiometric nickel-catalyzed conditions, no product was observed, and only demethylated anilinium salt was recovered.



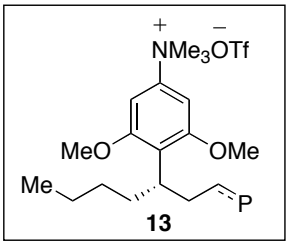
(14)

While an explanation for the unique effectiveness of the benzyl group in the transmetalation cross-coupling partner is unclear, it was carried on to the real system.

Investigation into the real system involved determination of the optimal protecting group for the cross-coupling reaction.

IV. Synthesis of Trimethylanilinium Salts with Different Functionalities.

The effect of the protecting groups on the functionality installed within the coupling fragments was unpredictable, similar to the previous section (vide infra). It was foreseen that the same unpredictability would occur with the oxidative addition partner – the trimethylanilinium salt **13**. With the functionality seven carbons away from the reacting center, the effect was not expected to be as pronounced as with the potassium trifluoroborate salt **12**. However, the protecting group would still have to be stable to the very basic conditions.



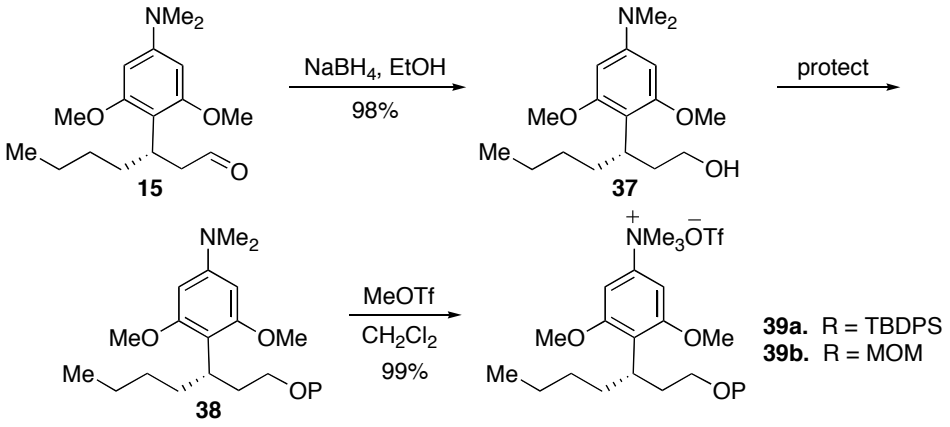
13

i. *Protected alcohols as oxidation state surrogates.*

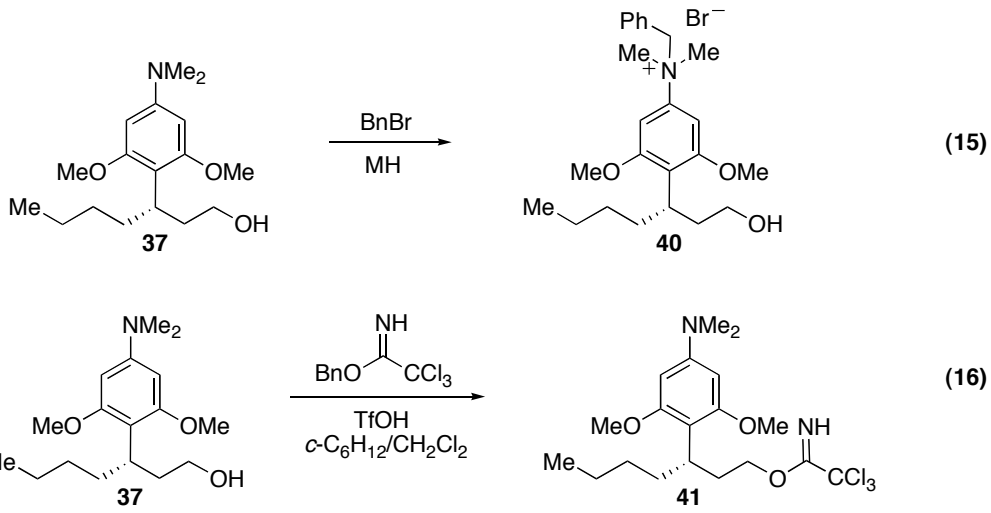
The first set of anilinium salts tested in the desired cross-coupling with borate **12d** contained an unprotected alcohol and its protected counterparts. The preparation of organocatalytic adduct **15** was discussed in chapter 3, from which the product was isolated with 93% ee at the benzylic stereocenter (Scheme 7). Reduction of the aldehyde was accomplished using sodium borohydride to furnish alcohol **37** in excellent yield. The free alcohol was protected as the TBDPS ether **38a** (TBDPS-Cl, Et_3N) and the MOM

(**38b**) ether (MOM-Cl, KH). Quaternization of the dimethylaniline with methyl triflate completed the syntheses of trimethylanilinium triflates **39**.

Scheme 7. **Preparation of trimethylanilinium salts 39.**



Preparation of the benzyl analogue proved difficult. However, the unique effectiveness of the benzyl ether protecting group in the potassium trifluoroborate salt studies required perserverence. However, benzyl protection of dimethylaniline **37** using various techniques was unfortunately unsuccessful. In the presence of benzyl halides, the anilinium salts were formed (eq. 15). In the presence of excess reagents (KH, BnBr), the actual protection was slow and inefficient. Alternatively, installation of the benzyl ether via the benzyl trichloroacetimidate transferred the imido group of the trichloroacetimidate to the substrate instead of the benzyl group (eq. 16).



In order to circumvent the issues associated with benzyl protection in the presence of the basic dimethylaniline moiety, the dimethylamine unit was replaced with a pyrrolidine. The nitrogen lone pair of the conformationally fixed pyrrolidine is delocalized in the adjacent aromatic π-system (Fig. 10), whereas the lone pair of the dimethylamine remains associated with the nitrogen without significant delocalization. Thus, the pyrrolidine moiety should not interfere with benzyl bromide.

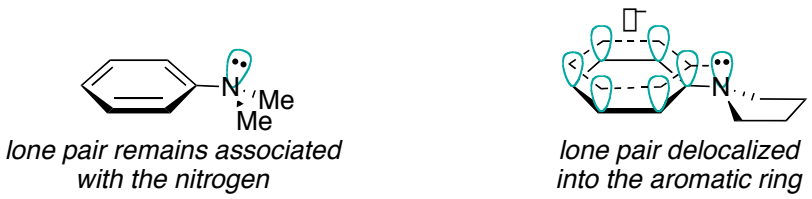


Figure 10. Dimethylaniline versus phenylpyrrolidine.

This delocalization has been observed experimentally and computationally. Laurence and co-workers have studied the effects of hydrogen bonding on a variety of

anilines and other heteroaromatic systems.[24] They were able to assess whether the hydrogen bond is associated with the nitrogen of the amine or whether it is associated with the π-system. They concluded that for dimethylaniline, the hydrogen bond is in proximity to the nitrogen (Fig. 11A) while it is centered on the phenyl ring for *N*-phenylpyrrolidine (Fig. 11B).

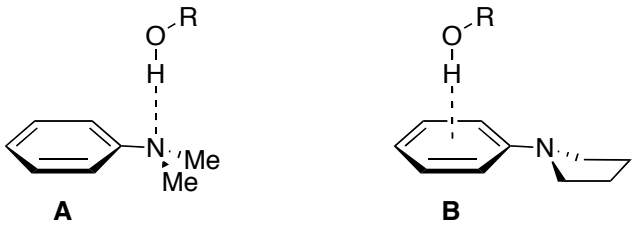


Figure 11. Location of a hydrogen bond on dimethylaniline and phenylpyrrolidine.

This modified aniline should be fully compatible with the current synthetic methods because (i) it has been demonstrated to be capable of organocatalytic Friedel-Crafts nucleophilic conjugate additions to enals,[25] and (ii) it has been shown that the pyrrolidinoanilinium triflates can couple to aryl boronic acids in the same manner as the trimethylanilinium triflates without appreciable loss in efficiency (Fig. 12).[26]

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[24] Marquis, E.; Graton, J.; Berthelot, M.; Planchat, A.; Laurence, C. *Can. J. Chem.* **2004**, *82*, 1413. For a study on the electron localization on DMAP and PPY, see: Heinrich, M. R.; Lisa, H. S.; Mayr, H.; Steglich, W.; Zipse, H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4826.

[25] Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*. 333.

[26] This reactivity was also noted by Dr. Simon Blakey in his original studies on the Suzuki cross-couplings with quaternized anilinium salts. Blakey, S. B. B. unpublished results.

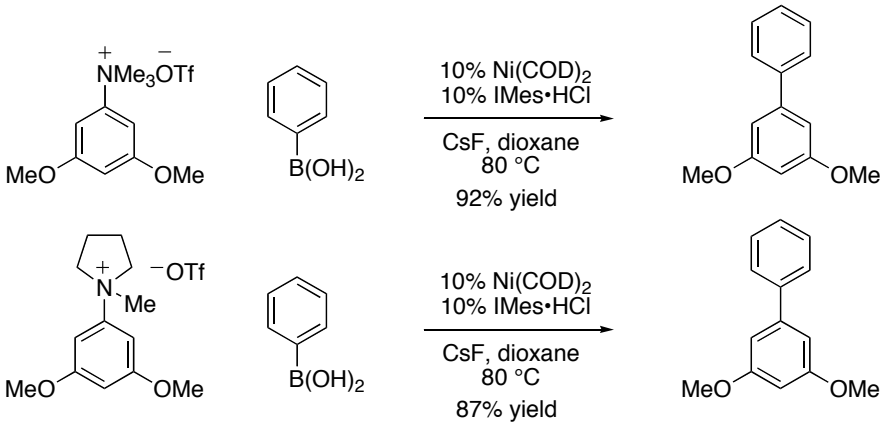
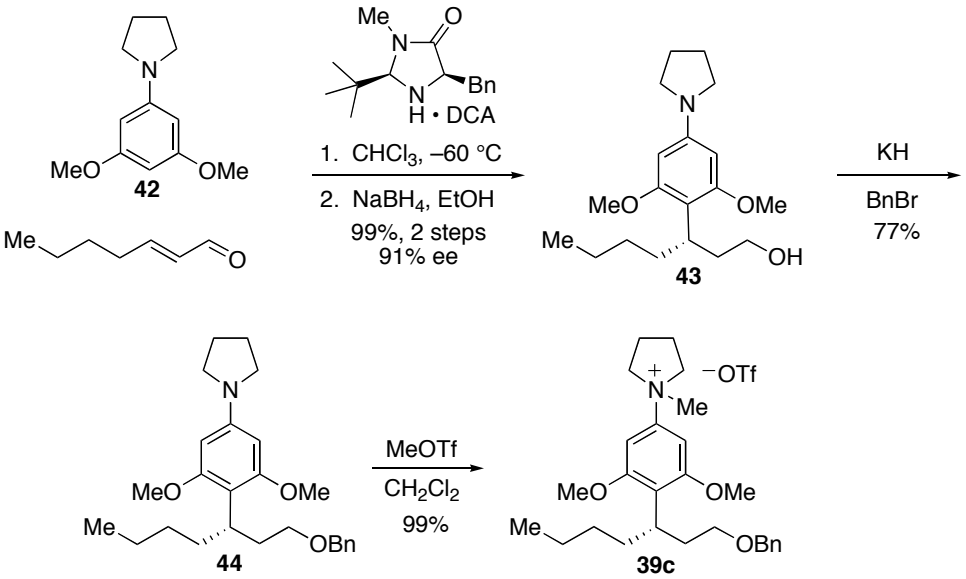


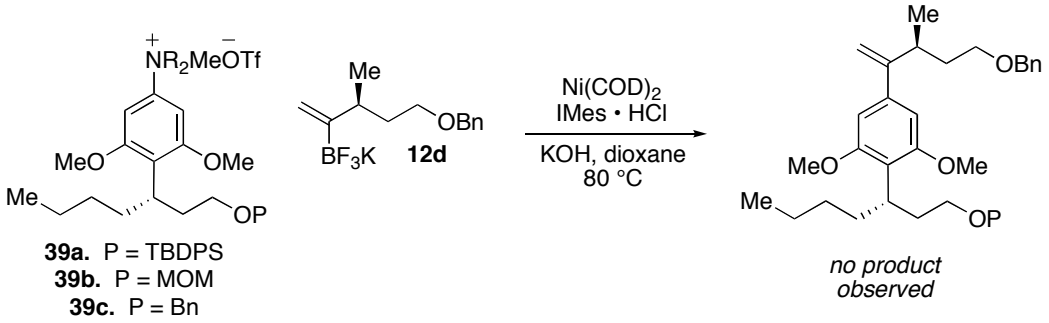
Figure 12. Cross-coupling with a pyrrolidino-anilinium salt.

The organocatalytic 1,4-conjugate addition of 1-(3,5-dimethoxyphenyl)-pyrrolidine **42** into 2-heptenal followed by in situ borohydride reduction of the aldehyde provided adduct **43** in excellent yield and enantioselectivity for the two step process (Scheme 8). Gratifyingly, benzyl protection of this system with benzyl bromide proceeded uneventfully to give the desired benzyl ether **43** in good yield. Quaternization of the pyrrolidine nitrogen with methyl triflate furnished the anilinium salt **39c**, finally providing access to the elusive benzyl ether functionality on the alkyl chain of the anilinium triflate.

Scheme 8. Synthesis of a benzyl-protected anilinium salt.



Using the optimized conditions for cross-couplings with potassium trifluoroborate salts, the cross-coupling with anilinium ions **39a–c** was attempted with benzyl-protected BF_3K salt **12d**. However, there was no instance in which carbon-carbon bond formation was observed (eq. 17). This lack of reactivity was especially surprisingly as model studies had shown that the benzyl moiety was seemingly compatible with cross-coupling on the truncated anilinium salt **1** (eq. 12).



(17)

The expected byproduct, demethylated starting material **38** and **44**, was observed in less than full mass recovery (Fig. 13). The remainder of the mass was unidentifiable decomposition products of the anilinium salt. The BF_3K salt **12d** was also unstable under these reaction conditions, as it could not be recovered upon aqueous workup. Small amounts of the corresponding boronic acid **45** or protodeborylation product **46** were observed after chromatography.

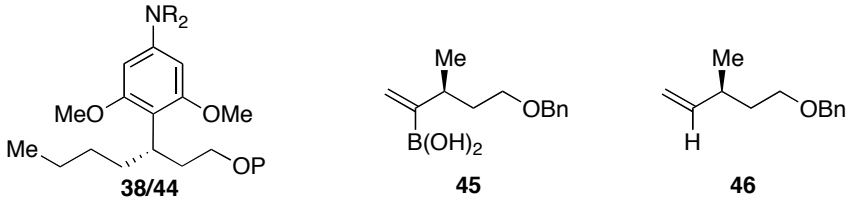


Figure 13. Isolated side-products of the cross-coupling in equation 17.

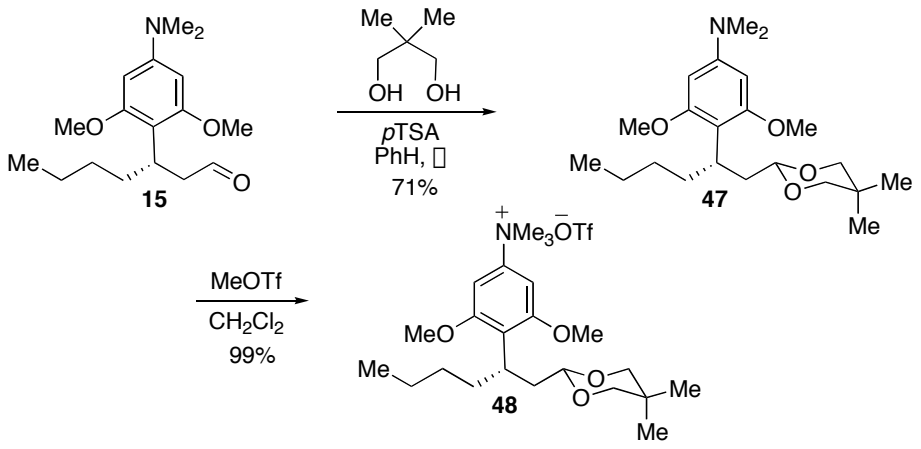
Upon consideration, it was thought that cleavage of the TBDPS in **39a** would result in the free alcohol **37**, which would consume the nickel in the reaction. Benzyl ethers and MOM ethers are known to be good metal chelating moieties, and so **39b** and **c** could conceivably coordinate the nickel and thus prevent the desired reaction from occurring.

ii. *Electron-withdrawing group on the alkyl side chain.*

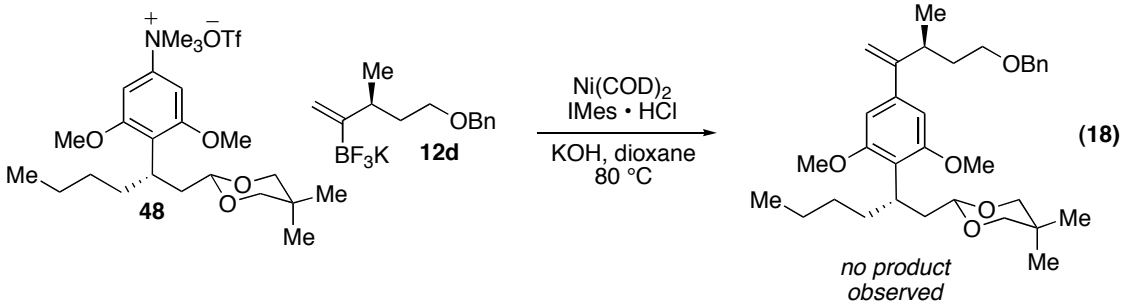
Alternatively, the aldehyde **15** could be masked as the acetal, which should not be susceptible to base-mediated cleavage. Aldehyde **15** was converted to the 4,4-

dimethyldioxolane **47** by condensation with 2,2-dimethylpropane diol (Scheme 9). Quaternization with methyl triflate furnished dioxolane anilinium salt **48** as a white solid.

Scheme 9. Installation of a dimethyldioxolane protecting group.



Cross-coupling of this system with BF_3K salt **12d** yielded no desired product (eq. 18). The recovered side products were dimethylaniline **47** and small amounts of boronic acid **45** and terminal olefin **46** (Fig. 13).

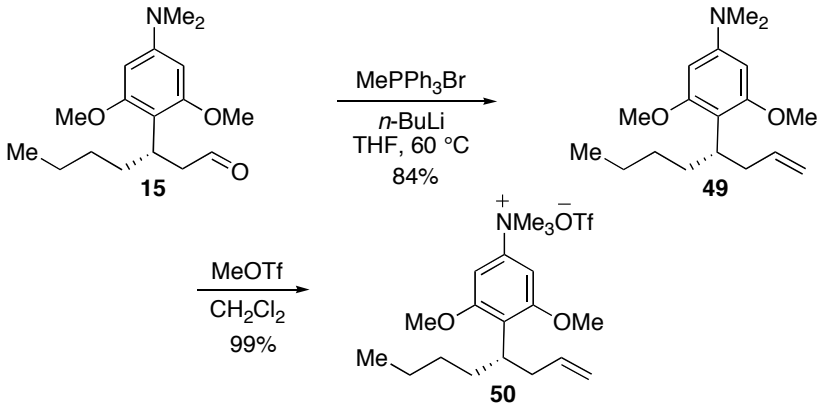


iii. *Simple alkenyl functionality on the alkyl chain.*

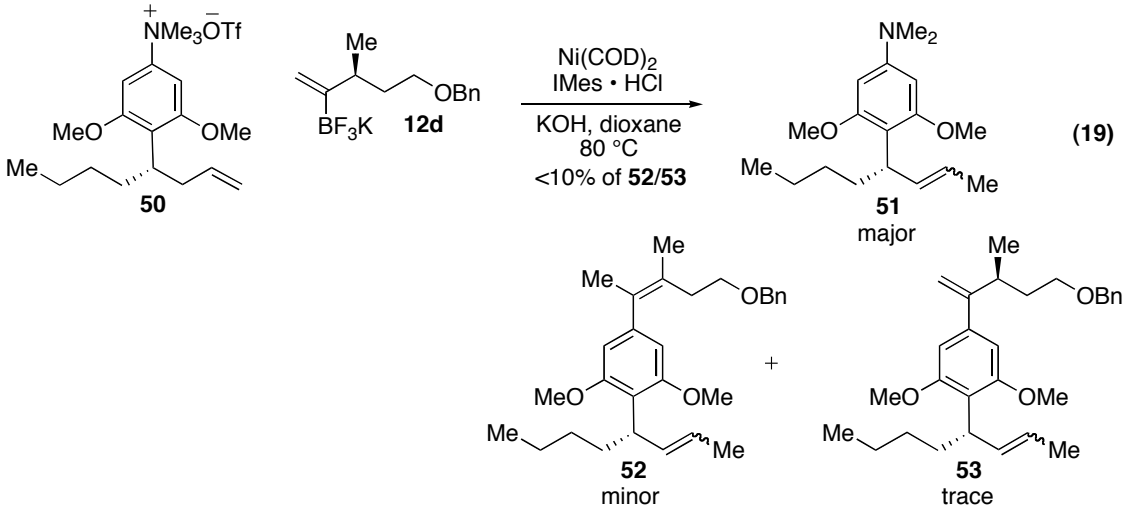
An olefin was chosen as a protecting group because it (i) is necessary for the cross-metathesis/dimerization strategy and (ii) both alcohol and aldehyde protecting

groups have had no success thus far. Trimethylanilinium salt **50** was synthesized in two steps from the enantioenriched product of the organocatalytic reaction **15**. Wittig olefination using methyl triphenylphosphonium bromide required heating to effect the olefination; the one carbon homologation was accomplished at 60 °C in excellent yield (Scheme 10). Quaternization of *N,N*-dimethylaniline **49** was done with methyl triflate in dichloromethane. Quantitative recovery of the product **50** was achieved through trituration of the reaction solution, which yielded a white crystalline solid after filtration.

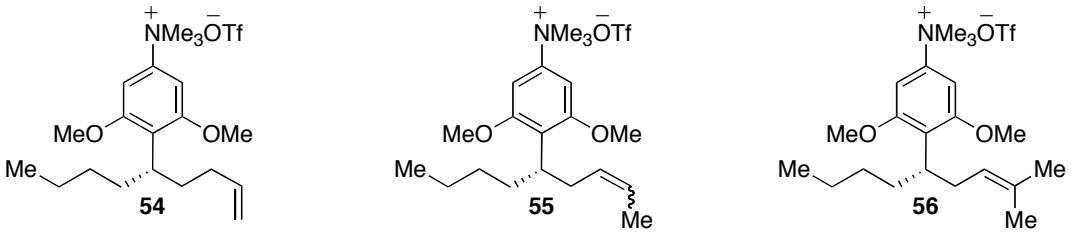
Scheme 10. Synthesis of methylene trimethylanilinium salt 50.



Cross-coupling with benzyl-protected vinyl potassium trifluoroborate salt **12d** was performed (eq. 19) using the optimized conditions developed in section I. The major isolated product was the demethylated anilinium salt, which is thought to be the product of nickel oxidative insertion into the nitrogen-methyl bond of the anilinium ion (see chapter 3). The minor product **52** isolated in less than 10% yield was the desired cross-coupled product. However, the terminal olefins were isomerized to a significant extent. The migration of the terminal olefin to a more substituted, more stable disubstituted one (**48**) was a cause for concern.



While migration of the terminal olefin in the trimethylanilinium cross-coupling partner was not desired, it was an issue that could be overcome by moving the terminal olefin (**54**) or by adding substitution to the olefin. The di- or tri-substituted olefin (**55** and **56**, respectively) would hopefully be stable to the reaction conditions.



However, the inability to suppress migration of the 1,1-disubstituted olefin of the BF_3K salt to the tetrasubstituted olefin seen in the more abundant cross-coupled product **52** seemed to be an insurmountable problem. As shown in figure 14, the tetrasubstituted olefin that was observed in compound **52** cannot be functionalized to access any of the

cylindrocyclophanes. Furthermore, cross-coupling with trisubstituted vinyl BF_3K salts like **57** was unsuccessful in this system.

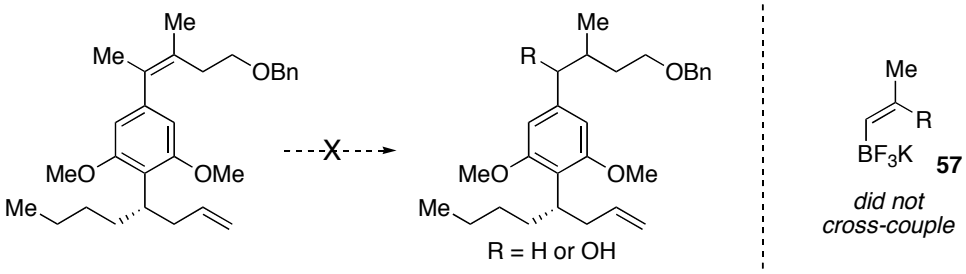
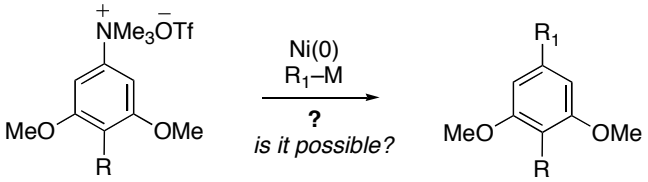


Figure 14. A non-productive route with the current cross-coupling strategy.

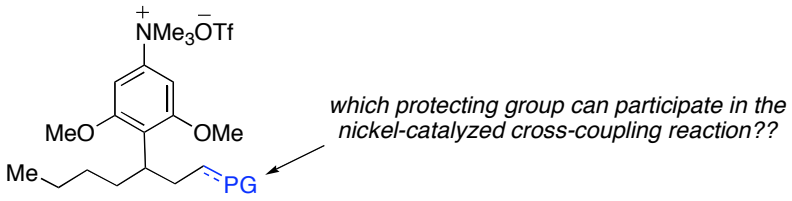
V. Investigation into Suzuki Cross-Couplings with Fully Functionalized *N,N,N*-Trimethylanilinium Triflates.

It became clear that the strategy of cross-coupling with 1,1-disubstituted potassium trifluoroborate salts was not going to be viable due to the deleterious olefin isomerization that may be the product of nickel hydrides generated during the catalytic pathway. However, before considering another route to the original ring-closing metathesis dimerization partner **11** that was proposed in the retrosynthesis in figure 3, it was imperative to determine if cross-coupling with the 3,5-dimethoxy-*N,N,N*-trimethylanilinum system with substitution in the 4-position were indeed possible.



Furthermore, the role of the substituent on the alkyl chain in the 4-position of the trimethylanilinium salt needed to be elucidated. While the olefinic substrate **50** provided

the only detectable amount of cross-coupled product, the yield of the reaction was too low to draw any valuable conclusions and thus this question needed a more thorough investigation.



i. *Cross-coupling with substitution in the 4-position.*

In order to ascertain the reactivity of the electron-rich anilinium systems that are required for the syntheses of the cylindrocyclophanes, cross-couplings using the conditions reported by Blakey and MacMillan were conducted with phenylboronic acid.[27] Phenylboronic acid undergoes rapid transmetalation, thus eliminating any issues associated with a slow transmetalation partner. The intended purpose of this study was to address the capacity of the different trimethylanilinium salts as oxidative addition cross-coupling partners in this nickel(0)-catalyzed reaction.

Cross-coupling of the model system 3,5-dimethoxy-*N,N,N*-trimethylanilinium triflate (**1**) was run as a control experiment (Fig. 15). The cross-coupled product **58** was obtained in 92% yield, which is in agreement with the reported yield. Cross-coupling with trimethylanilinium salt **50** (the only viable substrate from the studies in the previous section) with phenylboronic acid gave an 84% yield of biphenyl product **59**. As seen

[27] Blakey, S. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 6491.

with the previous studies, there was about 50% isomerization of the terminal olefin to the internal position. However, this simple experiment proved that the more electron-rich systems are indeed capable of undergoing oxidative addition in an event where there is a facile transmetalation.

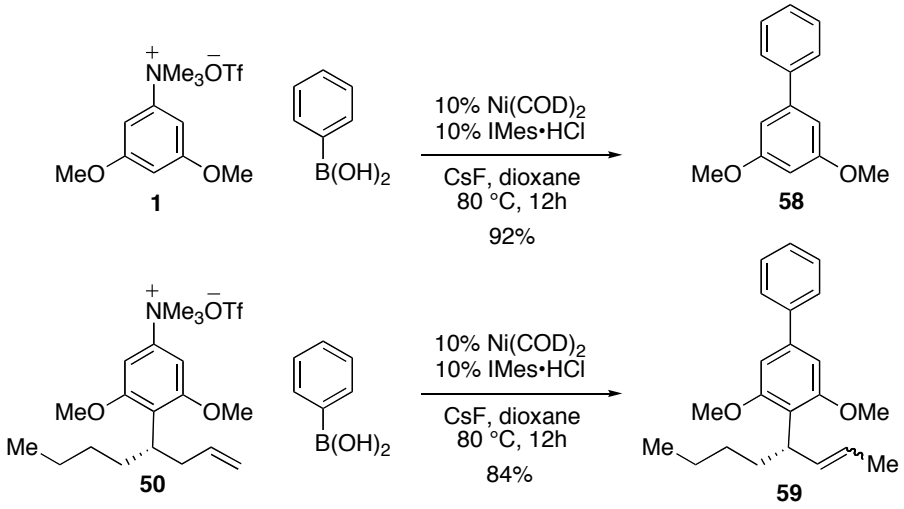
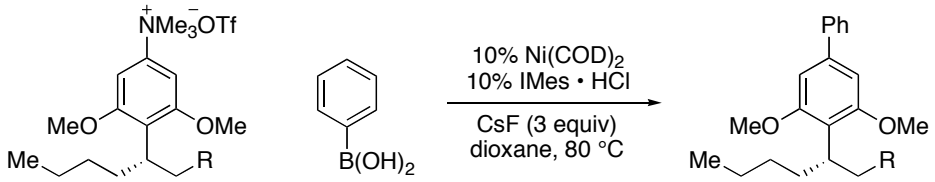


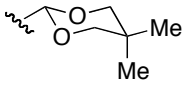
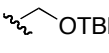
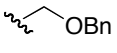
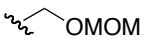
Figure 15. Substitution in the 4-position of the anilinium salt was tolerated.

ii. *Exploration into the role of functionality on the anilinium salt.*

Despite the successful coupling with **50** in figure 15, the role of the functional group on the alkyl chain remained unclear. Table 1 shows the reaction of various anilinium salts synthesized in section III of this chapter with phenylboronic acid in the conditions shown in figure 15.

Table 1. Phenylboronic acid Suzuki cross-couplings with various anilinium salts.



Entry	1	2	3	4	5
	R					
			OTBDPS	OBn	OMOM
Yield	84%*	20%	NP	NP	NP

* terminal olefin was isomerized to the internal position

Of the various functionalized trimethylanilinium salts prepared in section III, only two of them show any reactivity in the present system (Table 1, entries 1 and 2), and of these, the terminal olefinic functionality was the only one to form the biaryl system in good yields. Furthermore, this was the only system that cross-coupled at all in the cylindrocyclophane system. The dioxolanyl moiety furnished its respective biphenyl product in 20% yield, while no coupled product was observed in the reaction where ethereal linkages were present in the aliphatic chain.

The reason for the particular effectiveness of the olefinic substrate **47** was not clear. It was hypothesized that it could be a chelation effect in which reversible binding of the nickel to the olefin directed the nickel to the site of oxidative addition (Fig. 16A). Conversely, it could be a subtle electronic effect. The lack of product formation in entries 3–5 of table 1 could be due to donation of electron density from the ether oxygen into the aromatic system, thus increasing the difficulty of the original oxidative addition (Fig. 16B). However, it would be difficult to probe the electronic effect in further detail

as electron-withdrawing groups were already seen to be incompatible with the basic conditions of the cross-coupling.

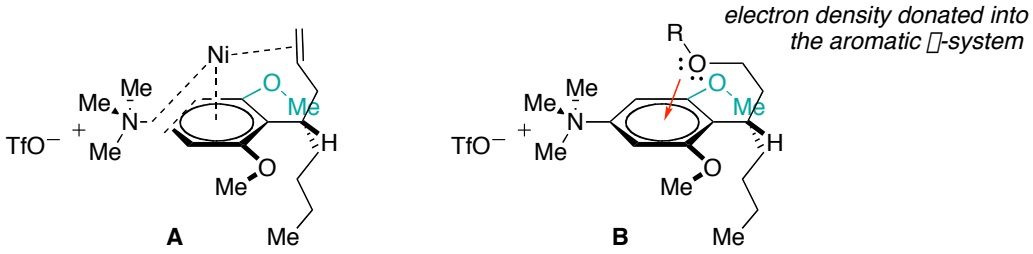
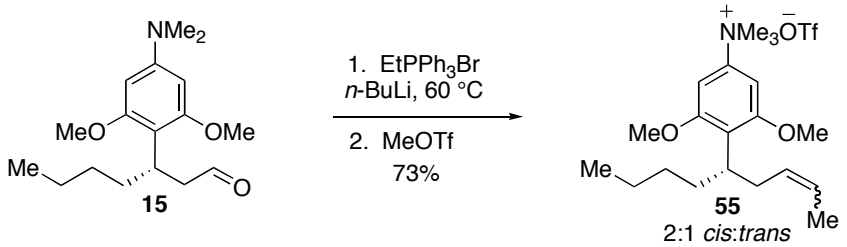
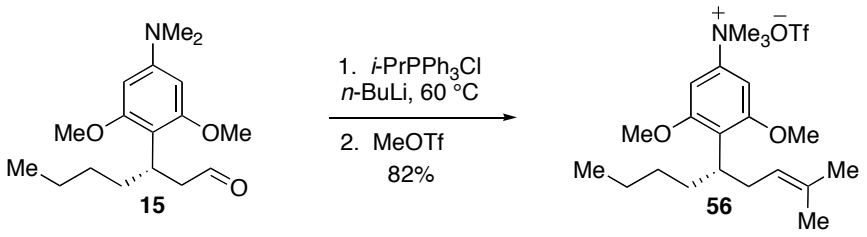


Figure 16. Possible directing of the nickel by an olefin on alkyl chain.

The chelation hypothesis shown in figure 15A was examined by preparing other trimethylanilinium substrates with a variety of pendant olefins from chiral aldehyde **15**. In order to prevent the olefin isomerization observed with a terminal olefin in figure 11, the di- and tri-substituted olefin analogues were synthesized by a Wittig reaction with ethyl and isopropyl triphenylphosphonium halides, respectively (eqs. 20 and 21). Reaction with ethyl triphenylphosphonium bromide provided the product in approximately a 2:1 mixture of *cis* to *trans* olefin isomers (eq. 20). The *cis* and *trans* olefins could not be separated and the mixture was carried forward. Quaternization of the nitrogen furnished anilinium triflates **55** and **56.**



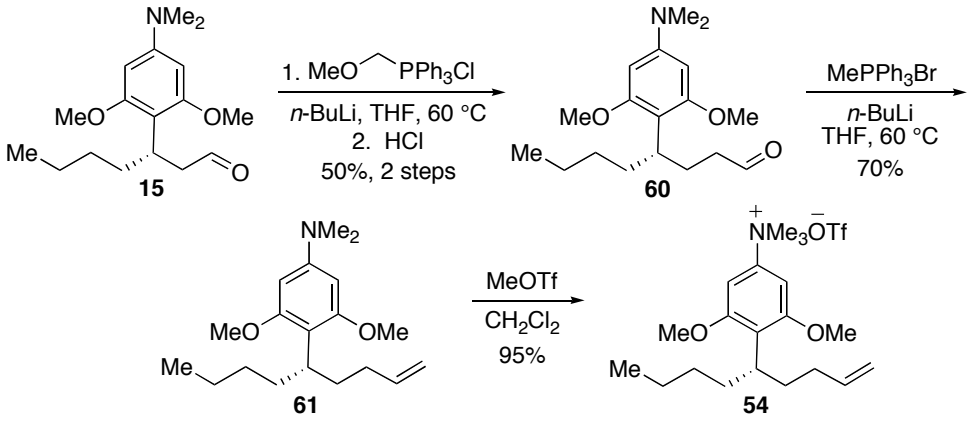
(20)



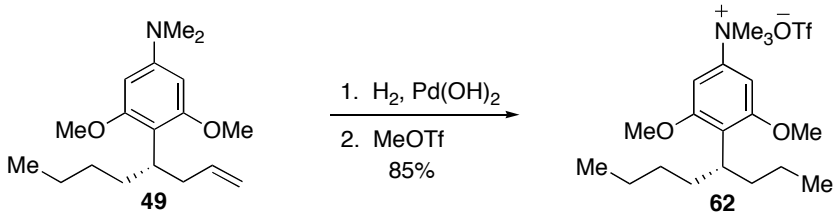
(21)

The next substrate of interest was one that would use the olefin isomerization to its advantage. Isomerization in this system would place the unsaturation in the correct position for further dimerization to the macrocycle. Preparation of this substrate commenced with aldehyde **15**, upon which a one carbon homologation was performed. Wittig reaction with methoxymethyl triphenylphosphonium chloride produced a methyl enol ether, which could be converted to aldehyde **60** with an acidic workup (Scheme 11). Subsequent Wittig olefination furnished terminal olefin **61**, which was transformed into the trimethylanilinium salt **54**.

Scheme 11. Synthesis of trimethylanilinium triflate with extended terminal olefin.



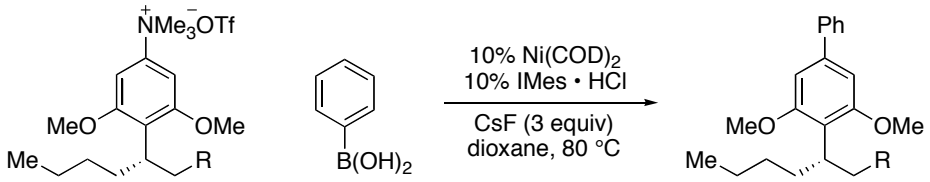
Finally, a substrate lacking unsaturation was prepared to test the chelation hypothesis. This trimethylanilinium salt **62** was synthesized from aniline **49** by hydrogenation of the terminal olefin and quaternization with methyl trifluoromethanesulfonate.



(22)

The four substrates **54**–**56** and **62** were cross-coupled with phenyl boronic acid under $Ni(COD)_2$ catalytic conditions in order to compare the results with the original substrate **50** (Table 2, entry 1, 84% yield) in equation 21. Gratifyingly, the 1,2-disubstituted olefin **55** coupled efficiently to form the biphenyl with a slight decrease in yield (entry 2, 60% yield). More importantly, there was no olefin isomerization observed in the isolated product. Also, as predicted, the product from reaction of **54** was isolated (entry 3, 41% yield), demonstrating that the olefin will indeed isomerize to a more stable position as desired in this system. Cross-coupling with trisubstituted olefin **56** was expected to hinder the directing effect of the nickel (Fig. 12) due to increased steric bulk around the coordination site. The yield for this system decreased as expected (entry 4, 12% yield). More surprisingly, however, was the fact that the reaction did proceed for a substrate that should be incapable of directing the nickel to the aromatic C–N bond to facilitate oxidative addition (entry 5, 22% yield).

Table 2. Testing the directing effect of pendant olefins on the aliphatic side chain.



Entry	1	2	3	4	5
	R	Me		Me, Me	Me
Yield	84%*	60%	41%*	12%	22%

* terminal olefin was isomerized to the internal position

Based on the collective information obtained from table 2, it appears that the cross-coupling is effective when there are no heteroatoms in the aliphatic chain extending from the four position of the aromatic moiety. However, placing a disubstituted olefin on this pendant alkyl chain can increase the yield. This may serve to direct the nickel into proximity with the aromatic C–N bond by reversible chelation to the olefin (Fig. 17).

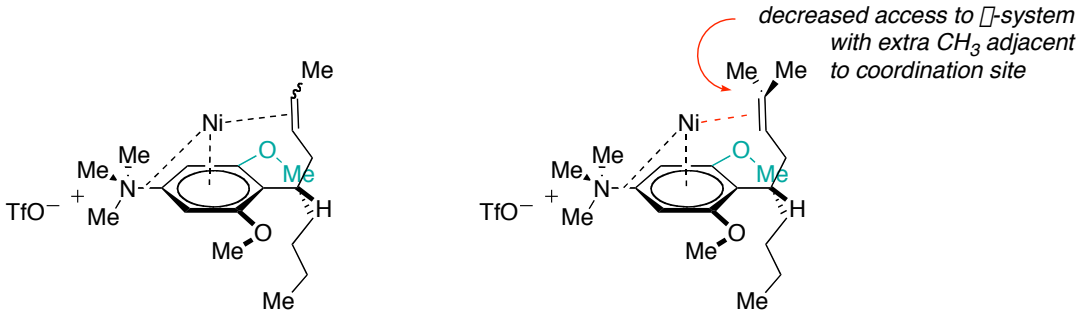


Figure 17. Decreased directing capability with a more substituted olefin.

Using this insight into the role of the functionality on the trimethylanilinium salt, a third synthetic strategy was planned using the trimethylanilinium triflate with a 1,2-disubstituted olefin on the alkyl chain.

Conclusion.

A new synthetic strategy to cylindrocyclophane A featuring a cross-coupling of an alkenyl potassium trifluoroborate salt with trimethylanilinium salts was investigated. A variety of 1,1-disubstituted vinyl potassium trifluoroborate salts were synthesized and tested for reactivity as a transmetalation partner with a model system. Of the differentially protecting substrates surveyed, only the benzyl-protected substrate affected the nickel(0)-catalyzed cross-coupling.

Using this uniquely effective transmetalation partner, a variety of protecting groups on the anilinium salt were tested in the cross-coupling. Reactivity of these systems decreased in comparison with the model system and significant amounts of nickel-catalyzed olefin isomerization were observed. Due to the inability to suppress this isomerization, the synthetic strategy utilizing 1,1-disubstituted vinyl potassium trifluoroborate salts was abandoned. However, in order to explain the concomitant lack of reactivity, an investigation into the role of an appropriate protecting group on the anilinium salt was conducted and revealed a pendant olefin to be uniquely effective. This study would prove crucial to further investigations, described in chapter 5.

Supporting Information.

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[28] Dioxane preparation was three-fold: (i) dried by distillation from sodium, (ii) degassed for 20 minutes with argon, and (iii) further deoxygenated by the freeze-pump thaw method. All other solvents were purified according to the method of Grubbs.[29] Non-aqueous reagents were transferred under nitrogen via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using flash chromatography on Silicycle 230-400 mesh silica gel. Thin-layer chromatography (TLC) was performed Silicycle 0.25 mm silica gel plates. Visualization of the developed chromatogram was performed by fluorescence quenching or by anisaldehyde, $KMnO_4$, or ceric ammonium molybdenate stain.

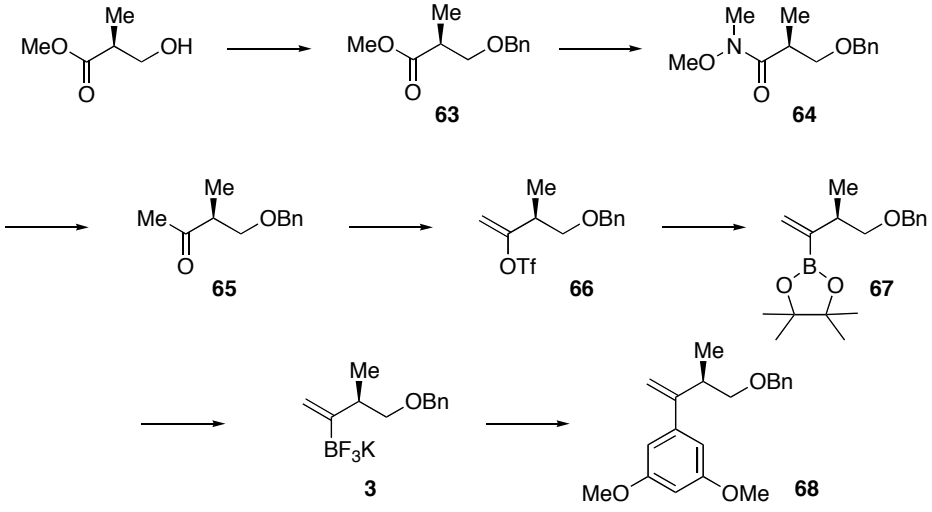
^1H and ^{13}C NMR spectra were recorded on a Mercury 300 Spectrometer (300 MHz and 75 MHz) as noted, and are internally referenced to residual protio solvent signals ($CDCl_3$ = 7.26 ppm, C_6D_6 = 7.16 ppm, D_6-acetone = 2.05 ppm). Data for ^1H NMR are reported as follows: chemical shift (ppm), multiplicity (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. 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 chromatography (GC) was performed on

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

[29] Pangborn, A.B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518./

Hewlett-Packard 6850 and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using a Bodman Chiraldex Γ-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. Analytical supercritical fluid chromatography (SFC) was perfomed on a Berger Instruments SFC with built-in photometric detector (l = 214 nm) using Daicel Chiracel OJ-H, OD-H, AS-H, and AD-H columns (25 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.

*Synthesis of potassium vinyltrifluoroborate salt **3** and cross-coupling onto model system:*



(*S*)-Methyl 3-(benzyloxy)-2-methylpropanoate (63). Methyl ester **63** was prepared in identical manner as reported in chapter 3. Spectral characterization was identical to literature report.[30] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5H, Ph**H**), 4.52 (s, 2H, OC**H**$_2$Ph), 3.71 (s, 3H, OC**H**$_3$), 3.62 (dd, 1H, *J* = 7.2, 9.3 Hz, C**H**HOBn), 3.48 (dd, 1H, *J* = 5.7, 9.3 Hz, CH**H**OBn), 2.79 (ddq, 1H, *J* = 5.7, 7.2, 7.2 Hz, C**H**CH$_3$); 1.20 (d, 1H, *J* = 7.2 Hz, CHC**H**$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 138.1, 128.3, 127.6, 127.5, 73.1, 71.9, 51.7, 40.2, 14.0.

(*S*)-3-(Benzyloxy)-*N*-methoxy-*N*,2-dimethylpropanamide (64). The hydrochloride acid salt of *N*-methoxymethylamine (8.08 g, 82.9 mmol) was quickly flame-dried under vacuum and kept under argon. Methyl ester **63** (11.5 g, 55.2mmol) was added in mL THF (0.5M) and the resultant slurry was cooled to –20 °C. Isopropylmagnesium chloride (102 mL, 204 mL, 2.0 M in THF) was added dropwise over 15 minutes. The reaction was warmed to –10 °C at which point TLC analysis confirmed reaction completion. Saturated ammonium chloride was added *slowly* to quench the reaction. The biphasic mixture was separated and the aqueous layer was extracted with diethyl ether (3 x mL). The organic layers were dried with magnesium sulfate, filtered, and the solvents concentrated in vacuo. The resultant oil **64** was carried on directly to the next reaction (8.0 g, 61% yield). Spectral characterization was identical to literature report.[30] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5H, Ph**H**), 4.52 (q, 2H, *J* = 12.0 Hz, OC**H**$_2$Ph), 3.69 (s, 3H, OC**H**$_3$), 3.72 (dd, 1H, *J* = 8.4, 8.4 Hz, C**H**HOBn), 3.66 (s, 3H, OC**H**$_3$), 3.42 (dd, 1H, *J* =

[30] Paterson, I.; Norcross, K. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287.

6.0, 9.0 Hz, CH**H**OBn), 3.27 (ddq, 1H, *J* = 6.0, 6.9, 8.4 Hz, C**H**CH_3), 3.20 (s, 3H, NC$\mathbf{H_3}$), 1.11 (d, 1H, *J* = 6.9 Hz, CHC$\mathbf{H_3}$).

(*S*)-4-(Benzyloxy)-3-methylbutan-2-one (65). Weinreb amine **64** (2.9 g, 12.2 mmol) was dissolved in 41 mL diethyl ether (0.3 M) at 0 °C under argon. Methyl magnesium bromide (5.31 mL, 15.83 mmol, 2.0M in THF) was added dropwise via syringe. The reaction was stirred at 0 °C for 2 h and then warmed slowly to ambient temperature. The reaction was filtered over a silica plug with excess diethyl ether to remove any amine products. The ether layers were concentrated in vacuo to provide spectroscopically pure methyl ketone **65** (2.33 g, 99% yield). Spectral characterization was identical to literature report.[31] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5H, Ph**H**), 4.49 (s, 2H, OC$\mathbf{H_2}$Ph), 3.62 (dd, 1H, *J* = 7.8, 9.0 Hz, C**H**HOBn), 3.48 (dd, 1H, *J* = 5.4, 9.0 Hz, CH**H**OBn), 3.27 (ddq, 1H, *J* = 5.4, 7.2, 7.8 Hz, C**H**CH_3), 2.18 (s, 3H, COC$\mathbf{H_3}$), 1.09 (d, 1H, *J* = 7.2 Hz, CHC$\mathbf{H_3}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.1, 138.0, 128.3, 127.6, 127.5, 73.2, 72.0, 47.2, 29.0, 13.4.

(*S*)-4-(Benzyloxy)-3-methylbut-1-en-2-yl trifluoromethanesulfonate (66). A flame-dried, argon-filled system was charged with freshly distilled diisopropylamine (4.88 mL, 34.8 mmol) and 70 mL THF (0.5M) and cooled to –78 °C. *n*-BuLi (13.9 mL, 34.8 mmol, 2.5M in hexanes) was added via syringe. The reaction was stirred as –78 °C for 10 min and warmed to 0 °C for 20 minutes. The reaction was recooled to –78 °C and methyl ketone **65** (6.69g, 34.8 mmol) was added in 10 mL THF. The enolate solution was stirred

[31] White, J. D.; Reddy, G. N.; Spessard, G. O. *J. Chem. Soc., Perkin Trans. 1* **1993**, *7*, 759.

at this temperature for 20 minutes. *N*-Phenyltriflamide (13.05g, 36.5 mmol) was dissolved in 50 mL THF and added to the reaction. After warming slowly to 0 °C for 20 minutes, the reaction was quenched with the slow addition of brine. The biphasic mixture was diluted with ethyl acetate. The organic layer was separated and then washed with 1N NaOH (3 x 150 mL). The ethyl acetate layer was dried with magnesium sulfate, filtered and concentrated in vacuo. The residue was immediately subjected to flash chromatography (1:3 CH_2Cl_2/hexanes) to provide triflate **66** as a light yellow oil (8.61 g, 77% yield). IR (film) 2973, 2862, 1714, 1458, 1359, 1179, 1097, 1028, 738, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5H, Ph**H**), 5.20 (d, 1H, J = 3.9 Hz, C=C**H**H), 5.03 (dd, 1H, J = 0.9, 3.9 Hz, C=CH**H**), 4.54 (s, 2H, OC**H**$_2$Ph), 3.54 (dd, 1H, J = 6.3, 9.3 Hz, C**H**HOBn), 3.46 (dd, 1H, J = 5.7, 9.3 Hz, CH**H**OBn), 2.73 (ddq, 1H, J = 5.7, 6.3, 7.2 Hz, C**H**CH_3); 1.21 (d, 1H, J = 7.2 Hz, CHC**H**$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) 158.2, 137.9, 128.4, 127.7, 127.6, 104.0, 73.2, 71.3, 39.1, 31.6, 14.9. ^{19}F NMR (282 MHz, $CDCl_3$) δ –74.3. HRMS (FAB+) exact mass calculated for $[MH]^+$ ($C_{13}H_{15}F_3O_4S$) requires *m/z* 324.0643, found *m/z* 324.0653.

(*R*)-2-(4-(Benzyloxy)-3-methylbut-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (67). A flame-dried flask was charged with bispinacolatodiboron (3.53 g, 13.9 mmol), $PdCl_2(PPh_3)_2$ (266 mg, 0.379 mmol), triphenylphosphine (199 mg, 0.758 mmol), and potassium phenoxide[32] (2.50 g, 19.0 mmol). Vinyl triflate **66** (4.1 g, 12.6 mmol) was added in 75 mL toluene (0.167M). This heterogeneous mixture was heated to 55 °C for 6 h. The reaction was cooled to ambient temperature and quenched with water. The

[32] Rahim, M. A.; Matsui, Y.; Matsuyama, T.; Kosugi, Y. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2191.

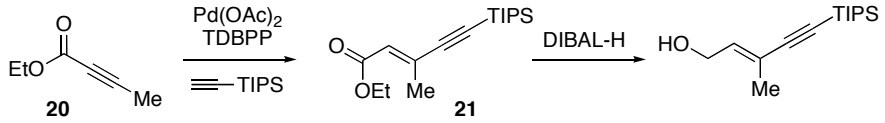
aqueous layer was separated and extrated with benzene (3 x mL). The benzene layers were dried with sodium sulfate and concentrated in vacuo. Flash chromatography (5% ethyl acetate/hexanes) provided the title compound as a clear oil (2.76 g, 74%yield). IR (film) 2977, 2931, 2861, 1612, 1372, 1309, 1145, 1097, 968, 852, 736, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) □ 7.37 (m, 5H, Ph**H**), 5.83 (d, 1H, *J* = 2.7 Hz, C=C**H**H), 5.66 (d, 1H, *J* = 02.4 Hz, C=CH**H**), 4.52 (s, 2H, OC**H**$_2$Ph), 3.78 (s, 6H, OC**H**$_3$), 3.52 (dd, 1H, *J* = 6.6, 9.0 Hz, C**H**HOBn), 3.35 (dd, 1H, *J* = 7.2, 9.0 Hz, CH**H**OBn), 2.71 (ddq, 1H, *J* = 6.6, 6.9, 6.9 Hz, C**H**CH_3); 1.24 (s, 6H, C(C**H**$_3$)$_2$), 1.23 (s, 6H, C(C**H**$_3$)$_2$), 1.09 (d, 1H, *J* = 6.9 Hz, CHC**H**$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) d 138.9, 128.5, 128.2, 127.5, 127.3, 83.2, 74.9, 72.7, 39.1, 24.7, 24.6, 16.8. HRMS (EI+) exact mass calculated for $[M•]^+$ ($C_{18}H_{27}BO_3$) requires *m/z* 302.2056, found *m/z* 302.2060. □$_D$ (c = 0.98, $CHCl_3$) = +2.0.

Potassium (*R*)-(4-(benzyloxy)-3-methylbut-1-en-2-yl)trifluoroborate (3). To a solution of pinacol boronic ester **67** (2.19 g, 7.25 mmol) in 14.5 mL diethyl ether (0.5 M), potassium hydrogen difluoride (2.00 g, 25.4 mmol) was added. Water (6.6 mL, 1.1 M) was added dropwise to this mixture, which was then stirred at room temperature for 4 h. The water and ether layers were removed and the salt mixture was dried under high vacuum for 3 h. Water was added to dissolve the solids. This aqueous layer was then extracted with 20% diethyl ether/hexanes (4 x 40 mL) to remove organic impurities. The aqueous layer was concentrated and the resultant salt mixture was taken up in hot acetone. The acetone layer was filtered to remove excess KF and concentrated to provide the BF_3K salt **3** as a white solid (1.2 g, % yield). This solid was further dried in a vacuum dessicator for 48 h prior to use. IR (film) 2978, 2932, 2866, 1612, 1372, 1308, 1145,

1097, 968, 852, 736, 697 cm^{-1}. ^1H NMR (300 MHz, CD_3COCD_3) δ 7.32 (m, 5H, Ph**H**), 5.12 (d, 1H, *J* = 4.5 Hz, C=C**H**H), 4.95 (broad s, 1H, C=CH**H**), 4.48 (q, 2H, *J* = 6.0 Hz, OC**H**$_2$Ph), 3.64 (dd, 1H, *J* = 4.8, 9.0 Hz, C**H**HOBn), 3.24 (dd, 1H, *J* = 9.0, 9.0 Hz, CH**H**OBn), 2.60 (ddq, 1H, *J* = 4.8, 6.9, 9.0 Hz, C**H**CH_3); 1.06 (d, 1H, *J* = 6.9 Hz, CHC**H**$_3$). ^{13}C NMR (75 MHz, CD_3COCD_3) 139.7, 128.0, 127.3, 126.9, 113.3, 76.0, 72.1, 39.0, 17.4. ^{19}F NMR (282 MHz, CD_3COCD_3) δ –142.3. ^{11}B NMR (160 MHz, CD_3COCD_3) δ 3.2. HRMS (FAB+) exact mass calculated for $[MH - K]^+$ ($C_{12}H_{15}BOF_3$) requires *m/z* 243.1168, found *m/z* 243.1167.

(*R*)-1-(4-(Benzyloxy)-3-methylbut-1-en-2-yl)-3,5-dimethoxybenzene (68). A flame-dried 2-dram vial was charged with 3,5-dimethoxy-*N,N,N*-trimethylanilinium triflate (**1**) (17.3 mg, 0.050 mmol), BF_3K salt **67** (17 mg, 0.0675 mmol), $Ni(COD)_2$ (4.1 mg, 0.015 mmol), IMes • HCl (5.3 mg, 0.015 mmol) and potassium hydroxide (21 mg, 0.15 mmol) in a nitrogen-filled glove box. The reaction vessel was sealed with a Teflon cap and removed from the box. The vial was then placed under positive argon pressure in order to add 0.5 mL deoxygenated dioxane. The reaction vial was sealed and heated to 80 °C for 18 h. The reaction was cooled to room temperature and quenched with 5 mL water. The aqueous layer was extracted with ethyl acetate (3 x 5 mL). The organic layers were filtered over a silica plug and concentrated. The conversion was determined by ^1H NMR by reference to an internal standard (4-dimethylaminoacetophenone) to be approximately 35%. ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 5H, Ph**H**), 6.51 (d, 2H, *J* = 2.4 Hz, Ar**H**), 6.39 (t, 1H, *J* = 2.4 Hz, Ar**H**), 5.26 (d, 1H, *J* = 0.9 Hz, C=C**H**H), 5.06 (d, 1H, *J* = 0.9 Hz, C=CH**H**), 4.49 (d, 2H, *J* = 5.5 Hz, OC**H**$_2$Ph), 3.78 (s, 6H, OC**H**$_3$), 3.54 (dd, 1H, *J* = 5.4,

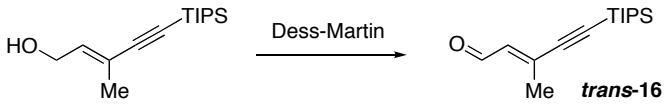
9.0 Hz, C**H**HOBn), 3.32 (dd, 1H, *J* = 7.2, 9.0 Hz, CH**H**OBn), 2.97 (ddq, 1H, *J* = 5.4, 6.9, 9.0 Hz, C**H**CH_3); 1.20 (d, 1H, *J* = 6.9 Hz, CHC**H**$_3$). ^{13}C NMR (75 MHz, $CDCl_3$). 160.5, 151.7, 144.8, 138.6, 128.3, 127.5, 127.4, 112.4, 105.0, 99.2, 74.7, 73.0, 55.3, 38.6, 17.4. HRMS (FAB+) exact mass calculated for $[MH]^+$ ($C_{20}H_{24}O_3$) requires *m*/*z* 312.1726, found *m*/*z* 312.1730.



(*E*)-3-Methyl-5-(triisopropylsilyl)pent-2-en-4-yn-1-ol. Palladium acetate (40 mg, 0.178 mmol) and TDBPP (158 mg, 0.356 mmol) were placed under argon in a Schlenk flask. THF (18 mL, 0.5 M) was added. To this solution, 1 g of ethyl-2-butynoate (**20**, 8.9 mmol) and 3.9 mL triisopropylsilylacetylene (17.8 mmol) were added. After 48 h at room temperature, the reaction was evaporated in vacuo and loaded directly onto a silica compound. Flash chromatography (0 to 3% ethyl acetate/hexanes) provided ester **21** (1.55 g, 59% yield).

The enyne product was dissolved in THF (10.5 mL, 0.5M) under argon and cooled to –78 °C. DIBAL-H (7.9 mL, 7.89 mmol) was added via syringe at –78 °C and slowly warmed to room temperature. 1N NaOH was carefully added to dissolve the aluminum salts. Once the reaction turned homogenous, the aqueous layer was extracted with diethyl ether (3 x 30 mL). The ether layers were dried with magnesium sulfate, filtered and the solvent removed via rotary evaporator. The residue was subjected to silica gel chromatography (5 to 20% ethyl acetate/hexanes) to provide the allylic alcohol

(848 mg, 64% yield). Spectral data characterization matches literature precedent.[33] ^{1}H NMR (300 MHz, $CDCl_3$). δ 6.04 (tq, 1H, *J* = 1.2, 6.6 Hz, C=C**H**); 4.22 (t, 2H, *J* = 2.1 Hz, C$\mathbf{H_2}$OH); 1.84 (s, 3H, C$\mathbf{H_3}$); 1.42 (m, 1H, O**H**); 1.07 (m, 21H, TIPS). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.7, 120.8, 107.5, 92.3, 59.2, 18.5, 17.5, 11.2.



(*E*)-3-Methyl-5-(triisopropylsilyl)pent-2-en-4-ynal (*trans*-16). Dess-Martin periodinane (309 mg, 0.729 mmol) was added to a solution of the corresponding allylic alcohol (184.1 mg, 0.729 mmol) in 1.5 mL dichloromethane (0.5 M). After 45 minutes, 1N NaOH was added and the reaction was stirred for 15 minutes. The aqueous layer was extracted with dichloromethane (2 x 5 mL). The organic layer was dried with magnesium sulfate, filtered, and concentrated in vacuo. Enal ***trans*-16** was isolated as a light yellow oil (164 mg, 90% yield). Spectral data characterization matches literature precedent.[34] IR (film) 2944, 2867, 2145, 1682, 1613, 1463, 1384, 1197, 1072, 997, 883, 679 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.03 (d, 1H, *J* = 7.8 Hz, C**H**O), 6.23 (dq, 1H, *J* = 1.2, 8.1 Hz, C=C**H**); 2.30 (d, 3H, *J* = 1.2 Hz, C$\mathbf{H_3}$); 1.09 (m, 21H, TIPS). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.1, 139.9, 133.9, 105.4, 104.8, 18.5, 18.1, 11.2. HRMS (FAB+) exact mass calculated for $[MH]^+$ ($C_{15}H_{25}OSi$) requires *m/z* 249.1675, found *m/z* 249.1684.

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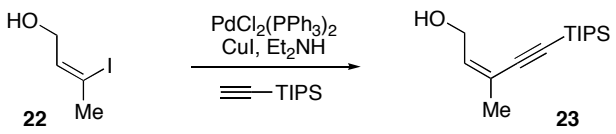
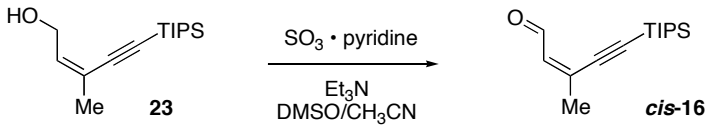
[33] (a) Roush, W. R.; Brown, B. *J. Am. Chem. Soc.* **1993**, *115*, 2268. (b) Waser, J.; Gonzalez-Gomez, J. C.; Nambu, H.; Huber, P.; Carreira, E. M. *Org. Lett.* **2005**, *7*, 4249.

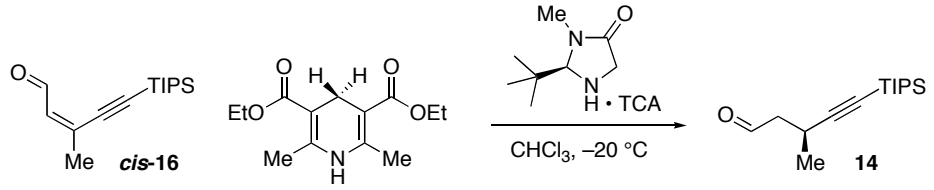
[34] Barluenga, J.; Mateos, C.; Aznar, F.; Valdes, C. *J. Org. Chem.* **2004**, *69*, 7114.



(*Z*)-3-Methyl-5-(triisopropylsilyl)pent-2-en-4-yn-1-ol (23). (Z)-3-Iodo-2-buten-1-ol **(22)** (6.0 g, 30.3 mmol) was taken up in freshly distilled diethylamine (60 mL, 0.5 M). $PdCl_2(PPh_3)_2$ (425 mg, 0.605 mmol) and copper(I) iodide (58 mg, 0.303 mmol) were added to the solution and stirred for 10 min under argon in the dark. Triisopropylsilyl-acetylene (8.15 mL, 36.3 mmol) was added slowly via syringe and stirred at room temperature for 24 h. If the reaction was not complete, it was recharged with palladium and stirred until completion. After the reaction was judged complete by TLC analysis, it was quenched with 125 mL saturated ammonium chloride. The aqueous layer was extracted with diethyl ether (3 x 100 mL). The organic layer was dried with magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography (20% diethyl ether/hexanes) provided the title compound as a dark oil (7.64 g, 99% yield). IR (film) 3317 (broad), 2943, 2866, 2140, 1463, 1383, 1320, 1171, 1013, 996, 882, 677, 660 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$). □ 5.89 (tq, 1H, *J* = 1.5, 6.9 Hz, C=C**H**); 4.35 (m, 2H, C$\mathbf{H_2}$OH); 1.89 (d, 3H, *J* = 1.2 Hz, C$\mathbf{H_3}$); 1.64 (m, 1H, O**H**); 1.08 (m, 21H, TIPS); ^{13}C NMR (75 MHz, $CDCl_3$). □ 136.3, 121.1, 105.0, 96.0, 61.5, 23.2, 18.6, 11.2; HRMS (EI+) exact mass calculated for $[M\bullet]^+$ ($C_{15}H_{28}OSi$) requires *m/z* 252.1910, found *m/z* 252.1910.

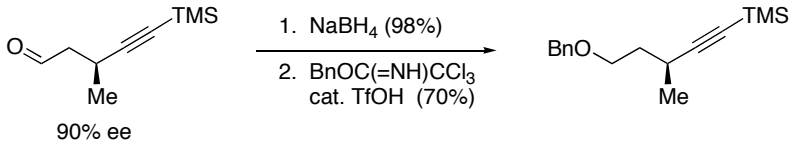


(*Z*)-3-Methyl-5-(triisopropylsilyl)pent-2-en-4-ynal (*cis*-16). Allylic alcohol **23** (7.6 g, 30.1 mmol) was dissolved in 133 mL DMSO and 167 mL dichloromethane at 0 °C. Triethylamine (8.38 mL, 60.3 mmol) was added followed by SO_3-pyridine (9.59 g, 60.3 mmol). The reaction mixture was stirred at room temperature until all of the SO_3-pyridine complex dissolved, at which point the oxidation was complete. The reaction was quenched with 150 mL saturated $NaHCO_3$ and allowed to stir for 30 minutes. The aqueous layer was separated and extracted with diethyl ether (2 x 150 mL). The ether layer was washed with a saturated copper(II) sulfate solution (2 x 150 mL). The copper sulfate solution was back-extracted with 100 mL diethyl ether. The ether layers were combined and washed with brine. They were then dried with magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography provided the (*Z*)-enal ***cis*-16** as a yellow oil (5.4 g, 72% yield). IR (film) 2943, 2866, 2140, 1681, 1596, 1463, 1383, 1319, 1172, 1102, 884, 678 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) 10.08 (d, 1H, J = 8.1 Hz, C**H**O), 6.17 (dq, 1H, J = 1.2, 8.4 Hz, C=C**H**); 2.13 (d, 3H, J = 1.5 Hz, C$\mathbf{H_3}$); 1.82 (m, 21H, TIPS); ^{13}C NMR (75 MHz, $CDCl_3$). 192.8, 142.4, 135.7, 104.0, 102.9, 25.0, 18.6, 11.1; HRMS (EI+) exact mass calculated for $[M\bullet]^+$ ($C_{15}H_{26}OSi$) requires *m/z* 250.1753, found *m/z* 250.1759.



(*S*)-3-Methyl-5-(triisopropylsilyl)pent-4-ynal (14). IR (film) 2943, 2865, 2167, 1729, 1463, 1387, 1323, 1074, 996, 883, 676, 660 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) 9.82 (t, 1H, *J* = 2.4 Hz, C**H**O), 3.01 (ddq, 1H, *J* = 6.6, 6.9, 7.2, C**H**CH_3); 2.57 (ddd, 1H, *J* = 2.1, 7.2, 16.5 Hz, CH**H**); 2.49 (ddd, 1H, *J* = 2.1, 6.6, 16.5 Hz, C**H**H); 1.26 (d, 1H, *J* = 6.9 Hz, CHC**H$_3$**), 1.04 (m, 21H, TIPS); ^{13}C NMR (75 MHz, $CDCl_3$). 201.2, 111.0, 81.7, 50.0, 21.8, 21.2, 18.6, 11.1; HRMS (EI+) exact mass calculated for $[M\bullet]^+$ ($C_{15}H_{28}OSi$) requires *m/z* 252.1910, found *m/z* 252.1905. $[\alpha]_D$ (c = 1.15, $CHCl_3$) = +11.40

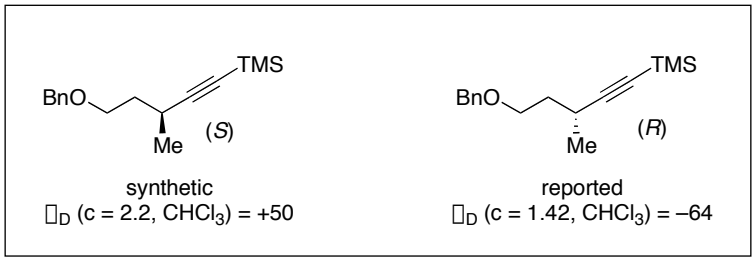
Proof of enantioselectivity by comparison to a literature compound:

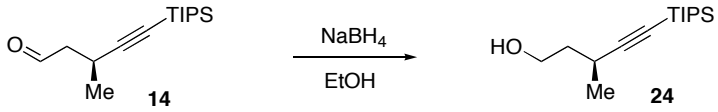


The trimethylsilyl version of the chiral aldehyde was prepared in the same manner as described for the triisopropylsilyl substrate **14**. The enantioselectivity was assessed on the aldehyde by gas chromatography on a chiral -TA column (50 °C isotherm, 34.50 min retention for (*R)*, 35.37 min retention for (*S*)). The aldehyde was reduced and protected as the benzyl group in order to correlate it to the (*R*) alkyne compound reported by Overman.[39] All spectral characterization matched. The optical rotations, however,

[39] Overman, L. E.; Bell, K. L.; Ito, F. *J. Am. Chem. Soc.* **1984**, *106*, 4192.

proved that the organocatalytic hydride reduction chemistry was furnishing the (*S*) enantiomer of the product.

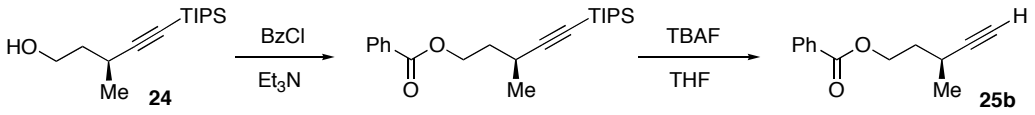




(*S*)-3-Methyl-5-(triisopropylsilyl)pent-4-yn-1-ol (24). Aldehyde **14** (1 g, 3.96 mmol) was taken up in 8 mL ethanol at room temperature. Sodium borohydride (377 mg, 9.91 mmol) was added. The reaction was completed after 15 minutes. Saturated $NaHCO_3$ was added to quench the reaction. After the boron salts were dissolved, the aqueous layer was extracted with diethyl ether (3 x 20 mL). The ether layers were washed with brine, dried with magnesium sulfate, filtered, and removed in vacuo. Flash chromatography (6 to 12 to 20% ethyl acetate/hexanes) provided alcohol **24** as a slightly yellow oil (0.93 g, 93% yield). IR (film) 3330 (broad), 2941, 2864, 2164, 1463, 1384, 1326, 1050, 994, 881, 677, 656 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.81 (m, 2H, C**H**$_2$OH), 2.64 (m, 1H, C**H**CH_3); 1.96 (bs, 1H, O**H**); 1.69 (m, 2H, C**H**$_2$$CH_2OH$); 1.22 (d, 1H, J = 7.2 Hz, CHC**H**$_3$), 1.05 (m, 21H, TIPS); ^{13}C NMR (75 MHz, $CDCl_3$). δ 113.1, 80.9, 61.4, 39.5, 24.0, 21.5, 18.0, 11.2; HRMS (FAB+) exact mass calculated for $[MH]^+$ ($C_{15}H_{31}OSi$) requires m/z 255.2144, found m/z 255.2152. $[\alpha]_D$ (c = 1.29, EtOH) = +35.7

Typical synthetic sequence for preparation of potassium trifluoroborate salts

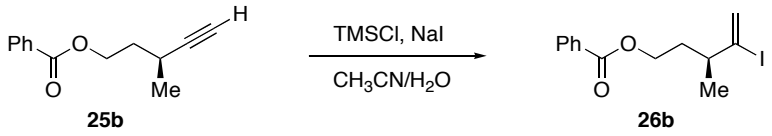
*For the benzoyl-protected BF_3K salt **12b**:*



(*S*)-3-Methylpent-4-ynyl benzoate (25b). Alcohol **24** (200 mg, 1.19 mmol) was dissolved in 2.4 mL dichloromethane at 0 °C. Triethylamine (0.174 mL, 1.25 mmol) and a catalytic amount of DMAP were added. Benzoyl chloride (0.145 mL, 1.25 mmol) was added via syringe and the reaction was slowly warmed to ambient temperature. The reaction was quenched with 5 mL saturated ammonium chloride and the aqueous layer was extracted with diethyl ether (3 x 5 mL). The ether layers were dried with magnesium sulfate, filtered, and the ether removed in vacuo. The crude residue was taken directly onto the silyl deprotection step.

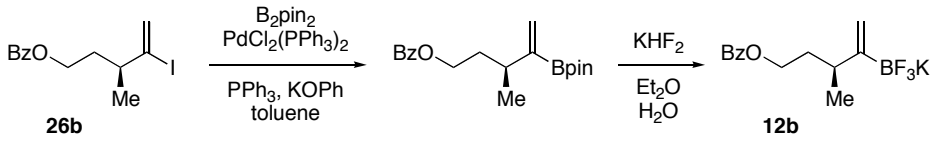
The crude residue (181 mg) was diluted in 14.4 mL THF at room temperature. TBAF (0.70 mL, 0.70 mmol, 1M solution in THF) was added. After 20 minutes, the reaction was complete by TLC analysis. 10 mL of saturated ammonium chloride was added and the biphasic mixture was separated. The aqueous layer was extracted with dichloromethane (2 x 10 mL) and filtered over a pad of silica gel. The organic solvent was remove in vacuo to provide the terminal alkyl **25b** as spectroscopically pure (121 mg, 92% yield). ^{1}H NMR (300 MHz, $CDCl_3$) □ 8.04 (m, 2H, Ph**H**), 7.55 (ddt, 1H, *J* = 1.5, 2.7, 7.5 Hz, Ph**H**), 7.43 (m, 2H, Ph**H**), 4.47 (m, 2H, OC**H$_2$**), 2.69 (m, 1H, C**H**CH_3), 2.09 (d, 1H, *J* = 2.4 Hz, alkyne-**H**), 1.91 (m, 2H, OCH_2(C**H$_2$**), 1.27 (d, 3H, *J* = 6.9 Hz,

$CHCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) d 166.5, 132.9, 130.3, 129.4, 128.3, 87.5, 69.1, 69.1, 62.9, 35.5, 22.8, 20.9.



25b **26b**

(*S*)-4-Iodo-3-methylpent-4-enyl benzoate (26b). In the dark under argon, freshly distilled trimethylsilylchloride (0.22 mL, 1.72 mmol) was added via syringe to a 2-dram vial charged with sodium iodide (258 mg, 1.72 mmol), water (15 μL, 0.860 mmol), and acetonitrile (1.72 mL, 0.25 M). The reaction was stirred for 15 minutes to allow for the generation of HI. Terminal alkyne **25b** (87 mg, 0.430 mmol) was added in about 0.3 mL acetonitrile. The reaction was stirred for 4 h. The acidic solution was diluted with 8 mL water and stirred for 15 minutes. The aqueous layer was then extracted with diethyl ether (3 x 10 mL). The ether later was filtered over silica and concentrated in a foil-wrapped flask to keep out light. The residue was subjected to rapid column chromatography (5% ethyl acetate/hexanes) in the dark to provide vinyl iodide **26b** as a dark orange oil (128 mg, 90% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (dt, 2H, *J* = 1.5, 6.9 Hz, Ph**H**), 7.56 (ddt, 1H, *J* = 1.5, 2.7, 7.5 Hz, Ph**H**), 7.44 (m, 2H, Ph**H**), 6.20 (dd, 1H, *J* = 0.6, 1.2 Hz, =CH**H**), 5.77 (d, 1H, *J* = 1.2 Hz, =C**H**H), 4.20-4.40 (m, 2H, OC$\mathbf{H_2}$), 2.08 (m, 1H, C**H**CH_3), 1.67-1.90 (m, 2H, OCH_2(C$\mathbf{H_2}$), 1.08 (d, 3H, *J* = 6.6 Hz, CHC$\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 132.9, 130.2, 129.5, 128.3, 125.2, 121.3, 62.6, 43.2, 34.9, 21.6

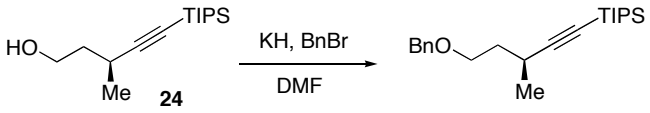


Potassium (*S*)-4-trifluoroboryl)-3-methylpent-4-enyl benzoate (12b). Vinyl iodide **26b** (128 mg, 0.388 mmol) in 2.3 mL toluene was added to a flask containing bispinacolatodiboron (108 mg, 0.427 mmol), $PdCl_2(PPh_3)_2$ (8.2 mg, 0.01166 mmol), triphenylphosphine (6.1 mg, 0.233 mmol), and potassium phenoxide (77 mg, 0.582 mmol). The reaction vial was sealed, wrapped in foil, and heated to 50 °C for 18 h. The reaction was quenched with water and the aqueous layer extracted with toluene. The toluene layer was filtered over silica and concentrated. The product was isolated by preparative TLC to afford the dioxaborolane.

The corresponding dioxaborolane (55 mg, 0.167 mmol) was taken up in 0.33 mL diethyl ether. Potassium hydrogen difluoride (37 mg, 0.467 mmol) was added. 0.15 mL water was added dropwise and the biphasic mixture was vigorously stirred at room temperature for 30 minutes. The water and ether layers were removed in vacuo and placed under high vacuum for 12 h. 5 mL reagent acetone was added to dissolve the desired potassium trifluoroborate salt and not the excess potassium salts. These potassium salts were filtered away and the acetone layer was concentrated via rotary evaporator to an amorphous solid that formed a solid under high vacuum. The white salt was taken up in water and washed with 20% diethyl ether/hexanes to remove undesired organic products. The water was removed in vacuo, providing potassium trifluoroborate salt **12b** as a white solid (865 mg, 57% yield). ^{1}H NMR (300 MHz, $(CD_3)_2CO$) □ 8.02 (m, 2H, Ph**H**), 7.61 (dt, 1H, *J* = 1.5, 7.5 Hz, Ph**H**), 7.49 (m, 2H, Ph**H**), 5.07 (d, 1H, *J* =

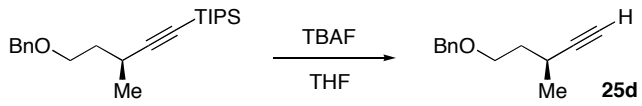
5.1 Hz, C=C**H**H), 4.92 (broad s, 1H, C=CH**H**), 4.20-4.36 (m, 2H, BzOC**H**$_2$), 2.41 (m, 1H, C**H**CH$_3$); 1.67-1.78 (m, 2H, CHC**H**$_2$), 1.09 (d, 3H, *J* = 6.9 Hz, CHC**H**$_3$). ^{13}C NMR (75 MHz, $(CD_3)_2CO$) d 166.8, 133.5, 131.8, 130.0, 129.2, 113.8, 65.6, 38.6, 35.9, 21.9. ^{19}F NMR (282 MHz, $(CD_3)_2CO$) –141.2.

*For the benzyl-protected BF_3K salt **12d**:*

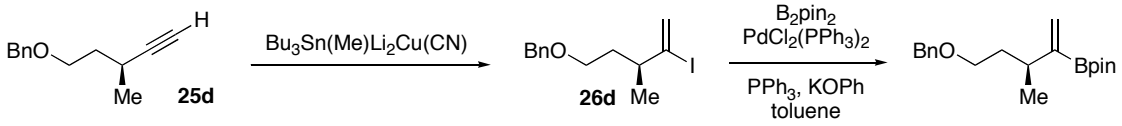


(*S*)-(5-(Benzyloxy)-3-methylpent-1-ynyl)triisopropylsilane. Sodium hydride (293 mg, 7.32 mmol, 60% in mineral oil) was washed three times with excess hexanes to remove oil prior to use. To sodium hydride at 0 °C was added alcohol **24** (0.93 g, 3.66 mmol) in 7.3 mL DMF (0.5 M) followed by benzyl bromide (0.65 mL, 5.49 mmol). The reaction was warmed to room temperature overnight. An aqueous 1N LiOH solution (10 mL) was added to convert excess benzyl bromide to benzyl alcohol, thus facilitating clean separation of the product. 10 mL water was added and the basic aqueous layer was extracted with diethyl ether (3 x 20 mL). The ether layers were dried with magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography provided the title compound (840 mg, 67% yield). IR (film) 2941, 2864, 2163, 1461, 1453, 1364, 1114, 1098, 993, 881, 730, 694, 674 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) 7.34 (m, 5H, Ph**H**), 4.51 (d, 2H, *J* = 1.5 Hz, OC**H**$_2$Bn), 3.62-3.73 (m, 2H, C**H**$_2$OBn), 2.70 (m, 1H, C**H**CH$_3$); 1.73 (m, 2H, C**H**$_2$CH$_2$OBn); 1.20 (d, 1H, *J* = 6.9 Hz, CHC**H**$_3$), 1.04 (m, 21H, TIPS). ^{13}C NMR (75 MHz, $CDCl_3$). 138.5, 128.3, 127.6, 127.5, 113.1, 80.0, 73.2, 68.4, 37.1, 23.9,

21.4, 18.6, 11.2; HRMS (FAB+) exact mass calculated for [MH – H2]$^+$ ($C_{22}H_{35}OSi$) requires *m/z* 343.2457, found *m/z* 343.2466. $[\alpha]_D$ (c = 1.01, EtOH) = +48.10.



(*S*)-((3-Methylpent-4-ynyloxy)methyl)benzene (25d). TBAF (2.52 mL, 2.52 mmol, 1M solution in THF) was added to a solution of the TIPS-alkyne (790 mg, 2.30 mmol) in 11.5 mL THF (0.2 M). The reaction was followed by TLC analysis. After 4 h, the reaction was quenched with saturated ammonium chloride. The aqueous layer was separated and extracted with diethyl ether (3 x 10 mL). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography (3% ethyl acetate/hexanes) provided the terminal alkyne **25d** (272 mg, 63% yield). IR (film) 2921, 2850, 2146, 1722, 1600, 1453, 1361, 1114, 1207, 1097, 1070, 732, 696 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5H, Ph**H**), 4.52 (s, 2H, OC**H$_2$**Bn), 3.62 (m, 2H, C**H$_2$**OBn), 2.63 (m, 1H, C**H**CH$_3$); 2.04 (d, 1H, *J* = 0.6 Hz, alkyne-**H**), 1.75 (m, 2H, C**H$_2$**CH$_2$OBn); 1.20 (d, 1H, *J* = 6.9 Hz, CHC**H$_3$**); ^{13}C NMR (75 MHz, $CDCl_3$). δ 138.5, 128.3, 127.6, 127.5, 113.1, 80.0, 73.2, 68.4, 37.1, 23.9, 21.4, 18.6, 11.2; HRMS (EI+) exact mass calculated for [M•]$^+$ ($C_{13}H_{15}O$) requires *m/z* 187.1123, found *m/z* 187.1130.



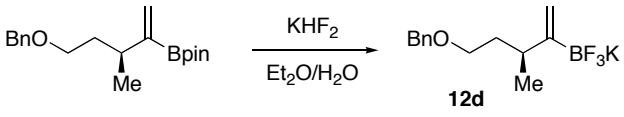
(*S*)-2-(5-(Benzyloxy)-3-methylpent-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. All glassware used in this reaction was flame-dried under vacuum. To a –20 °C solution of hexabutylditin (0.363 mL, 0.725 mmol) in 1.38 mL THF was added *n*-BuLi (0.310 mL, 0.725 mmol, 2.34 M in hexanes) via syringe. The reaction was stirred for 15 minutes and cooled to –78 °C. Methyllithium (0.449 mL, 0.691 mmol, 1.6 M in hexanes) was added. This solution was stirred for 15 minutes, after which copper(I) cyanide (62 mg, 0.691 mmol) was added quickly as a solid and the flask was repurged with argon. This mixture was stirred for 30 minutes at –78 °C.

Meanwhile, alkyne **26** (65 mg, 0.345 mmol) was dissolved in 0.35 mL THF. The alkyne solution was transferred via syringe to the stannylcuprate solution at –78 °C. The reaction was warmed slowly to room temperature at which point the reaction turned red. 1 mL saturated ammonium chloride was added, causing the reaction to change from a red color to black. The aqueous layer was extracted with diethyl ether (3 x 3 mL) and dried by filtration over silica. The organic solvent was removed in vacuo and flash chromatography (gradient elution: 0 to 10% ethyl ether/hexanes) provided the product, which was carried directly onto the next step.

At –78 °C, a solution of vinyl stannane in 0.4 mL dichloromethane was treated with iodine (90 mg, 0.36 mmol). The reaction was monitored by TLC analysis as it was slowly warmed to room temperature. Upon completion, the excess iodine was quenched

with saturated sodium thiosulfate. The aqueous layer was extracted with 10% ethyl acetate/hexanes. The organic layers were filtered over silica gel to provide the vinyl iodides that were used directly in the palladium cross-coupling.

A flame-dried flask was charged with bispinacolatodiboron (147 mg, 0.526 mmol), $PdCl_2(PPh_3)_2$ (11 mg, 0.0158 mmol), triphenylphosphine (11 mg, 0.0316 mmol), and potassium phenoxide[32] (104 mg, 0.789 mmol). The vinyl iodide was added in 3 mL toluene (0.167 M). This heterogeneous mixture was heated to 55 °C for h. The reaction was cooled to ambient temperature and quenched with water. The aqueous layer was separated and extracted with benzene (3 x mL). The benzene layers were dried with sodium sulfate and concentrated in vacuo. Flash chromatography (5% ethyl acetate/hexanes) provided the title compound as a clear oil (135 mg, 32% yield). ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.32 (m, 5H, Ph**H**), 5.75 (d, 1H, *J* = 3.0 Hz, C=C**H**H), 5.58 (d, 1H, *J* = 3.3 Hz, C=CH**H**), 4.48 (s, 2H, OC**H$_2$**Ph), 3.44 (m, 2H, C**H$_2$**OBn), 2.46 (m, 1H, C**H**CH_3), 1.85 (m, 1H, CHC**H**H), 1.68 (m, 1H, CHCH**H**), 1.25 (s, 12H, 2 x C(C**H$_3$)$_2$**), 1.06 (d, 1H, *J* = 6.9 Hz, CHC**H$_3$**). ^{13}C NMR (75 MHz, $CDCl_3$) □ 138.8, 128.3, 127.7, 127.6, 127.4, 83.1, 72.8, 69.1, 36.6, 35.6, 24.72, 24.68, 20.5.

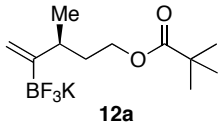


12d

Potassium (*S*)-(5-(benzyloxy)-3-methylpent-1-en-2-yl)trifluoroborate (12d). The corresponding dioxaborolane (1.635 g, 5.17 mmol) described in the previous entry was taken up in 10.4 mL diethyl ether. Potassium hydrogen difluoride (1.39 g, 17.58 mmol) was added. 5.2 mL water was added dropwise and the biphasic mixture was vigorously

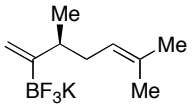
stirred at room temperature for 30 minutes. The water and ether layers were removed in vacuo and placed under high vacuum for 12 h. 20 mL reagent acetone was added to dissolve the desired potassium trifluroborate salt and not the excess potassium salts. These potassium salts were filtered away and the acetone layer was concentrated via rotary evaporator to a white opaque oil that formed an amorphous solid under high vacuum. The white salt was taken up in water and washed with 20% diethyl ether/hexanes to remove undesired organic products. The water was removed in vacuo, providing potassium trifluoroborate salt **12d** as a white solid (865 mg, 57% yield). IR (film) 3031, 2958, 2864, 2122, 1620, 1454, 1408, 1365, 1208, 1083, 1028, 974, 923, 736, 698 cm^{-1}. ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 7.31 (m, 5H, Ph**H**), 5.00 (d, 1H, *J* = 4.5 Hz, C=C**H**H), 4.85 (broad s, 1H, C=CH**H**), 4.43 (s, 2H, OC**H**$_2$Ph), 3.46 (dt, 1H, *J* = 6.3, 9.0 Hz, C**H**HOBn), 3.43 (dt, 1H, *J* = 6.3, 9.3 Hz, CH**H**OBn), 2.32 (tq, 1H, *J* = 6.9, 7.2 Hz, C**H**CH_3); 1.91 (m, 1H, CHC**H**H), 1.51 (m, 1H, CHCH**H**), 0.99 (d, 3H, *J* = 6.9 Hz, CHC**H**$_3$). ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 140.5, 128.9, 128.2, 128.1, 127.8, 112.7, 72.9, 70.8, 38.0, 37.0, 25.0, 21.7. ^{19}F NMR (282 MHz, $(CD_3)_2CO$) δ –141.2. HRMS (FAB–) exact mass calculated for $[M–K]^-$ ($C_{13}H_{17}BF_3$) requires *m/z* 257.1325, found *m/z* 257.1326. $[\alpha]_D$ (c = 0.95, EtOH) = +4.5.

Spectral Data for potassium pivaloyl- and isoprenyltrifluoroborate salts:



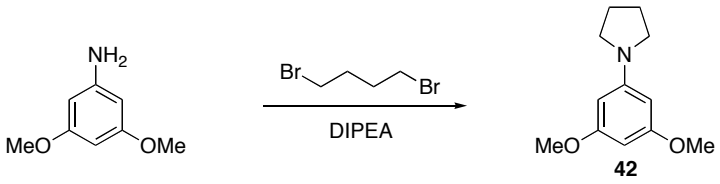
12a

Potassium (*S*)-4-(trifluoroboryl)-3-methylpent-4-enyl 2,2-dimethylpropanoate (12a). ^{1}H NMR (300 MHz, $(CD_3)_2CO$) 5.00 (d, 1H, *J* = 4.8 Hz, C=C**H**H), 4.84 (broad s, 1H, C=CH**H**), 3.89-4.03 (m, 2H, BzOC**H$_2$**), 2.24 (m, 1H, C**H**CH$_3$); 1.84 (m, 1H, CHC**H**H), 1.51 (m, 1H, CHCH**H**), 1.11 (s, 9H, CO(C**H$_3$**)$_3$), 0.99 (d, 3H, *J* = 7.2 Hz, CHC**H$_3$**). ^{13}C NMR (75 MHz, $(CD_3)_2CO$) 178.6, 113.9, 74.9, 64.9, 39.2. 38.5. 35.9. 27.6, 25.3, 21.9. ^{19}F NMR (282 MHz, $(CD_3)_2CO$) –141.0.

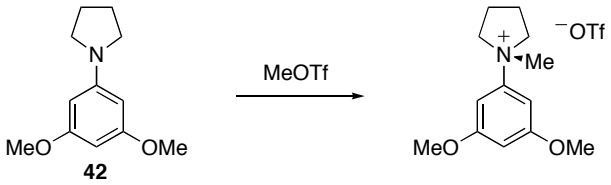


12f

Potassium (*S*)-(3,6-dimethylhepta-1,5-dien-2-yl)trifluoroborate (12f). IR (film) 3031, 2958, 2864, 2122, 1620, 1454, 1408, 1365, 1208, 1083, 1028, 974, 923, 736, 698 cm^{-1}. ^{1}H NMR (300 MHz, $(CD_3)_2CO$) 5.16 (tq, 1H, *J* = 1.5, 6.3 Hz, C=C**H**), 4.98 (d, 1H, *J* = 5.1 Hz, C=C**H**H), 4.81 (broad s, 1H, C=CH**H**), 2.21 (m, 2H, C**H$_2$**), 1.91 (m, 1H, C**H**CH$_3$); 1.63 (s, 3H, =C(**Me**)(Me)), 1.56 (s, 3H, =C(Me)(**Me**)), 0.93 (d, 3H, *J* = 6.9 Hz, CHC**H$_3$**). ^{13}C NMR (75 MHz, $(CD_3)_2CO$) 130.0, 126.9, 114.6, 111.5, 40.5, 35.8, 26.0, 20.4, 17.9. ^{19}F NMR (282 MHz, $(CD_3)_2CO$) –142.1. HRMS (FAB$^-$) exact mass calculated for [M–K]$^-$ ($C_9H_{15}BF_3$) requires *m/z* 191.1219, found *m/z* 191.1210. $[\alpha]_D$ (c = 0.80, EtOH) = –9.9.

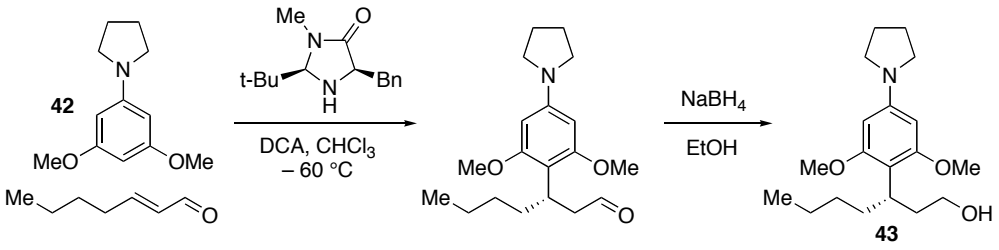


1-(3,5-Dimethoxyphenyl)pyrrolidine (42). 3,5-Dimethoxyaniline (2.3 g, 15.0 mmol) was taken up in 30 mL toluene (0.5 M). Diisopropylethylamine (5.75 mL, 33 mL) and 1,4-dibromobutane (2.0 mL, 16.5 mmol) were added and this reaction was refluxed to 85 °C for 16 h. The reaction was cooled to ambient temperature and quenched with water to remove the salts that had precipitated out of solution. Dichloromethane was added and the biphasic mixture was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL) and dried with magnesium sulfate. The organic solvents were removed in vacuo and flash chromatography provided pyrrolidine **42** as a light yellow oil (2.45 g, 79% yield). IR (film) 2961, 2839, 1615, 1576, 1485, 1464, 1354, 1319, 1226, 1204, 1149, 1068, 926, 801, 679cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) 5.86 (t, 1H, *J* = 2.4 Hz, Ar**H**), 5.75 (d, 2H, *J* = 2.1 Hz, Ar**H)**, 3.77 (s, 6H, O**C**$\mathbf{H_3}$), 3.26 (m, 4H, N-**C**$\mathbf{H_2}$$(CH_2)_2$**C**$\mathbf{H_2}$-), 1.97 (m, 4H, N-$CH_2$(**C**$\mathbf{H_2}$$)_2$$CH_2$-); ^{13}C NMR (75 MHz, $CDCl_3$)) d 161.5, 149.6, 90.7, 87.8, 55.1, 47.7, 25.4. HRMS (FAB+) exact mass calculated for $[MH]^+$ ($C_{12}H_{17}NO_2$) requires *m/z* 207.1259, found *m/z* 207.1259.



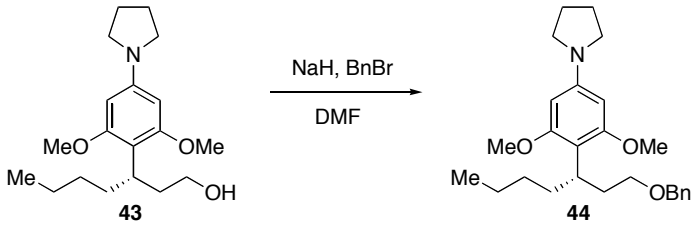
1-(3,5-Dimethoxyphenyl)-1-methylpyrrolidinium trifluoromethanesulfonate. Phenyl pyrollidine **42** (500 mg, 2.41 mmol) was dissolved in 4.8 mL dichloromethane (0.5 M).

Methyl trifluoromethanesulfonate (0.57 mL, 5.06 mmol) was added via syringe. The reaction was stirred at room temperature for 20 minutes and the reaction was triturated with hexanes to precipitate the desired product as a whitish solid (850 mg, 95% yield). IR (film) 2979, 1604, 1487, 1450, 1424, 1268, 1208, 1153, 1063, 1035, 823, 691, 643 cm^{-1}. ^1H NMR (300 MHz, $(CD_3)_2CO$) 7.06 (d, 2H, *J* = 2.1 Hz, Ar**H**), 6.70 (t, 1H, *J* = 2.1 Hz, Ar**H**), 3.89 (s, 6H, OC**H**$_3$), 4.47 (m, 2H, N-C**H**H$(CH_2)_2$CH**H**-). 4.16 (m, 2H, N-CH**H**$(CH_2)_2$C**H**H-), 3.61 (s, 3H, NC**H**$_3$), 2.43 (m, 4H, N-CH_2(C**H**$_2$)$_2$$CH_2$-);$^{13}C$ NMR (75 MHz, $(CD_3)_2CO$). 162.7, 149.8, 102.0, 100.7, 66.7, 56.4, 55.2, 29.0, 21.4. ^{19}F NMR (282 MHz, $(CD_3)_2CO$). –78.9. HRMS (FAB+) exact mass calculated for $[MH]^+$ ($C_{13}H_{20}NO_2$) requires *m/z* 222.1494, found *m/z* 222.1502.



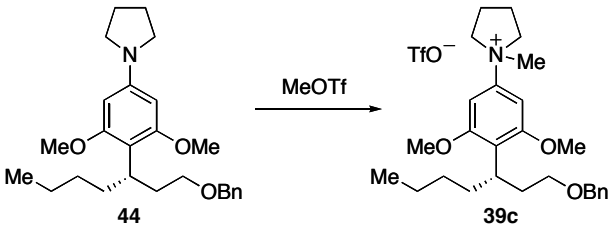
(*S*)-3-(2,6-Dimethoxy-4-(pyrrolidin-1-yl)phenyl)heptan-1-ol (43). 3,5-Dimethoxy-phenyl-*N*-phenylpyrrolidine **42** (500 mg, 2. 41 mmol) was dissolved in 4.8 mL chloroform (0.5M). (2*R*,5*R*)-2-*tert*-butyl-5-benzylimidazolidinone (59.4 mg, 0.241 mmol) and dichloroacetic acid (18 mL, 0.241 mmol) was added and the solution was cooled to –60 °C. Once cooled to this temperature, 2-heptenal (0.95 mL, 7.24 mmol) was added via syringe. The reaction was stirred to – 60 °C for 72 h. The solvent was removed in vacuo. The crude residue was carried directly onto the next step.

The crude residue was taken up in 2 mL EtOH and 8 mL CH_2Cl_2. Sodium borohydride (360 mg, 9.1 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 (6 to 10% EtOAc/hexanes) provided the primary alcohol **99** as a yellow oil (776 mg, 99% yield). IR (film) 3420 (bs), 2954, 2931, 2857, 1613, 1568, 1506, 1465, 1253, 1207, 1127, 1107, 798 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 5.77 (s, 2H, Ar**H**); 3.78 (s, 6H, OC**H**$_3$); 3.47 (m, 1H, ArC**H**); 3.29 (m, 2H, C**H**$_2$OH); 3.29 (m, 4H, N-C**H**$_2$(CH_2)$_2$C**H**$_2$-), 2.09 (broad dd, 1H, *J* = 3.0, 5.1 Hz, OH); 2.00 (m, 4H, N-CH_2(C**H**$_2$)$_2$$CH_2$-); 1.75-2.00 (m, 3H, C**H**$_2$CHC**H**H); 1.56 (m, 1H, CHCH**H**), 1.04-1.3 (m, 4H, C**H**$_2$C**H**$_2$$CH_3$); 0.83 (t, 3H, *J* = 7.2 Hz, CH_2C**H**$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) □ 159.3, 147.3, 108.5, 88.9, 61.8, 55.5, 40.7, 36.6, 33.6, 30.8, 30.6, 22.8, 14.1. The enantiomeric ratio was determined by SFC using a Chiralcel AD-H column (5–50% methanol/CO_2, 35 °C, 100 bar, 4 mL/min, ramp rate = 5%/min); major enantiomer (t_r = 3.89 min) and minor enantiomer (t_r = 3.54 min).



(*S*)-1-(4-(1-(Benzyloxy)heptan-3-yl)-3,5-dimethoxyphenyl)pyrrolidine (44). Potassium hydride (345 mg, 2.55 mmol, 30% in mineral oil) was washed with hexanes three times and dried on a high vacuum line prior to use. Alcohol **43** (410 mg, 1.27 mmol) in 12.7 mL THF (0.1 M) was added to the KH under Ar at ambient temperature.

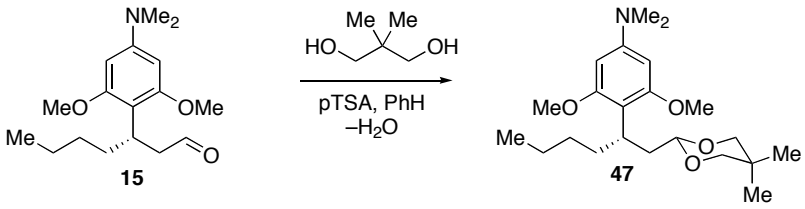
Benzyl bromide (0.3 mL, 2.55 mmol) was added via syringe. After 3 h, the reaction was quenched with water and stirred until all salts were dissolved in the water layer. The biphasic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 15 mL). The organic layers were dried with magnesium sulfate, filtered, and the solvents removed in vacuo. The crude residue was immediately loaded onto a silica gel column. Flash chromatography (4 to 10% ethyl acetate/hexanes) provided the benzyl ether **44** as a very viscous yellow oil (372 mg, 71% yield). ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.31 (m, 5H, Ph**H**), 5.77 (s, 2H, Ar**H**); 4.41 (s, 2H, OC**H**$_2$Ph), 3.76 (s, 6H, OC**H**$_3$); 3.36 (t, 2H, *J* = 7.5 Hz, C**H**$_2$OBn); 3.32 (m, 1H, ArC**H**); 3.30 (m, 4H, N-C**H**$_2$(CH_2)$_2$C**H**$_2$-), 2.16 (m, 1H, CHC**H**H); 2.00 (m, 4H, N-CH_2(C**H**$_2$)$_2$$CH_2$-); 1.90 (m, 1H, CHCH**H**); 1.80 (m, 1H, CHCH**H**), 1.57 (m, 1H, CHC**H**H), 1.02-1.32 (m, 4H, C**H**$_2$C**H**$_2$$CH_3$); 0.82 (t, 3H, *J* = 7.2 Hz, CH_2C**H**$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) □ 159.0, 147.2, 139.2, 128.2, 127.5, 127.2, 108.7, 88.9, 72.7, 70.3, 55.5, 47.6, 34.0, 33.9, 31.4, 30.4, 25.4, 22.9, 14.1.



44 39c

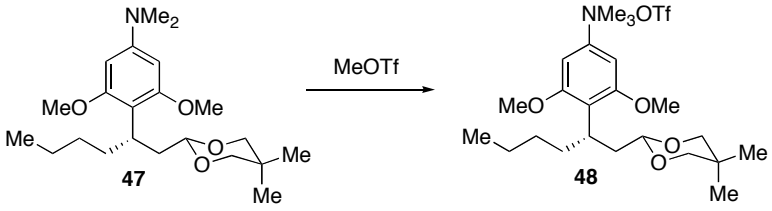
(*S*)-1-(4-(1-(Benzyloxy)heptan-3-yl)-3,5-dimethoxyphenyl)pyrrolidine *N*-methyl trifluoromethanesulfonate (39c). Dimethylaniline **44** (2.05 g, 4.98 mmol) was dissolved in 25 mL dichloromethane. Methyl triflate (0.59 mL, 5. 23 mmol) was added via syringe. The reaction was stirred for 30 minutes. Attempts to triturate or recrystallize the product by the addition of hexanes or ether were unsuccessful as the product **39c** rapidly forms an oil. Therefore, the solvents were removed in vacuo and the oil **39c** (2.85

g, 97% yield) was thoroughly dried on a high vacuum line for 24 h and stored in a vacuum dessicator for 48 h prior to use. IR (film) 2954, 2927, 2856, 1600, 1457, 1425, 1256, 1134, 1030, 638 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 5H, Ph**H**), 6.77 (s, 2H, Ar**H**), 4.38 (s, 2H, OC**H**$_2$Ph), 4.35-4.42 (m, 2H, NC**H**$_2$), 3.80-3.91 (m, 2H, NC**H**$_2$), 3.84 (s, 6H, OC**H**$_3$), 3.49 (s, 3H, NC**H**$_3$), 3.46 (m, 1H, ArC**H**), 3.30 (t, 2H, J = 7.5 Hz, C**H**$_2$OBn), 3.34-2.47 (m, 4H, N(CH_2C**H**$_2$)$_2$), 2.09 (m, 1H, C**H**HCH$_2$OBn); 1.96 (m, 1H, CH**H**CH$_2$OBn); 1.69-1.83 (m, 1H, CHC**H**H), 1.52- 1.64 (m, 1H, CHCH**H**), 0.9-1.3 (m, 4H, C**H**$_2$C**H**$_2$$CH_3$), 0.81 (t, 3H, J = 7.2 Hz, CH_2C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$). δ 159.6, 145.3, 138.8, 128.2, 127.4, 127.3, 123.7, 122.8, 118.6, 96.8, 72.7, 69.5, 65.9, 56.3, 55.0, 33.0, 32.7, 32.0, 30.2, 22.7, 20.9, 14.0. ^{19}F NMR (282 MHz, $CDCl_3$). δ –78.4. HRMS (FAB+) exact mass calculated for [MH – MeOTf]$^+$ ($C_{27}H_{40}NO_3$) requires m/z 426.3008, found m/z 426.2988. $[\alpha]_D$ (c = 1.2, $CHCl_3$) = +8.80



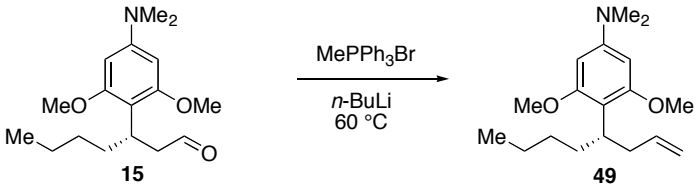
(*S*)-4-(1-(5,5-Dimethyl-1,3-dioxan-2-yl)hexan-2-yl)-3,5-dimethoxy-*N*,*N*-dimethylaniline (47). A solution of aldehyde **15** (293 mg, 1.0 mmol), 2,2-dimethylpropanediol (160 mg, 1.2 mmol), and *p*TSA (30 mg, 0.2 mmol) in benzene (10 mL, 0.1 M) was equipped with a Dean-Stark condenser and heated to 80 °C for 12 h. The reaction was cooled to room temperature, filtered over a silica plug with excess ethyl acetate, and the solvents removed by rotary evaporation. Flash chromatography (5 to 10% ethyl acetate/hexanes) provided the title compound **47** as a viscous yellow oil (271

mg, 72% yield). IR (film) 2953, 2854, 1613, 1568, 1466, 1392, 1362, 1237, 1206, 1128, 1103, 1005, 796 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) 5.92 (s, 2H, Ar**H**), 4.11 (dd, 1H, *J* = 3.0, 7.5 Hz, OC**H**O), 3.77 (s, 6H, OC$\mathbf{H_3}$), 3.54 (ddd, 2H, *J* = 3.0, 10.8, 20.4 Hz, OC**H**$H_{(dioxolane)}$), 3.37 (m, 1H, ArC**H**), 3.28 (app t, 2H, *J* = 11.4 Hz, OCH**H**$_{(dioxolane)}$), 2.95 (s, 6H, NC$\mathbf{H_3}$), 2.18 (ddd, 1H, *J* = 3.3, 10.2, 13.5 Hz, C**H**H**CMe$_{2(dioxolane)}$**), 1.89 (ddd, 1H, *J* = 5.4, 7.8, 13.2 Hz, CH**H**$CMe_{2(dioxolane)}$), 1.77 (m, 1H, CHCH**H**), 1.53 (m, 1H, CHC**H**H), 1.04-1.31 (m, 4H, C$\mathbf{H_2}$C$\mathbf{H_2}$$CH_3$), 1.17 (s, 3H, C(C$\mathbf{H_3}$)$_2$); 0.80 (t, 3H, *J* = 6.6 Hz, CH_2C$\mathbf{H_3}$), 0.64 (s, 3H, C(C$\mathbf{H_3}$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$). 159.9, 150.0, 109.9, 102.3, 90.3, 77.2, 77.2, 40.7, 39.1, 33.7, 31.6, 30.3, 30.2, 30.1, 23.2, 22.9, 22.6, 21.9, 14.1. HRMS (FAB+) exact mass calculated for $[MH]^+$ ($C_{22}H_{37}NO_4$) requires *m/z* 379.2723, found *m/z* 379.2732.



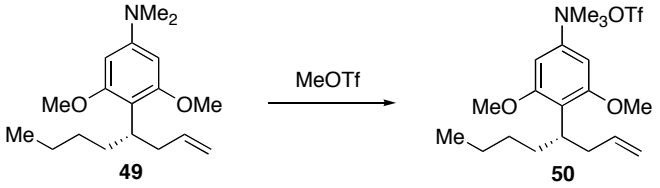
(*S*)-4-(1-(5,5-Dimethyl-1,3-dioxan-2-yl)hexan-2-yl)-3,5-dimethoxy-*N*,*N*,*N*-trimethyl-anilinium trifluoromethanesulfonate (48). Dimethylaniline **47** (238 mg, 0.627 mmol) was dissolved in 2 mL dichloromethane. Methyl trifluoromethanesulfone (75 L, 0.659 mmol) was added via syringe. The reaction was stirred for 10 minutes at room temperature, after which time 20 mL hexanes was added to precipitate the product out of solution. After filtration of this mixture, the product was isolated as a solid (300 mg, 89% yield). IR (film) 2956, 2857, 1600, 1469, 1426, 1258, 1146, 1031, 923, 733, 640 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) 6.85 (s, 2H, Ar**H**), 4.08 (dd, 1H, *J* = 3.6, 6.9 Hz,

OC**H**O), 3.87 (s, 6H, OC**H**$_3$), 3.73 (s, 9H, NC**H**$_3$), 3.47-3.57 (m, 3H, ArC**H** and OC**H**$_{2(\text{dioxolane})}$), 3.28 (app t, 2H, J = 11.1 Hz, OC**H**$_{2(\text{dioxolane})}$), 2.11 (ddd, 1H, J = 3.6, 9.3, 13.2 Hz, CHC**H**H); 1.95 (m, 1H, CHCH**H**); 1.75 (m, 1H, CHC**H**H), 1.56 (m, 1H, CHCH**H**), 1.04-1.37 (m, 4H, C**H**$_2$C**H**$_2$CH$_3$), 1.14 (s, 3H, C(C**H**$_3$)$_2$), 0.79 (t, 3H, J = 7.2 Hz, CH$_2$C**H**$_3$), 0.65 (s, 3H, C(C**H**$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$). 159.6, 145.9, 138.8, 123.8, 101.7, 95.9, 77.2, 57.2, 38.3, 32.8, 31.6, 30.6, 30.1, 30.1, 23.1, 22.7, 22.6, 21.8, 14.1, 14.0. ^{19}F NMR (282 MHz, $CDCl_3$). –78.5. HRMS (FAB+) exact mass calculated for $[MH - OTf]^+$ ($C_{23}H_{40}NO_4$) requires m/z 394.2957, found m/z 394.2942.



(*S*)-3,5-Dimethoxy-*N*,*N*-dimethyl-4-(oct-1-en-4-yl)aniline (49). A mixture of methyl triphenylphosphonium bromide (1.43 g, 4.0 mmol) in 10 mL THF (0.2 M) was cooled to 0 °C under an argon atmosphere. *n*-BuLi (1.44 mL, 3.6 mmol, 2.5M in hexanes) was added dropwise via syringe to form a bright red solution indicative of ylid formation. The ylid was warmed to room temperature for 20 minutes and aldehyde **15** (586 mg, 2.0 mmol) was added in about 1 mL THF. The reaction flask was equipped with a reflux condenser and heated to 60 °C for 2 h. The reaction was followed by TLC analysis. The reaction was cooled to room temperature and filtered over a pad of silica gel with diethyl ether. The organic layers were concentrated and subjected to flash chromatography (4 to 10% ethyl acetate/hexanes) to provide the title compound as a light yellow oil (453 mg, 78% yield). ^{1}H NMR (300 MHz, $CDCl_3$) 5.93 (s, 2H, Ar**H**), 5.34 (ddt, 1H, J = 6.9,

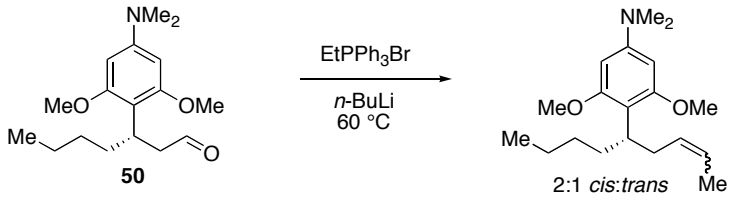
7.2, 13.2 Hz, C**H**=CH_2), 4.86 (m, 2H, CH=C**H**$_2$), 3.78 (s, 6H, OC**H**$_3$), 3.24 (m, 1H, ArC**H**), 2.94 (s, 6H, NC**H**$_3$), 2.52 (m, 1H, C**H**HCH=), 2.39 (m, 1H, CH**H**CH=), 1.75 (m, 1H, CHCH**H**), 1.57 (m, 1H, CHC**H**H), 1.04-1.31 (m, 4H, C**H**$_2$C**H**$_2$$CH_3$), 0.82 (t, 3H, *J* = 7.2 Hz, CH_2C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$). 159.6, 150.0, 139.5, 113.9, 110.4, 90.3, 55.7, 40.7, 38.6, 34.6, 33.2, 30.4, 22.9, 14.1. HRMS (FAB+) exact mass calculated for $[MH]^+$ ($C_{18}H_{28}NO_2$) requires *m/z* 290.2120, found *m/z* 290.2129.



49 **50**

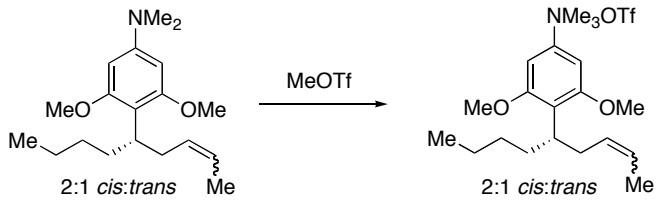
(*S*)-3,5-Dimethoxy-*N*,*N*,*N*-trimethyl-4-(oct-1-en-4-yl)anilinium trifluoromethanesulfonate (50). Dimethylaniline **49** (120 mg, 0.411 mmol) was dissolved in 2 mL dichloromethane. Methyl trifluoromethanesulfone (51 L, 0.452 mmol) was added via syringe. The reaction was stirred for 10 minutes at room temperature, after which time 20 mL hexanes was added to precipitate the product out of solution. After filtration of this mixture, the product was isolated as a solid (140 mg, 98% yield). IR (film) 2956, 2855, 1600, 1468, 1425, 1378, 1257, 1146, 1102, 1031, 923, 738, 637 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) 6.84 (s, 2H, Ar**H**), 5.61 (ddt, 1H, *J* = 6.9, 7.2, 13.2 Hz, C**H**=CH_2), 4.84 (m, 2H, CH=C**H**$_2$), 3.87 (s, 6H, OC**H**$_3$), 3.73 (s, 9H, NC**H**$_3$), 3.39 (m, 1H, ArC**H**), 2.50 (m, 1H, C**H**HCH=), 2.37 (m, 1H, CH**H**CH=), 1.75 (m, 1H, CHCH**H**), 1.59 (m, 1H, CHC**H**H), 0.90-1.31 (m, 4H, C**H**$_2$C**H**$_2$$CH_3$), 0.82 (t, 3H, *J* = 7.5 Hz, CH_2C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$). 159.8, 145.8, 138.0, 123.9, 114.9, 95.8, 57.3, 56.3, 37.5, 35.1, 32.3,

30.3, 22.7, 14.0. ^{19}F NMR (282 MHz, $CDCl_3$). –78.1. HRMS (FAB+) exact mass calculated for $[MH]^+$ ($C_{19}H_{32}NO_2$) requires *m/z* 306.2433, found *m/z* 306.2437.



(*S*)-3,5-Dimethoxy-*N*,*N*-dimethyl-4-(non-2-en-5-yl)aniline.[40] A mixture of ethyl triphenylphosphonium bromide (11.1 g, 28.0 mmol) in 30 mL THF (0.5 M) was cooled to 0 °C under an argon atmosphere. *n*-BuLi (11.5 mL, 26.6 mmol, 2.3M in hexanes) was added dropwise via syringe to form a bright red solution indicative of ylid formation. The ylid was warmed to room temperature for 20 minutes and aldehyde **15** (4.4 g, 15.0 mmol) was added in about 1 mL THF. The reaction flask was equipped with a reflux condenser and heated to 60 °C for 4 h. The reaction was followed by TLC analysis. The reaction was cooled to room temperature and filtered over a pad of silica gel with diethyl ether. The organic layers were concentrated and subjected to flash chromatography (3 to 10% ethyl acetate/hexanes) to provide the title compound as a light yellow oil (3.80 g, 83% yield). IR (film) 2954, 2931, 2956, 1613, 1568, 1506, 1465, 1359, 1254, 1207, 1132, 1008, 796 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) 5.94 (s, 2H, Ar**H**), 5.34 (m, 2H, C**H**=C**H**), 3.78 (s, 6H, OC$\mathbf{H_3}$), 3.23 (m, 1H, ArC**H**), 2.95 (s, 6H, NC$\mathbf{H_3}$), 2.34-2.56 (m, 2H, C$\mathbf{H_2}$CH=), 1.77 (m, 1H, CHCH**H**), 1.53 (m, 1H, CHC**H**H), 1.57 (*1.55*) (s, 3H, =CHC$\mathbf{H_3}$), 1.04-1.31 (m, 4H, C$\mathbf{H_2}$C$\mathbf{H_2}$CH$_3$), 0.83 (*0.80*) (t, 3H, *J* = 7.2 Hz, CH$_2$C$\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$). 159.7, 149.9, 131.0 (*131.9*), 123.2 (*124.3*), 110.7 (*111.0*),

90.3 (*90.5*), 55.7, 40.7 (*37.4*), 34.8 (*35.1*), 33.2 (*32.9*), 31.3, 30.5 (*30.49*), 22.9 (*18.0*), 14.1 (*12.8*).



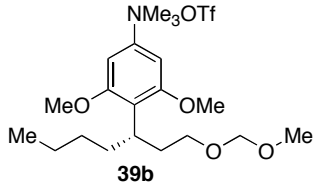
55

(*S*)-3,5-Dimethoxy-*N*,*N*,*N*-trimethyl-4-(non-2-en-5-yl)anilinium trifluoromethanesulfonate (55).[40] (*S*)-3,5-dimethoxy-*N*,*N*-dimethyl-4-(non-2-en-5-yl)aniline (601 mg, 1.97 mmol) was dissolved in 9.8 mL dichloromethane. Methyl trifluoromethanesulfone (234 μL, 2.07 mmol) was added via syringe. The reaction was stirred for 10 minutes at room temperature, after which time 50 mL hexanes was added to precipitate the product out of solution. After filtration of this mixture, the product was isolated as a pearly white solid (769 mg, 83% yield). IR (film) 2956, 2857, 1600, 1469, 1426, 1258, 1146, 1031, 923, 733, 640 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 2H, Ar**H**), 5.31 (m, 1H, C**H**=CH), 5.21 (m, 1H, CH=C**H**), 3.87 (*3.86*) (s, 6H, OC$\mathbf{H_3}$), 3.72 (s, 9H, NC$\mathbf{H_3}$), 3.41 (m, 1H, ArC**H**), 2.46 (m, 1H, C**H**HCH=), 2.35 (m, 1H, CH**H**CH=), 1.77 (m, 1H, CHCH**H**), 1.59 (m, 1H, CHC**H**H), 1.49 (*1.53*) (d, 3H, J = 6.3 Hz, =CHC$\mathbf{H_3}$), 0.88-1.30 (m, 4H, C$\mathbf{H_2}$C$\mathbf{H_2}$$CH_3$), 0.81 (*0.80*) (t, 3H, J = 7.2 Hz, CH_2C$\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$). δ 159.6, 145.9, 138.8, 123.8, 101.7, 95.9, 77.2, 57.2, 38.3, 32.8, 31.6, 30.6, 30.1, 30.1, 23.1, 22.7, 22.6, 21.8, 14.1, 14.0. ^{19}F NMR (282 MHz, $CDCl_3$). δ –78.5. HRMS (FAB+) exact mass calculated for $[MH - OTf]^+$ ($C_{20}H_{34}NO_2$) requires m/z 320.2590, found m/z 320.2583. $[\alpha]_D$ (c = 1.03, EtOH) = –4.86.

[40] Minor *trans* chemical shifts are noted in parentheses.

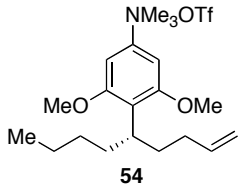
Spectral data for other synthesized trimethylanilinium salts.

General procedure for preparation of trimethylanilinium salts: Dimethylaniline substrate (1 equiv.) was dissolved in 0.5 M dichloromethane. Methyl trifluoromethanesulfone (1.05 equiv.) was added and stirred for 15–30 minutes. Hexanes or pentanes was added to precipitate out the trimethylanilinium salt, which was filtered and the solvent removed in vacuo.



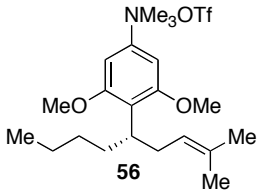
39b

(*S*)-3,5-Dimethoxy-4-(1-(methoxymethoxy)heptan-3-yl)-*N*,*N*,*N*-trimethylanilinium trifluoomethanesulfonate (39b). IR (film) 2958, 2928, 2850, 1599, 1468, 1426, 1376, 1257, 1152, 1107, 1031, 924, 639 cm^{-1}. ^1H NMR (300 MHz, $(CD_3)_2CO$) δ 7.26 (s, 2H, Ar**H**), 4.47 (d, 1H, *J* = 6.6 Hz, OC**H**HO), 4.43 (d, 1H, *J* = 6.3 Hz, OCH**H**O), 3.92 (s, 6H, OC$\mathbf{H_3}$), 3.88 (s, 9H, NC$\mathbf{H_3}$), 3.39 (ddt, 1H, *J* = 6.0, 6.0, 9.3 Hz, ArC**H**), 3.27 (m, 2H, C$\mathbf{H_2}$OMOM), 3.21 (s, 3H, OC$\mathbf{H_3}$), 2.09 (m, 1H, C**H**HCH$_2$O), 1.92 (m, 1H, CH**H**CH$_2$O), 1.83 (m, 1H, CHC**H**H), 1.62 (m, 1H, CHCH**H**), 0.93-1.32 (m, 4H, C$\mathbf{H_2}$C$\mathbf{H_2}$CH$_3$), 0.81 (t, 3H, *J* = 7.2 Hz, CH$_2$C$\mathbf{H_3}$); ^{13}C NMR (75 MHz, $(CD_3)_2CO$). δ 160.5, 147.5, 123.5, 97.9, 96.9, 67.2, 57.7, 56.8, 54.8, 34.1, 33.5, 32.7, 31.0, 23.3, 14.3. ^{19}F NMR (282 MHz, $(CD_3)_2CO$). δ –78.9. HRMS (FAB+) exact mass calculated for $[MH]^+$ ($C_{20}H_{36}NO_4$) requires *m/z* 354.2644, found *m/z* 354.2644. $[\alpha]_D$ (c = 1.0, EtOH) = +0.59



54

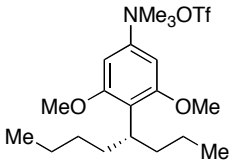
(*S*)-3,5-Dimethoxy-*N*,*N*,*N*-trimethyl-4-(non-1-en-5-yl)anilinium trifluoromethanesulfonate (54). IR (film) 2968, 2922, 2856, 1598, 1468, 1425, 1376, 1259, 1222, 1156, 1031, 923, 739, 637 cm^{-1}. ^1H NMR (300 MHz, $(CD_3)_2CO$) 7.26 (s, 2H, Ar**H**), 5.77 (ddt, 1H, *J* = 6.0, 7.5, 9.6 Hz, C**H**=CH_2), 4.86 (m, 2H, C**H**=CH_2), 3.92 (s, 6H, OC$\mathbf{H_3}$), 3.89 (s, 9H, NC$\mathbf{H_3}$), 3.40 (m, 1H, ArC**H**), 1.55-2.00 (m, 6H, C$\mathbf{H_2}$CHC$\mathbf{H_2}$C$\mathbf{H_2}$CH=), 0.93-1.32 (m, 4H, C$\mathbf{H_2}$C$\mathbf{H_2}$$CH_3$), 0.81 (t, 3H, *J* = 7.2 Hz, CH_2C$\mathbf{H_3}$); ^{13}C NMR (75 MHz, $(CD_3)_2CO$). 160.0, 157.2, 139.9, 123.7, 114.5, 98.6, 57.7, 35.5, 33.5, 33.4, 33.2, 31.1, 23.3, 14.3. ^{19}F NMR (282 MHz, $(CD_3)_2CO$). –78.9. HRMS (FAB+) exact mass calculated for $[MH]^+$ ($C_{20}H_{34}NO_2$) requires *m/z* 320.2590, found *m/z* 320.2591. $[\alpha]_D$ (c = 0.74, EtOH) = +2.9



56

(*S*)-3,5-Dimethoxy-*N*,*N*,*N*-trimethyl-4-(2-methylnon-2-en-5-yl)anilinium trifluoromethanesulfonate (56). IR (film) 2956, 2849, 1598, 1466, 1424, 1262, 1226, 1146, 1207, 1157, 1032, 637 cm^{-1}. ^1H NMR (300 MHz, $(CD_3)_2CO$) 7.24 (s, 2H, Ar**H**), 5.01 (tq, 1H, *J* = 1.5, 7.2 Hz, C**H**=C), 3.92 (s, 6H, OC$\mathbf{H_3}$), 3.86 (s, 9H, NC$\mathbf{H_3}$), 3.38 (m, 1H, ArC**H**), 2.38 (m, 2H, C$\mathbf{H_2}$CH=), 1.87 (m, 1H, CHCH**H**), 1.62 (m, 1H, CHC**H**H), 1.56 (s,

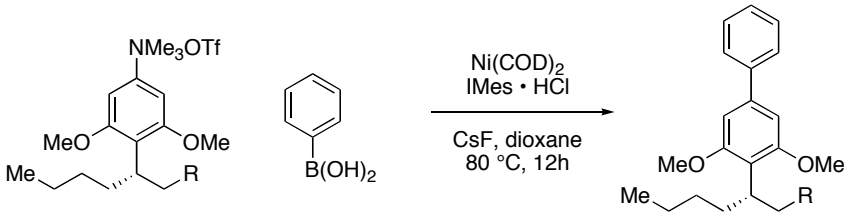
3H, C=C(**Me**)(Me)), 1.49 (s, 3H, C=C(Me)(**Me**)), 0.93-1.32 (m, 4H, C**H**$_2$C**H**$_2$CH$_3$), 0.80 (t, 3H, *J* = 7.2 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (75 MHz, (CD$_3$)$_2$CO). 160.5, 147.3, 132.0, 124.6, 124.1, 97.9, 57.7, 56.8, 36.4, 32.9, 32.5, 31.1, 25.8, 23.4, 17.7, 14.3. ^{19}F NMR (282 MHz, (CD$_3$)$_2$CO). –78.9. HRMS (FAB+) exact mass calculated for [MH]$^+$ (C$_{21}$H$_{36}$NO$_2$) requires *m/z* 334.2746, found *m/z* 334.2744. $[\alpha]_D$ (c = 1.0, EtOH) = –1.2



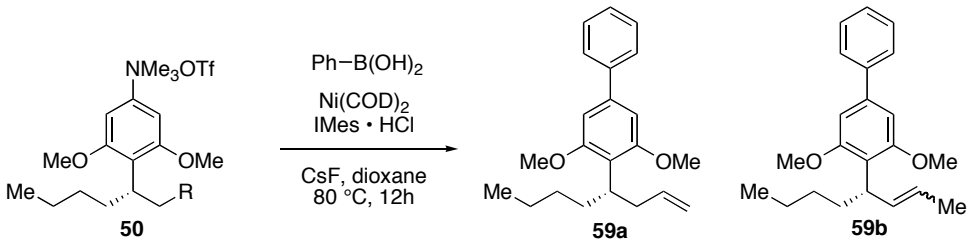
62

(*R*)-3,5-Dimethoxy-*N*,*N*,*N*-trimethyl-4-(octan-4-yl)anilinium trifluoromethane-sulfonate (62). IR (film) 2958, 2917, 2850, 1599, 1463, 1422, 1261, 1222, 1153, 1135, 1031, 637 cm^{-1}. ^{1}H NMR (300 MHz, (CD$_3$)$_2$CO) 7.25 (s, 2H, Ar**H**), 3.91 (s, 6H, OC**H**$_3$), 3.88 (s, 9H, NC**H**$_3$), 3.39 (tt, 1H, *J* = 5.7, 9.0 Hz, ArC**H**), 1.82 (m, 2H, CHC**H**$_2$), 1.58 (m, 2H, C**H**$_2$CH), 1.56 (s, 3H, C=C(**Me**)(Me)), 1.49 (s, 3H, C=C(Me)(**Me**)), 0.93-1.32 (m, 6H, C**H**$_2$C**H**$_2$CH$_3$ and C**H**$_2$CH$_3$), 0.81 (t, 3H, *J* = 7.2 Hz, CH$_2$C**H**$_3$), 0.80 (t, 3H, *J* = 7.2 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (75 MHz, (CD$_3$)$_2$CO). 160.7, 129.8, 124.6, 124.1, 97.8, 57.7, 56.8, 36.3, 35.6, 33.7, 31.1, 23.4, 21.9, 14.4, 14.3. ^{19}F NMR (282 MHz, (CD$_3$)$_2$CO). –78.9. HRMS (FAB+) exact mass calculated for [MH]$^+$ (C$_{19}$H$_{34}$NO$_2$) requires *m/z* 308.2590, found *m/z* 308.2591. $[\alpha]_D$ (c = 1.0, EtOH) = –1.5

General procedure for cross-coupling of trimethylanilinium salts with $PhB(OH)_2$:



Inside a glovebox, a flame-dried 2-dram vial was charged with the desired trimethylanilinium salt (0.044 mmol), phenylboronic acid (8 mg, 0.066 mmol), Ni(COD)2 (1.2 mg, 0.0044 mmol), IMes • HCl (1.5 mg, 0.0044 mmol), and cesium fluoride (20 mg, 0.132 mmol). The vial was sealed with a teflon septum and cap and removed from the glovebox. The vial was placed under positive argon pressure while 0.3 mL dioxane was added (0.15 M). The vial was then sealed and heated to 80 °C for 12 h, after which the reaction was cooled to room temperature and quenched with 1N HCl. This facilitates purification by forming the salt of the dimethylaniline by-product, which is eliminated in the aqueous layer. The aqueous layer was then extract with ethyl acetate, washed with brine, and dried with magnesium sulfate. The organic layers were removed in vacuo, and the product was isolated by flash column chromatography.



(*S*)-3,5-Dimethoxy-4-(oct-1-en-4-yl)biphenyl (59a) and (*S*)-3,5-dimethoxy-4-(oct-2-en-4-yl)biphenyl (59b). Trimethylanilinium salt **50** (20 mg) was cross-coupled

according to the general procedure. A 1:1 mixture of isomerized and unisomerized biphenyl product was isolated (12 mg, 84% yield).

(*S*)-3,5-Dimethoxy-4-(oct-1-en-4-yl)biphenyl (59a) ^{1}H NMR (300 MHz, $CDCl_3$) 7.59 (m, 2H, Ph**H**), 7.43 (m, 2H, Ph**H**), 7.36 (m, 1H, Ph**H**), 6.74 (s, 2H, Ar**H**), 5.73 (ddt, 1H, *J* = 6.9, 7.2, 13.2 Hz, C**H**=CH_2), 4.89 (m, 2H, CH=C**H$_2$**), 3.85 (s, 6H, OC**H$_3$**), 3.41 (m, 1H, ArC**H**), 2.57 (m, 1H, C**H**HCH=), 2.48 (m, 1H, CH**H**CH=), 1.82 (m, 1H, CHCH**H**), 1.62 (m, 1H, CHC**H**H), 1.04-1.38 (m, 4H, C**H$_2$**C**H$_2$**CH_3), 0.82 (t, 3H, *J* = 7.2 Hz, CH_2C**H$_3$**).

(*S*)-3,5-Dimethoxy-4-(oct-2-en-4-yl)biphenyl (59b). ^{1}H NMR (300 MHz, $CDCl_3$) 7.59 (m, 2H, Ph**H**), 7.43 (m, 2H, Ph**H**), 7.36 (m, 1H, Ph**H**), 6.74 (s, 2H, Ar**H**), 5.94 (ddq, 1H, *J* = 1.5, 9.0, 15.0 Hz, C**H**=CHMe), 5.36-5.54 (m, 1H, CH=C**H**Me), 3.86 (*3.87*) (s, 6H, OC**H$_3$**), 3.94 (*4.33*) (dt, 1H, *J* = 7.8, 15.3 Hz, ArC**H**), 1.77 (dt, 1H, *J* = 7.5, 7.5 Hz, C**H$_2$**CH), 1.65 (*1.66*) (dd, 3H, *J* = 1.8, 6.3 Hz =CHC**H$_3$**), 1.04-1.38 (m, 4H, C**H$_2$**C**H$_2$**CH_3), 0.84 (t, 3H, *J* = 7.2 Hz, CH_2C**H$_3$**).

C h a p t e r 5

A Formal Synthesis of Cylindrocyclophane A: Cross-Coupling with an Activated Vinyl Stannane.

The difficulties associated with the key cross-coupling that arose in the first-generation approach to cylindrocyclophane A prompted the investigation of an alternative route using a different transmetalation partner. As demonstrated in chapter 4, an unwanted side reaction of nickel(0) catalysis was isomerization of terminal olefins present on either the oxidative addition or transmetalation partner. A new synthetic strategy would require that functionality of the cross-coupling substrate be unaffected by an olefin isomerization event.

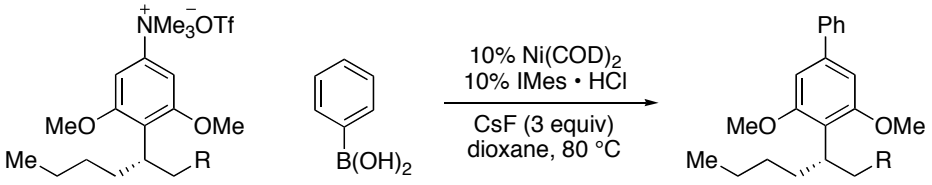
I. Revisiting the olefin isomerization problem.

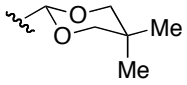
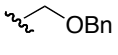
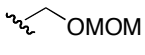
i. *Trimethylanilinium salt.*

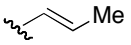
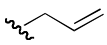
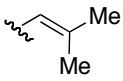
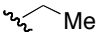
Chapter 4 ended with a study into which substituents were tolerated under the nickel(0)-catalyzed cross-coupling conditions (*vide infra*). Table 1 summarizes the results of an investigation into which functionality on the alkyl chain of the trimethylanilinium salt is tolerated under these conditions. The most promising substrate comprised a terminal olefin on the alkyl chain at the 4-position (entry 1). Though carbon-carbon bond formation was effected in 84% yield, there was a significant amount of isomerization of the terminal olefin to the 1,2-disubstituted olefin. In order to

circumvent this problem, a variety of more substituted alkenes were synthesized and subjected to the cross-coupling conditions (entries 6–8). The 1,2-disubstituted system coupled efficiently (60% yield) and, more importantly, the position of the olefin remained unchanged (entry 6). Therefore, this second-generation synthetic strategy will focus on cross-coupling with this trimethylanilinium salt.

Table 1. Trimethylanilinium salts that can participate in cross-coupling.



Entry	1	2	3	4	5
R					
Yield	84%*	20%	NP	NP	NP

Entry	6	7	8	9
R				
Yield	60%	41%*	12%	22%

* terminal olefin was isomerized to the internal position

ii. *Transmetalation partner.*

Due to the observation that 1,1-disubstituted vinyl potassium trifluoroborate salts also isomerized when cross-coupled to the desired trimethylanilinium salt (Chapter 4), substrates of these types were no longer considered. The first approach to seeking out a new coupling partner was to use a BF_3K salt that would *purposely* isomerize into a

desirable position. For instance, if an allyl-derived BF_3K salt coupled with the optimal trimethylanilinium salt **1**, the allylic product would isomerize under the reaction conditions into a position that would prove useful to the overall synthesis (Fig. 1).

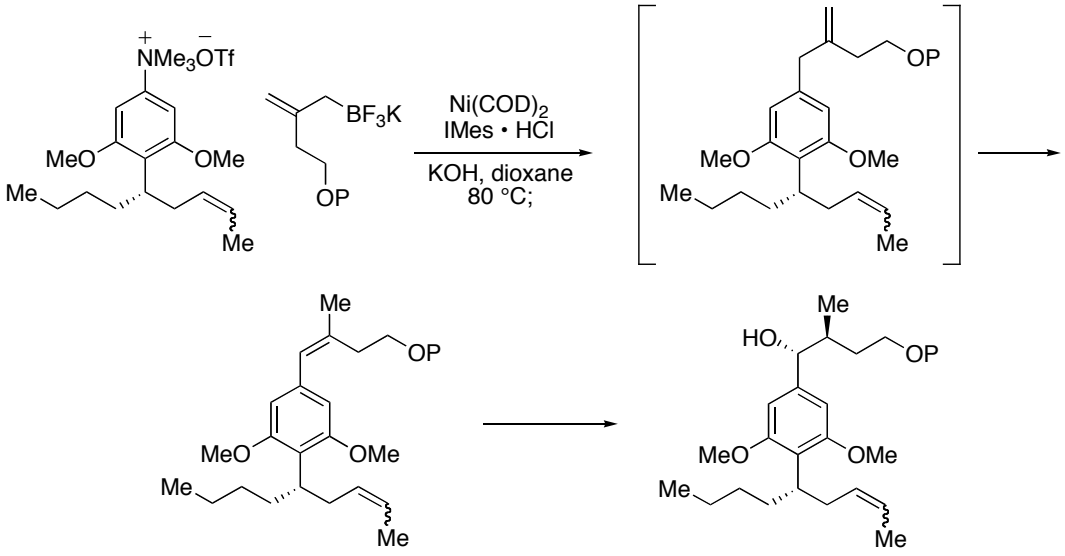
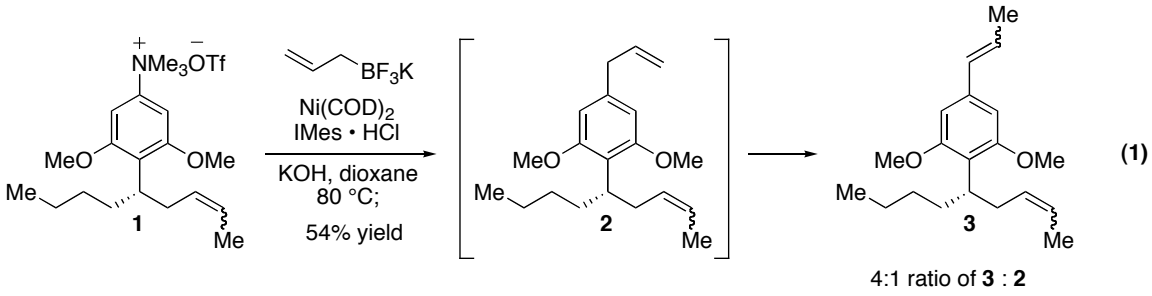


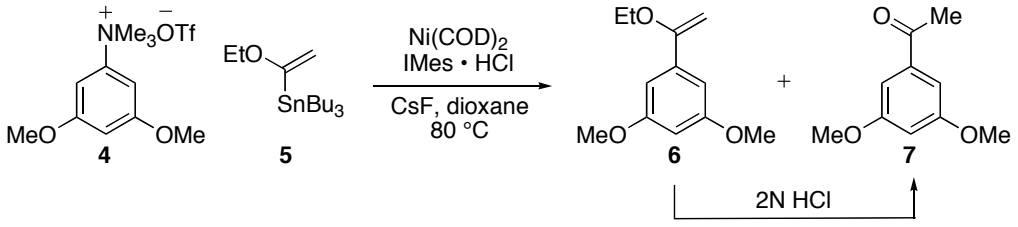
Figure 1. A selective olefination isomerization required for further functionalization.

This strategy was first probed with potassium allyltrifluoroborate to see if it isomerized under the nickel(0) reaction conditions; allyl BF_3K did indeed cross-couple in 54% yield to give predominantly isomerized styrene **3** (eq. 1). In order to make the above cross-coupling strategy applicable to the total synthesis of cylindrocyclophanes F, a single product of the olefin isomerization would have to be produced in order to conduct further chemistry in a stereoselective manner. Based on the mixture of olefin isomers observed in **3**, the unsatisfactory control of the isomerization process was deemed to be not suitable for construction of the natural product.

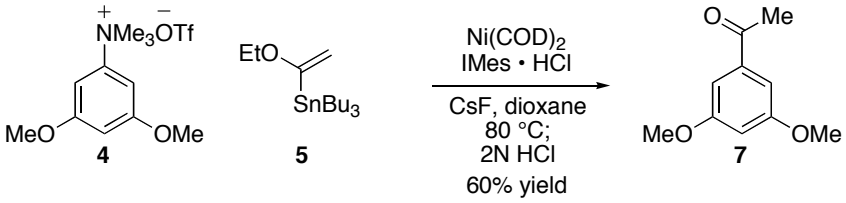


(1)

It had previously been shown that activated α-ethoxyvinyl tributyltin (**5**) coupled to the model system **4** to afford a mixture of 1-(1-ethoxyvinyl)-3,5-dimethoxybenzene (**6**) and 3,5-dimethoxyacetophenone (**7**) (eq. 2). Not surprisingly, enol ether **6** converts to methyl ketone **7** upon exposure to silica gel. By pre-treating the silica gel with triethylamine, the ethyl enol ether **6** could be cleanly isolated. Alternatively, stirring the completed reaction with 2N aqueous HCl provided full conversion to the methyl ketone in a 60% yield (eq. 3).



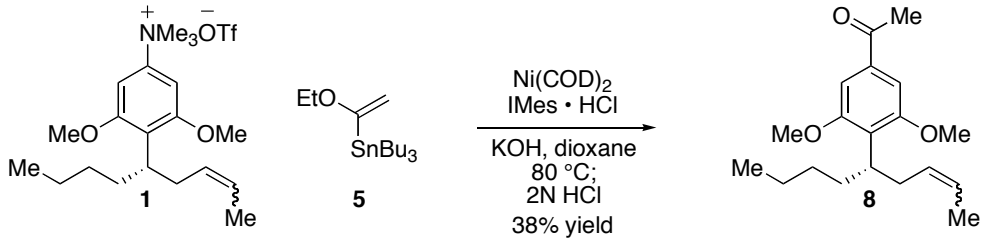
(2)



(3)

This result became more useful when it proved to be applicable to the cross-coupling of stannane **2** with the more electron-rich trimethylanilinium salt **1**. After an

aqueous acidic quench, the methyl ketone **8** was isolated in 38% yield (eq. 4). Encouraged by this result, a new retrosynthetic plan was devised using trimethylanilinium salt **1** with an activated β-ethoxyvinylstannane, such as **5**.



(4)

II. Progress Towards the Total Synthesis of Cylindrocyclophane A.

i. *Retrosynthetic strategy.*

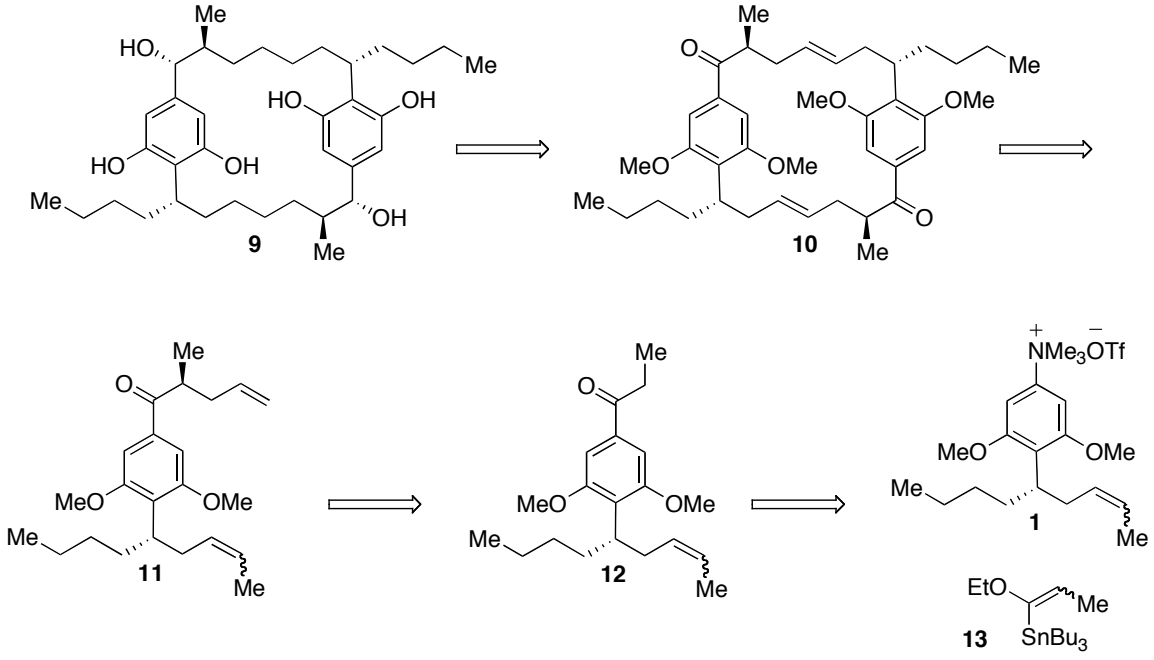
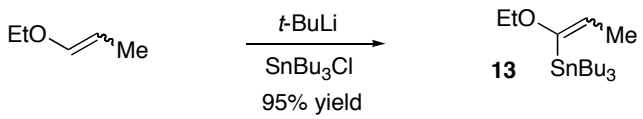


Figure 2. Revised retrosynthetic plan.

As in the first-generation approach, a strategy employing a ring-closing metathesis dimerization of **11** was adopted to form diketone **10**, which is an intermediate en route to the C_2-symmetric cylindrocyclophane A (**9**) (Fig. 2). Dimerization precursor **11** could be prepared by an asymmetric allylation of ethyl ketone **12**. Given the precedent of cross-coupling with activated stannanes, access to ethyl ketone **12** via a Stille coupling of stannane **13** and trimethylanilinium triflate **1** was not foreseen to be problematic.

ii. *Stille cross-coupling with trimethylanilinium salt 1.*

Tributyl(1-ethoxyprop-1-enyl)stannane (**13**) was synthesized in a single transformation from commercially available 1-ethoxyprop-1-ene via lithiation of the β-vinyl proton and quenching with tributyltin chloride (eq. 5).[1]



(5)

Initial exploration into the desired cross-coupling of stannane **13** and anilinium salt **1** showed the reaction to be operative, although it appeared that catalytic turnover was not being achieved (Table 2, entry 1). In order to try to increase the reaction efficiency, a survey of phosphine, phenanthroline, and *N*-heterocyclic carbenes was

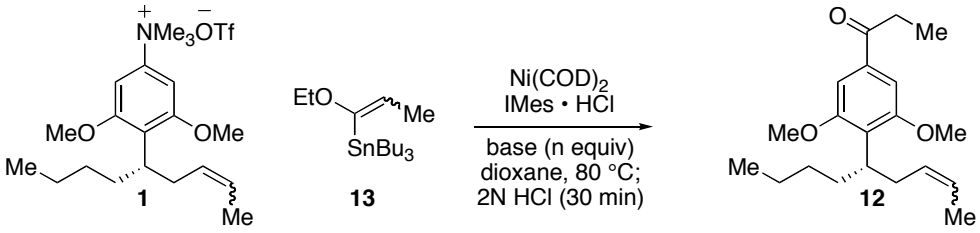
[1] Quintard, J. P.; Elissando, B.; Pereye, M. *J. Org. Chem.* **1983**, *48*, 1559.

conducted. Only IMes • HCl gave any of cross-coupled product **12**; all the other ligands demethylated trimethylanilinium triflate **1** at different rates. A survey of more soluble fluoride sources (Table 2) demonstrated that cesium fluoride was the most effective base, though it was interesting to note that TBAT[2] did function as a fluoride source in the reaction (entry 3). However, this result was not pursued because its byproduct, fluorotriphenylsilane (Ph_3SiF), could not be separated from the product.

While less than three equivalents of cesium fluoride still showed reactivity (1.5 and 2 equivalents, 22 and 26% yield), more than five equivalents increased the rate of demethylation of the trimethylanilinium salt. Using three equivalents of cesium fluoride, the yield could be increased to 52% (entry 6) by allowing the crude reaction mixture to stir for 6 hours in 2N HCl at room temperature after the reaction was completed. It could be speculated that extended exposure to strong acidic conditions serves two purposes: (i) it allows for more complete protonation of the dimethylaniline side-product, thus facilitating subsequent workup procedures, and (ii) it consumes any nickel remaining in the crude reaction mixture, which may still be coordinated to the product.

[2] TBAT = tetrabutylammonium triphenyldifluorosilicate, $[Bu_4N][Ph_3SiF_2]$

Table 2. Survey of fluoride sources in the Stille cross-coupling.



entry	base	equiv.	yield (%)
1	CsF	3	38
2	TBAF	3	NR
3	TBAT	3	23
4	CsF	1.5	22
5	CsF	2	26
6[a]	CsF	3	52

[a] 2N HCl workup allowed to stir for 6 hours

With ethyl ketone **12** in hand, an asymmetric allylation was required to install the stereochemistry of the methyl stereocenter. There are numerous methods available to install an allyl group enantioselectively, however, the first challenge undertaken was to do an achiral allylation in order to obtain an assay for the diastereomers that would be produced in the reaction (Fig. 3). Simple allylation of the lithium enolate provided four diastereomers of the desired product **14**. Due to the presence of (*E*/*Z*) olefin geometries, there were a total of eight possible stereoisomers. The olefins were subsequently hydrogenated to give **15**, which now only consisted of four diastereomers.

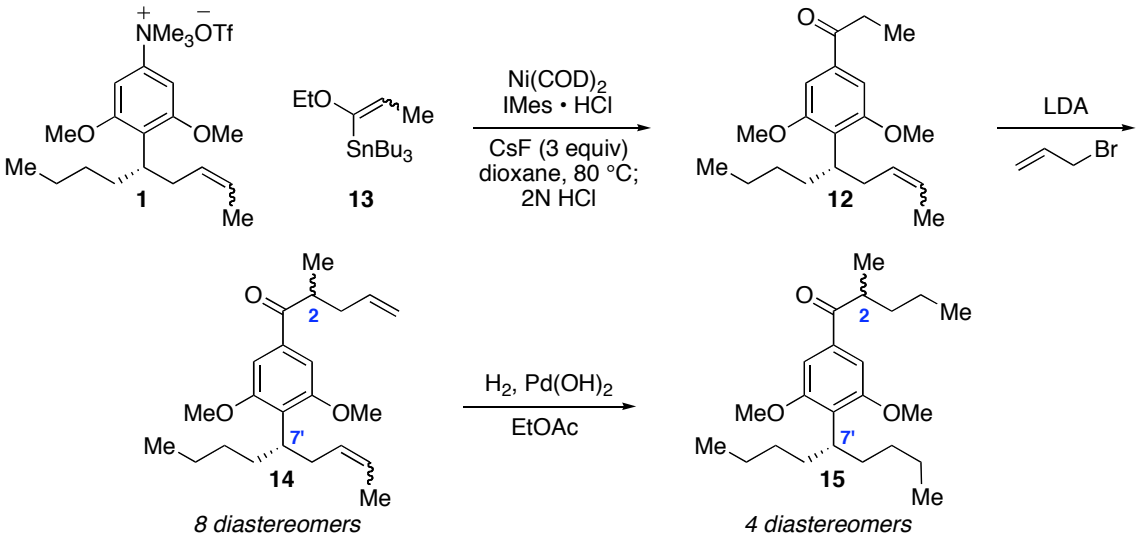


Figure 3. An achiral allylation for an assay.

The diastereomers of ketone **15** were not detectable by ^{1}H NMR, as should be expected because the two stereocenters at C2 and C7' are not within proximity to each other. Likewise, separation of the stereoisomers by chiral gas chromatography was unsuccessful. Ketones **14** and **15** were unexpectedly non-polar, thus all available methods of separation by liquid chromatography proved ineffective.

The inability to obtain a spectrometric or chromatographic method to determine the selectivity at the C2 stereocenter suggested that a diastereoselective allylation should be utilized (Fig. 4). By employing a chiral auxiliary, the diastereoselection should be easily assessed by ^{1}H NMR analysis on a substrate such as **16**.

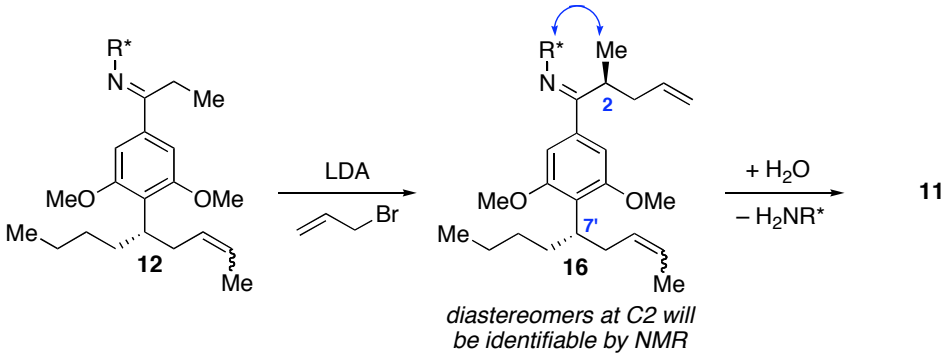
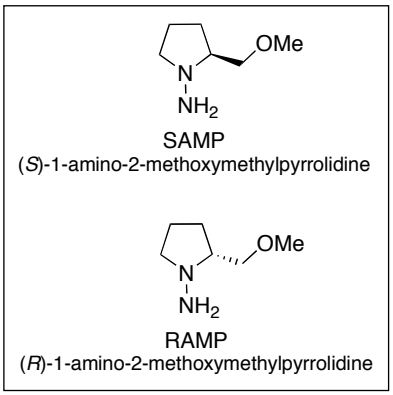


Figure 4. Allylic alkylation with a chiral auxiliary to facilitate the determination of diastereoselectivity.

iii. *Diastereoselective allylic allylation with chiral hydrazones.*



In 1976, Enders and co-workers reported that the RAMP and SAMP hydrazones of a variety of ketones and aldehydes underwent diastereoselective alkylations in the presence of various electrophiles.[3] The mild conditions used in the construction and removal of the hydrazones have made them an attractive protocol in natural product synthesis. As illustrated in figure 5, Nicolaou has used this alkylation methodology on both ketone- and aldehyde-derived SAMP hydrazones in the total

[3] (a) Enders, D.; Eichenauer, H. *Angew. Chem. Int. Ed.* **1976**, *15*, 549. (b) Enders, D.; Eichenauer, H. *Tetrahedron Lett.* **1977**, *47*, 191. (c) For a comprehensive review on the SAMP/RAMP-hydrazone methodology, see: Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253.

syntheses of swinholide A (an antifungal and cytotoxic marine isolate)[4] and CP-225,917 (a potent inhibitor of squalene synthase and Ras farnesyl transferase).[5]

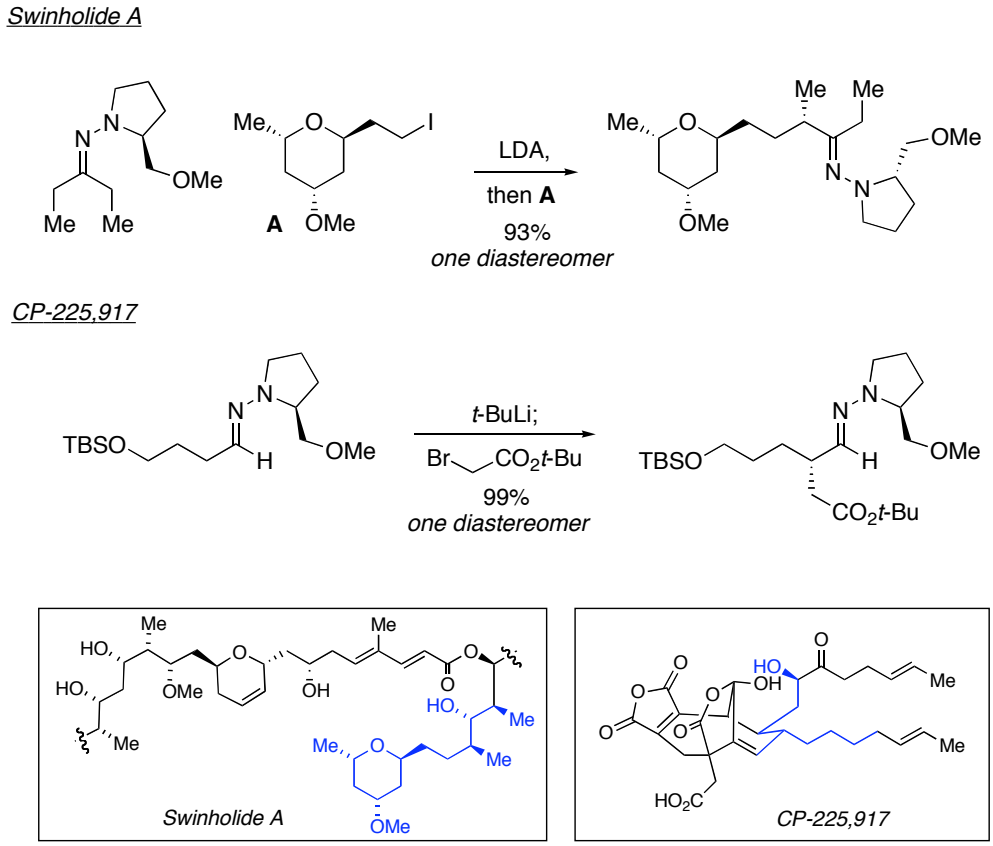


Figure 5. SAMP-hydrazone alkylations in natural product synthesis.

In the enolization step, four different azaenolate geometries corresponding to rotation around the C=C and C–N bonds are possible. In the presence of lithium bases, only one of these four azaenolates is observed. In both cyclic and acyclic systems, this $E_{CC}Z_{CN}$ species is favored (Fig. 6). This has been confirmed with trapping experiments,[6]

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[4] (a) Nicolaou, K. C.; Patron, A. P.; Ajito, K.; Richter, P. K.; Khatuya, H.; Bertinato, P.; Miller, R. A.; Tomaszewski, M. *Chem. Eur. J.* **1996**, *2*, 847. (b) Nicolaou, K. C.; Ajito, K.; Patron, A. P.; Khutaya, H.; Richter, P. K.; Bertinato, P. *J. Am. Chem. Soc.* **1996**, *118*, 3059.

[5] Nicolaou, K. C.; Harter, M. W.; Boulton, L.; Jandeleit, B. *Angew. Chem. Int. Ed.* **1997**, *36*, 1194.

[6] (a) Enders, D.; Eichenauer, H. *Chem Ber.* **1979**, *112*, 2933. (b) Enders, D.; Eichenauer, H.; Baus, U.; Schubert, H.; Kremer, K. A. *Tetrahedron* **1984**, *40*, 1345. (c) Endrs, D.; Baus, U. *Liebigs. Ann.* **1983**, 1439.

x-ray analysis,[7] and spectroscopic investigations.[8] In monomeric structure **17EZ**, the methoxy group of the pyrrolidine coordinates the lithium atom of the lithio enehydrazide intramolecularly. Electrophilic attack on this rigid intermediate is biased by the conformation of the catalyst and proceeds with high levels of diastereodifferentiation. Based on these models that Enders proposed,[3c] it was determined that the (*S*)-enantiomeric series of the chiral hydrazones (SAMP, SAEP, SAPP) would be required for the proposed synthesis.

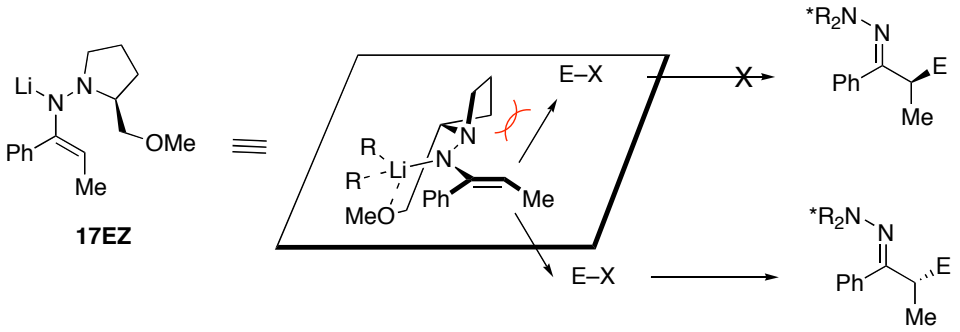

Figure 6. Diastereoselective alkylation of SAMP hydrazone.

In order to test the levels of diastereoselectivity of the allylation, a model study was done using phenyl ethyl ketone **18**. The conditions reported to form SAMP hydrazones on phenyl ketones required neat reaction conditions, elevated temperatures, and long reaction times. In order to make this procedure useful in an advanced stage of a synthesis a new procedure had to be developed in order to avoid using an excess of the phenyl ketone. Using reaction conditions developed for less sterically-demanding ketones (TsOH, benzene), the SAMP-hydrazone **19** of ketone **18** was isolated after 144

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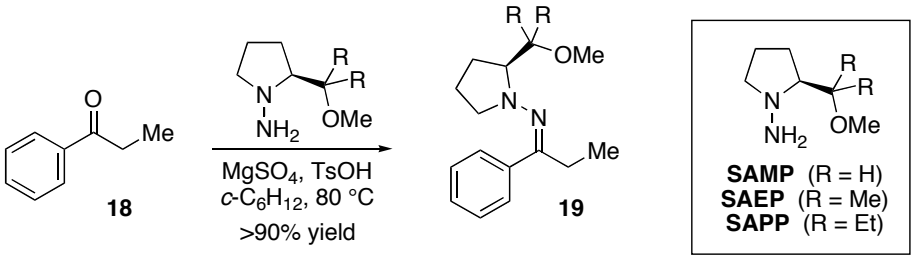
[7] Enders, D.; Bachstadter, G.; Kremer, K. A. M.; Marsch, M.; Harms, K.; Boche, G. *Angew. Chem. Int. Ed.* **1988**, *27*, 1522.

[8] (a) Davenport, K. G.; Eichenauer, H.; Enders, D.; Newcomb, M.; Bergbreiter, D. E. *J. Am. Chem. Soc.* **1979**, *101*, 5654. (b) Ahlbrecht, H.; Duber, E. O.; Enders, D.; Eichenauer, H.; Weuster, P. *Tetrahedron Lett.* **1978**, *19*, 3691.

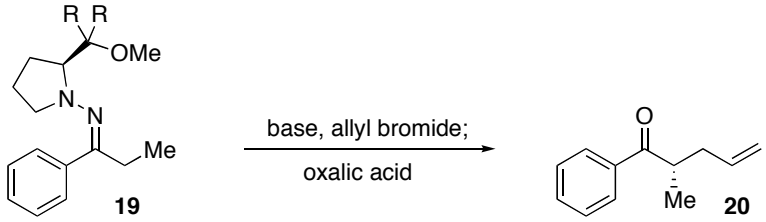
hours in only 44% yield. After some investigation, it was found that the addition of magnesium sulfate accelerated the condensation by removing water from the reaction mixture. In addition, changing the solvent to cyclohexane facilitated the condensation in less than 24 hours, with yields consistently above 90% (eq. 6).



(6)

The allylic alkylation of the lithio enehydrazide was examined using allyl bromide as the electrophile (Table 3). The enantiomeric excess was determined by analysis of the ketone **20**, which was obtained after cleavage of the corresponding hydrazone in the presence of oxalic acid.

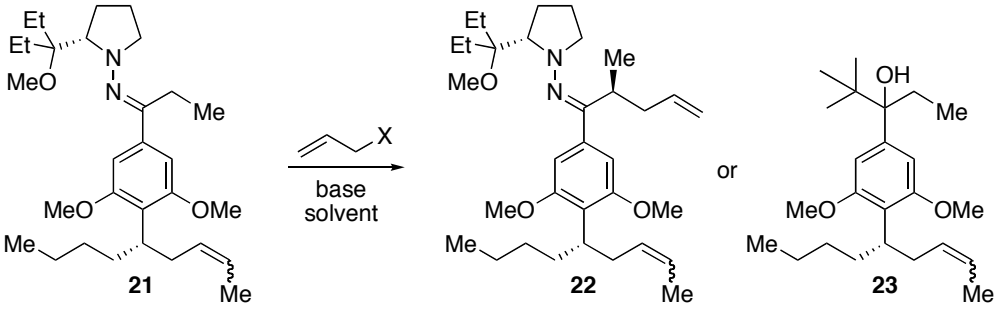
Table 3. Diastereoselective alkylation with SAMP-derivatives.



entry	R	base	ee (%)
1	H	*n*-BuLi	NR
2	H	LDA	10
3	H	LiTMP	16
4	H	*t*-BuLi	70
5	Me	*t*-BuLi	82
6	Et	*t*-BuLi	91

Different lithium bases were screened in the alkylation of the SAMP hydrazone of **19** (R = H). While LDA, LiTMP, and *tert*-butyllithium effected complete conversion to the product, *t*-BuLi gave higher levels of enantioselectivity (entries 2–4, 90% ee vs. 10 and 16% ee). Other combinations of bases and solvents with the SAMP hydrazone did not increase the selectivity of this reaction. The effect of the size of the substitutents on the pyrrolidine ring of the chiral auxiliary was examined next. It was found that by changing from the SAMP (R = H) to the SAEP (R = Me) hydrazone, the enantioselectivity increased (entries 4 and 5, 70 to 82% ee). Ultimately, the SAPP (R = Et) hydrazone provided ketone **20** with synthetically useful levels of enantioselectivity (91% ee, entry 6). Alkylation with SAPP was thus carried over to the desired system of cylindrocyclophane A.

Table 4. Diastereoselective alkylation with SAPP-hydrazone 21.



entry	X	solvent	base	product
1	Br	THF	*t*-BuLi	**23**
2	Br	hexanes	*t*-BuLi	**23**
3	Br	Et_2O	*t*-BuLi	**23**
4	I	THF	*n*-BuLi	NR
5	I	THF	LDA	NR
6	Br	THF	LDA	NR
7	Br	THF	LiTMP	NR

SAPP hydrazone **21** was reactive under the conditions developed in table 3. As shown in table 4, the desired allylated product **22** was not isolated. Instead the tertiary alcohol **23** was obtained when *t*-BuLi was used as a base. It seemed surprising that a large nucleophilic base such as *tert*-butyllithium would be able to attack the C=N bond that resides in such a sterically hindered environment (Fig. 7). Thus it was thought that less nucleophilic and/or smaller bases would prevent this pathway. However, variation in the source of the base or the leaving group on the allyl electrophile did not affect any reaction (Table 4, entries 4–6). Despite attempts to suppress this side reaction by altering solvents (entries 1–3), this undesired reaction was found to dominate the diastereoselective allylation of substrate **21**.

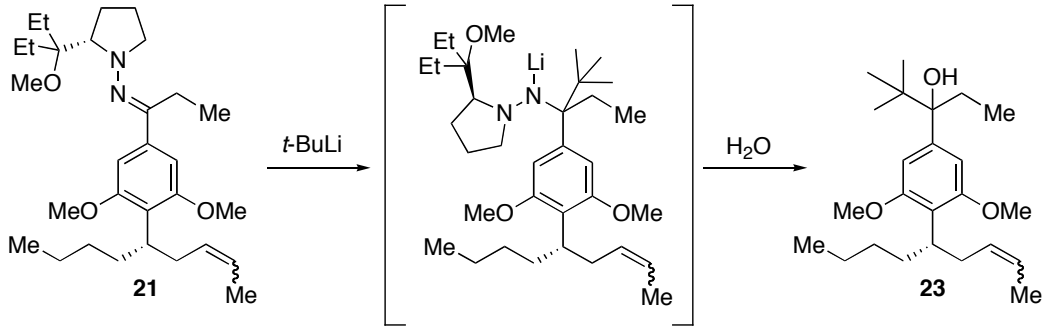


Figure 7. Addition to C=N bond in the diastereoselective alkylation.

Despite other efforts to change the SAPP hydrazone to the SAEP and SAMP derivatives, the nucleophilic addition to the C=N bond prevailed. This deleterious side reaction proved insurmountable and thus an alternative allylic alkylation protocol was pursued.

iv. *Asymmetric allylic alkylation using the Tsuji reaction*

While the asymmetric allylic alkylation (AAA) of ketone enolates is one of the most challenging reactions in organic synthesis, it is also one of the most important.[9] This asymmetric alkylation of ketones is complicated by the need to control the enolate geometry, which in turn dictates selectivity. Because of this constraint, initial reports of an asymmetric catalytic enolate allylation focused on cyclic ketones where the enolate geometry is fixed by the carbocycle. Stoltz[10] reported the first asymmetric Tsuji allylation[11] of cyclic enol carbonates using a palladium-catalyzed system with the PHOX ligands[12] (Fig. 8). Likewise, Trost employed phenanthroline-based P/N ligands with a palladium catalyst to effect a similar allylation with good levels of enantioselectivity. [13]

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[9] (a) Trost, B. M.; Lee, C. In *Catalytic Asymmetric Synthesis, 2nd Ed.* Ojima, I. Ed., Wiley-VCH: New York, 2000. pp 593–649. (b) Pflatz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*, Jacobsen, E N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 2, pp 833–884. (c) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (d) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813.

[10] Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044.

[11] (a) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140. (b) Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 1793.

[12] For a review on N/P ligands, see: (a) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336. (b) Williams, J. M. J. *Synlett* **1996**, 705.

[13] Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846.

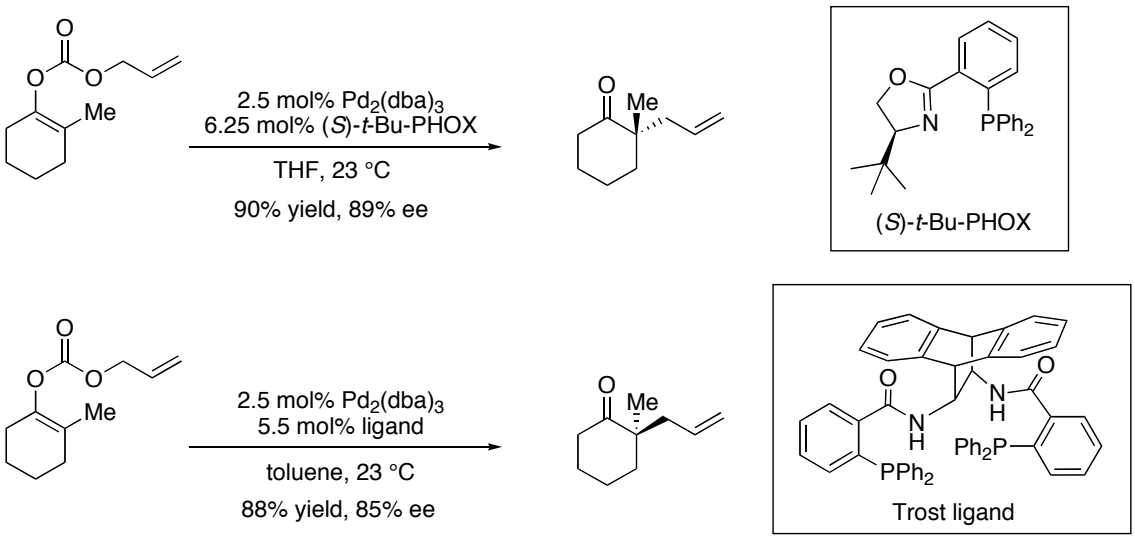


Figure 8. AAA of cyclie ketones by Stoltz and Trost.

While both of these examples are seminal contributions to AAA, they are limited to cases where the enolate geometry is fixed. Acyclic substrates in these systems gave lower levels of enantioselectivities. To date, the most selective AAA of acyclic systems was reported by Trost at the end of 2005 in which he again used the phenanthroline-based P/N ligand with a palladium(II) catalyst to effect a highly selective allylation on a wide range of ketones (Fig. 9).[14]

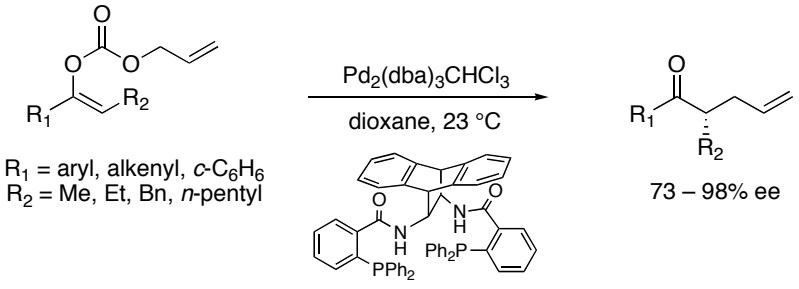


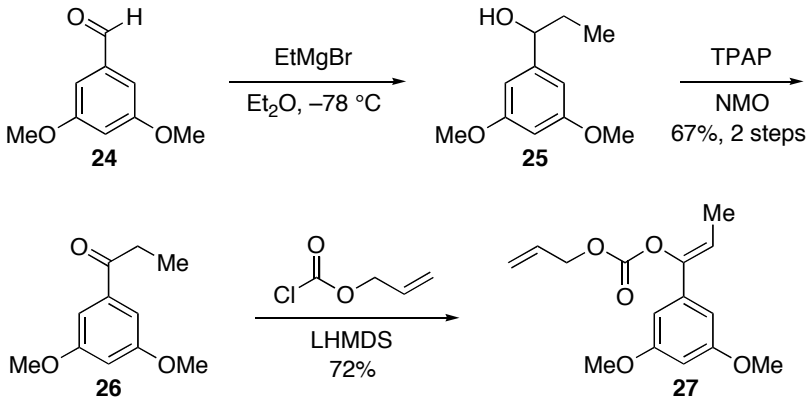
Figure 9. Trost's AAA of acyclic systems.

[14] Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 17180.

Based on this precedent, the asymmetric acyclic Tsuji-Trost reaction was chosen as the next step of the synthesis. Trost did not demonstrate how an electron-rich system such as **12** would perform in the AAA.

The model system allyl carbonate **27** necessary for the Tsuji-Trost allylic alkylation was synthesized in three steps from 3,5-dimethoxybenzaldehyde **24** (Scheme 1). Addition of ethylmagnesium bromide followed by TPAP oxidation[15] provided the desired ethyl ketone **26** in 67% yield for the two step sequence. Selective (*Z*)-enolization in the presence of LHMDS and trapping with allyl chloroformate provided allyl carbonate **27** in good yield.[14]

Scheme 1. Synthesis of an allyl enol carbonate for AAA studies.

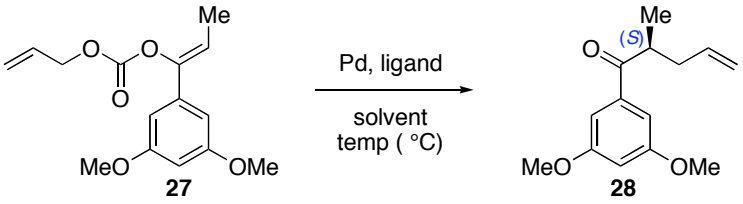


Exposure of **27** to the conditions reported by Trost (Fig. 9, ligand **A**, $Pd_2(dba)_3$, dioxane, 23 °C) provided an enantioenriched ketone with good enantioselectivity and full conversion (Table 5, entry 1). When the temperature was lowered to 4 °C in order to

[15] Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

increase the enantioselectivity, the dioxane began to freeze and lower conversion was noted (entry 2). Other solvents with a lower freezing point such as THF or toluene were not effective under Trost's conditions, even though THF was the solvent of choice in Stoltz's acyclic system. The ketone in question (**27**) should be more reactive due to the higher electron density on the aromatic moiety so it should be feasible to lower the temperature in order to obtain good levels of selectivity.

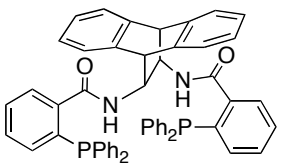
Table 5. Asymmetric allylic alkylation of model system 27.



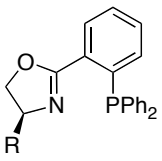
27 **28**

Reaction	Pd (mol%)	ligand	solvent	Temp (°C)	ee %	conversion
1	$Pd_2(dba)_3$•$CHCl_3$ (2.5)	**A**	dioxane	RT	85 (S)	100%
2	$Pd_2(dba)_3$•$CHCl_3$ (2.5)	**A**	dioxane	4	87 (S)	~60%
3	$Pd_2(dba)_3$ (5)	**B**	THF	RT	73 (R)	100%
4	$Pd_2(dba)_3$ (5)	**C**	THF	RT	64 (R)	100%
5	$Pd_2(dba)_3$ (5)	**B**	THF	4	78 (R)	100%
6	$Pd_2(dba)_3$ (5)	**B**	THF	–10	89 (R)	50%
7	$Pd_2(dba)_3$ (5)	**B**	THF	–20	91 (R)	50%
8	$Pd_2(dba)_3$ (5)	**B**	THF	–30	91 (R)	low
9	$Pd_2(dba)_3$ (5)	**D**	THF	–20	ND	ND
10	$Pd_2(dba)_3$ (10)	**E**	THF	–20	91 (S)	71% I.Y.**

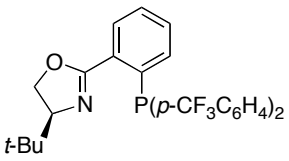
** 100% conversion, 18h



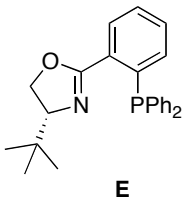
A



B (R = *t*-Bu)
C (R = *i*-Pr)



D



E

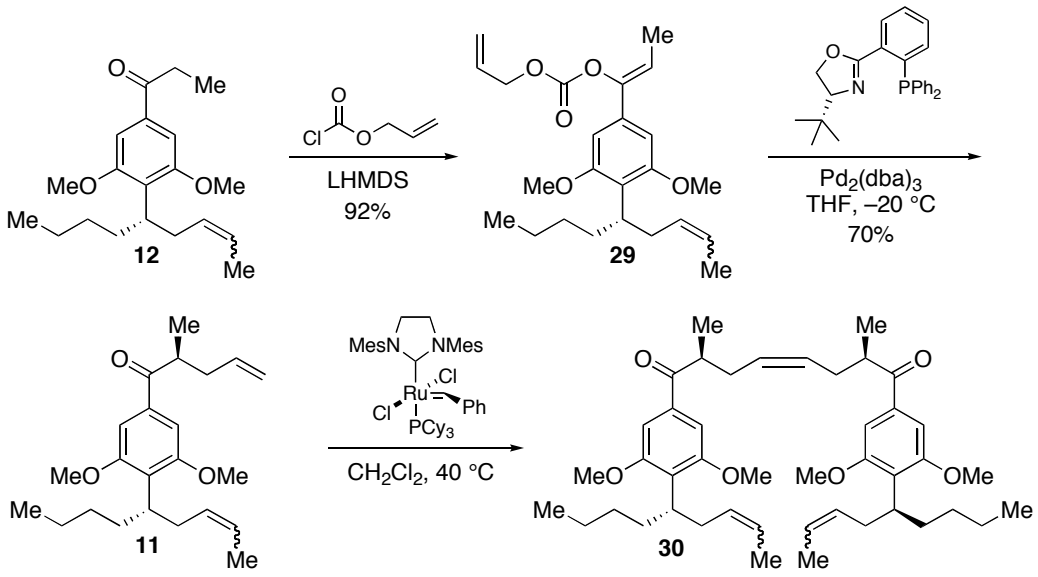
Using 5 mol% (*S*)-*t*-Bu-PHOX ligand **B** with 5 mol% $Pd_2(dba)_3$ in THF at room temperature, 100% conversion and 73% ee was obtained for the product (entry 3). Meanwhile, other PHOX derivatives **C** and **D** were not as selective in this sytem (entries 4 and 9). The reaction was rapid at room temperature and complete within a few hours. Levels of enantioselectivity greater than 90% were quickly realized when the temperature of the system was lowered to –30 °C (entries 5–8, 78–91% ee), but the reaction efficiency decreased with the lower temperatures. In order to overcome this, the catalyst loading was increased from 5 mol% to 10 mol% (entry 10). Now enantioriched ketone **28** was isolated in 71% yield with a synthetically useful 91% ee. This reaction represents the first example of employing Stoltz's Tsuji AAA to access such high levels of enantioselection on an acyclic ketone.

III. Formal Synthesis of Cylindrocyclophane A.

Application of these low temperature Tsuji-Trost AAA conditions to the desired system proceeded as expected and provided the desired product in 70% yield at –10 °C (Scheme 2). While the diastereomeric ratio could not be determined spectroscopically or chromatographically, dimerization of the molecule to the conformationally-rigid macrocycle should allow for diastereomeric determination. However, a survey of the macrocyclization/dimerization of **11** with a variety of metathesis catalysts, solvents, and

concentrations only formed the head-to-head dimer **30** via cross-metathesis of the terminal olefins.

Scheme 2. Successful Tsuji-Trost allylic alkylation.

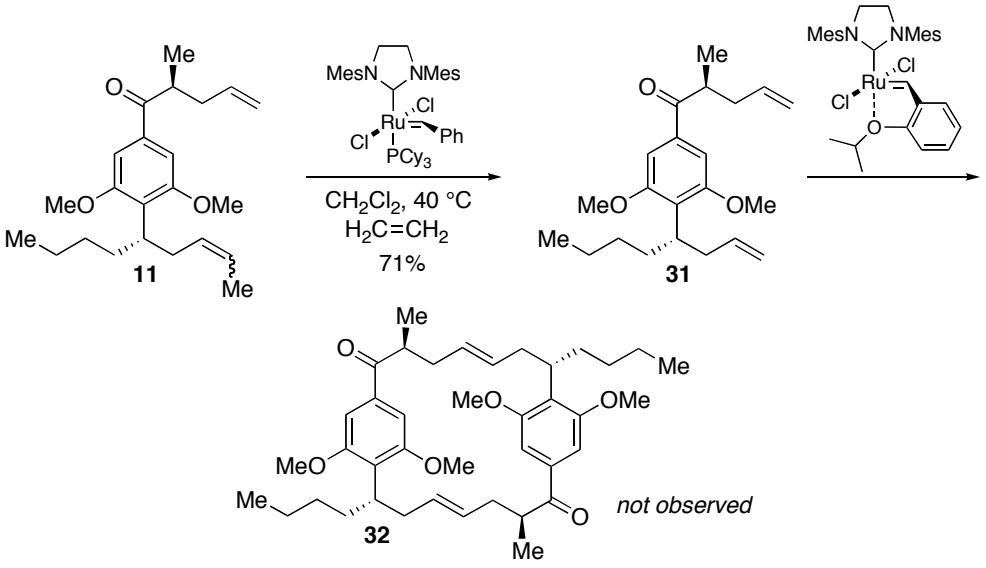


Conversion of the disubstituted olefin in **11** to the terminal olefin should allow for the reversible ring-closing metathesis dimerization that was demonstrated by Smith.[16] Olefin cross-metathesis with ethylene provided diene **31**, which was an advanced intermediate in the Smith synthesis.[16c] However, substrate **31** was not subjected to ring-closing metathesis conditions, presumably due to issues associated with catalyst deactivation by coordination of the carbonyl. Therefore, the ketone in **31** had to be reduced and protected before the metathesis dimerization event could be conducted.

[16] (a) Smith, A. B. III; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **1999**, *121*, 7423. (b) Smith, A. B. III; Koamin, S. A.; Adams, C. M.; Paone, D. V. *J. Am. Chem. Soc.* **2000**, *122*, 4984. (c) Smith, A. B. III; Adams, C. M.; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 5925.

Since Smith's article in 2000, there have been newer, more active metathesis catalysts reported.[17] Other studies have also shown that ketones can be coordinated to external Lewis acids in the presence of metathesis catalysts, thus allowing for them to be present in olefin metathesis reactions.[18] Yet in this system, the Grubbs-Hoveyda ruthenium metathesis catalyst was ineffective in the ring-closing dimerization (Scheme 3).

Scheme 3. Latest metathesis technology was ineffective for RCM dimerization



Based on time and material restrictions, this project will remain an unfinished story. However, what remains to be tried in this system is the addition of an external boron[18a] or titanium[18b] Lewis acid to the metathesis reaction to render the carbonyl in **31** incapable of coordination to the ruthenium catalyst (Fig. 10). After successful formation

[17] (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168. (b) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973. (c) Bujok, R.; Bienick, M.; Masnyk, M.; Michrowska, A.; Sarosiek, A.; Stepowska, H.; Arlt, D.; Grela, K. *J. Org. Chem.* **2004**, *69*, 6894.

[18] (a) Vedrenne, E.; Dupont, H.; Oualef, S.; Elkaim, L.; Grimaud, L. *Synlett* **2005**, *4*, 670. (b) Furstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130.

of the bisketone macrocycle **32**, hydrogenation of the olefins, diastereoselective reduction of the ketone, and deprotection of the aromatic methyl ethers would furnish cylindrocyclophane A (**9**).

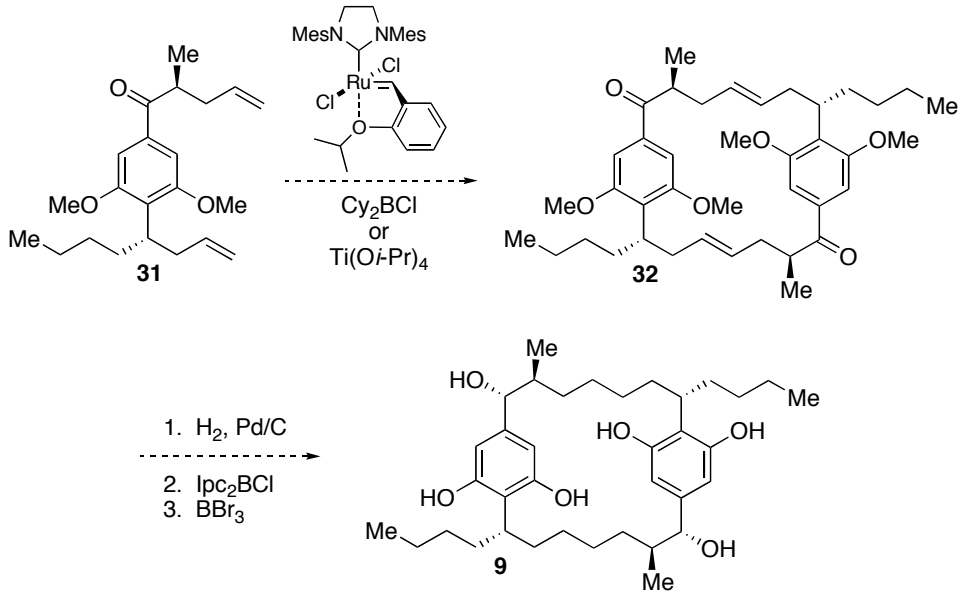
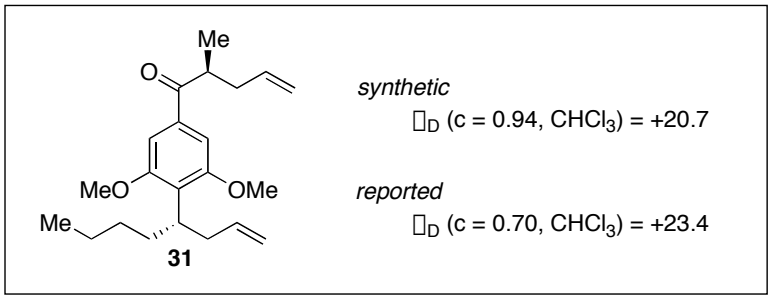


Figure 10. Remaining synthetic sequence to the natural product.

Despite being unable to form the macrocycle, diene **31** represents a compound that could be compared to a known substrate that was reported by Smith in the total synthesis of cylindrocyclophane A (Fig. 11).[16c] It was concluded by comparison of optical rotation data that a good level of diastereoselectivity was installed via the Tsuji-Trost palladium-catalyzed asymmetric allylic alkylation.



Synthesis of diene **31** therefore constitutes a formal synthesis of cylindrocyclophane A. The intermediate contains the required functionality necessary to complete a total synthesis of the natural product, which would require six steps from diene **31** (Fig. 11).

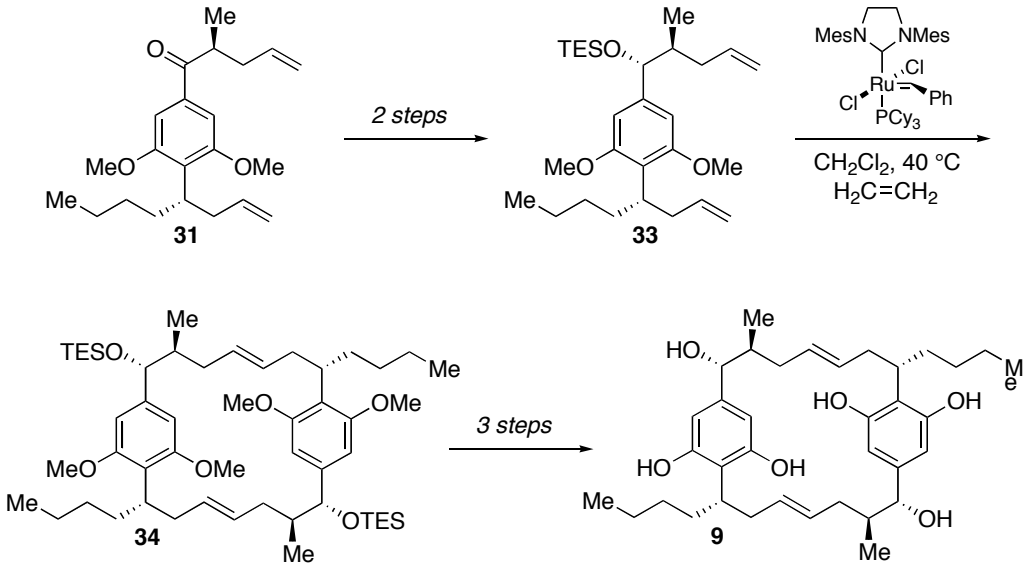


Figure 11. Completion of the synthesis of cylindrocyclophane A by Smith's route.

Conclusion.

A formal synthesis of cyclindrocyclophane A is reported herein. This synthetic strategy featured two methodologies developed within the MacMillan lab: (i) an organocatalytic 1,4-addition of an electron-rich aniline into an □,□-unsaturated aldehyde and (ii) a nickel(0)-catalyzed Stille cross-coupling of an activated vinyl stannane with a trimethylanilinium salt. Elaboration to the natural product highlighted a

diastereoselective asymmetric catalytic allylic alkylation of an enol allyl carbonate catalyzed by palladium(II) and the *t*-Bu-PHOX ligand. This allylated ketone was then correlated to the spectroscopic data reported by Smith for an advanced intermediate in his synthesis of cylindrocyclophane A.

Supporting Information.

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[19] Dioxane preparation was threefold: (i) dried by distillation from sodium, (ii) degassed for 20 minutes with argon, and (iii) further deoxygenated by the freeze-pump thaw method. All other solvents were purified according to the method of Grubbs.[20] Non-aqueous reagents were transferred under nitrogen via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using flash chromatography on Silicycle 230-400 mesh silica gel. Thin-layer chromatography (TLC) was performed on Silicycle 0.25 mm silica gel plates. Visualization of the developed chromatogram was performed by fluorescence quenching or by anisaldehyde, $KMnO_4$, or ceric ammonium molybdenate stain.

^1H 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_6D_6 = 7.16 ppm, D_6-acetone = 2.05 ppm). Data for ^1H NMR are reported as follows: chemical shift (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. 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

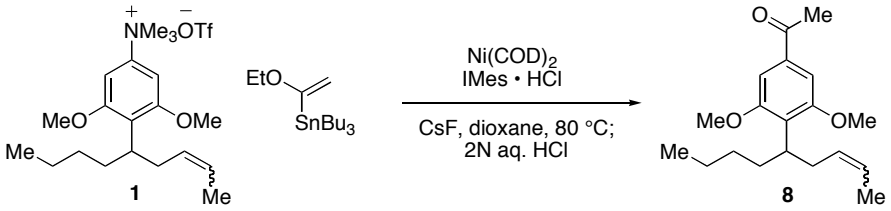
[19]Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals, 3rd ed.*; Pergamon Press, Oxford, 1988.

[20] Pangborn, A.B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518./

of Technology mass spectral facility. Gas chromatography (GC) was 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 Γ-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. Analytical supercritical fluid chromatography (SFC) was perfomed on a Berger Instruments SFC with built-in photometric detector (λ = 214 nm) using Daicel Chiracel OJ-H, OD-H, AS-H, and AD-H columns (25 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.

1-(3,5-Dimethoxyphenyl)ethanone (7). In a glove box under nitrogen, a flame-dried Schlenk flask was charged with anilinium salt **4** (51.8 mg, 0.15 mmol), Ni(COD)$_2$ (8.2 mg, 0.03 mmol), IMes • HCl (10.5 mg, 0.03 mmol), and cesium fluoride (68.2 mg, 0.45 mmol). The Schlenk was sealed and removed from the box. It was placed under positive argon pressure so that Γ-ethoxytributylstannane (100 ΓL, 0.30 mmol) and dioxane (1.5 mL, 0.1 M) could be added via syringe. The Schlenk was sealed and the reaction vessel was heated at 80 °C for 12 h. The reaction was cooled to room temperature, at which

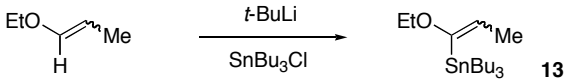
point 2N HCl was added. After stirring for an hour, the acidic layer was extracted with ethyl acetate. The organic layers were washed with brine, dried with magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography of the crude residue provided the title compound **7** as a clear oil (32 mg, 60% yield). Spectroscopic data was consistent with commercially available material.



1-(3,5-Dimethoxy-4-(non-2-en-5-yl)phenyl)ethanone (8).[21] In a glove box under nitrogen, a flame-dried Schlenk flask was charged with anilinium salt **1** (230 mg, 0.49 mmol), $Ni(COD)_2$ (40 mg, 0.147 mmol), IMes • HCl (50 mg, 0.147 mmol), and cesium fluoride (223 mg, 1.47 mmol). The Schlenk was sealed and removed from the box. It was placed under positive argon pressure so that □-ethoxytributylstannane (330 □L, 0.98 mmol) and dioxane (4.9 mL, 0.1 M) could be added via syringe. The Schlenk was sealed and the reaction vessel was heated at 80 °C for 12 h. The reaction was cooled to room temperature, at which point 2N HCl was added. After stirring for an hour, the acidic layer was extracted with ethyl acetate. The organic layers were washed with brine, dried with magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography of the crude residue provided the title compound **8** as a clear oil (56 mg, 38% yield). IR (film) 2956, 2929, 2857, 1684, 1577, 1456, 1412, 1312, 1223, 1209, 1101 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) □ 7.11 (s, 2H, Ar**H**), 5.29 (m, 2H, C**H**=C**H**), 3.85 (s, 6H, OC**H**$_3$), 3.40

[21] Chemical shifts of the minor olefin isomer are noted in the spectroscopic data in parentheses in italics.

(m, 1H, ArC**H**), 2.59 (s, 3H, COC**H**$_3$), 2.55 (m, 1H, CH**H**CH=), 2.39 (m, 1H, C**H**HCH=), 1.84 (m, 1H, CHCH**H**), 1.64 (m, 1H, CHC**H**H), 1.50 (*1.54*) (d, 3H, *J* = 5.4 Hz, =CHC**H**$_3$), 0.96-1.42 (m, 4H, C**H**$_2$C**H**$_2$CH$_3$), 0.92 (t, 3H, *J* = 7.2 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 197.7, 159.1, 135.9, 129.9 (*130.7*), 127.7 (*127.9)*, 123.9 (*125.1)*, 104.3, 104.2, 55.8, 35.7 (*36.0)*, 32.5 (*32.3)*, 30.4 (*30.6)*, 27.8, 26.8, 26.5, 22.8, 17.5, 14.1 (*13.6).*

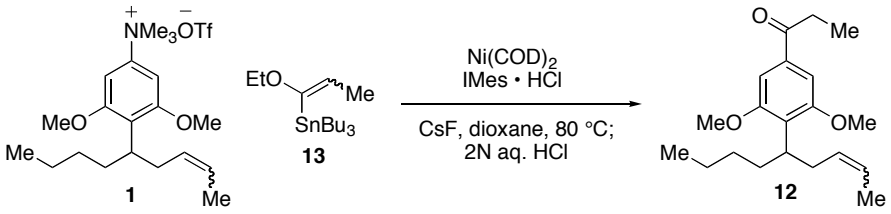


13

Tributyl(1-ethoxyprop-1-enyl)stannane (13).[21] Ethyl-2-propenyl ether (8.6 g, 100 mmol) was taken up in 36 mL THF at –78 °C under argon. *Tert*-butyllithium (47 mL, 1.6M in hexanes) was added slowly via syringe. The reaction was warmed slowly to 0 °C over 3h. After recooling the system to –78 C, tributyltin chloride (6.8 mL, 25 mmol) was added via sringe. The reaction was stirred for –78 °C for 30 minutes before warming to room temperature. 100 mL saturated ammonium chloride was added to quench the reaction. The aqueous layer was separated and extracted with hexanes (2 x 100 mL). The hexanes layer was dried with magnesium sulfate and passed over alumina to remove any trace amounts of $SnBu_3OH$. Removal of the organic solvents provided the title compound as a clear oil (8.4 g, 90% yield). Spectroscopic data were consistent with values previously reported material in the literature.[1,22] ^{1}H NMR (300 MHz, $CDCl_3$) 5.27 (q, 1H, *J* = 6.6 Hz, J_{Sn} = 46.2, 48.6 Hz, =C**H**), 3.62 (*3.69*) (q, 2H, *J* = 6.9 Hz, OC**H**$_2$CH$_3$), 1.59 (*1.66*) (d, 3H, *J* = 6.6 Hz, =CHC**H**$_3$), 1.43-1.60 (m, 6H,

[22] Sato, N.; Narita, N. *Synthesis* **2001**, *10*, 1551.

$SnC\mathbf{H_2}CH_2CH_2CH_3$), 1.23-1.38 (m, 6H, $SnCH_2C\mathbf{H_2}CH_2CH_3$), 1.22 (*1.24*) (t, 3H, *J* = 7.5 Hz, $OCH_2C\mathbf{H_3}$), 0.80-0.99 (m, 6H, $SnCH_2CH_2C\mathbf{H_2}C\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$)[23] 165.8 (*163.4*), 105.5 (*118.0*), 62.7 (*67.4*), 41.0 (*31.9*), 29.1, 28.6, 27.3, 13.7, 10.2; ^{119}Sn NMR (186 MHz, C_6D_6) –158.9 (*–154.4*); HRMS (EI+) exact mass calculated for $[M\bullet]^+$ ($C_{17}H_{36}OSn$) requires *m/z* 376.1788, found *m/z* 376.1798.

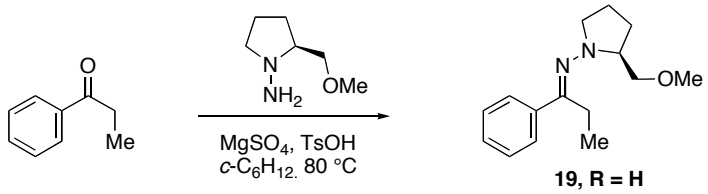


1-(3,5-Dimethoxy-4-(non-2-en-5-yl)phenyl)propan-1-one (12).[21] In a glove box under nitrogen, a flame-dried Schlenk flask was charged with anilinium salt **1** (1.6 g, 3.4 mmol), $Ni(COD)_2$ (281 mg, 1.02 mmol), IMes • HCl (348 mg, 1.02 mmol), and cesium fluoride (1.55 g, 10.2 mmol). The Schlenk was sealed and removed from the box. It was placed under positive argon pressure so that -ethoxytributylstannane **13** (2.40 mL, 6.8 mmol) and dioxane (34 mL, 0.1 M) could be added via syringe. The Schlenk was sealed and the reaction vessel was heated at 80 °C for 12 h. The reaction was cooled to room temperature, at which point 2N HCl was added. After stirring for 6 hours, the acidic layer was extracted with ethyl acetate. The organic layers were washed with brine, dried with magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography of the crude residue provided the title compound **12** as a clear oil (564 mg, 52% yield).IR (film) 2957, 2926, 2855, 1684, 1577, 1462, 1413, 1376, 1300, 1208, 1200, 1163, 1132,

[23] 13C NMR of this substrate had multiple satellite peaks in the alkyl region of the spectra. Only the major peaks are listed here. Minor olefin isomers are noted in italics in parentheses.

1104, 860, 801 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) □ 7.13 (s, 2H, Ar**H**), 5.30 (m, 2H, C**H**=C**H**), 3.84 (s, 6H, OC**H$_3$**), 3.41 (m, 1H, ArC**H**), 2.98 (*2.975*) (q, 2H, *J* = 7.2 Hz, COC**H$_2$**CH_3), 2.56 (m, 1H, CH**H**CH=), 2.38 (m, 1H, C**H**HCH=), 1.84 (m, 1H, CHCH**H**), 1.62 (m, 1H, CHC**H**H), 1.50 (*1.54*) (d, 3H, *J* = 6.3 Hz, =CHC**H$_3$**), 1.223 (*1.227*) (t, 3H, *J* = 6.9 Hz, $COCH_2$C**H$_3$**), 0.96-1.42 (m, 4H, C**H$_2$**C**H$_2$**CH_3), 0.81 (t, 3H, *J* = 7.2 Hz, CH_2C**H$_3$**); ^{13}C NMR (75 MHz, $CDCl_3$). □200.4, 159.1, 135.7 (*130.8*), 129.9 (*127.4*), 123.9 (*125.1)*, 104.0, 103.9, 55.8, 35.7 (*35.9)*, 32.5 (*32.3)*, 31.6, 30.6, 30.4 (*30.38)*, 29.7, 22.8, 17.9, 14.1 (*12.7)*, 8.4. HRMS (EI+) exact mass calculated for $[M•]^+$ ($C_{20}H_{30}O_3$) requires *m/z* 318.2195, found *m/z* 318.2207. □$_D$ (c = 0.64, EtOH) = –4.1.

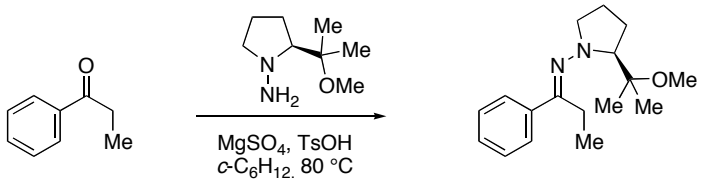
General Procedure for Preparation of SAMP/SAEP/SAPP Hydrazones from the Corresponding Ketones: Ketone (1 mmol) was taken up in cyclohexane (2 mL, 0.5 M) at room temperature. Hydrazone (2 mmol), magnesium sulfate (400 mg), and a catalytic amount of *p*-toluenesulfonic acid were added. The reaction was refluxed with at 80 °C until the starting material was consumed. When the reaction was completed, it was cooled to room temperature and loaded directly onto a silica column. Flash chromatography (solvents noted below) provided the hydrazones.



19, R = H

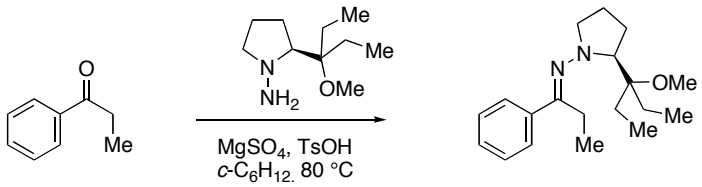
(*S*)-2-(Methoxymethyl)-*N*-(1-phenylpropylidene)pyrrolidin-1-amine (19, R = H). Propiophenone (0.133 mL), SAMP (0.268 mL), magnesium sulfate (400 mg), catalytic

TsOH, cyclohexane (2 mL). Flash chromatography (5% ethyl acetate/hexanes) provided the hydrazone as an orange oil (215 mg, 87% yield). Spectroscopic data was consistent with that previously reported material in the literature.[24]



19, R = Me

(*S*)-2-(2-Methoxypropan-2-yl)-*N*-(1-phenylpropylidene)pyrrolidin-1-amine (19, R = Me). Propiophenone (66.5 μL, 0.5 mmol), SAEP (158 mg, 1 mmol), magnesium sulfate (200 mg), catalytic TsOH, cyclohexane (1 mL). Flash chromatography (5% ethyl acetate/hexanes) provided the hydrazone as a yellow oil (124 mg, 90% yield). Spectroscopic data were consistent with values previously reported in the literature.[24a,b]



19, R = Et

(*S*)-2-(3-Methoxypentan-3-yl)-*N*-(1-phenylpropylidene)pyrrolidin-1-amine (19, R = Et). Propiophenone (66.5 μL, 0.5 mmol), SAPP (186 mg, 1 mmol), magnesium sulfate (200 mg), catalytic TsOH, cyclohexane (1 mL). Flash chromatography (5% ethyl acetate/hexanes) provided the hydrazone as a yellow oil (124 mg, 91% yield). Spectroscopic data were consistent with values previously reported in the literature.[24a]

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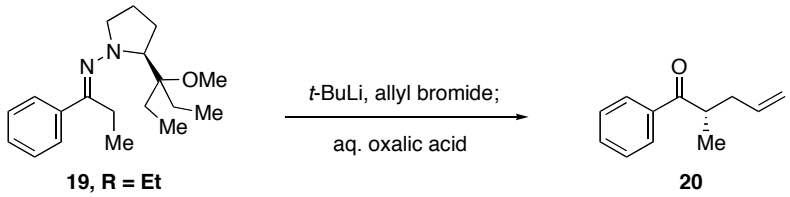
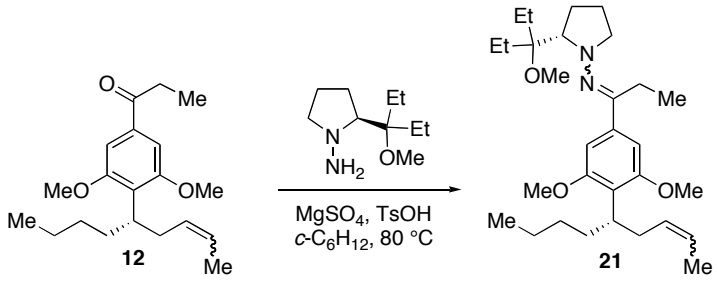
[24] (a) Enders, D.; Meyer, I.; Runsink, J.; Raabe, G. *Heterocycles* **199**, *50*, 995. (b) Enders, D.; Bushan, V. *Tetrahedron Lett.* **1988**, *29*, 2437. (c) Enders, D.; Eichenauer, H.; Baus, U.; Schubert, H.; Kremer, K. Am. M. *Tetrahedron* **1984**, *40*, 1365.

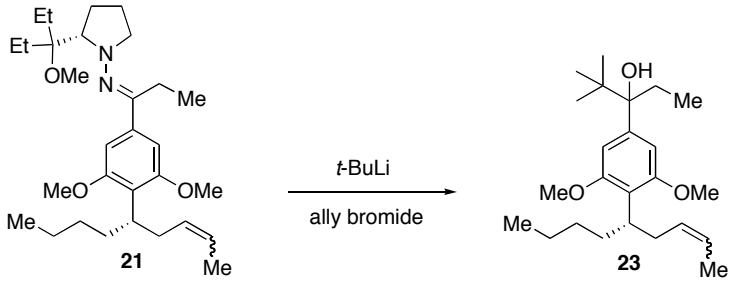


(*S*)-2-Methyl-1-phenylpent-4-en-1-one (20). At –78 °C under argon, *tert*-butyllithium (0.19 mL, 0.325 mmol) was added to a solution of hydrazone **19** (24.5 mg, 0.0812 mmol) in 0.54 mL THF (0.15 M). The solution turned light orange in color. The reaction was stirred at –78 °C for 30 min and then warmed to 0 °C for 2 h. After recooling the system to –78 °C, allyl bromide (28 μL, 0.325 mmol) was added via syringe. The reaction was stirred for 30 minutes at –78 °C and slowly warmed to room temperature. 2 mL diethyl ether was added to dilute the reaction. The ether layer was washed with water and then filtered over silica. 1 mL aq. 1N oxalic acid was added and the solution was heated at 35 °C for 2 h. The reaction was then sampled for GC analysis. Spectroscopic data were consistent with values previously reported in the literature.[14] The enantiomeric ratio was determined by GC analysis using a Bodman Chiralsex B-DM guard column (90° isotherm, 40 minutes); *(S)* isomer t_r = 43.40 min, *(R)* isomer t_r = 43.33 min.



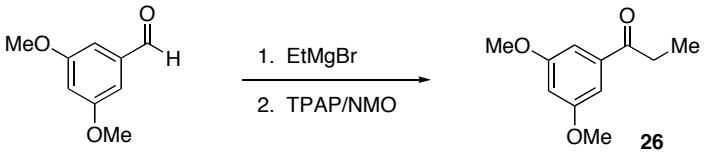
(*S*)-*N*-(1-(3,5-Dimethoxy-4-((*S*)-non-2-en-5-yl)phenyl)propylidene)-2-(3-methoxypentan-3-yl)pyrrolidin-1-amine (21).[21] Ketone **12** (318 mg, 1 mmol) was

taken up in cyclohexane (2 mL, 0.5 M) at room temperature. Hydrazone (372 mg, 2 mmol), magnesium sulfate (400 mg), and a catalytic amount of *p*-toluenesulfonic acid were added. The reaction was refluxed at 80 °C until the starting material was consumed. When the reaction was completed, it was cooled to room temperature and loaded directly onto a silica column. Flash chromatography (5% ethyl acetate/hexanes) provided hydrazone **21** as an orange oil (315 mg, 65% yield). IR (film) 2956, 2932, 2858, 1604, 1564, 1462, 1409, 1339, 1208, 1131, 1102 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) □ 6.85 (s, 2H, Ar**H**), 5.29 (m, 2H, C**H**=C**H**), 3.81 (s, 6H, OC**H**$_3$), 3.52 (d, *J* = 3.6, 9.0 Hz, C**H**HOMe), 3.37 (s, 3H, OC**H**$_3$), 3.26-3.44 (m, 4H, C**H**$_2$NCHC**H**), 2.81 (q, 2.51, *J* = 7.5 Hz, C**H**$_2$CH$_3$), 2.62 (dt, 1H, *J* = 5.7, 5.7 Hz, NC**H**), 2.51 (m, 1H, ArC**H**), 2.41(m, 2H, C**H**$_2$CH=), 2.06 (m, 1H, pyrrolidine), 1.67-1.93 (m, 3H, pyrrolidine), 1.55 (*1.53*) (d, 3H, *J* = 7.2 Hz, =CHC**H**$_3$), 1.11 (t, 3H, *J* = 7.5 Hz, CH$_2$C**H**$_3$), 0.96-1.32 (m, 4H, C**H**$_2$C**H**$_2$CH$_3$), 0.81 (t, 3H, *J* = 7.2 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$). □ 166.0, 158.1, 136.6, 130.5 (*131.3*), 123.5 (*124.7*), 122.7, 103.1 (*103.2)*, 104.7, 75.7, 66.6, 59.2, 56.0, 55.6, 35.4 (*35.7)*, 32.7 (*32.6*), 30.9, 30.5 (*30.4*), 26.7, 22.8, 22.7, 22.5, 14.1 (*12.7)*, 12.0.



3-(3,5-Dimethoxy-4-((*S*)-non-2-en-5-yl)phenyl)-2,2-dimethylpentan-3-ol (23). At –78 °C under argon, *tert*-butyllithium (0.19 mL, 0.325 mmol) was added to a solution of

hydrazone **21** (24.5 mg, 0.0812 mmol) in 0.54 mL THF (0.15 M). The solution turned orangish-yellow. The reaction was stirred at –78 °C for 30 min and then warmed to 0 °C for 2 h. After recooling the system to –78 °C, allyl bromide (28 μL, 0.325 mmol) was added via syringe. The reaction was stirred for 30 minutes at –78 °C and slowly warmed to room temperature. 2 mL diethyl ether was added to dilute the reaction. The ether layer was washed with water, filtered over silica, and concentrated in vacuo. Flash chromatography (5 to 10% ethyl acetate/hexanes) provided the tertiary alcohol **23** (59 mg, 79% yield). IR (film) 2957, 2934, 2859, 1606, 1575, 1463, 1411, 1366, 1239, 1208, 1200, 1133, 1099, 972, 837 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.52 (s, 2H, Ar**H**), 5.29 (m, 2H, C**H**=C**H**), 3.76 (s, 6H, OC$\mathbf{H_3}$), 3.29 (m, 1H, ArC**H**), 2.51 (m, 1H, CH**H**CH=), 2.37 (m, 1H, C**H**HCH=), 2.14 (m, 1H, CC**H**HCH_3), 1.85 (m, 1H, CCH**H**CH_3), 1.82 (m, 1H, CHCH**H**), 1.67 (broad t, 1H, *J* = 1.2 Hz, O**H**), 1.62 (m, 1H, CHC**H**H), 1.47 (*1.52*) (d, 3H, *J* = 4.2 Hz, =CHC$\mathbf{H_3}$), 0.92 (s, 9H, C(C$\mathbf{H_3}$)$_3$), 0.96-1.36 (m, 4H, C$\mathbf{H_2}$C$\mathbf{H_2}$CH_3), 0.81 (t, 3H, *J* = 7.2 Hz, CH_2C$\mathbf{H_3}$), 0.71 (t, 3H, *J* = 7.2 Hz, CCH_2C$\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$). δ 158.1, 141.8 (*141.7*), 130.5 (*131.4*), 123.4 (*124.6*), 104.7 (*104.8)*, 104.7, 81.5, 55.9, 38.4 (*36.9)*, 35.3 (*35.5)*, 32.8 (*32.6*), 31.0, 30.6 (*30.5*), 26.9, 26.0, 22.8 (*22.6*), 14.3 (*12.7)*, 8.2.

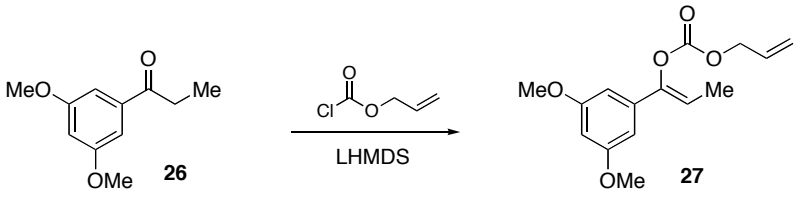


26

1-(3,5-Dimethoxyphenyl)propan-1-one (26). Ethylmagnesium bromide (20.5 mL, 51.8 mmol, 2.5 M solution in ether) was added to a solution of 3,5-dimethoxybenzaldehyde (**21**, 5.0 g, 30.4 mmol) in 100 mL THF (0.3 M) at –78 C under argon. The reaction was

warmed to room temperature over 1.5 h. 150 mL saturated ammonium chloride was added. The aqueous layer was separated and extracted with ethyl acetate (3 x 100 mL). The organic layers were dried with magnesium sulfate, filtered over a pad of silica gel, and concentrated in vacuo to provide alcohol **25** as a yellow oil.

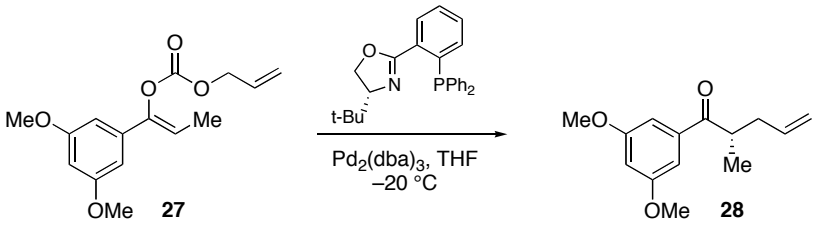
The above alcohol **25** was dissolved in 60 mL CH_2Cl_2 (0.2 M) at room temperature under argon. Morpholine *N*-oxide (NMO, 7.0 g, 60 mmol) and 5.0 mg activated 4Å mol sieves were added. This mixture was stirred for 30 minutes before TPAP (264 mg, 0.75 mmol) was added. Upon completion, the reaction was loaded directly onto a silica column that had a pad of Celite on top. Chromatography (20% diethyl ether/pentanes) provided the ketone **26** as a white solid (3.85 mg, 67% yield for 2 steps). Spectroscopic data were consistent with values previously reported in the literature.[25]



(*Z*)-Allyl 1-(3,5-dimethoxyphenyl)prop-1-enyl carbonate (27). LHMDS (0.61 M) was freshly prepared: *n*-butyllithium (2.19 mL, 5 mmol) was added to a solution of HMDS (5 mmol) in 5 mL THF at 0 °C. The reaction was warmed to room temperature before use. Ketone **26** (278 mg, 1.44 mmol) was take up in THF (5.8 mL, 0.25 M) at 0 °C under argon. LHMDS (3.56 mL, 0.61 M) was added via syringe. The reaction was stirred for 2.5h at 0 °C, after which it was cooled to –78 °C. Allyl chloroformate (0.28 mL, 2.60

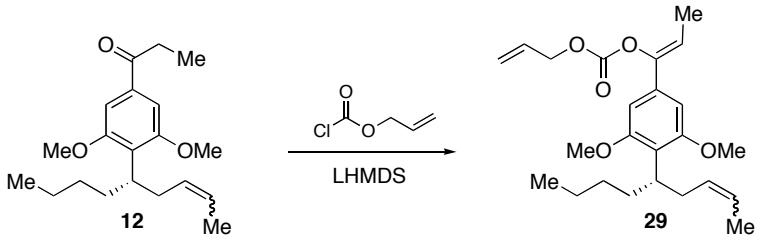
[25] Cannon, J. R.; Cheong, P. K.; Fallick, C. J.; Hamilton, B. H.; McDonald, I. A.; Vinciguerra, G. *Aust. J. Chem.* **1973**, *26*, 799.

mmol) was added via syringe. The reaction was warmed to room temperature and stirred for 10 h. The reaction was quenched with saturated ammonium chloride. The aqueous layer was separated and extracted with ethyl acetate (2 x 10 mL). The organic layers were dried and concentrated in vacuo. Flash chromatography (5% ethyl acetate/hexanes) provided the enol ether **27** (288 mg, 72% yield). IR (film) 2941, 2840, 1761, 1594, 1457, 1425, 1238, 1206, 1157, 1066, 976 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.58 (d, 2H, *J* = 2.1 Hz, Ar**H**), 6.40 (t, 1H, *J* = 2.1 Hz, Ar**H**), 5.96 (ddt, 1H, *J* = 5.4, 10.8, 17.4 Hz, C**H**=CH_2), 5.85 (q, 1H, *J* = 6.9 Hz, =C**H**CH_3), 5.39 (ddt, 1H, *J* = 1.5, 1.5, 15.4 Hz, CH=C**H**H), 5.30 (ddt, 1H, *J* = 1.5, 1.5, 10.2 Hz, CH=CH**H**), 3.78 (s, 6H, OC$\mathbf{H_3}$), 1.77 (d, 3H, *J* = 7.2 Hz, =CHC$\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$). δ 160.8, 152.7, 147.1, 136.8, 131.2, 119.2, 113.5, 102.6, 100.4, 69.0, 55.3, 11.3. HRMS (EI+) exact mass calculated for $[M•]^+$ ($C_{15}H_{18}O_5$) requires *m/z* 278.1154, found *m/z* 278.1158.



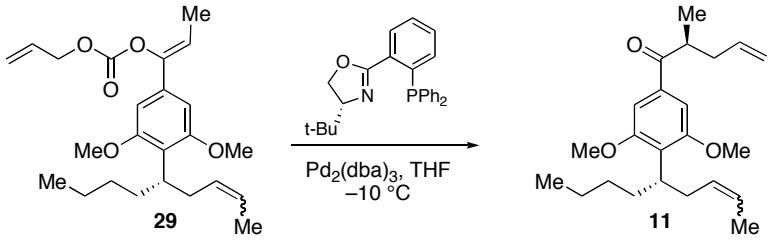
(*S*)-1-(3,5-Dimethoxyphenyl)-2-methylpent-4-en-1-one (28). A flame-dried 2-dram vial was charged with $Pd_2(dba)_3$ (5.0 mg, 0.00543 mmol) and (*R*)-*t*-Bu)-PHOX (5.3 mg, 0.0136 mmol). 1 mL THF was added and this mixture was stirred at room temperature for 30 minutes, after which it was cooled to –20 °C. Enol carbonate **27** (15 mg) in 0.63 mL THF was added. The reaction was stirred for 20 h and filtered over a pad of silica to remove trace metal and ligand before removal of the solvent. The residue was purified

by preparative TLC (5% ethyl acetate/hexanes) to afford the title compound **28** (9 mg, 71% yield, 91% ee). IR (film) 2925, 2854, 1684, 1593, 1458, 1426, 1360, 1294, 1206, 1157, 1068, 1005 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) 7.08 (d, 2H, *J* = 2.4 Hz, Ar**H**), 6.45 (t, 1H, *J* = 2.4 Hz, Ar**H**), 5.77 (m, 1H, C**H**=CH_2), 5.02 (m, 2H, CH=C$\mathbf{H_2}$), 3.84 (s, 6H, OC$\mathbf{H_3}$), 3.46 (ddq, 1H, *J* = 1.5, 6.9, 14.4 Hz, C**H**CH_3), 2.55 (dtt, 1H, *J* = 1.2, 6.3, 14.4 Hz, CHC**H**H), 2.18 (m, 1H, CHCH**H**), 1.19 (d, 3H, *J* = 6.9 Hz, CHC$\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$). 200.5, 160.9, 138.4, 135.8, 116.8, 106.1, 105.0, 55.6, 40.6, 37.7, 17.1. HRMS (EI+) exact mass calculated for $[M\bullet]^+$ ($C_{14}H_{18}O_3$) requires *m/z* 234.1256, found *m/z* 234.1245. $[\alpha]_D$ (c = 1.0, EtOH, 91% ee) = +19.0. The enantiomeric ratio was determined by HPLC analysis using a Chiralcel ODH and ODH guard column (2.0% isopropanol/hexanes, 254 nm, 1.0 mL/min); *(S)* isomer t_r = 14.09 min, *(R)* isomer t_r = 15.84 min.



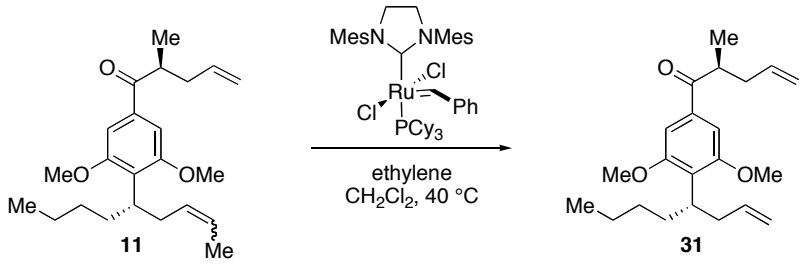
Allyl (1*Z*)-1-(3,5-dimethoxy-4-((*S*)-non-2-en-5-yl)phenyl)prop-1-enyl carbonate (29). LHMDS (0.61 M) was freshly prepared: *n*-butyllithium (2.19 mL, 5 mmol) was added to a solution of HMDS (5 mmol) in 5 mL THF at 0 °C. The reaction was warmed to room temperature before use. The ketone **12** (26 mg, 0.0817 mmol) was taken up in THF (0.33 mL, 0.25 M) at 0 °C under argon. LHMDS (0.23 mL, 0.123 mmol, 0.61 M) was added via syringe. The reaction was stirred for 2.5 h at 0 °C, after which it was cooled to –78 °C. Allyl chloroformate (18 L, 0.148 mmol) was added via syringe. The reaction was

warmed to room temperature and stirred for 10 h. The reaction was quenched with saturated ammonium chloride. The aqueous layer was separated and extract with ethyl acetate (2 x 10 mL). The organic layers were dried and concentrated in vacuo. Flash chromatography (0 to 3% ethyl acetate/hexanes) provided the enol ether **29** (31 mg, 94% yield). IR (film) 2956, 2933, 2858, 1764, 1580, 1452, 1416, 1238, 1209, 1133, 963, 810, 783 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) □ 6.71 (s, 2H, Ar**H**), 5.81 (dddd, 1H, *J* = 5.7, 5.7, 10.5, 16.5 Hz, C**H**=CH_2), 5.40 (m, 1H, CH=C**H**H), 5.28 (complex m, 3H, C**H**=C**H** and CH=C**H**H), 5.03 (d, 2H, *J* = 5.7 Hz, OC**H**$_2$CH), 3.76 (*3.75*) (s, 6H, OC**H**$_3$), 3.29 (m, 1H, ArC**H**), 3.18 (m, 1H, C**H**CH=), 2.88 (m, 1H, CH**H**CH=), 2.33-2.55 (m, 3H, CHC**H**$_2$), 1.81 (m, 1H, CH_2CH**H**), 1.63 (m, 1H, CH_2CH**H**), 1.46 (dt, 3H, *J* = 1.2, 3.0 Hz, =CHC**H**$_3$), 1.15 (dt, 3H, *J* = 3.3, 7.5 Hz, =CHC**H**$_3$), 0.96-1.2 (m, 2H, C**H**$_2$$CH_3$), 0.82 (*0.81*) (t, 3H, *J* = 6.9 Hz, CH_2C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$). □ 157.8, 151.6, 135.4, 131.4 (*131.0*), 130.2 (*130.1*), 123.7 (*125.0*), 122.8 (*123.0*), 119.5, 119.5, 105.8 (*105.9*), 93.2, 55.9, 40.4, 35.4 (*35.7*), 32.6 (*32.3*), 30.8, 30.5 (*30.3*), 27.6, 22. 8, 17.9, 14.1 (*12.7*), 9.9; not stable to FAB or EI high resolution mass spectrometry. □$_D$ (c = 1.24, $CHCl_3$) = –5.53



(*S*)-1-(3,5-Dimethoxy-4-((*S*)-non-2-en-5-yl)phenyl)-2-methylpent-4-en-1-one (11). A flame-dried 2-dram vial was charged with $Pd_2(dba)_3$ (8.6 mg, 0.009363 mmol) and (*R*)-*t*-

Bu)-PHOX (9.1 mg, 0.0234 mmol). 2 mL THF was added and this mixture was stirred at room temperature for 30 minutes, after which it was cooled to –10 °C. Enol carbonate **29** (37 mg) in 0.80 mL THF was added. The reaction was stirred for 20 h and filtered over a pad of silica to remove trace metal and ligand before removal of the solvent. The residue was purified by preparative TLC (5% ethyl acetate/hexanes) to afford the title compound **11** (13 mg, 41% yield). IR (film) 2958, 2932, 2858, 1680, 1575, 1457, 1413, 1374, 1303, 1209, 1133, 915 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) 7.11 (s, 2H, Ar**H**), 5.81 (dddd, 1H, *J* = 6.9, 7.2, 9.9, 17.1 Hz, C**H**=CH_2), 5.65 (m, 2H, C**H**=C**H**), 5.07 (d, 1H, *J* = 17.1 Hz, CH=C**H**H), 5.03 (d, 1H, *J* = 10.2 Hz, CH=CH**H**), 3.84 (s, 6H, OC$\mathbf{H_3}$), 3.48 (m, 1H, ArC**H**), 3.39 (m, 1H, C**H**CH=), 2.56 (m, 1H, CH**H**CH=), 2.40 (ddd, 1H, *J* = 7.2, 7.2, 13.8 Hz, C**H**HCH=), 2.20 (ddd, 1H, *J* = 6.9, 7.2, 13.8 Hz, C**H**HCH=), 1.82 (m, 1H, CCH**H**), 1.62 (m, 1H, CHCH**H**), 1.50 (*1.54*) (d, 3H, *J* = 6.0 Hz, =CHC$\mathbf{H_3}$), 1.22 (d, 3H, *J* = 6.9 Hz, CHC$\mathbf{H_3}$), 0.96-1.36 (m, 4H, C$\mathbf{H_2}$C$\mathbf{H_2}$$CH_3$), 0.81 (*0.80*) (t, 3H, *J* = 7.2 Hz, CH_2C$\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$). 203.1, 159.0, 136.0 (*135.1*), 129.9 (*130.8*), 127.6 (*127.8*), 123.9 (*125.1*), 116.7, 104.2 (*104.3*), 55.7, 40.4, 37.8 (*36.5*), 35.7 (*36.0*), 32.5 (*32.3*), 30. 6, 30.4 (*30.3*), 22.8, 17.3 (*17.9*), 14.1 (*12.7*); HRMS (FAB+) exact mass calculated for $[MH]^+$ ($C_{23}H_{35}O_3$) requires *m/z* 359.2586, found *m/z* 359.2583.



(*S*)-1-(3,5-Dimethoxy-4-((*S*)-oct-1-en-4-yl)phenyl)-2-methylpent-4-en-1-one (31). A solution of diene **11** (12 mg, 0.033 mmol), Grubbs' second-generation catalyst (3 mg, 0.0036 mmol) in 3.6 mL CH_2Cl_2 (0.01 M) was degassed with ethylene for 10 minutes. The reaction was sealed and stirred at room temperature. After 24 h, another 3 mg of Grubbs' catalyst was added and stirred for another 6 h. This reaction was filtered over a pad of silica gel with excess CH_2Cl_2. After removal of the solvent, flash chromatography (3% ethyl acetate/pentanes) provided the title compound **31** (8 mg, 71% yield). IR (film) 2957, 2931, 2858, 1681, 1575, 1456, 1413, 1373, 1304, 1215, 1137, 1117, 912 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) □7.12 (s, 2H, Ar**H**), 5.81 (dddd, 1H, *J* = 6.9, 6.9, 10.2, 16.8 Hz, C**H**=CH_2), 5.65 (dddd, 1H, *J* = 6.9, 7.2, 9.9, 17.1 Hz, C**H**=CH_2), 5.07 (m, 1H, CH=C**H**H), 5.01 (m, 1H, CH=CH**H**), 4.91 (m, 1H, CH=C**H**H), 4.81 (m, 1H, CH=CH**H**), 3.76 (s, 6H, OC**H**$_3$), 3.48 (m, 1H, ArC**H**), 3.43 (m, 1H, C**H**CH=), 2.56 (m, 2H, C**HH**CH=), 2.41 (dd, 1H, *J* = 6.9, 6.9, 13.8 Hz, C**H**HCH=), 2.20 (dd, 1H, *J* = 6.9, 7.5, 13.8 Hz, C**H**HCH=), 1.81 (m, 1H, CCH**H**), 1.62 (m, 1H, CHCH**H**), 0.96-1.36 (m, 4H, C**H**$_2$C**H**$_2$$CH_3$), 0.81 (t, 3H, *J* = 7.2 Hz, CH_2C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$). □ 203.1, 159.0, 138.4, 136.0, 127.3, 116.7, 114.6, 104.3, 55.9, 40.4, 37.8, 37.8, 35.4, 32.4 , 30.3, 22.8, 17.3, 14.1 HRMS (FAB+) exact mass calculated for $[MH]^+$ ($C_{22}H_{33}O_3$) requires *m/z* 345.2430, found *m/z* 345.2445. □$_D$ (c = 0.98, $CHCl_3$) = +20.7. This spectral data is consisted with spectral data reported by Smith [(c = 0.70, $CHCl_3$) = +23.7].[16c]