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.

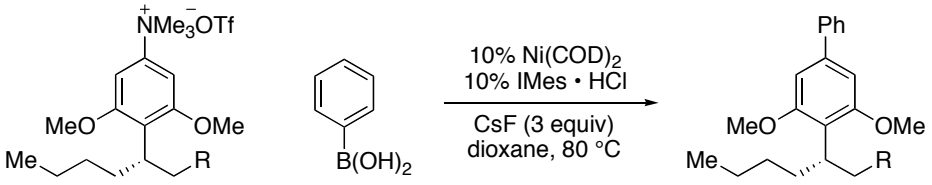
I. Revisiting the olefin isomerization problem.

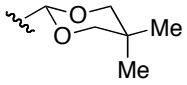
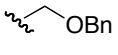
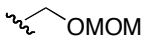
i. *Trimethylanilinium salt.*

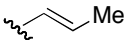
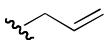
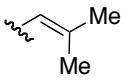
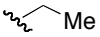
Chapter 4 ended with a study into which substituents were tolerated under the nickel(0)-catalyzed cross-coupling conditions (*vide infra*). Table 1 summarizes the results of an investigation into which functionality on the alkyl chain of the trimethylanilinium salt is tolerated under these conditions. 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).

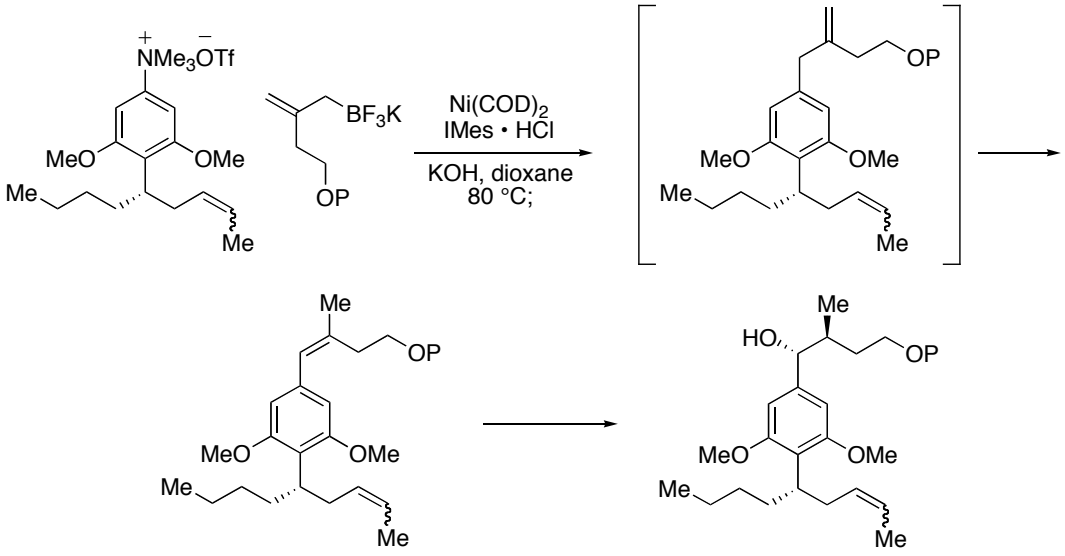
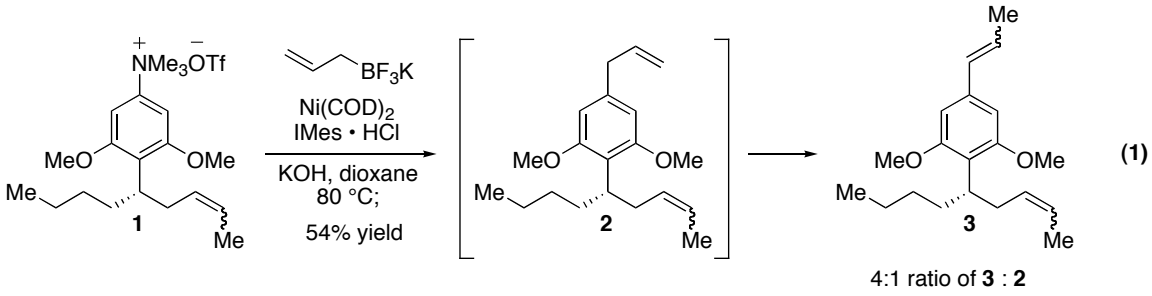


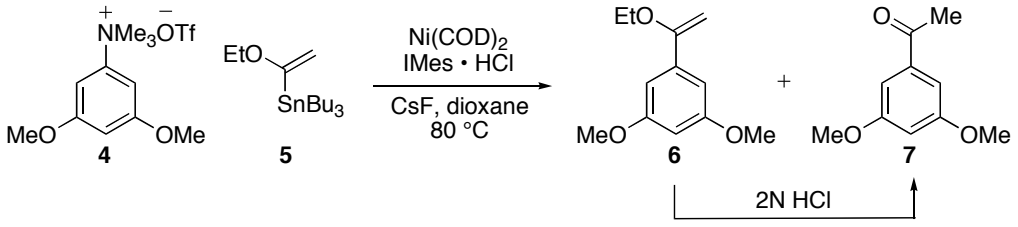
Figure 1. A selective olefination isomerization required for further functionalization.

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.

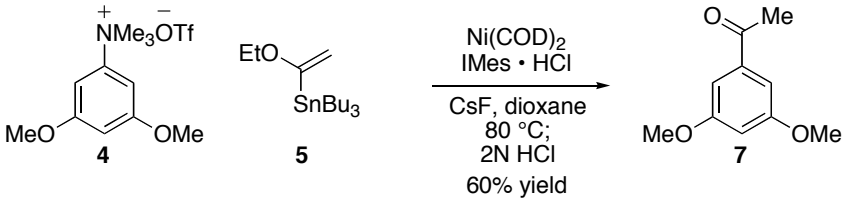


(1)

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).



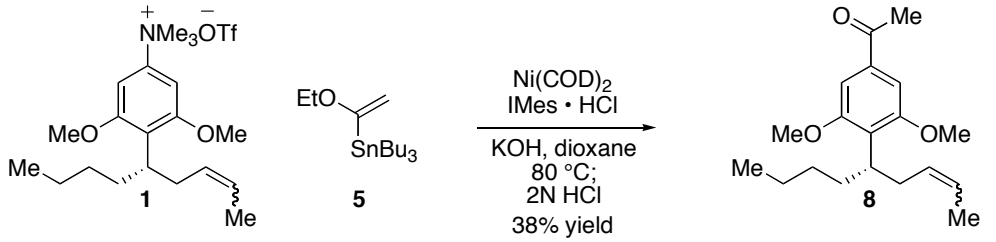
(2)



(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.*

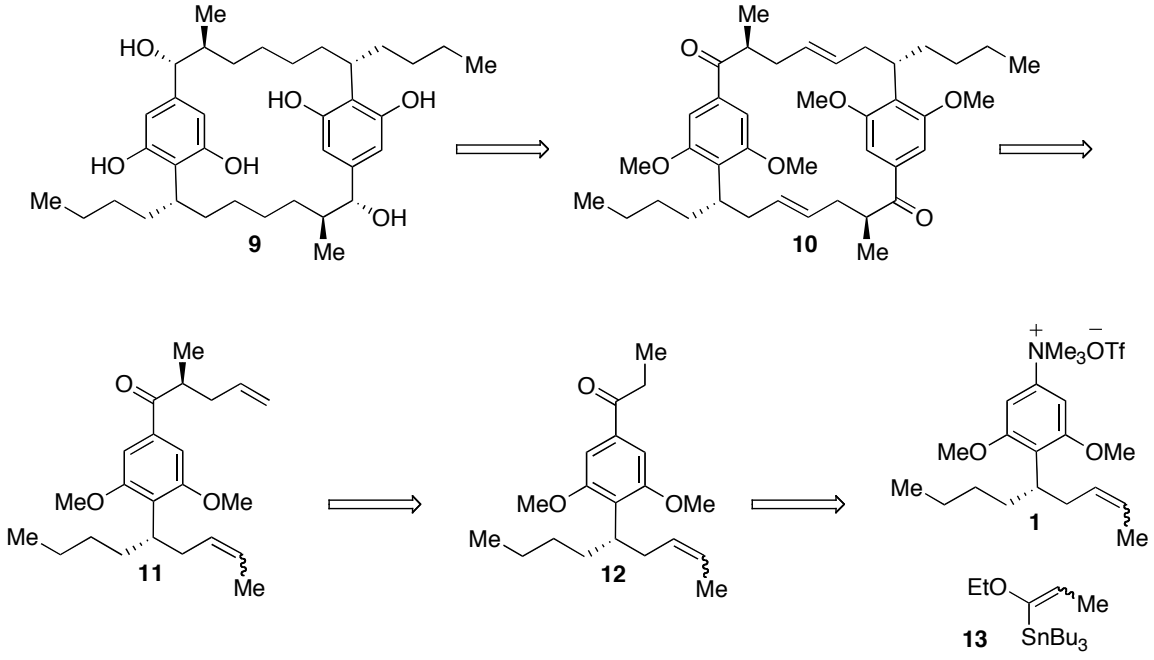
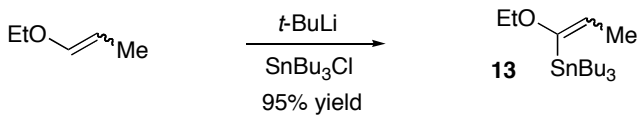


Figure 2. Revised retrosynthetic plan.

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

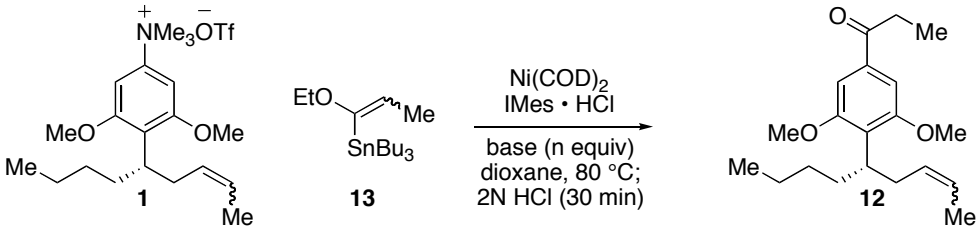
[1] Quintard, J. P.; Elissando, B.; Pereye, M. *J. Org. Chem.* **1983**, *48*, 1559.

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.

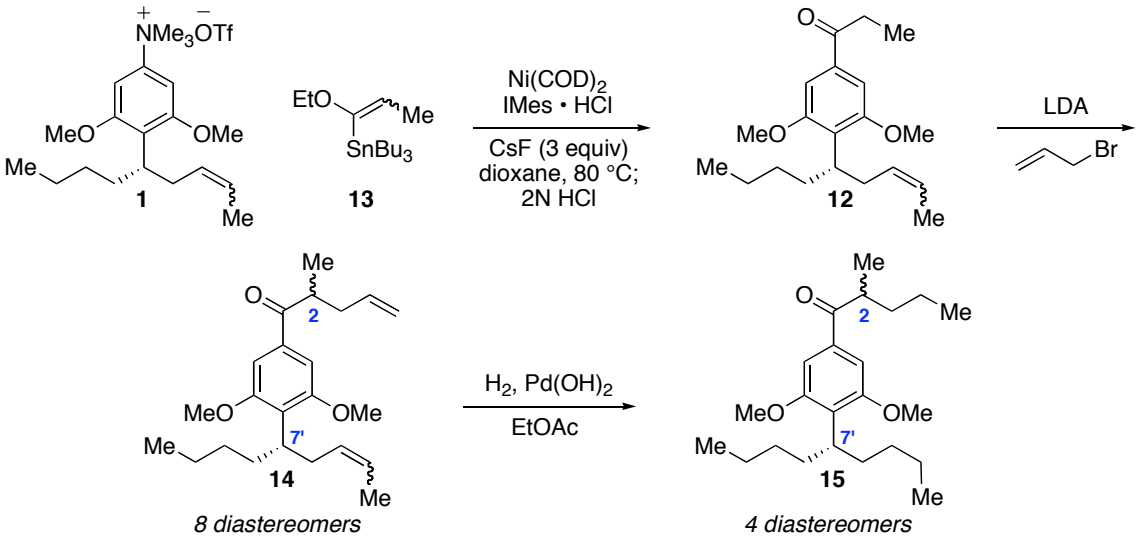


Figure 3. An achiral allylation for an assay.

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**.

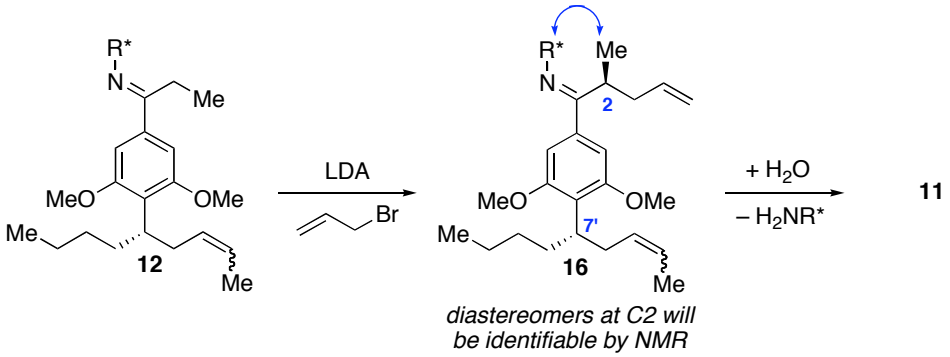
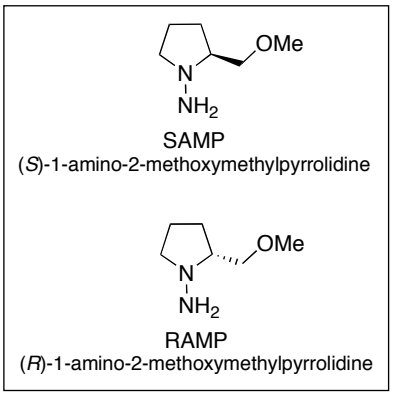


Figure 4. Allylic alkylation with a chiral auxiliary to facilitate the determination of diastereoselectivity.

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]

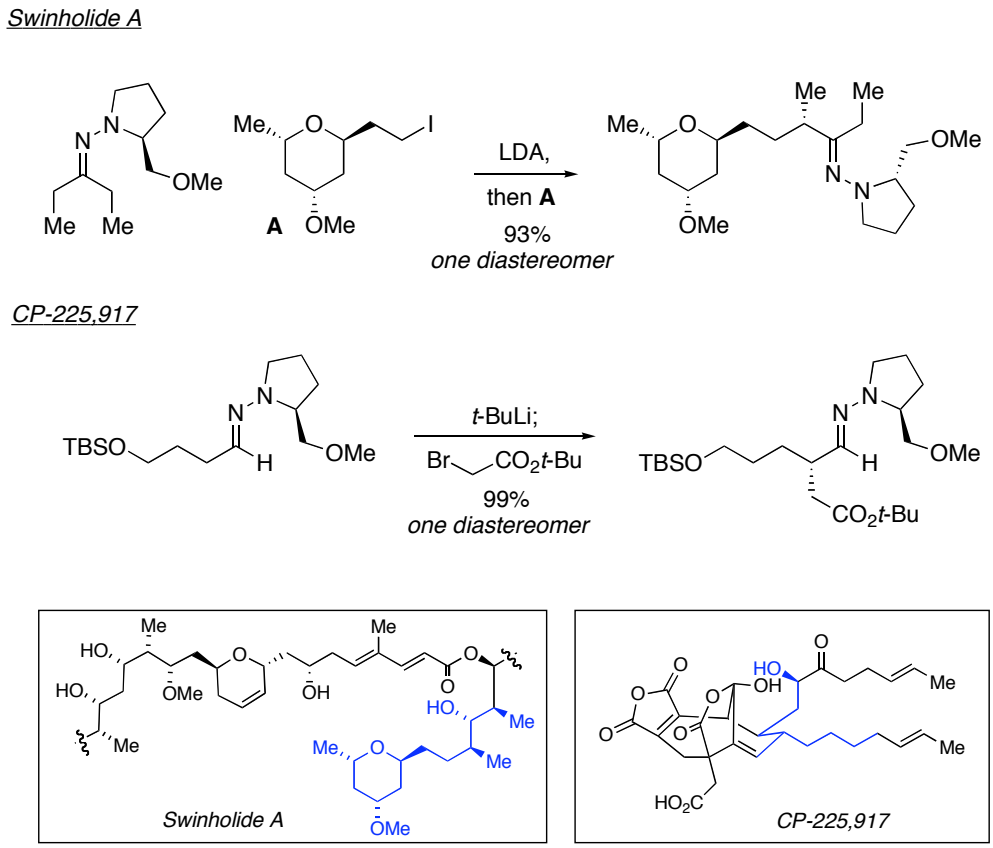


Figure 5. SAMP-hydrazone alkylations in natural product synthesis.

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.

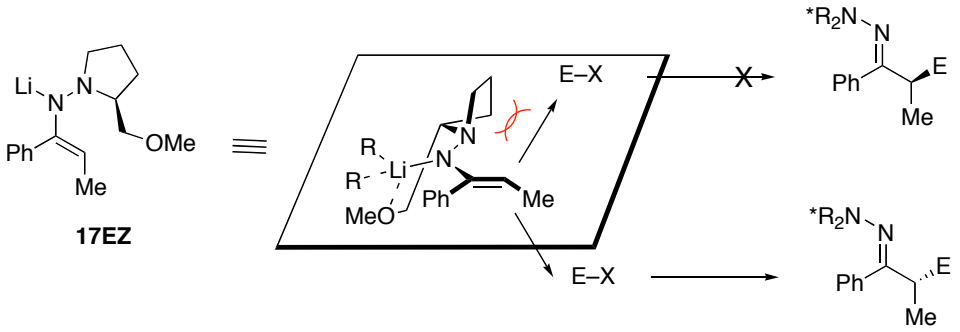

Figure 6. Diastereoselective alkylation of SAMP hydrazone.

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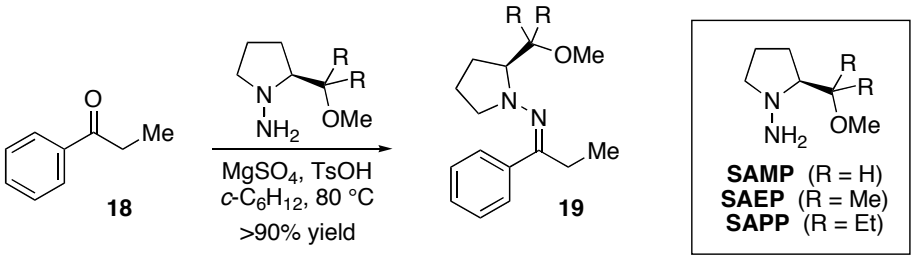
[7] Enders, D.; Bachstadter, G.; Kremer, K. A. M.; Marsch, M.; Harms, K.; Boche, G. *Angew. Chem. Int. Ed.* **1988**, *27*, 1522.

[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.

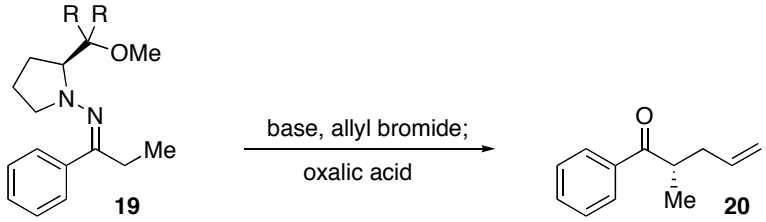
hours in only 44% yield. After some investigation, it was found that the addition of magnesium sulfate accelerated the condensation by removing water from the reaction mixture. In addition, changing the solvent to cyclohexane facilitated the condensation in less than 24 hours, with yields consistently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

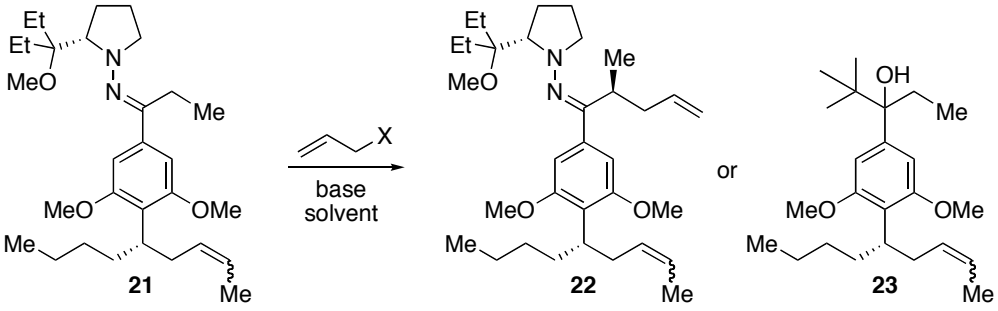
Table 3. Diastereoselective alkylation with SAMP-derivatives.



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**.

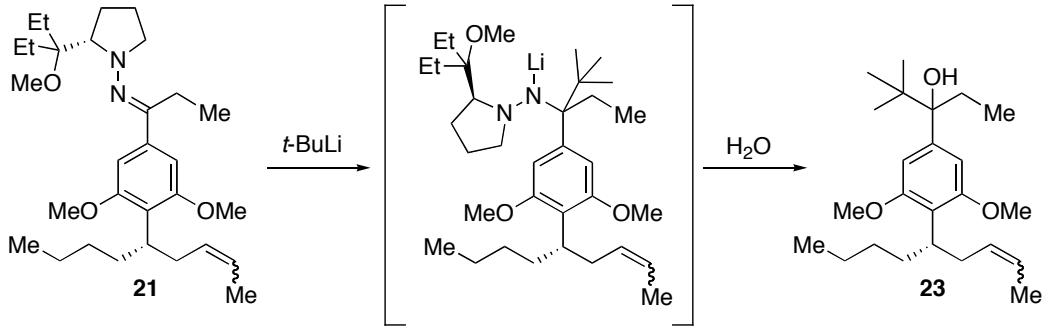


Figure 7. Addition to C=N bond in the diastereoselective alkylation.

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.

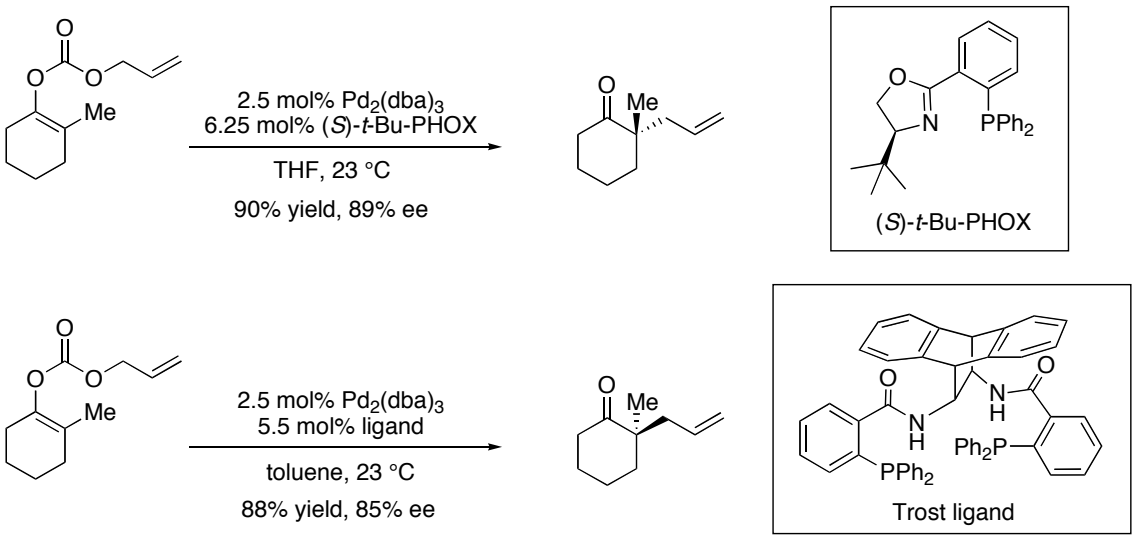


Figure 8. AAA of cyclie ketones by Stoltz and Trost.

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]

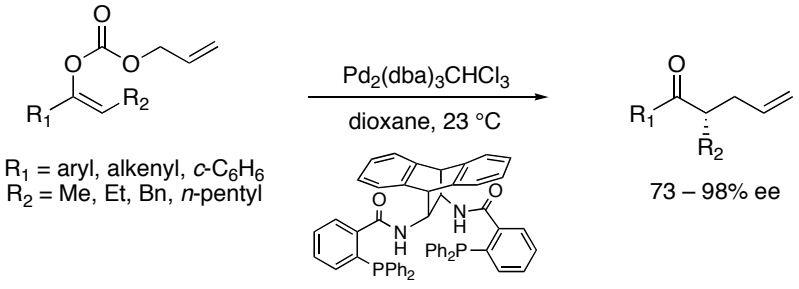


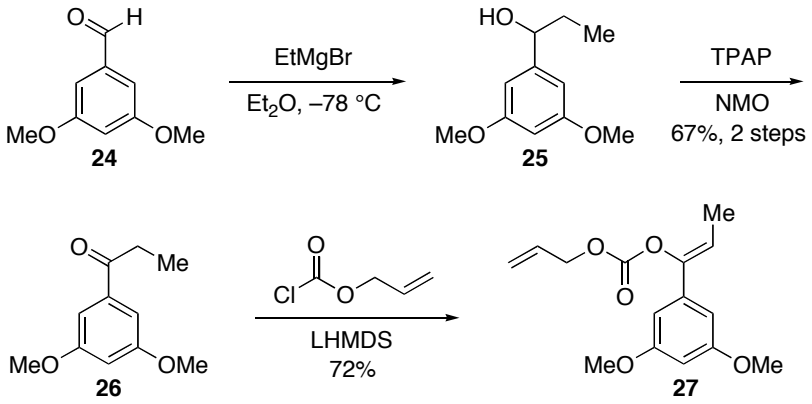
Figure 9. Trost's AAA of acyclic systems.

[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.

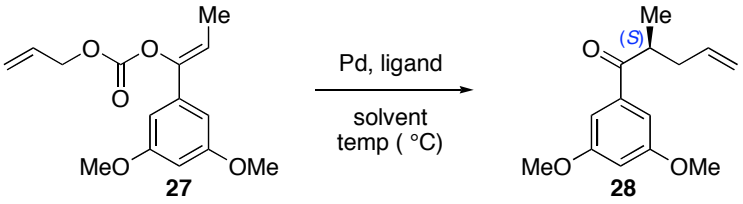


Exposure of **27** to the conditions reported by Trost (Fig. 9, ligand **A**, $Pd_2(dba)_3$, dioxane, 23 °C) provided an enantioenriched ketone with good enantioselectivity and full conversion (Table 5, entry 1). When the temperature was lowered to 4 °C in order to

[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.

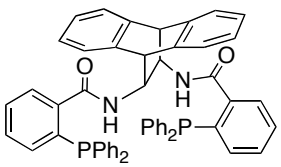
Table 5. Asymmetric allylic alkylation of model system 27.



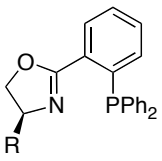
27 **28**

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.**

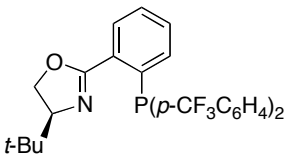
** 100% conversion, 18h



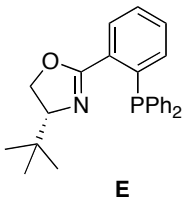
A



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



D



E

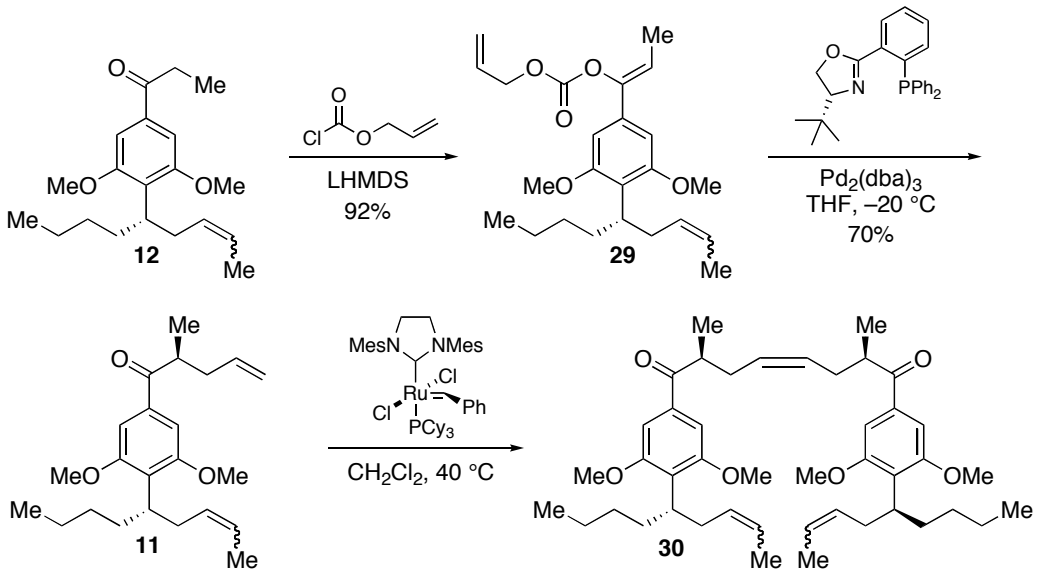
Using 5 mol% (*S*)-*t*-Bu-PHOX ligand **B** with 5 mol% $Pd_2(dba)_3$ in THF at room temperature, 100% conversion and 73% ee was obtained for the product (entry 3). Meanwhile, other PHOX derivatives **C** and **D** were not as selective in this sytem (entries 4 and 9). The reaction was rapid at room 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.

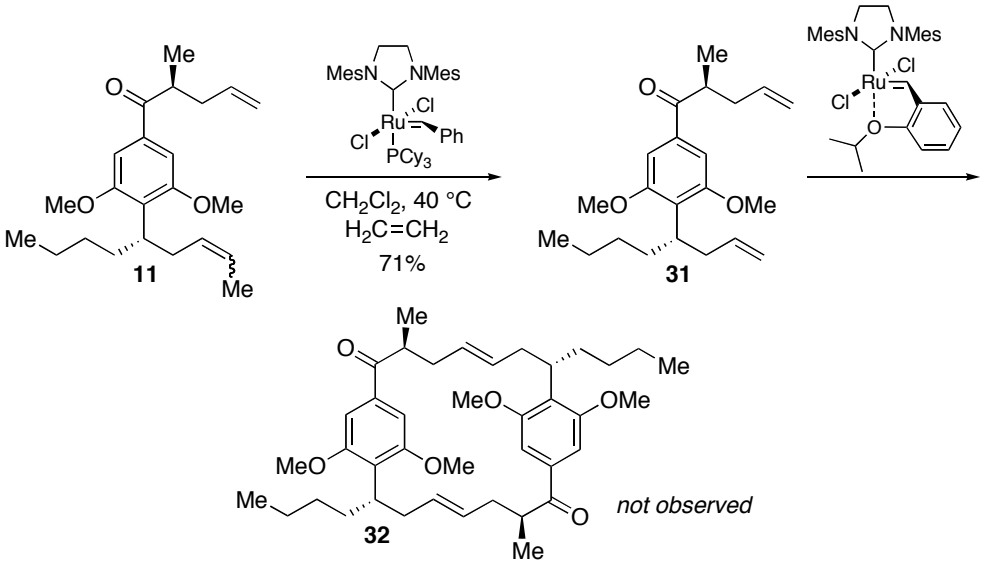


Conversion of the disubstituted olefin in **11** to the terminal olefin should allow for the reversible ring-closing metathesis dimerization that was demonstrated by Smith.[16] Olefin cross-metathesis with ethylene provided diene **31**, which was an advanced intermediate in the Smith synthesis.[16c] 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**).

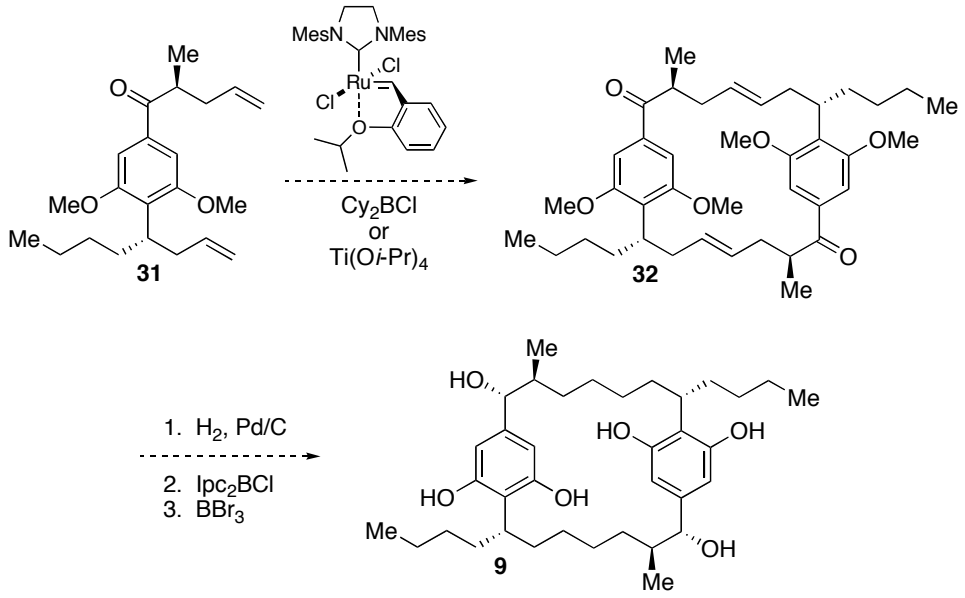
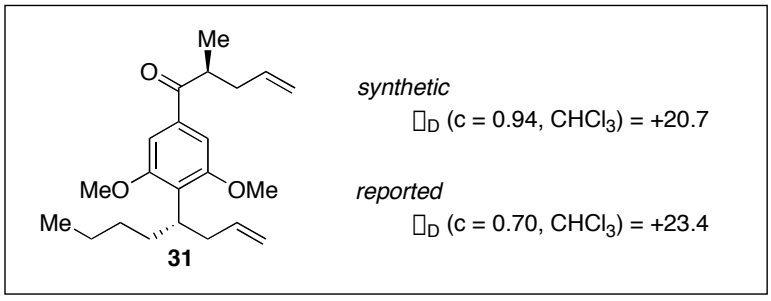


Figure 10. Remaining synthetic sequence to the natural product.

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).

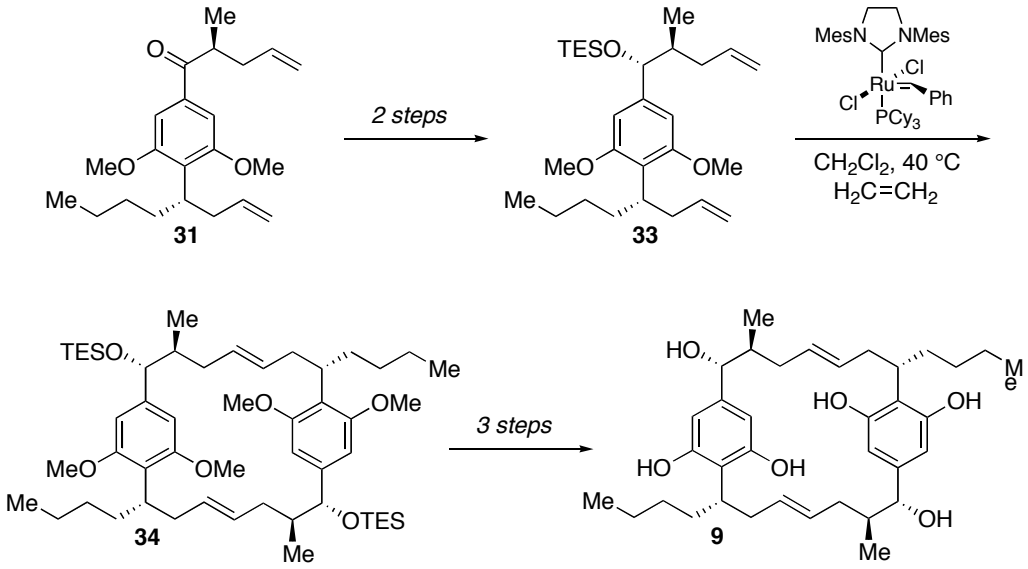


Figure 11. Completion of the synthesis of cylindrocyclophane A by Smith's route.

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

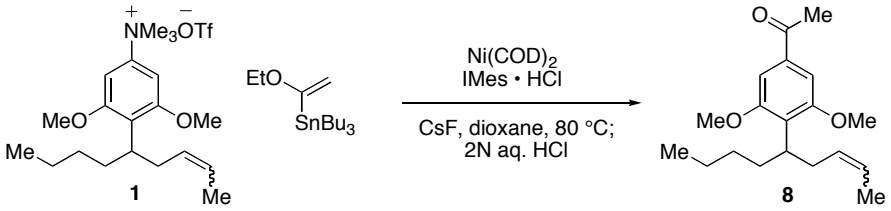
[19]Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals, 3rd ed.*; Pergamon Press, Oxford, 1988.

[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

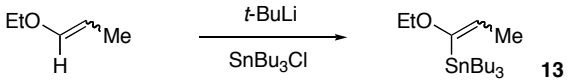
point 2N HCl was added. After stirring for an hour, the acidic layer was extracted with ethyl acetate. The organic layers were washed with brine, dried with magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography of the crude residue provided the title compound **7** as a clear oil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

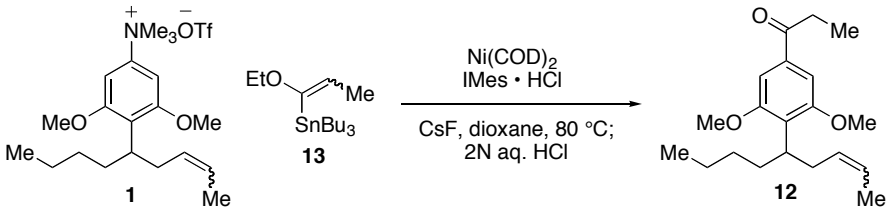


13

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.

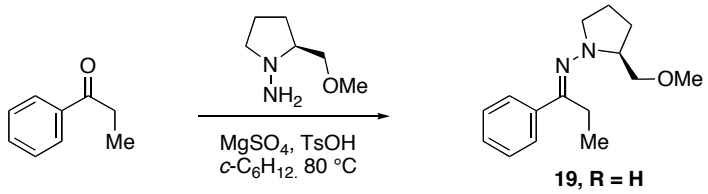


1-(3,5-Dimethoxy-4-(non-2-en-5-yl)phenyl)propan-1-one (12).[21] In a glove box under nitrogen, a flame-dried Schlenk flask was charged with anilinium salt **1** (1.6 g, 3.4 mmol), $Ni(COD)_2$ (281 mg, 1.02 mmol), IMes • HCl (348 mg, 1.02 mmol), and cesium fluoride (1.55 g, 10.2 mmol). The Schlenk was 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.

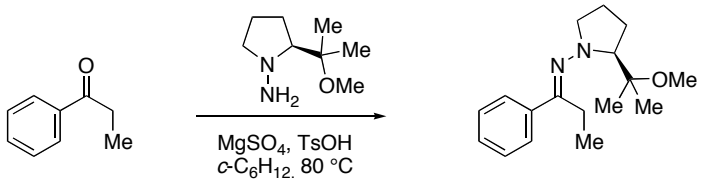
General Procedure for Preparation of SAMP/SAEP/SAPP Hydrazones from the Corresponding Ketones: Ketone (1 mmol) was taken up in cyclohexane (2 mL, 0.5 M) at room temperature. Hydrazone (2 mmol), magnesium sulfate (400 mg), and a catalytic amount of *p*-toluenesulfonic acid were added. The reaction was 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

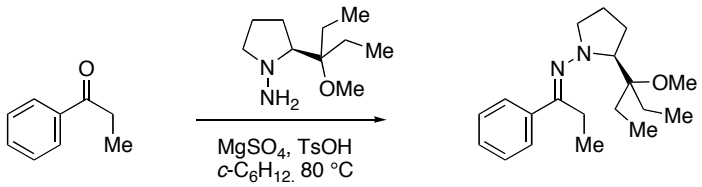
(*S*)-2-(Methoxymethyl)-*N*-(1-phenylpropylidene)pyrrolidin-1-amine (19, R = H). Propiophenone (0.133 mL), SAMP (0.268 mL), magnesium sulfate (400 mg), catalytic

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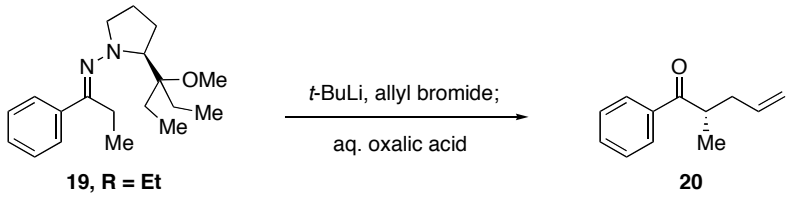
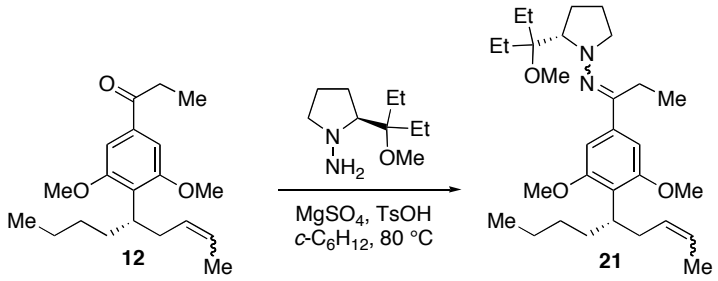
[24] (a) Enders, D.; Meyer, I.; Runsink, J.; Raabe, G. *Heterocycles* **199**, *50*, 995. (b) Enders, D.; Bushan, V. *Tetrahedron Lett.* **1988**, *29*, 2437. (c) Enders, D.; Eichenauer, H.; Baus, U.; Schubert, H.; Kremer, K. Am. M. *Tetrahedron* **1984**, *40*, 1365.

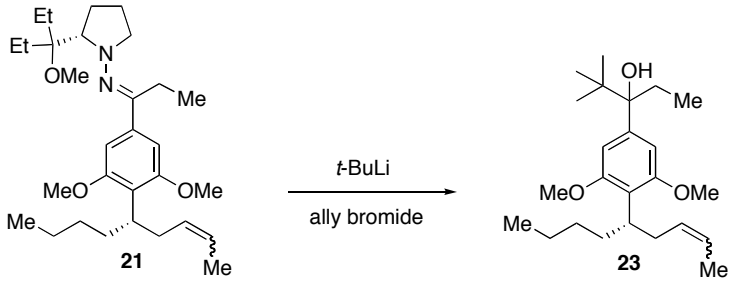


(*S*)-2-Methyl-1-phenylpent-4-en-1-one (20). At –78 °C under argon, *tert*-butyllithium (0.19 mL, 0.325 mmol) was added to a solution of hydrazone **19** (24.5 mg, 0.0812 mmol) in 0.54 mL THF (0.15 M). The solution turned light orange in color. The reaction was stirred at –78 °C for 30 min and then warmed 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.



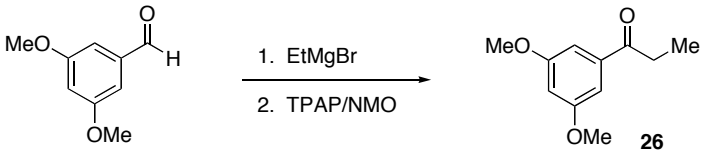
(*S*)-*N*-(1-(3,5-Dimethoxy-4-((*S*)-non-2-en-5-yl)phenyl)propylidene)-2-(3-methoxypentan-3-yl)pyrrolidin-1-amine (21).[21] Ketone **12** (318 mg, 1 mmol) was

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.

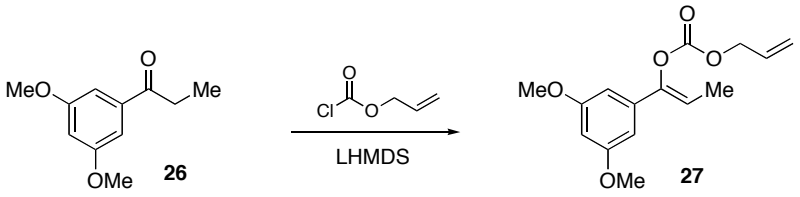


26

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.

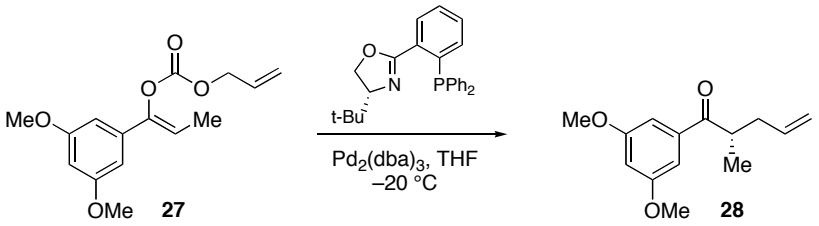
The above alcohol **25** was dissolved in 60 mL CH_2Cl_2 (0.2 M) at room temperature under argon. Morpholine *N*-oxide (NMO, 7.0 g, 60 mmol) and 5.0 mg activated 4Å mol sieves were added. This mixture was stirred for 30 minutes before TPAP (264 mg, 0.75 mmol) was added. Upon completion, the reaction 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

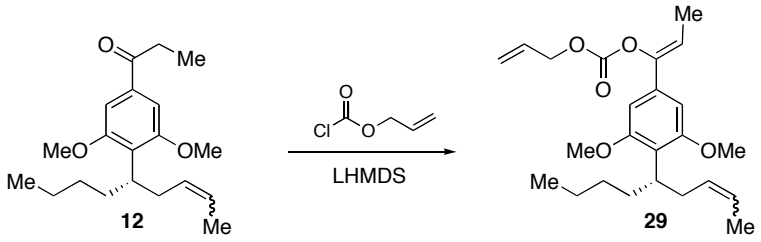
[25] Cannon, J. R.; Cheong, P. K.; Fallick, C. J.; Hamilton, B. H.; McDonald, I. A.; Vinciguerra, G. *Aust. J. Chem.* **1973**, *26*, 799.

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.



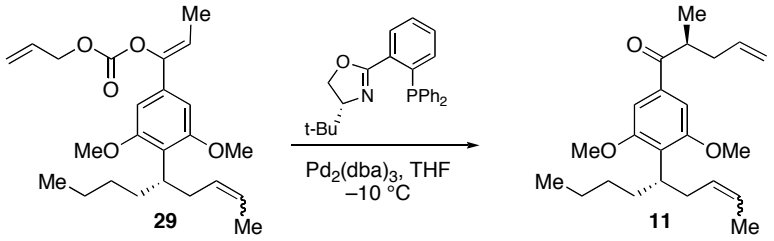
(*S*)-1-(3,5-Dimethoxyphenyl)-2-methylpent-4-en-1-one (28). A flame-dried 2-dram vial was charged with $Pd_2(dba)_3$ (5.0 mg, 0.00543 mmol) and (*R*)-*t*-Bu)-PHOX (5.3 mg, 0.0136 mmol). 1 mL THF was added and this mixture was stirred at room temperature for 30 minutes, after which it was cooled to –20 °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.



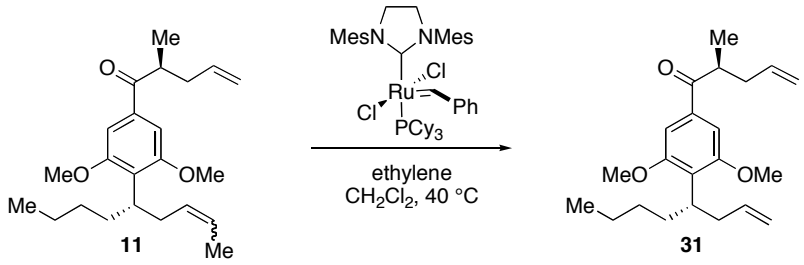
Allyl (1*Z*)-1-(3,5-dimethoxy-4-((*S*)-non-2-en-5-yl)phenyl)prop-1-enyl carbonate (29). LHMDS (0.61 M) was freshly prepared: *n*-butyllithium (2.19 mL, 5 mmol) was added to a solution of HMDS (5 mmol) in 5 mL THF at 0 °C. The reaction was warmed to room temperature before use. The ketone **12** (26 mg, 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]