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).

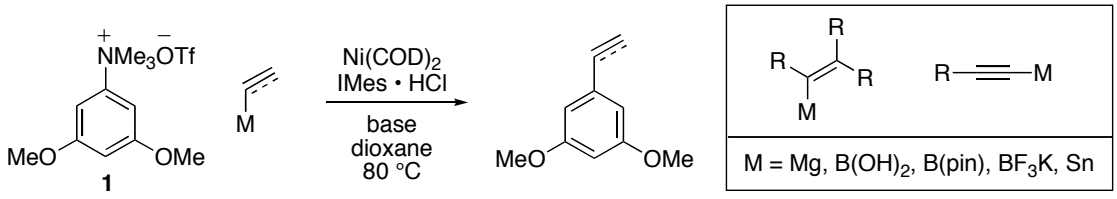
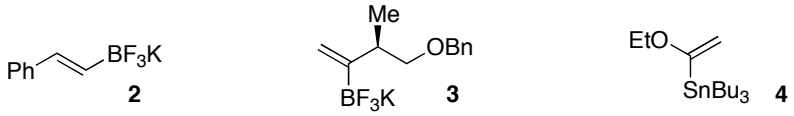


Figure 1. Transmetalation reagents operable with Ni(0) cross-coupling.

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).

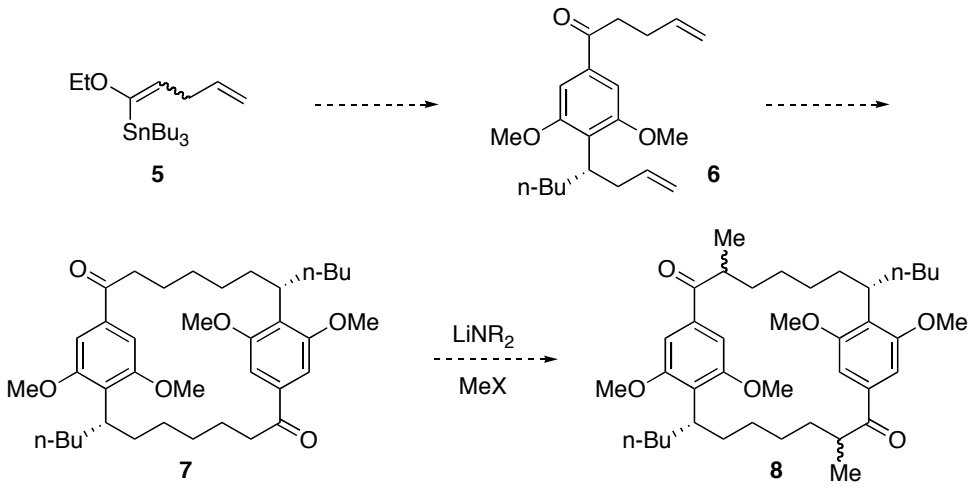


Figure 2. Lack of diastereocontrol in an alkylation of the macrocycle.

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.

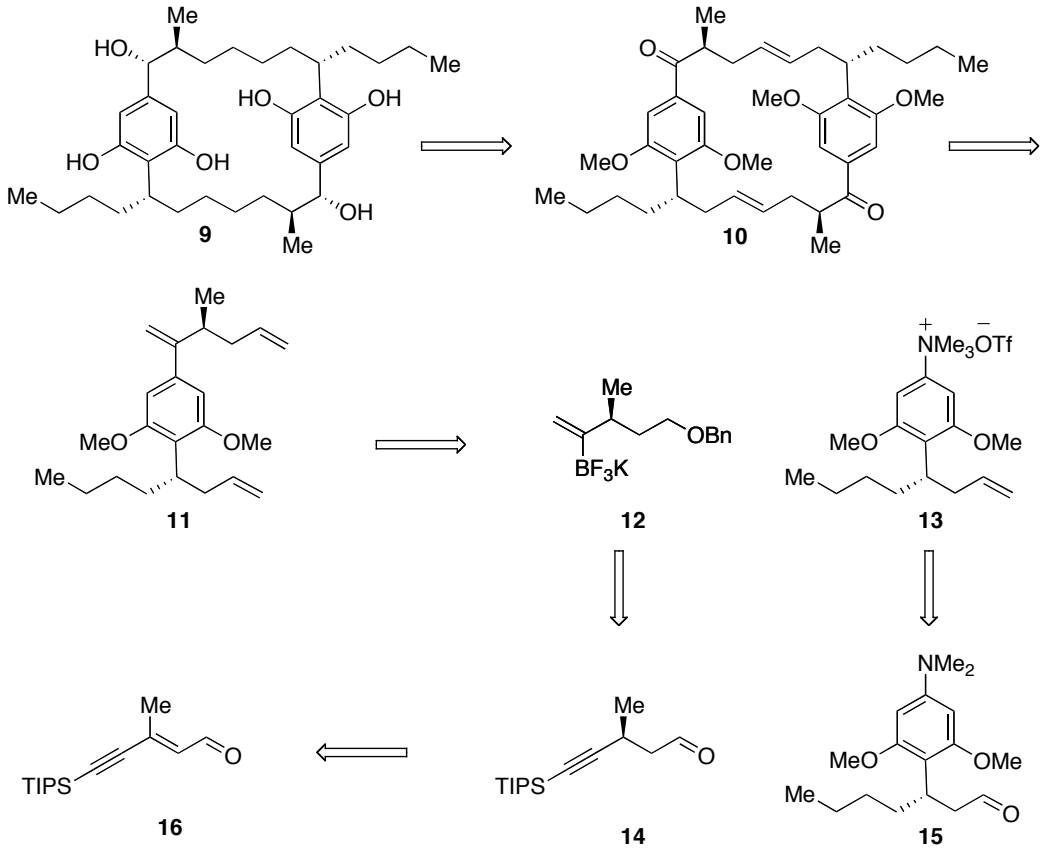
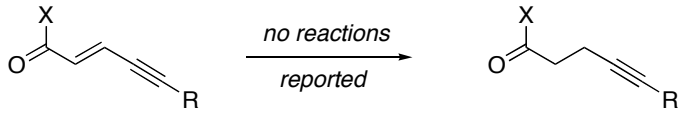


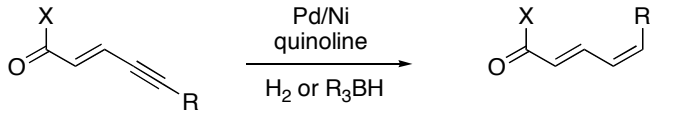
Figure 3. Retrosynthetic plan for cylindrocyclophane A.

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]

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[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.

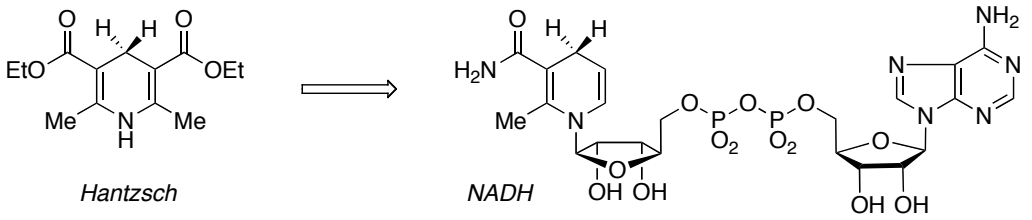
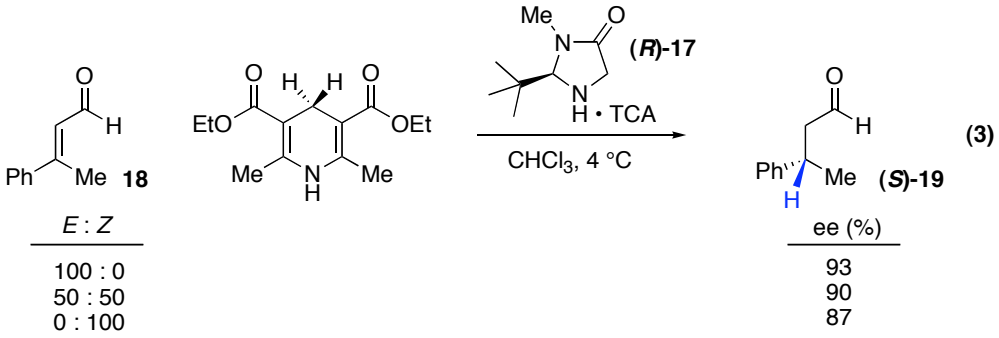


Figure 4. Hantzsch ester as a biological mimetic for NADH.

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.

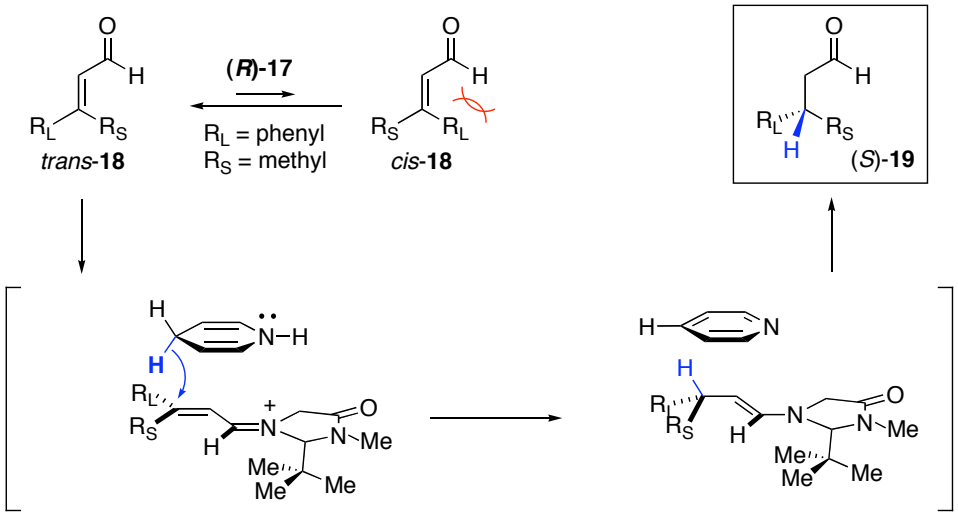
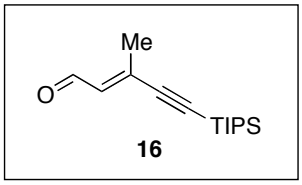


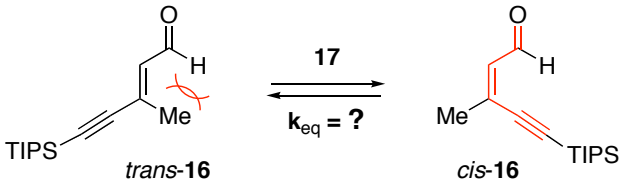
Figure 5. Catalyst-assisted isomerization of α,β-unsaturated aldehydes.



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.

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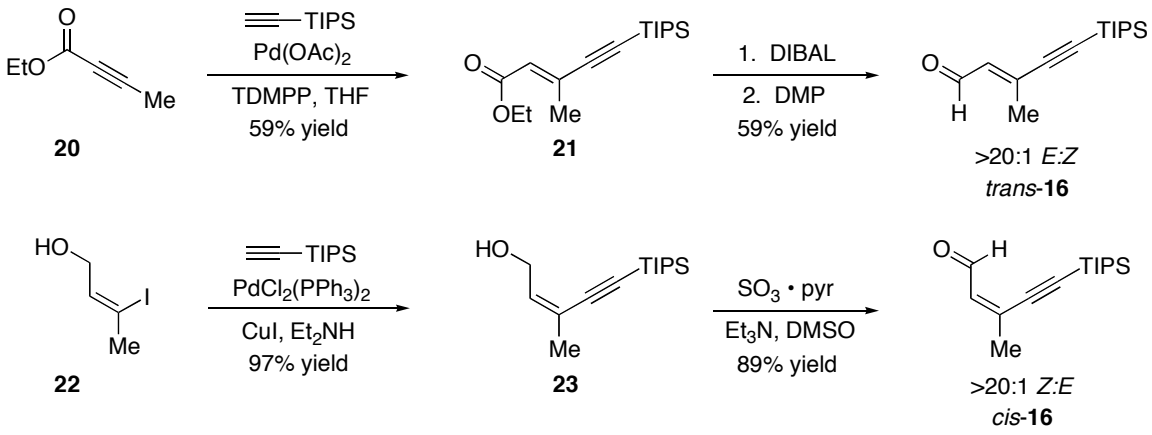
[8] Trost, B. M.; Sorum, M. T.; Chan, C.; Tuehter, G.. *J. Am. Chem. Soc.*. **1997**, *119*, 698.

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

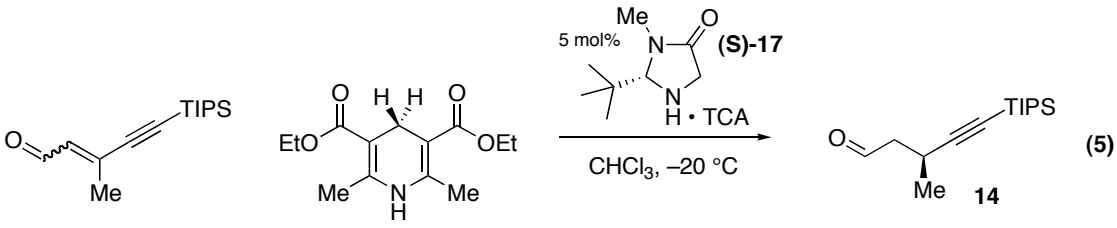
[10] Odedra, A.; Wu, C.-J.; Madhushaw, R. J.; Wang, S.-L.; Liu, R.-S. *J. Am. Chem. Soc.* **2003**, *125*, 9610.

[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.

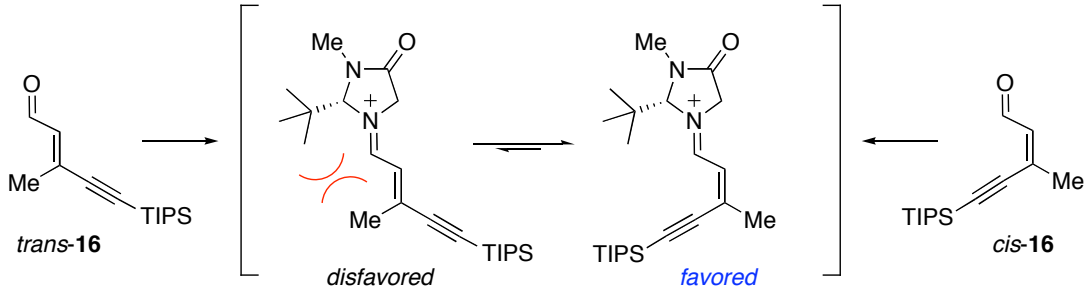
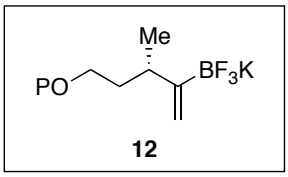


Figure 6. Sterics was the dominating factor in the iminium olefin isomerization.

III. Synthesis of Potassium Trifluoroborate Cross-Coupling Substrates.

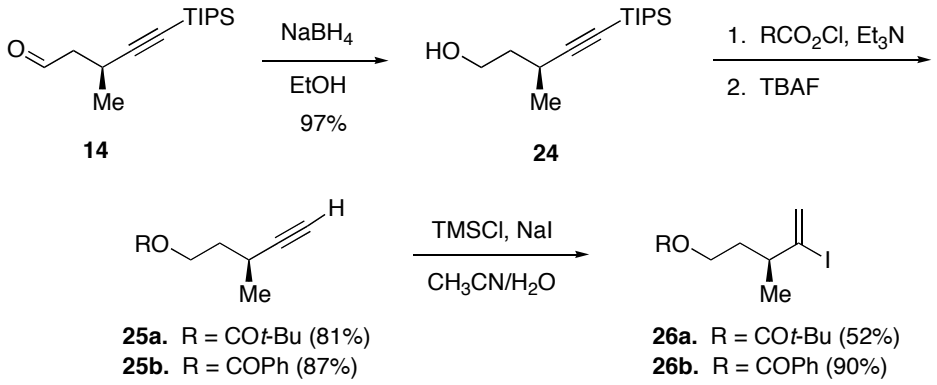
The choice of protecting group of potassium trifluoroborate salt **12** was crucial in the cross-coupling reaction with trimethylanilinium salt **13**. There were two considerations that were important: (i) the protecting group should withstand the basic conditions of refluxing KOH in dioxane and (ii) 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).

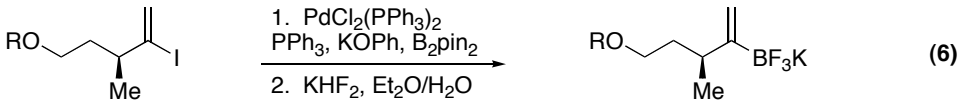
Scheme 2. Preparation of vinyl iodides with electron-withdrawing groups.



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

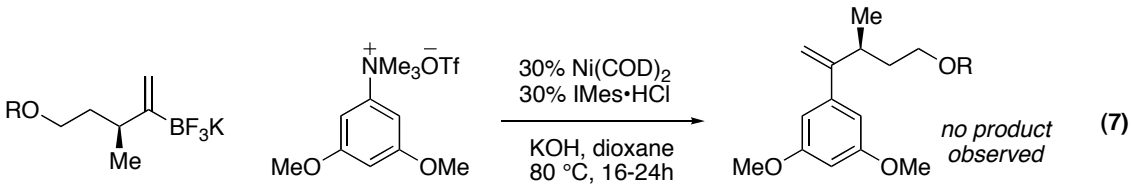
12a. R = CO*t*-Bu (30%)
12b. R = COPh (40%)

(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)

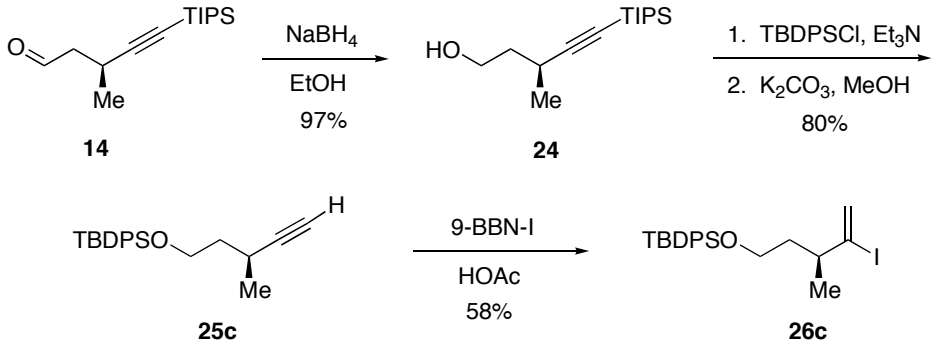
ii. ***A bulky silyl group as a choice of protecting group.***

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

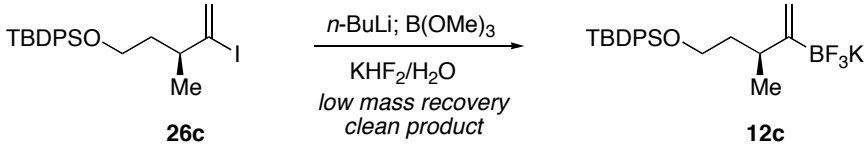
[15] Greene, T. W.; Wutts, P. G. M. In *Protective Groups in Organic Synthesis, 3td Ed.* Wiley: New York, 1999.

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.

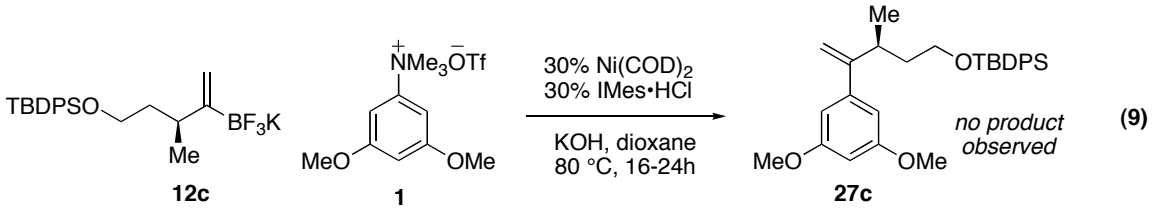


(8)

[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.

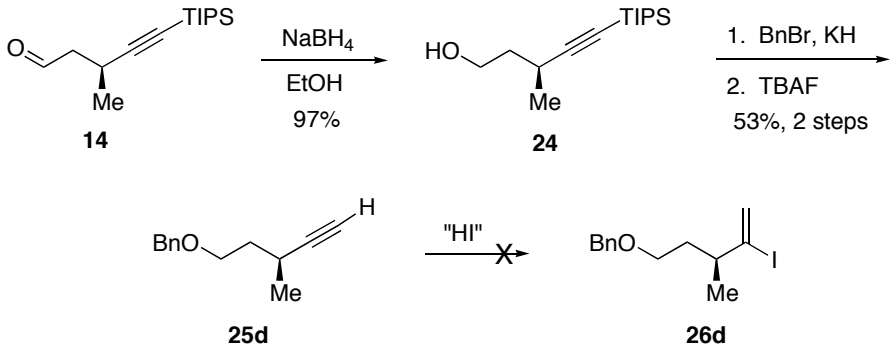


(9)

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.

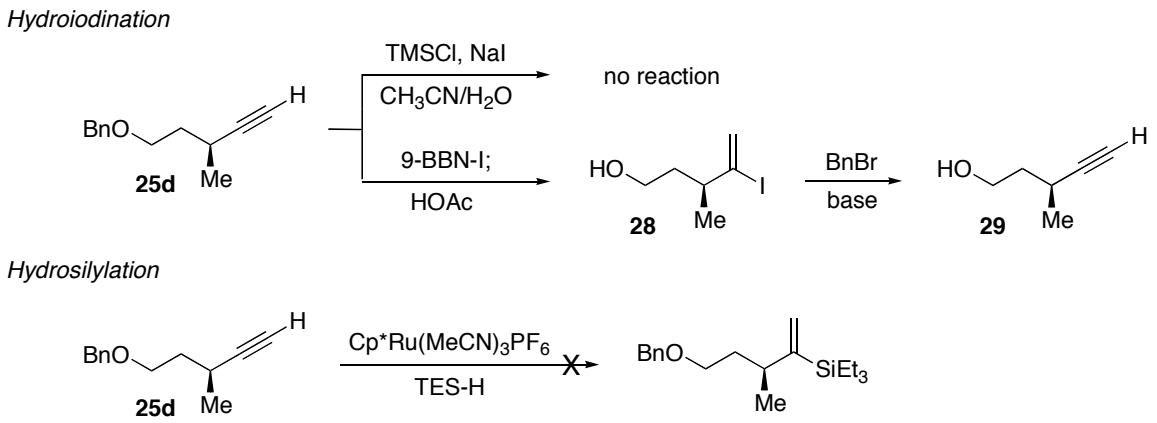


Figure 7. Unsuccessful attempts to functionalize the terminal alkyne.

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.

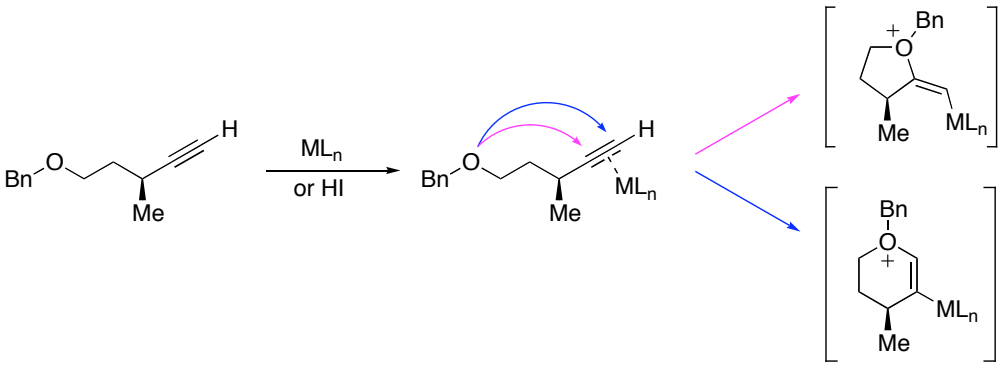
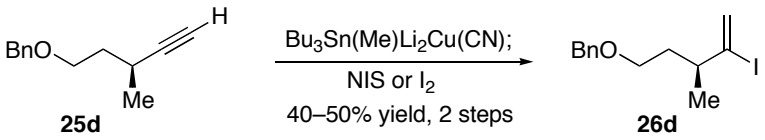


Figure 8. Intramolecular trap of ether oxygen onto the alkyne.

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).



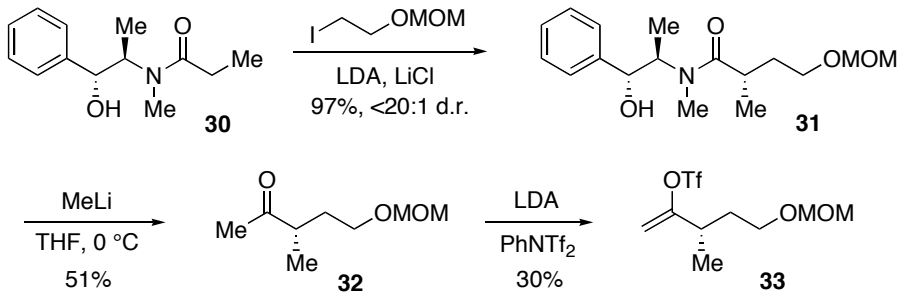
(10)

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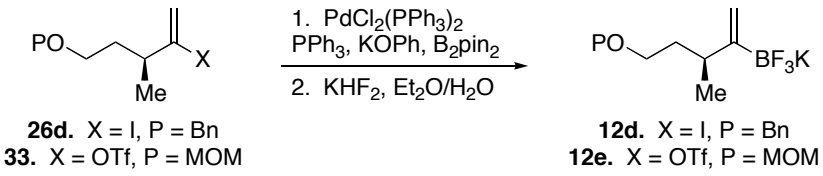
[22] Myers, A. G.; McKinstry, L. *J. Org. Chem.* **1996**, *61*, 2428.

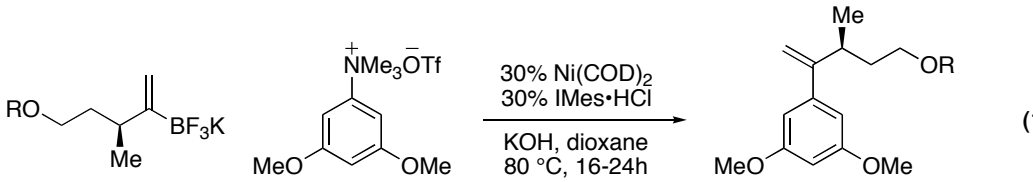


26d. X = I, P = Bn
33. X = OTf, P = MOM

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.



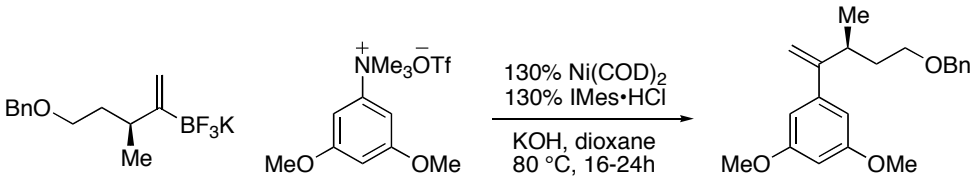
12d. R = Bn
12e. R = MOM

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]

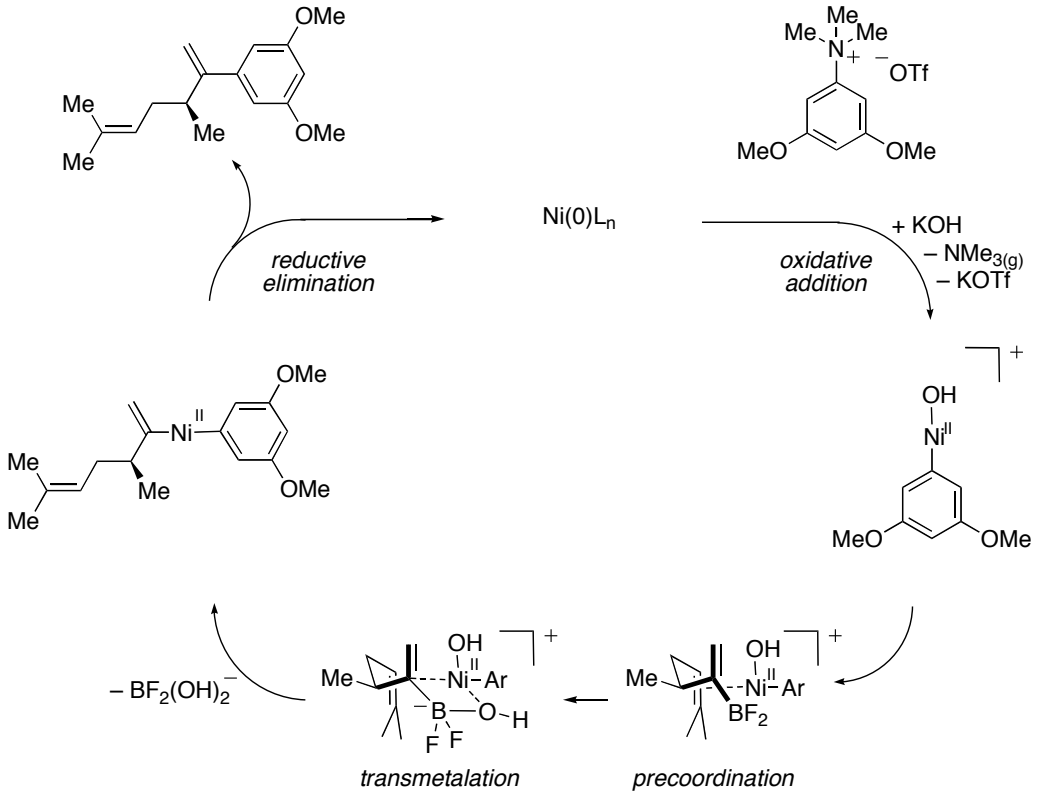
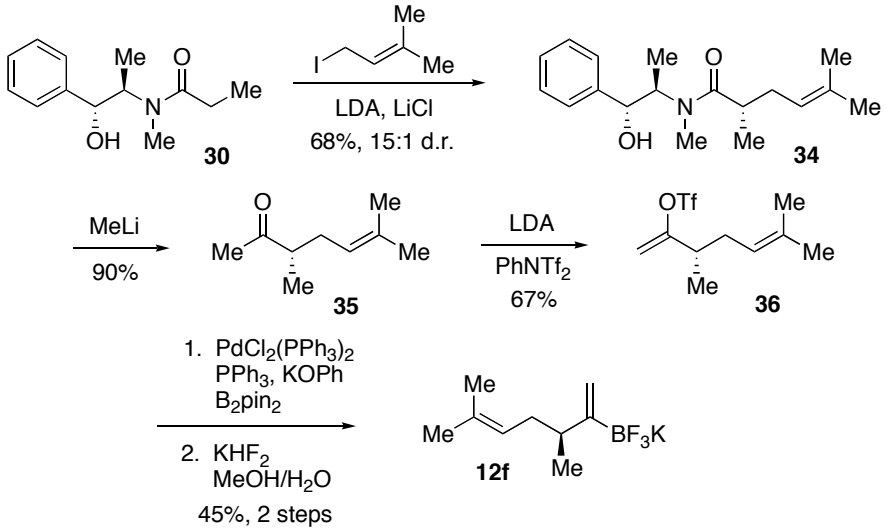


Figure 9. Facilitation of a transmetalation event with a pendant isoprenyl group.

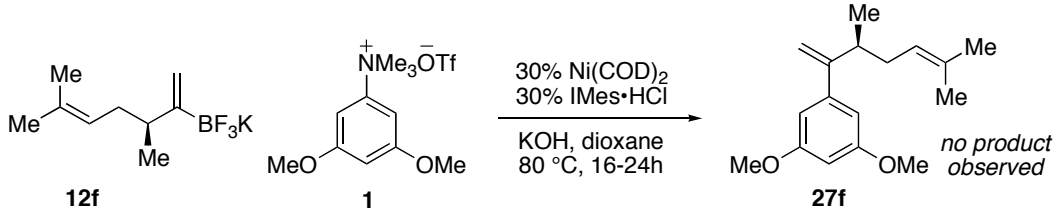
[23] For a discussion on the transmetalation of potassium organotrifluoroborates, see: Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461.

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.



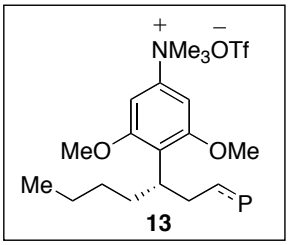
(14)

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.



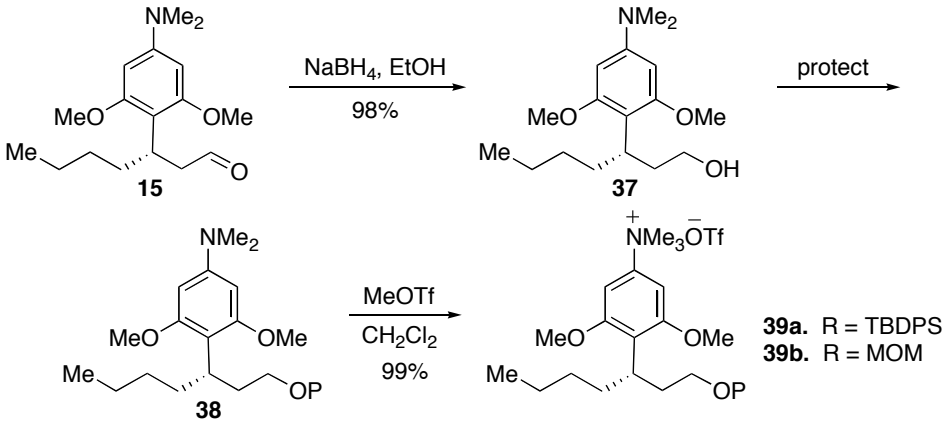
13

i. *Protected alcohols as oxidation state surrogates.*

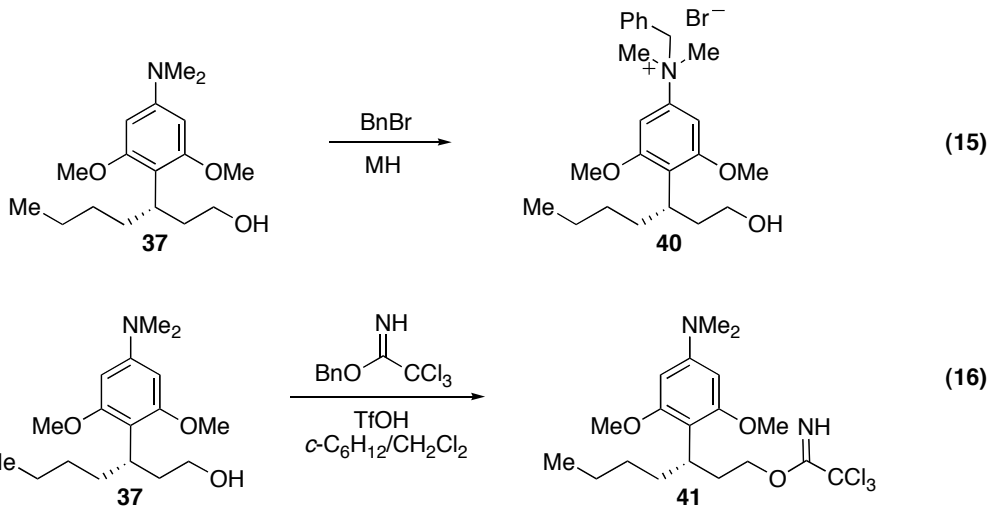
The first set of anilinium salts tested in the desired cross-coupling with borate **12d** contained an unprotected alcohol and its protected counterparts. The preparation of organocatalytic adduct **15** was discussed in chapter 3, from which the product was isolated with 93% ee at the benzylic stereocenter (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.

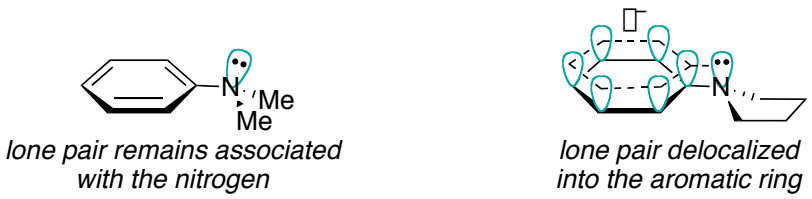


Figure 10. Dimethylaniline versus phenylpyrrolidine.

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).

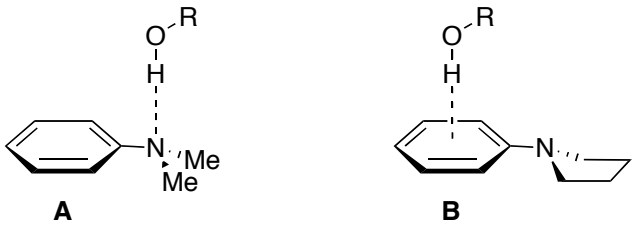


Figure 11. Location of a hydrogen bond on dimethylaniline and phenylpyrrolidine.

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]

---

[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.

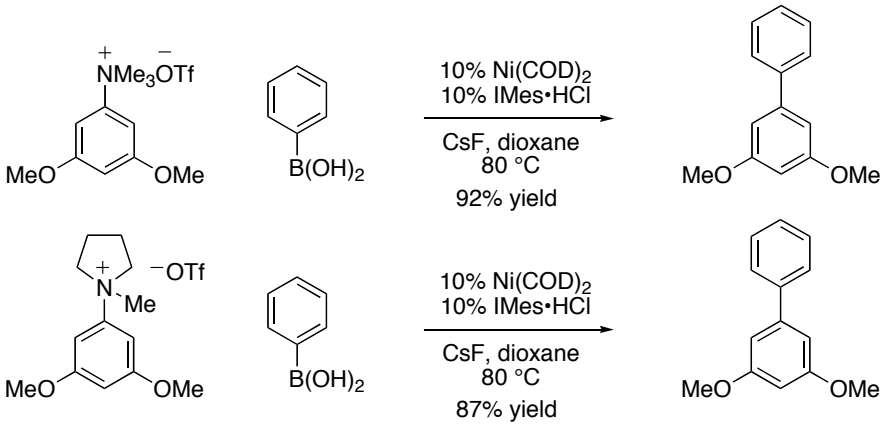
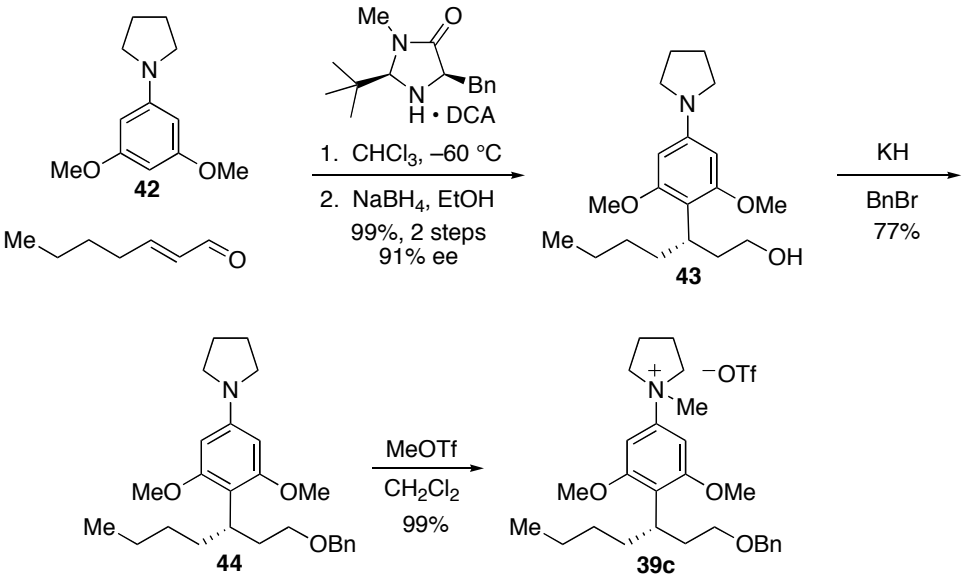


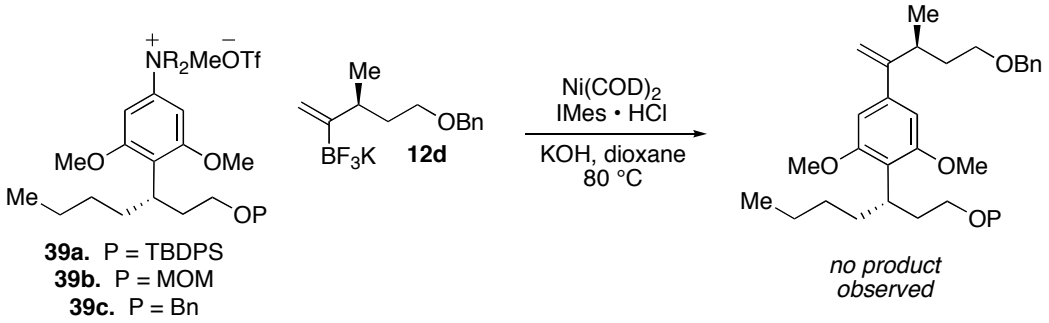
Figure 12. Cross-coupling with a pyrrolidino-anilinium salt.

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.

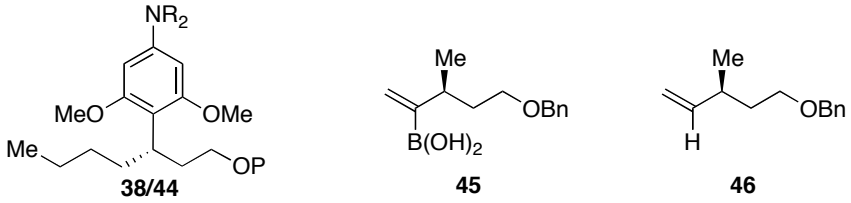


Figure 13. Isolated side-products of the cross-coupling in equation 17.

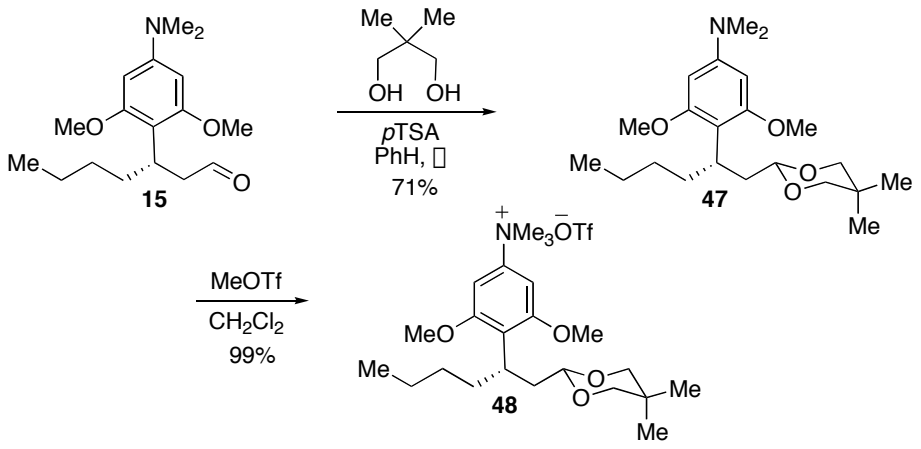
Upon consideration, it was thought that cleavage of the TBDPS in **39a** would result in the free alcohol **37**, which would consume the nickel in the reaction. Benzyl ethers and MOM ethers are known to be good metal chelating moieties, and so **39b** and **c** could conceivably coordinate the nickel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

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

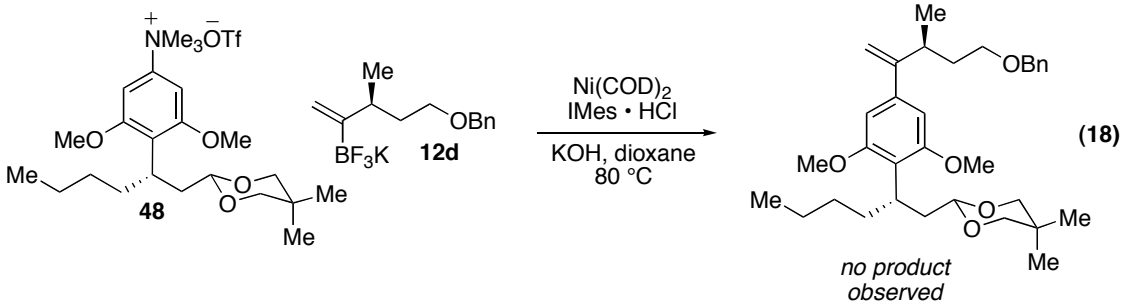
Alternatively, the aldehyde **15** could be masked as the acetal, which should not be susceptible to base-mediated cleavage. Aldehyde **15** was converted to the 4,4-

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).

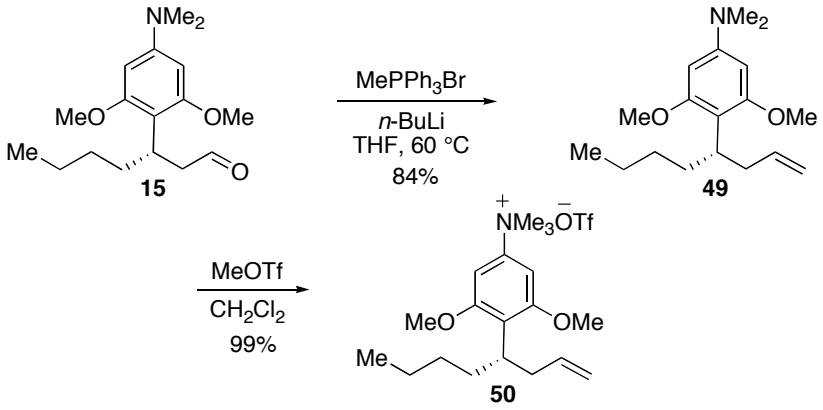


iii. *Simple alkenyl functionality on the alkyl chain.*

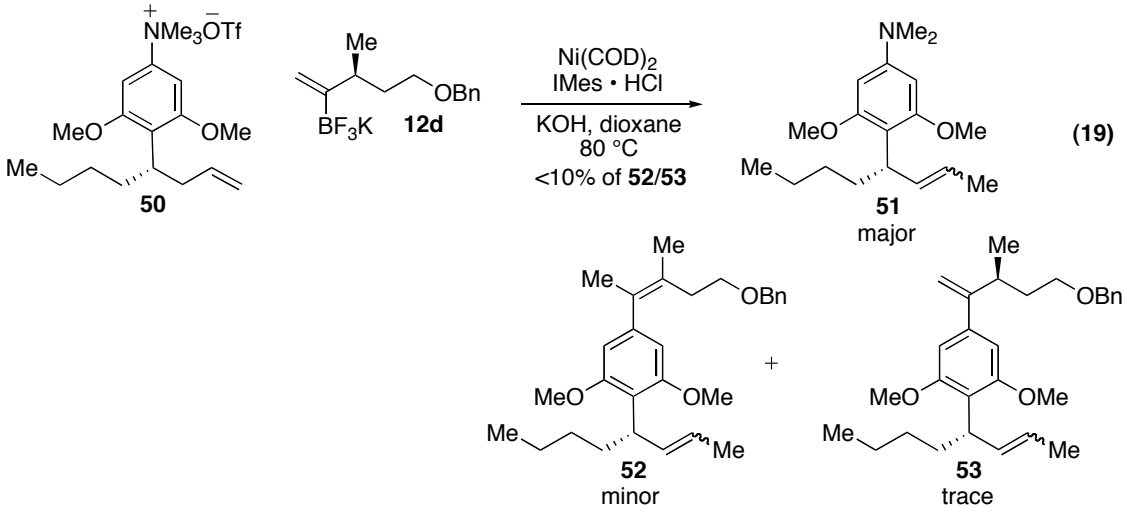
An olefin was chosen as a protecting group because it (i) is necessary for the cross-metathesis/dimerization strategy and (ii) both alcohol and aldehyde protecting

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.

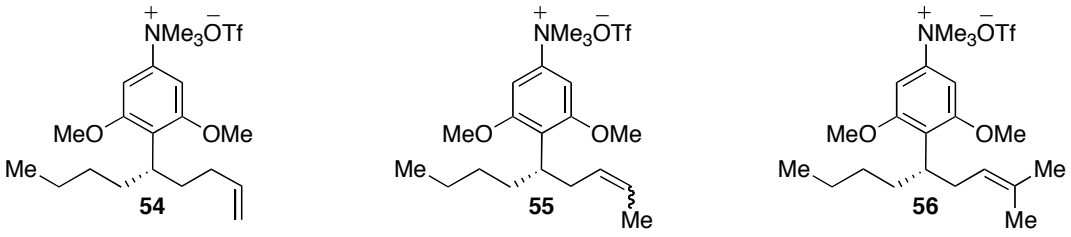
Scheme 10. Synthesis of methylene trimethylanilinium salt 50.



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.

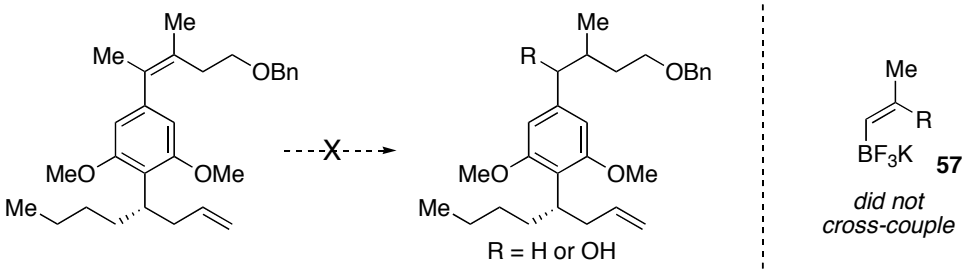
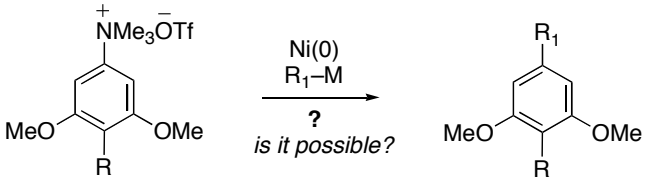


Figure 14. A non-productive route with the current cross-coupling strategy.

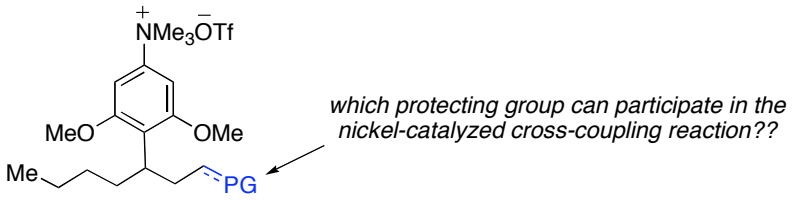
V. Investigation into Suzuki Cross-Couplings with Fully Functionalized *N,N,N*-Trimethylanilinium Triflates.

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.

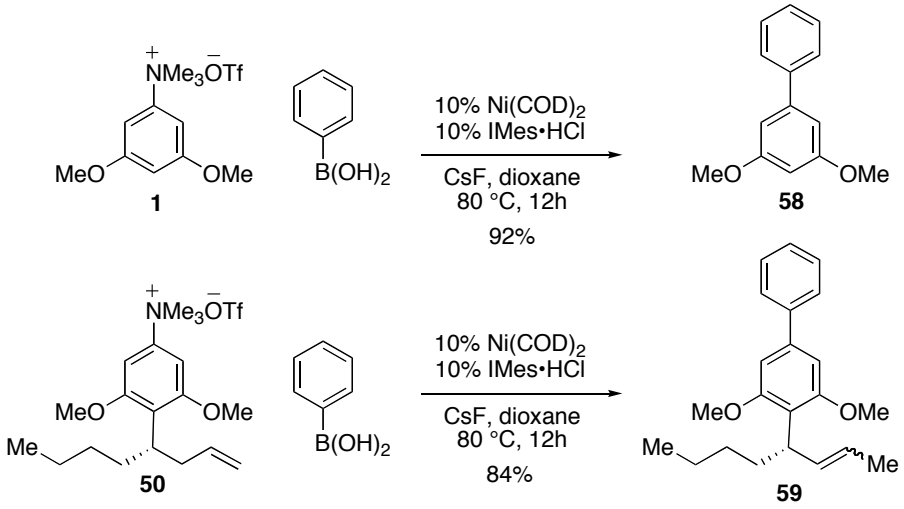
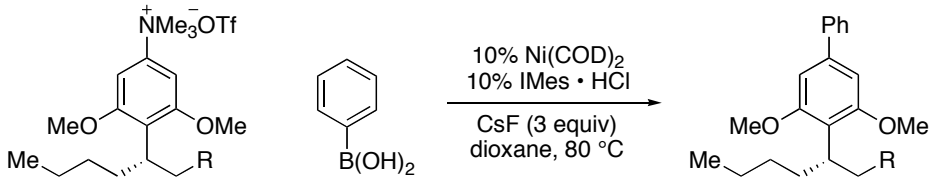


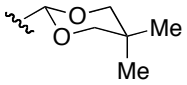
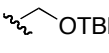
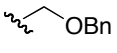
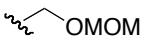
Figure 15. Substitution in the 4-position of the anilinium salt was tolerated.

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.

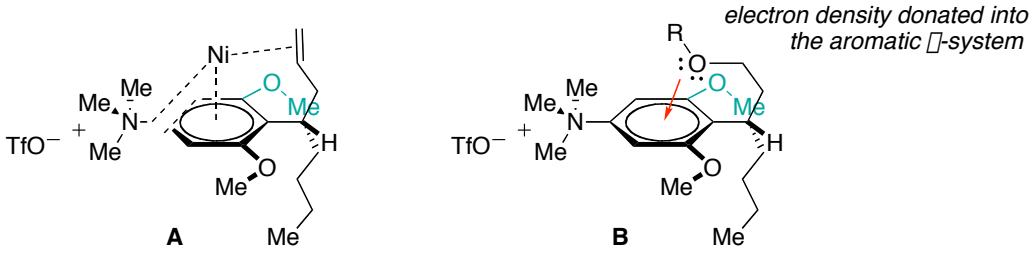
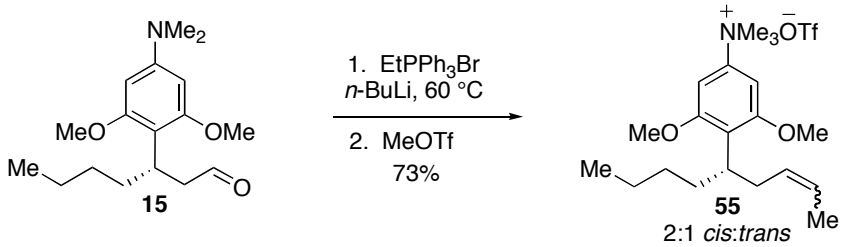
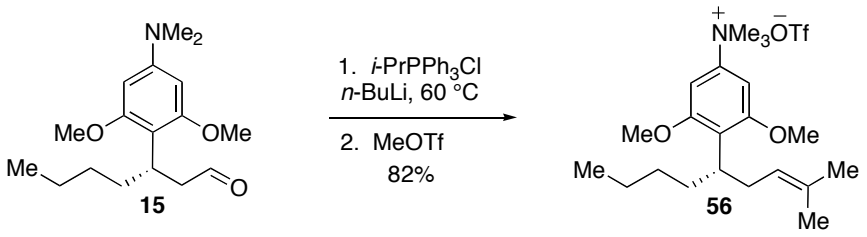


Figure 16. Possible directing of the nickel by an olefin on alkyl chain.

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.**



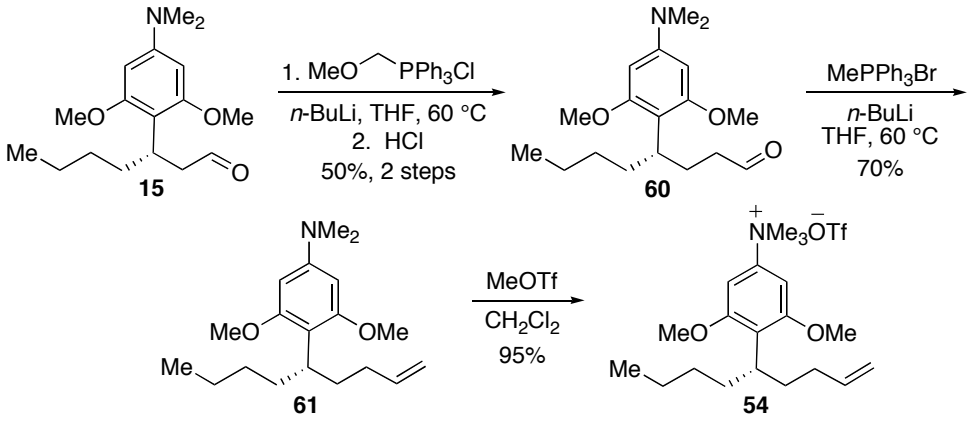
(20)



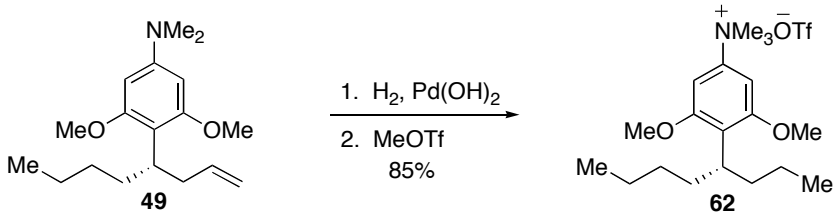
(21)

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.



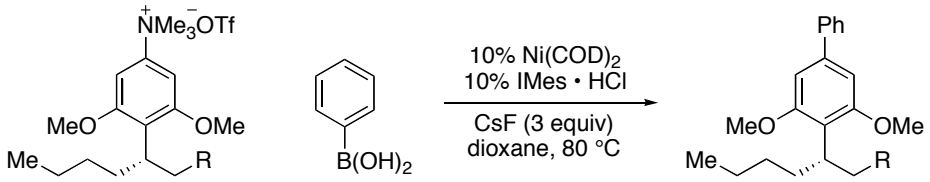
Finally, a substrate lacking unsaturation was prepared to test the chelation hypothesis. This trimethylanilinium salt **62** was synthesized from aniline **49** by hydrogenation of the terminal olefin and quaternization with methyl trifluoromethanesulfonate.



(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).

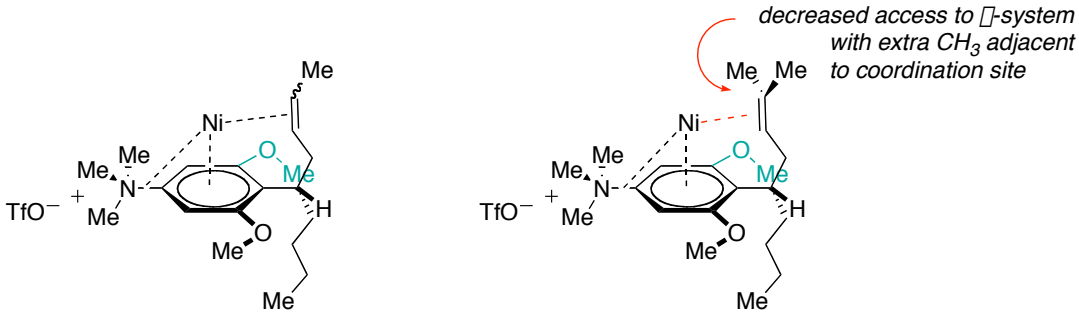


Figure 17. Decreased directing capability with a more substituted olefin.

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.

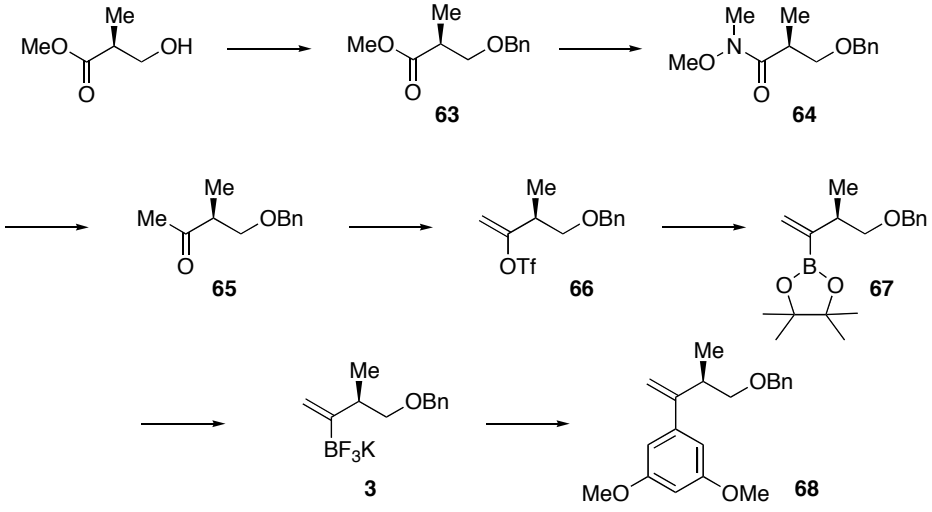
^1H and ^{13}C NMR spectra were recorded on a Mercury 300 Spectrometer (300 MHz and 75 MHz) as noted, and are internally referenced to residual protio solvent signals ($CDCl_3$ = 7.26 ppm, C_6D_6 = 7.16 ppm, D_6-acetone = 2.05 ppm). Data for ^1H NMR are reported as follows: chemical shift (ppm), multiplicity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

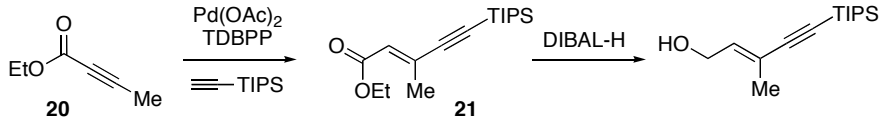
aqueous layer was separated and extrated with benzene (3 x mL). The benzene layers were dried with sodium sulfate and concentrated in vacuo. Flash chromatography (5% ethyl acetate/hexanes) provided the title compound as a clear oil (2.76 g, 74%yield). IR (film) 2977, 2931, 2861, 1612, 1372, 1309, 1145, 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,

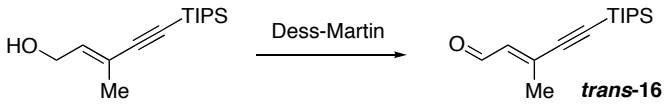
9.0 Hz, C**H**HOBn), 3.32 (dd, 1H, *J* = 7.2, 9.0 Hz, CH**H**OBn), 2.97 (ddq, 1H, *J* = 5.4, 6.9, 9.0 Hz, C**H**CH_3); 1.20 (d, 1H, *J* = 6.9 Hz, CHC**H**$_3$). ^{13}C NMR (75 MHz, $CDCl_3$). 160.5, 151.7, 144.8, 138.6, 128.3, 127.5, 127.4, 112.4, 105.0, 99.2, 74.7, 73.0, 55.3, 38.6, 17.4. HRMS (FAB+) 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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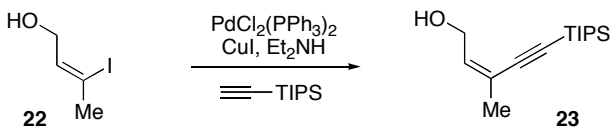
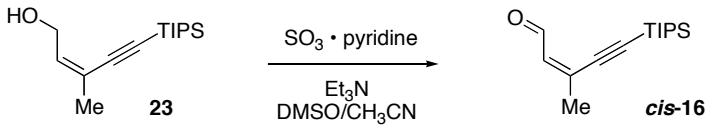
[33] (a) Roush, W. R.; Brown, B. *J. Am. Chem. Soc.* **1993**, *115*, 2268. (b) Waser, J.; Gonzalez-Gomez, J. C.; Nambu, H.; Huber, P.; Carreira, E. M. *Org. Lett.* **2005**, *7*, 4249.

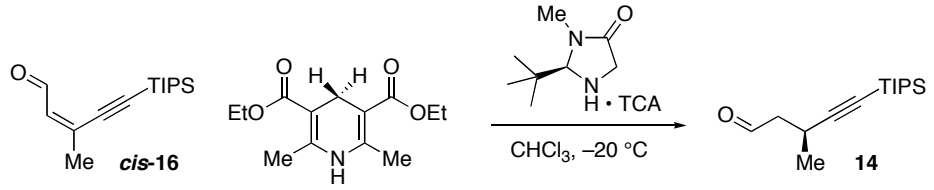
[34] Barluenga, J.; Mateos, C.; Aznar, F.; Valdes, C. *J. Org. Chem.* **2004**, *69*, 7114.



(*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.

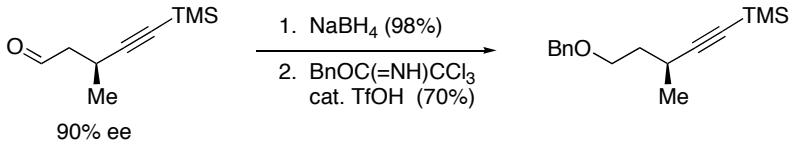


(*Z*)-3-Methyl-5-(triisopropylsilyl)pent-2-en-4-ynal (*cis*-16). Allylic alcohol **23** (7.6 g, 30.1 mmol) was dissolved in 133 mL DMSO and 167 mL dichloromethane at 0 °C. Triethylamine (8.38 mL, 60.3 mmol) was added followed by SO_3-pyridine (9.59 g, 60.3 mmol). The reaction mixture was stirred at room 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

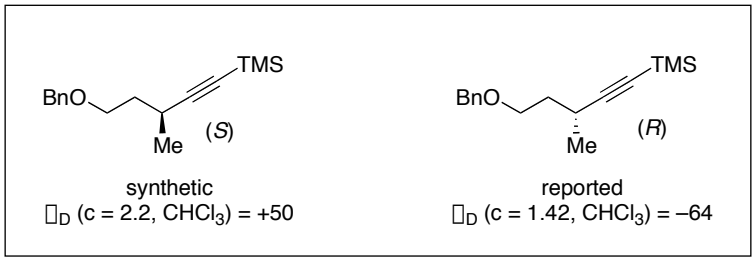
Proof of enantioselectivity by comparison to a literature compound:

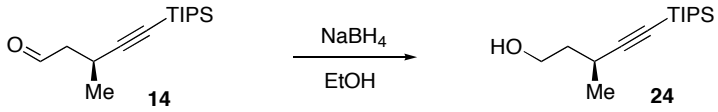


The trimethylsilyl version of the chiral aldehyde was prepared in the same manner as described for the triisopropylsilyl substrate **14**. The enantioselectivity was assessed on the aldehyde by gas chromatography on a chiral -TA column (50 °C isotherm, 34.50 min retention for (*R)*, 35.37 min retention 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.

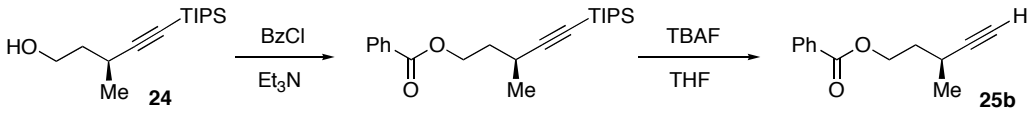




(*S*)-3-Methyl-5-(triisopropylsilyl)pent-4-yn-1-ol (24). Aldehyde **14** (1 g, 3.96 mmol) was taken up in 8 mL ethanol at room temperature. Sodium borohydride (377 mg, 9.91 mmol) was added. The reaction was completed after 15 minutes. Saturated $NaHCO_3$ was added to quench the reaction. After the boron 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

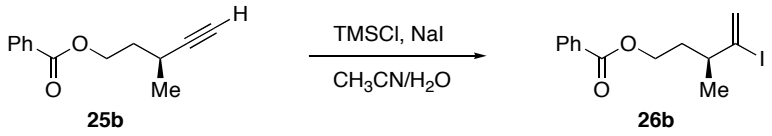
*For the benzoyl-protected BF_3K salt **12b**:*



(*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.

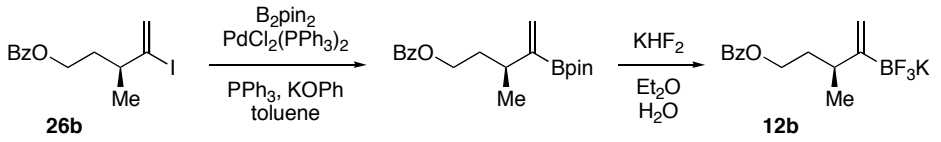
The crude residue (181 mg) was diluted in 14.4 mL THF at room temperature. TBAF (0.70 mL, 0.70 mmol, 1M solution in THF) was added. After 20 minutes, the reaction was complete by TLC analysis. 10 mL of saturated ammonium chloride was added and the biphasic mixture was separated. The aqueous layer was 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

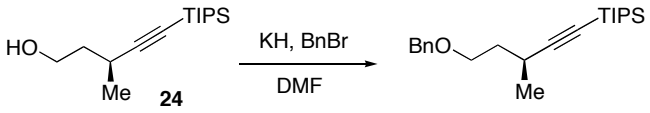


Potassium (*S*)-4-trifluoroboryl)-3-methylpent-4-enyl benzoate (12b). Vinyl iodide **26b** (128 mg, 0.388 mmol) in 2.3 mL toluene was added to a flask containing bispinacolatodiboron (108 mg, 0.427 mmol), $PdCl_2(PPh_3)_2$ (8.2 mg, 0.01166 mmol), triphenylphosphine (6.1 mg, 0.233 mmol), and potassium 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* =

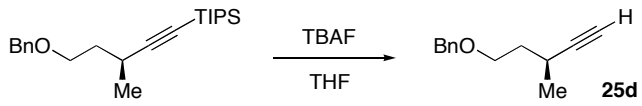
5.1 Hz, C=C**H**H), 4.92 (broad s, 1H, C=CH**H**), 4.20-4.36 (m, 2H, BzOC**H**$_2$), 2.41 (m, 1H, C**H**CH$_3$); 1.67-1.78 (m, 2H, CHC**H**$_2$), 1.09 (d, 3H, *J* = 6.9 Hz, CHC**H**$_3$). ^{13}C NMR (75 MHz, $(CD_3)_2CO$) d 166.8, 133.5, 131.8, 130.0, 129.2, 113.8, 65.6, 38.6, 35.9, 21.9. ^{19}F NMR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

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

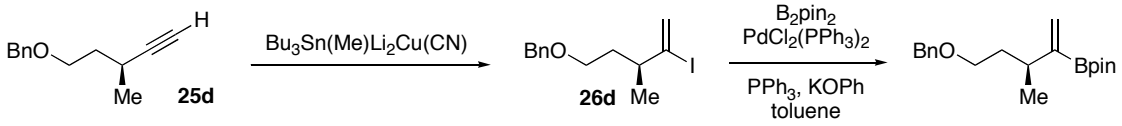


(*S*)-(5-(Benzyloxy)-3-methylpent-1-ynyl)triisopropylsilane. Sodium hydride (293 mg, 7.32 mmol, 60% in mineral oil) was washed three times with excess hexanes to remove oil prior to use. To sodium hydride at 0 °C was added alcohol **24** (0.93 g, 3.66 mmol) in 7.3 mL DMF (0.5 M) followed by benzyl bromide (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.



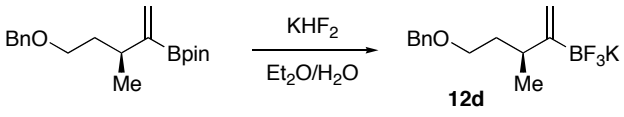
(*S*)-2-(5-(Benzyloxy)-3-methylpent-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. All glassware used in this reaction was flame-dried under vacuum. To a –20 °C solution of hexabutylditin (0.363 mL, 0.725 mmol) in 1.38 mL THF was added *n*-BuLi (0.310 mL, 0.725 mmol, 2.34 M in hexanes) via syringe. 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.

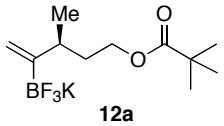


12d

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

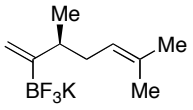
stirred at room temperature for 30 minutes. The water and ether layers were removed in vacuo and placed under high vacuum for 12 h. 20 mL reagent acetone was added to dissolve the desired potassium trifluroborate salt and not the excess potassium salts. These potassium salts were filtered away and the 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:



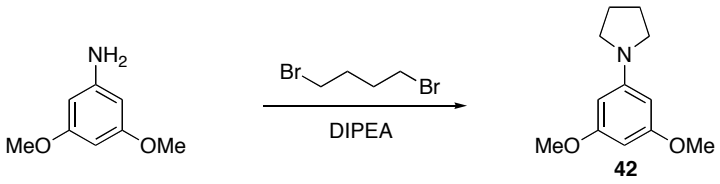
12a

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.

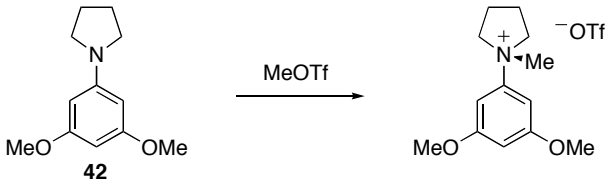


12f

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.

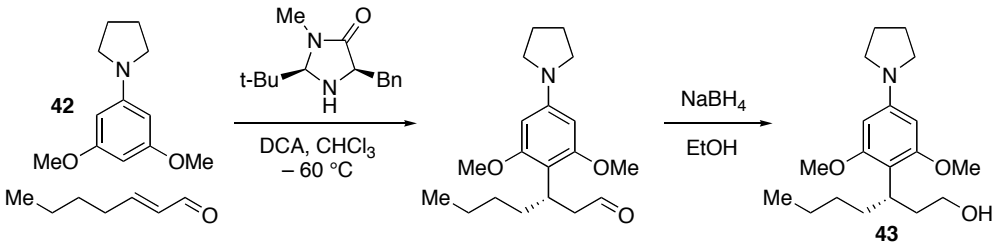


1-(3,5-Dimethoxyphenyl)pyrrolidine (42). 3,5-Dimethoxyaniline (2.3 g, 15.0 mmol) was taken up in 30 mL toluene (0.5 M). Diisopropylethylamine (5.75 mL, 33 mL) and 1,4-dibromobutane (2.0 mL, 16.5 mmol) were added and this reaction was refluxed to 85 °C for 16 h. The reaction was cooled to ambient temperature 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.



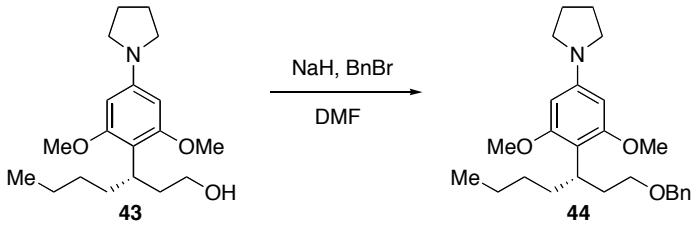
1-(3,5-Dimethoxyphenyl)-1-methylpyrrolidinium trifluoromethanesulfonate. Phenyl pyrollidine **42** (500 mg, 2.41 mmol) was dissolved in 4.8 mL dichloromethane (0.5 M).

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.



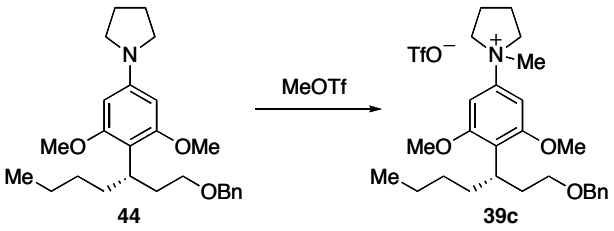
(*S*)-3-(2,6-Dimethoxy-4-(pyrrolidin-1-yl)phenyl)heptan-1-ol (43). 3,5-Dimethoxy-phenyl-*N*-phenylpyrrolidine **42** (500 mg, 2. 41 mmol) was dissolved in 4.8 mL chloroform (0.5M). (2*R*,5*R*)-2-*tert*-butyl-5-benzylimidazolidinone (59.4 mg, 0.241 mmol) and dichloroacetic acid (18 mL, 0.241 mmol) was 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.

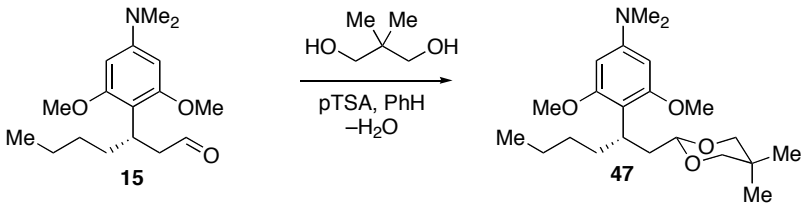
Benzyl bromide (0.3 mL, 2.55 mmol) was added via syringe. After 3 h, the reaction was quenched with water and stirred until all salts were dissolved in the water layer. The biphasic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 15 mL). The organic layers were dried with 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

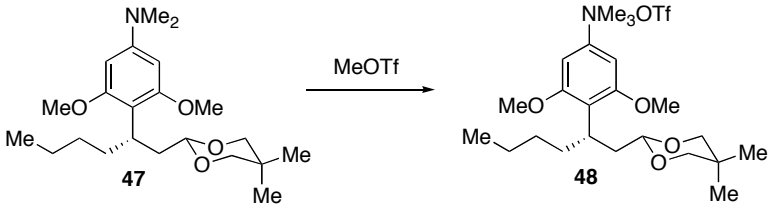
(*S*)-1-(4-(1-(Benzyloxy)heptan-3-yl)-3,5-dimethoxyphenyl)pyrrolidine *N*-methyl trifluoromethanesulfonate (39c). Dimethylaniline **44** (2.05 g, 4.98 mmol) was dissolved in 25 mL dichloromethane. Methyl triflate (0.59 mL, 5. 23 mmol) was added via syringe. The reaction was stirred for 30 minutes. Attempts 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



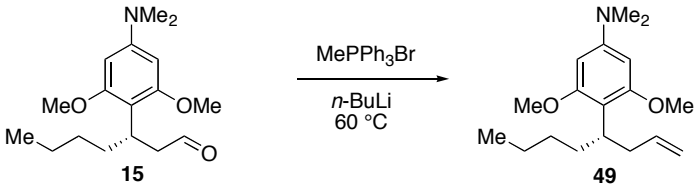
(*S*)-4-(1-(5,5-Dimethyl-1,3-dioxan-2-yl)hexan-2-yl)-3,5-dimethoxy-*N*,*N*-dimethylaniline (47). A solution of aldehyde **15** (293 mg, 1.0 mmol), 2,2-dimethylpropanediol (160 mg, 1.2 mmol), and *p*TSA (30 mg, 0.2 mmol) in benzene (10 mL, 0.1 M) was equipped with a Dean-Stark condenser and heated to 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.



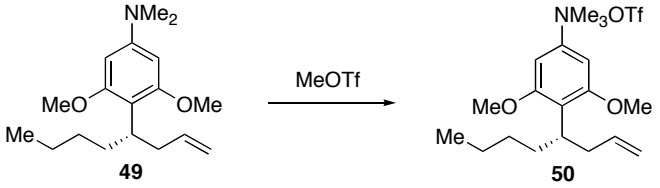
(*S*)-4-(1-(5,5-Dimethyl-1,3-dioxan-2-yl)hexan-2-yl)-3,5-dimethoxy-*N*,*N*,*N*-trimethyl-anilinium trifluoromethanesulfonate (48). Dimethylaniline **47** (238 mg, 0.627 mmol) was dissolved in 2 mL dichloromethane. Methyl trifluoromethanesulfone (75 L, 0.659 mmol) was added via syringe. The reaction was 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,

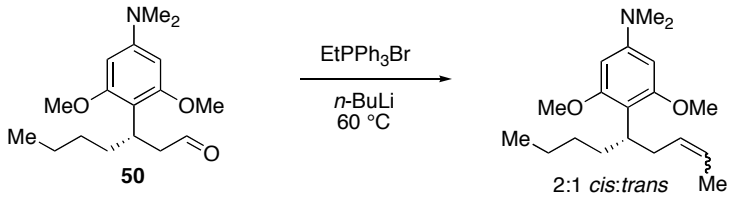
7.2, 13.2 Hz, C**H**=CH_2), 4.86 (m, 2H, CH=C**H**$_2$), 3.78 (s, 6H, OC**H**$_3$), 3.24 (m, 1H, ArC**H**), 2.94 (s, 6H, NC**H**$_3$), 2.52 (m, 1H, C**H**HCH=), 2.39 (m, 1H, CH**H**CH=), 1.75 (m, 1H, CHCH**H**), 1.57 (m, 1H, CHC**H**H), 1.04-1.31 (m, 4H, C**H**$_2$C**H**$_2$$CH_3$), 0.82 (t, 3H, *J* = 7.2 Hz, CH_2C**H**$_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**

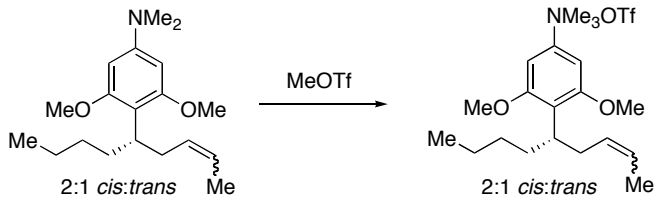
(*S*)-3,5-Dimethoxy-*N*,*N*,*N*-trimethyl-4-(oct-1-en-4-yl)anilinium trifluoromethanesulfonate (50). Dimethylaniline **49** (120 mg, 0.411 mmol) was dissolved in 2 mL dichloromethane. Methyl trifluoromethanesulfone (51 L, 0.452 mmol) was added via syringe. The reaction was stirred for 10 minutes at room 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*).



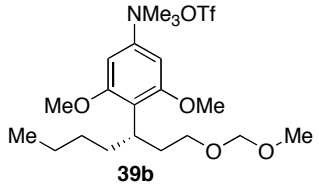
55

(*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.

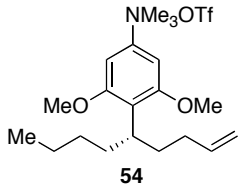
Spectral data for other synthesized trimethylanilinium salts.

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.



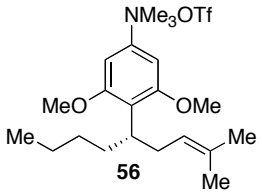
39b

(*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

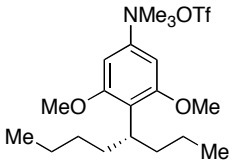
(*S*)-3,5-Dimethoxy-*N*,*N*,*N*-trimethyl-4-(non-1-en-5-yl)anilinium trifluoromethanesulfonate (54). IR (film) 2968, 2922, 2856, 1598, 1468, 1425, 1376, 1259, 1222, 1156, 1031, 923, 739, 637 cm^{-1}. ^1H NMR (300 MHz, $(CD_3)_2CO$) 7.26 (s, 2H, Ar**H**), 5.77 (ddt, 1H, *J* = 6.0, 7.5, 9.6 Hz, C**H**=CH_2), 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,

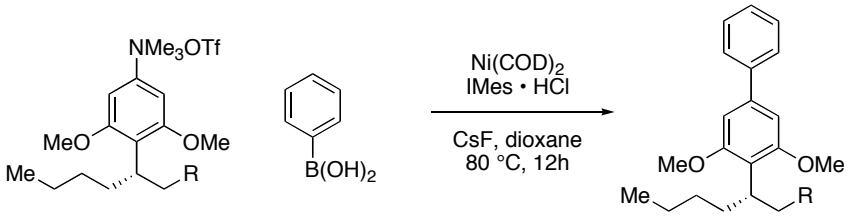
3H, C=C(**Me**)(Me)), 1.49 (s, 3H, C=C(Me)(**Me**)), 0.93-1.32 (m, 4H, C**H**$_2$C**H**$_2$CH$_3$), 0.80 (t, 3H, *J* = 7.2 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (75 MHz, (CD$_3$)$_2$CO). 160.5, 147.3, 132.0, 124.6, 124.1, 97.9, 57.7, 56.8, 36.4, 32.9, 32.5, 31.1, 25.8, 23.4, 17.7, 14.3. ^{19}F NMR (282 MHz, (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



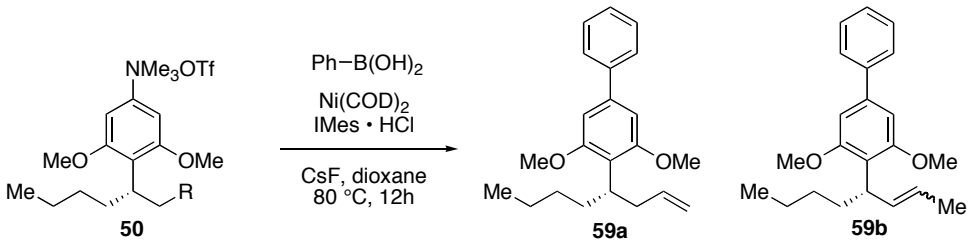
62

(*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$_3$**).