Method Development for the Stereoselective Synthesis of Heterocycles

by

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Dedication

To Doug, Chloe, Bandit and Milo

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List of Abbreviations

Ac.....Acyl
acac.....acetylacetonate
Ar.....aryl
BINAP.....2,2'-bis(diphenylphosphino)-1,1'-biphenyl
BINOL .....1,1'-bi-2-napthol
Bn.....benzyl
Boc.....tert-butyloxycarbonyl
Bu.....butyl
Bz.....benzoyl
ca.....approximately
Cy.....cyclohexyl
dba.....dibenzylideneacetone
Dpe-phos.....bis(2-diphenylphosphinophenyl)ether
dppb.....1,4-bis(diphenylphosphino)butane
dppe.....1,2-bis(diphenylphosphino)ethane
dppf.....1,1'-bis(diphenylphosphino)ferrocene
dr.....diastereomeric ratio
ee .....enantiomeric excess
equiv.....equivalents
ESI.....electrospray ionization
Et .....ethyl
h.....hour(s)
HPLC .....high performance liquid chromatography
iPr.....isopropyl
LAH .....lithium aluminum hydride

LC-MS .....liquid chromatography – mass spectrometry
Ln .....ligand
M .....molarity
Me .....methyl
NMR .....nuclear magnetic resonance
nOe .....nuclear Overhauser effect
nu.....nucleophile
tol .....tolyl
pg.....protecting group
Ph .....phenyl
pr .....propyl
rt .....room temperature
TBS .....tert-butyl-dimethylsilyl
TFA.....trifluoroacetic acid
THF.....tetrahedrofuran
TMS.....trimethylsilyl
Xantphos 9,9-dimethyl-bis-4,5-diphenylphosphinoxantphene

Abstract

Efforts made to improve the scope of palladium-catalyzed carboetherification and carboamination reactions are illustrated herein, and strategies for overcoming various limitations to the method are discussed. As described in this thesis, the synthesis of bis, fused and poly-substituted tetrahydrofurans, 1,3-oxazolidines, benzopyrans and benzoxepines was achieved through the palladium-catalyzing coupling of γ-hydroxy alkenes, O-vinyl-1, 2-amino alcohols, homoallylphenols and 2-(pent-4-en-1-yl)phenols with aryl and alkenyl halides, respectively. The synthesis of the aforementioned heterocycles represents a significant advancement in the methodology toward the eventual application of natural product synthesis, especially the annonaceous acetogenins.

In Chapter 2, a novel strategy for the synthesis of bis and fused tetrahydrofurans is described. Sequential Pd-catalyzed carboetherification reactions were performed to yield bis and fused THFs, which enabled access into biologically active compounds such as the annonaceous acetogenins. As described in Chapter 3, the diastereoselectivity of Pd-catalyzed carboetherification reactions of substrates bearing internal alkenes was improved by employing S-Phos, an electron-rich, bulky monodentate biaryl ligand, which promoted reductive elimination and suppressed β-hydride elimination. As a result, the synthesis of poly-substituted tetrahydrofurans was achieved in excellent diastereoselectivity, and biologically active compounds possessing this motif, such as Simplakidine A, a cytotoxic marine natural product, may be produced using the proposed methodology. In Chapter 4, the synthesis of 1,3-oxazolidines using a catalyst system based on S-Phos is described. The use of S-Phos promoted reductive elimination, which was disfavored due to the presence of electron withdrawing substituents on the substrate. Through the

work described in this thesis, 1,3-oxazolidines, an important structural motif in organic synthesis, can now be obtained using Pd-catalyzed carboamination reactions. A catalyst system composed of Pd2(dba)3/S-Phos also proved to be useful for the production of benzopyrans, which are common in antioxidants and were previously inaccessible through our methodology. As outlined in Chapter 5, the scope of the methodology was effectively expanded to include homoallylphenols, highlighting the ability of the catalyst to overcome entropic effects and the low nucleophilicity of phenols. Heterocycles containing 6-membered rings were produced in a convergent manner, allowing access into motifs common in biologically active materials. In Chapter 6, the methodology was further extended towards benzoxepines, enabling the synthesis of unique, biologically relevant materials.

Chapter 1: Background and Limitations of Palladium-Catalyzed Carboamination and Carboetherification Reactions

1.1 Background and Significance

Saturated heterocycles are commonplace structural units in natural products and biologically active compounds. Significantly, natural products containing tetrahydrofurans and benzopyrans show unique activity, especially the annonaceous acetogenins[1] and vitamin E derivatives[2], which possess antitumor properties (Figure 1-1). Benzoxepines and 1,3-oxazolidines also show wide-ranging biological activities, and the latter is used as a chiral auxiliary to effect stereoselective syntheses.[3, 4] Due to the importance of the aforementioned saturated heterocycles in medicinal and synthetic chemistry, myriad methods have been developed for their synthesis. Nevertheless, convergent synthetic methods that effect carbon-heteroatom and carbon-carbon bond formation and are amenable to the rapid production of analog libraries are relatively rare.[5] Thus, the research outlined in the present thesis is focused on the development of methodology for the stereoselective synthesis of saturated heterocycles, for the ultimate goal of the synthesis of biologically relevant molecules.

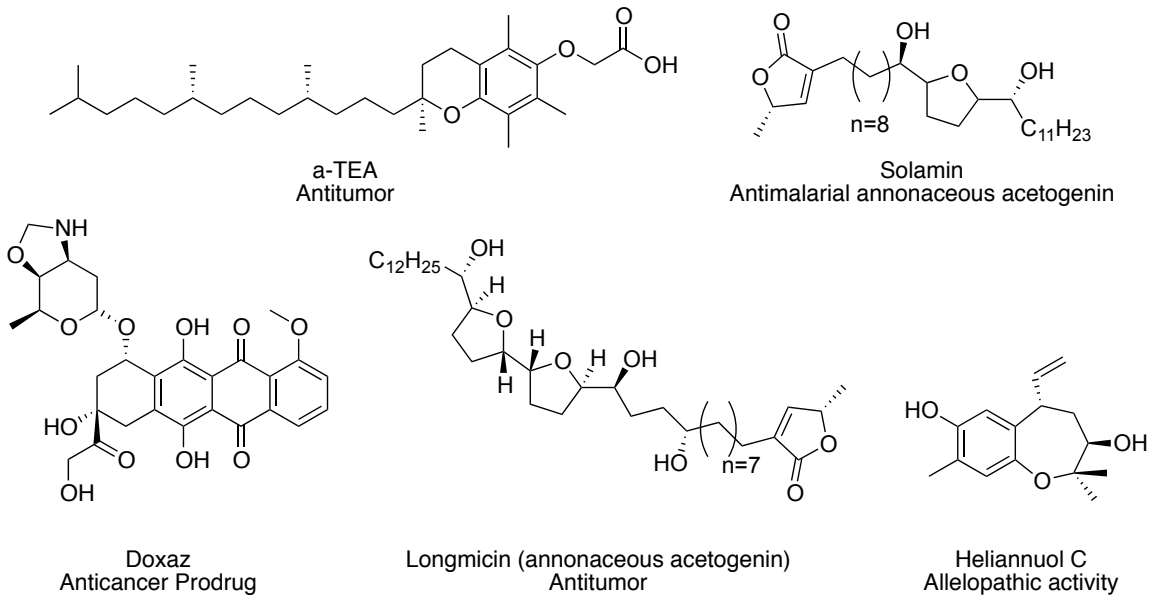
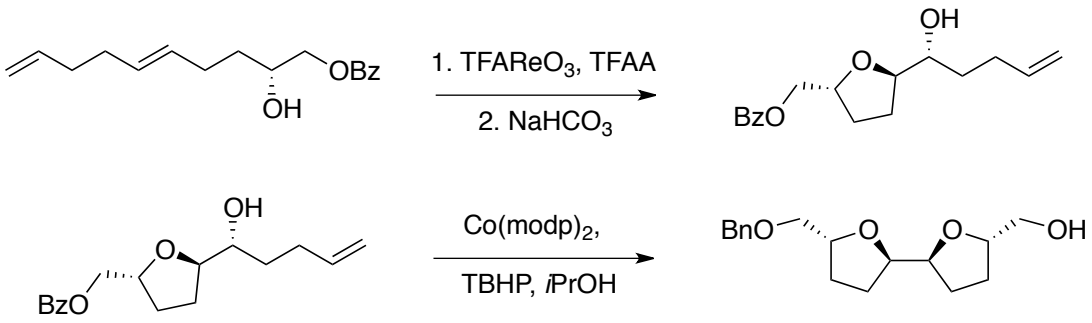


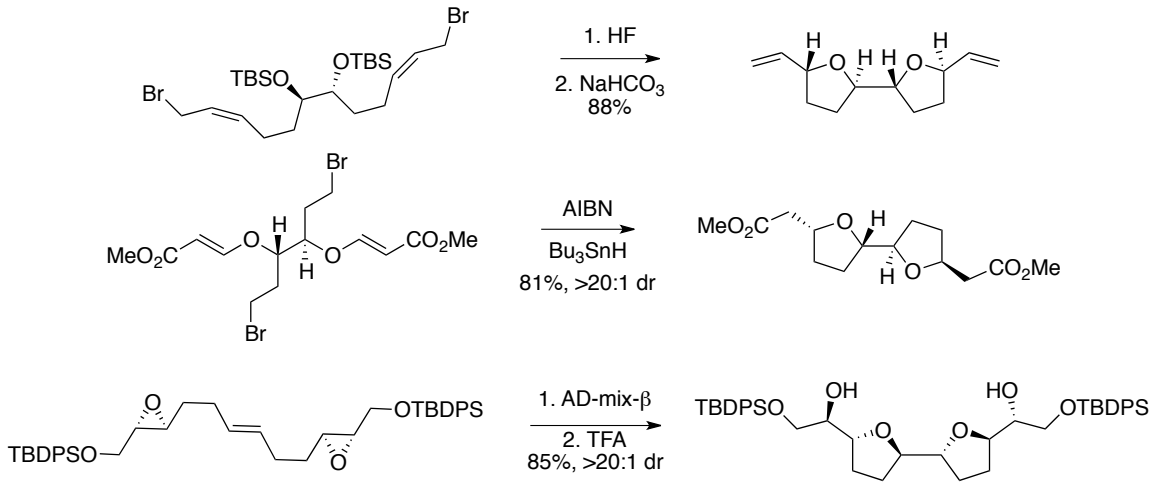
Figure 1.1. Examples of Heterocyclic Natural Products

As previously mentioned, the annonaceous acetogenins are diverse natural products of marine origin that contain a mono-, bis-, or tris-tetrahydrofuran core with flanking hydroxyl substituents at the 1' position.[6] Previous studies have shown that this motif is essential for biological activity, and many methods have been developed to produce both bis- and 2,1'-substituted tetrahydrofurans.[7] For instance, rhenium- and cobalt-catalyzed reactions have been used to transform γ-hydroxy alkenes into 1'-hydroxyl substituted tetrahydrofurans, as shown in Scheme 1-1.[8] Although these methods produce the desired motif in excellent yield and diastereoselectivity, they are not amenable for analog synthesis and the production of heterocyclic libraries, which are useful for studying structure-activity relationships. Moreover, these methods lack the ability to forge carbon-carbons, which is fundamental for creating structural complexity from simple starting materials.

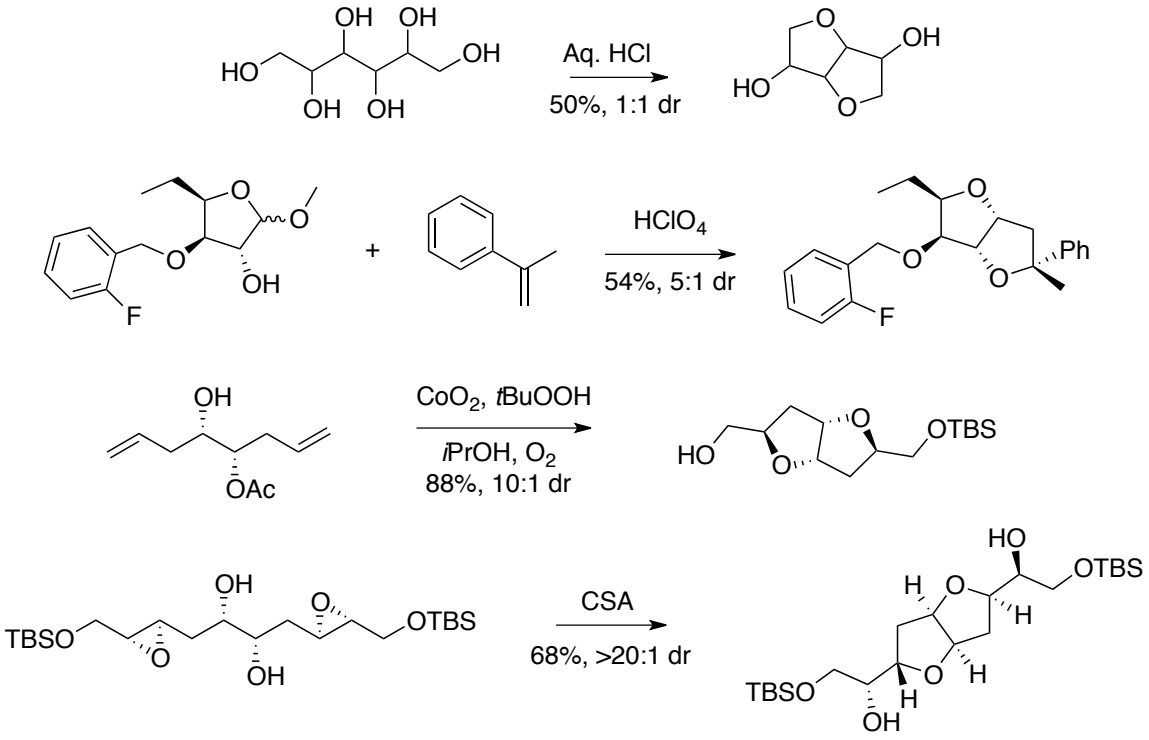


Scheme 1.1. Oxidative Cyclization Methods for the Synthesis of Bis-Tetrahydrofurans

Bis tetrahydrofurans are also synthesized via sequential ring-closing reactions (Scheme 1-2). Although ring closure is effected with these methods, carbon-carbon bond formation is not achieved, and additional steps must be conducted to install alkyl groups, which increases the number of steps of the overall synthesis. Methods typically used in tandem ring forming approaches include S_N2 reactions, radical cyclizations, and epoxide-opening reactions.[9, 10, 11] Similar strategies have been evoked to produce fused tetrahydrofurans, which are structurally interesting compounds displayed in diverse natural products. Common methods adopted for the synthesis of fused tetrahydrofurans are shown in Scheme 1-3, which highlight various reactions such as S_N1 and S_N2 reactions.[12] Similar to bis-THFs, fused tetrahydrofurans can also be synthesized via metal-catalyzed oxidative cyclization reactions and ring-opening of epoxides.[13]



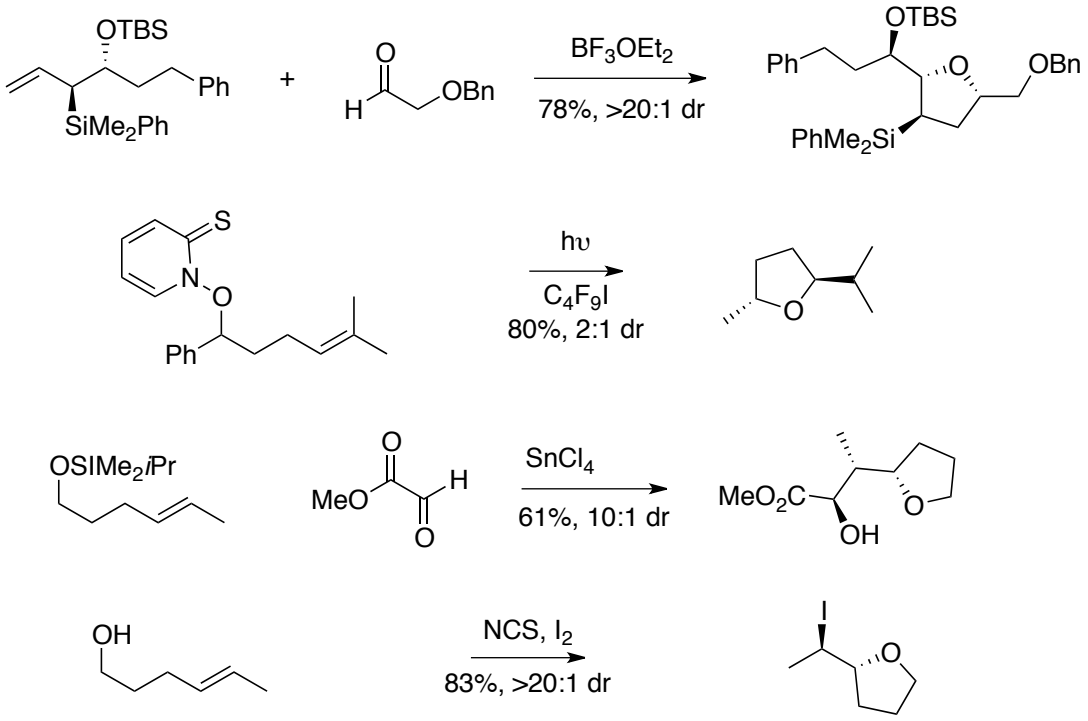
Scheme 1.2. Methods for the Synthesis of Bis-Tetrahydrofurans



Scheme 1.3. Methods for the Synthesis of Fused-Tetrahydrofurans

In contrast, substituents at the 1' position are often installed prior to THF formation, as illustrated in Scheme 1-4. Methods previously employed for the production of 2,1'-polysubstituted tetrahydrofurans include [3+2] annulation, radical cyclizations, Prins cyclizations and haloetherification. [14, 15, 16] Despite the application of a wide variety of different procedures for the synthesis of 2,1'-

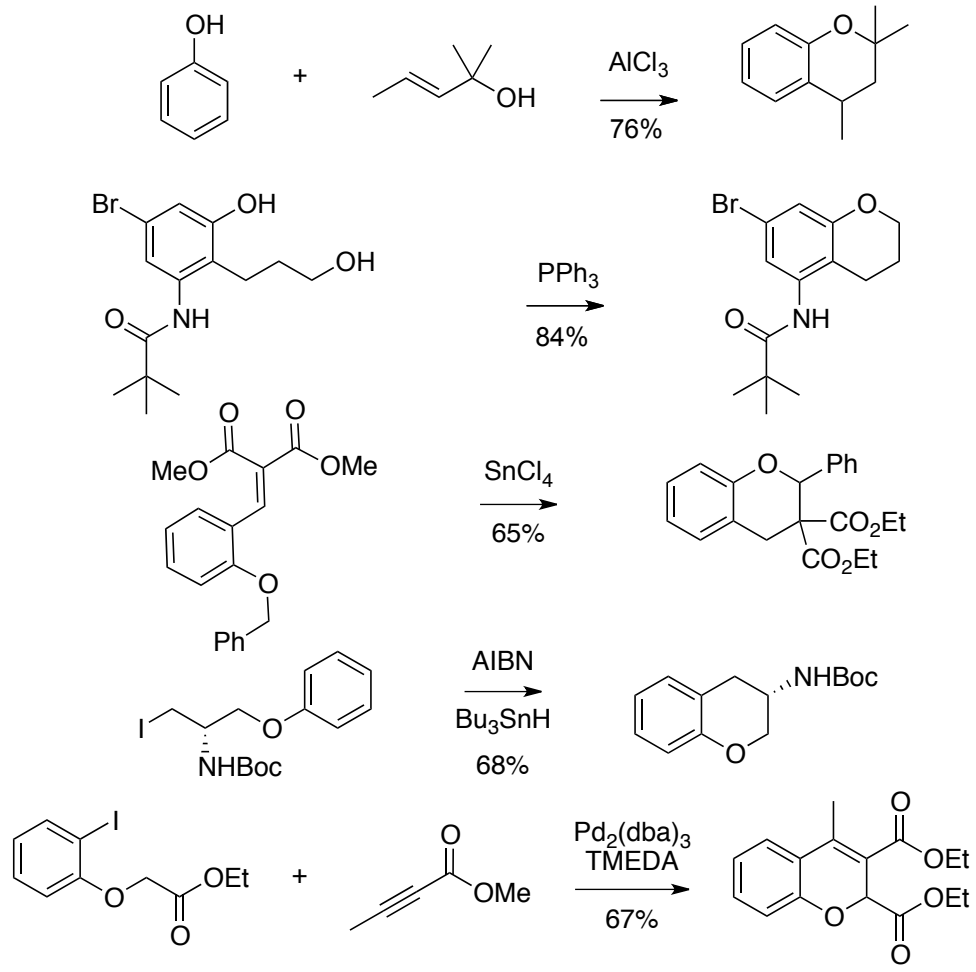
polysubstituted tetrahydrofurans, high diastereoselectivity is often difficult to achieve, and additional manipulations are often required to obtain the desired substitution pattern or to obtain the required functional group at the 1' position. Thus, a method that can produce 2,1'-substituted tetrahydrofurans in high diastereoselectivity is desirable.



Scheme 1.4. Methods Employed to Synthesize 2,1'-Polysubstituted Tetrahydrofurans

Benzopyrans and benzoxepines are 6- and 7-membered ring oxygenated heterocycles that display unique biological properties. For instance, benzopyrans are common antioxidants, and benzoxepines have shown allelopathic activity, as observed in heliannuol C.[17, 18] Although the synthesis of benzopyrans can be readily achieved via Freidel crafts or S_N2 reactions, the reaction conditions are often harsh and sensitive functional groups are not well-tolerated (Scheme 1-5). Alternative approaches for the synthesis of benzopyrans include C-H activation, radical cyclization and Pd-catalyzed reactions.[19, 20, 21] Nevertheless, these methods also suffer significant limitations, including the use of toxic reagents and

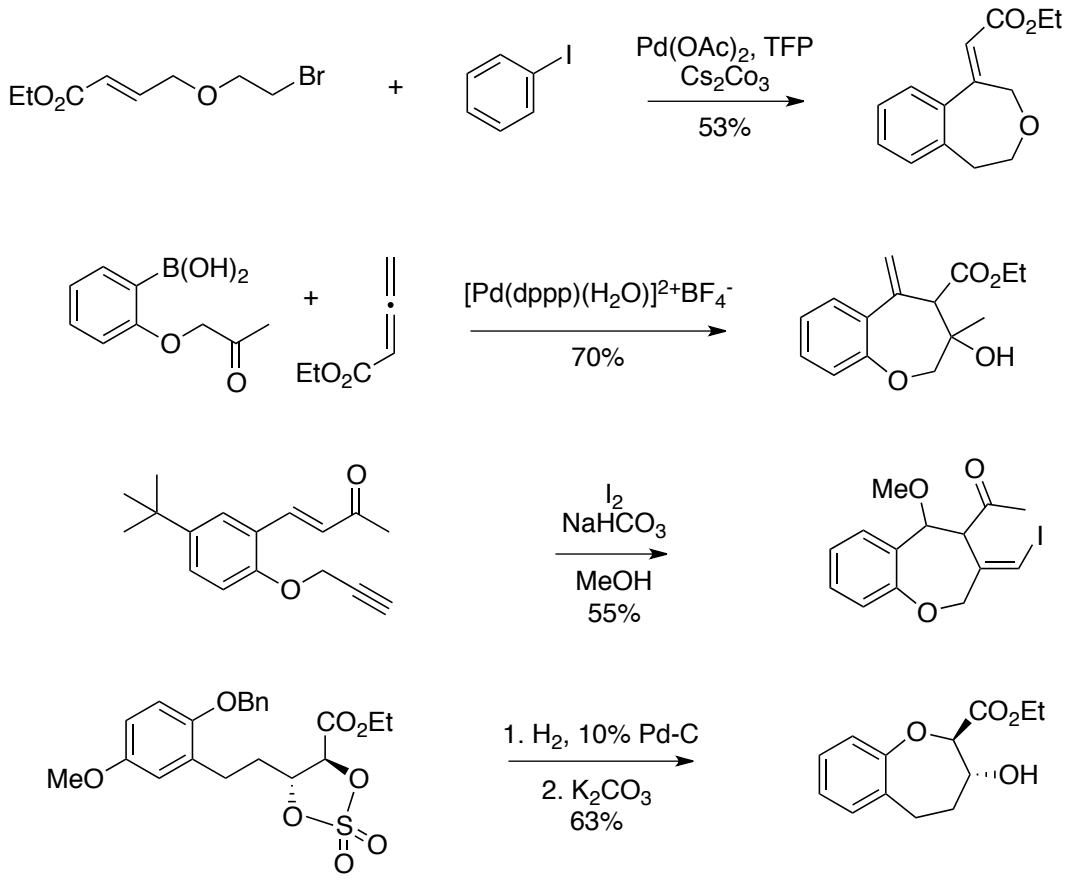
poor substrate scope. As evidenced, novel methodologies must be developed in order to access benzopyrans in a diastereoselective manner.



Scheme 1.5. Representative Methods for the Synthesis of Benzopyrans

On the other hand, due to the difficulty in overcoming entropic effects for the generation of 7-membered rings, relatively few methods have been developed for the synthesis of benzoxepines. Nevertheless, several Pd-catalyzed methods have been proposed, including sequential alkylation-alkenylation reactions and [5 + 2] annulation reactions (Scheme 1-6).[22, 23] More traditional approaches such as Grubb's catalysis, S_N2 reactions and iodination have also been employed; however, the yields of these reactions are often low or substrate-dependent.[24, 25, 26] As such, additional methodologies that can be used to synthesize

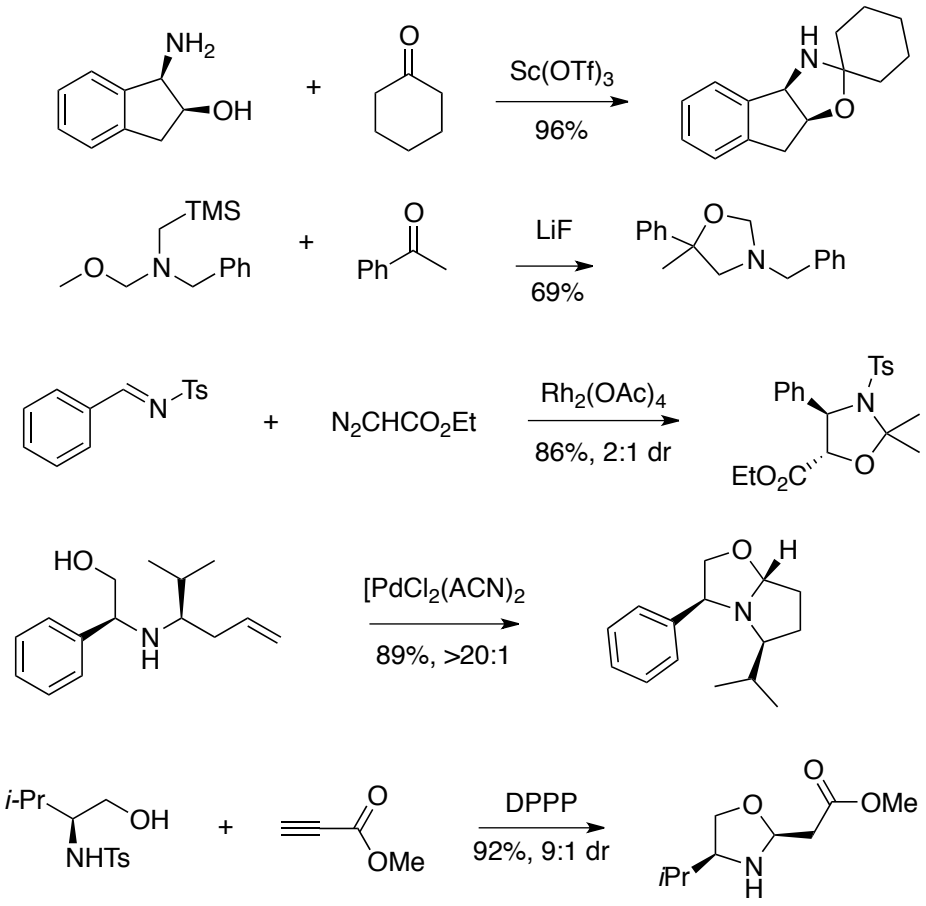
benzoxepines in an efficient and convergent manner would be useful tools for organic and medicinal chemists.



Scheme 1.6. Methods for the Synthesis of Benzoxepines

Lastly, 1,3-oxazolidines are often employed as chiral auxiliaries in organic reactions and display unique biological activity in their own right. Therefore, myriad methods have been employed to synthesize diastereomerically pure 1,3-oxazolidines, especially condensation reactions between 1,2 amino alcohols and ketones and cycloaddition reactions (Scheme 1-7).[27, 28] However, stereoselectivity is often difficult to achieve, especially when the formation of 2,5-*cis*-1,3-oxazolidines is desired. To this end, various Pd-catalyzed methods and tandem reactions based on Michael additions have been developed.[29, 30] Although the diastereoselectivity of these methods are high, carbon-carbon bond formation cannot be effected. Thus, a method that can achieve both high

diastereoselectivity and concomitant carbon-heteroatom and carbon-carbon bond formation is required to produce libraries of 1,3-oxazolidine chiral auxiliaries for stereoselective syntheses.



Scheme 1.7. Representative Methods for the Synthesis of 1,3-Oxazolidines

1.2 Introduction to Pd-Catalyzed Carboamination and Carboetherification Reactions

To address the lack of convergent synthetic methods for the production of heterocycles such as those listed above, research in the Wolfe lab is focused on the development of methodology for the synthesis of various types of saturated heterocycles.[31] In particular, palladium-catalyzed coupling reactions of γ-hydroxy alkenes and γ-amino alkenes with aryl and alkenyl halides have been developed to construct complex heterocycles in a stereoselective manner (Figure 1-2). For

instance, tetrahydrofurans, pyrrolidines, isoxazolidines,[32] piperazines,[33] morpholines,[34] imidazoldin-2-ones[35] and pyrrazolidines[36] have been synthesized using this methodology, which can effect carbon-heteroatom and carbon-carbon bond formation in a single step.

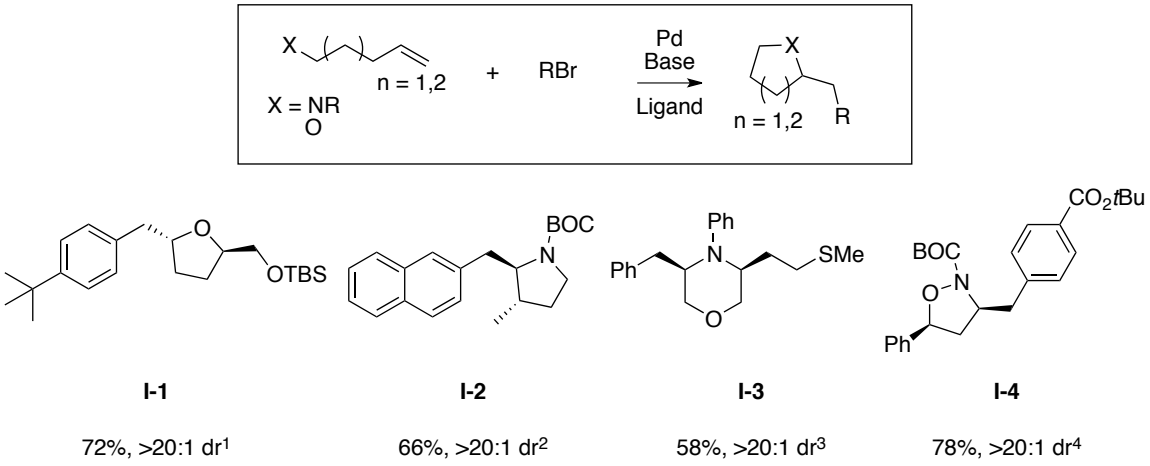
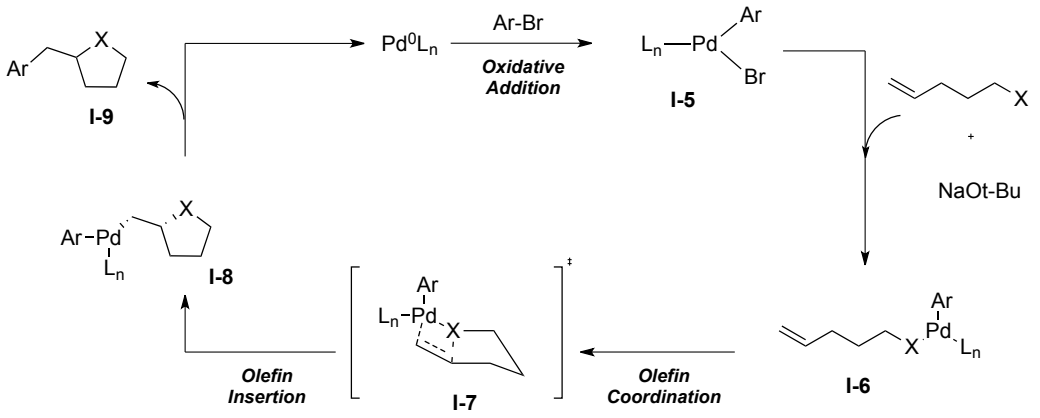


Figure 1.2. Palladium-Catalyzed Carboetherification and Carboamination Reactions for the Synthesis of Various Heterocycles

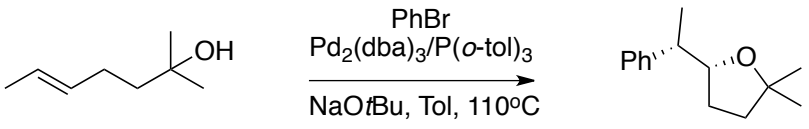
The mechanism of palladium-catalyzed carboetherification reactions has been studied in detail and is shown in Scheme 1-8.[37] The reaction begins with a Pd (0) species, which undergoes oxidative addition into the aryl or alkenyl halide bond to afford complex **I-5**. Coordination and deprotonation of the heteroatom to the substrate leads to **I-6**, which can coordinate the pendant alkene to produce **I-7**.[38] Subsequently, the coordinated alkene inserts into the Pd-heteroatom bond, resulting in the formation of **I-8**. Lastly, reductive elimination of Pd (II) affords a Pd (0) species, along with the final heterocyclic product (**I-9**).



Scheme 1.8. Proposed Mechanism of Palladium-Catalyzed Carboetherification and Carboamination Reactions

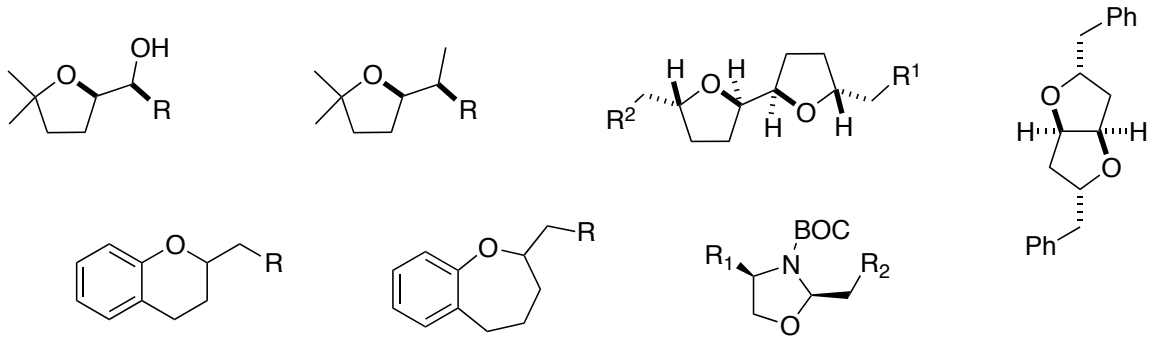
1.3 Limitations to the Method

Although Pd-catalyzed carboetherification and carboamination reactions have been shown to be powerful tools for the rapid synthesis of heterocyclic libraries, several limitations remained to be addressed. For instance, in carboetherification reactions of substrates bearing internal alkenes, the desired product was formed as a mixture of diastereomers (Scheme 1-9) due to competing beta-hydride elimination and reinsertion processes. These processes reduced the diastereoselectivity of the reaction and prevented the use of the method for the synthesis of the annonaceous acetogenins, which often possess functional groups at the 1' position.[39] This diverse family of natural products also often contains a bis-tetrahydrofuran core, which our group had not previously demonstrated was accessible via palladium-catalyzed carboetherification reactions.



Scheme 1.9. Pd-Catalyzed Carboetherification Reactions of Internal Alkene Substrates

Previously, large-ring heterocycles such as benzopyrans and benzoxepines could not be synthesized using our methodology due to entropic effects and the poor nucleophilicity of phenol. In addition, 1,3-oxazolidines were also inaccessible due to the presence of electron-withdrawing substituents, which suppressed reductive elimination, and the electron-rich nature of the cyclizing alkene. Scheme 1-10 illustrates several biologically relevant motifs that could not be synthesized due to limitations in the methodology that were overcome through the work described in this thesis.



Scheme 1.10. Heterocycles not Previously Accessible through Pd-Catalyzed Carboetherification and Carboamination Reactions

Considerable extensions have been made toward the eventual application of our methodology to the synthesis of biologically active compounds such as the annonaceous acetogenins, as outlined in this thesis. For instance, as described in Chapter 2, palladium-catalyzed carboetherification reactions have been extended to the synthesis of bis and fused tetrahydrofurans, which represents a significant advancement in the scope of our method. Most importantly, novel reaction conditions have been developed to synthesize diastereomerically pure 1'-substituted tetrahydrofurans from substrates bearing an internal alkene by effectively suppressing competing beta-hydride elimination and reinsertion processes, which lead to the production of the minor diastereomer. The optimized conditions and corresponding mechanistic implications are described in detail in Chapter 3, which outlines the use of a catalyst system containing S-phos, an electron-rich biaryl ligand known to enhance reductive elimination. Due

to the achievements described in Chapter 3, natural products containing polysubstituted tetrahydrofurans such as Simplakidine A can potentially be synthesized via Pd-catalyzed carboetherification reactions.

In addition to the limitations described above, Pd-catalyzed carboetherification reactions had not been applied to generate 6- or 7-membered rings, and electron-rich alkenes such as enol ethers had not been employed. Nevertheless, these constraints have been overcome using monodentate biaryl ligands. As described in Chapter 4, the synthesis of 1,3-oxazolidines through the palladium-catalyzed carboamination of O-vinyl-1,2-aminoalcohols was achieved using S-phos. This bulky monodentate ligand apparently enhanced reductive elimination, which was slowed due to the electronic effects of the heteroatom adjacent to the pendent alkene. As a result, the stereoselective synthesis of poly-substituted 1,3-oxazolidines can be attained using Pd-catalyzed carbamination reactions, allowing the production of extensive libraries of these heterocycles. Thus, through the work described in Chapter 4 of this thesis, a significant limitation to our methodology was addressed, and a novel method for the synthesis of 1,3-oxazolidines was developed.

As outlined in Chapters 5 and 6, the synthesis of 6- and 7-membered heterocycles was attained by developing reaction conditions based on S-phos and Ru-phos, respectively. The aforementioned ligands overcame the low nucleophilicity of the phenol substrate and entropic effects to form the desired product. Therefore, access into a new arena of natural product synthesis was enabled through the expansion of the substrate scope of Pd-catalyzed carboetherification reactions, which can effect both carbon-carbon and carbon-heteroatom bond formation in a single step, addressing the needs of the synthetic community for convergent and stereoselective methods.

1.4 References

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Chapter 2: Palladium-Catalyzed Carboetherification Reactions for the Synthesis of Bis- and Fused-Tetrahydrofurans

2.1 Introduction

A large number of interesting compounds contain attached-ring or fused-ring tetrahydrofuran scaffolds (Figure 2-1). The 2,6-dioxabicyclo[3.3.0]octane framework (**II-1**) is found in both naturally occurring[1] and synthetic molecules that are relevant to human health (e.g., **II-3**; antitumor activity)[2] and agriculture (e.g., **II-4**; herbicide).[3] Attached-ring tetrahydrofurans (**II-2**) are displayed in a vast number of natural products, including the annonaceous acetogenins,[4] of which asimicin (**II-5**) is a member.

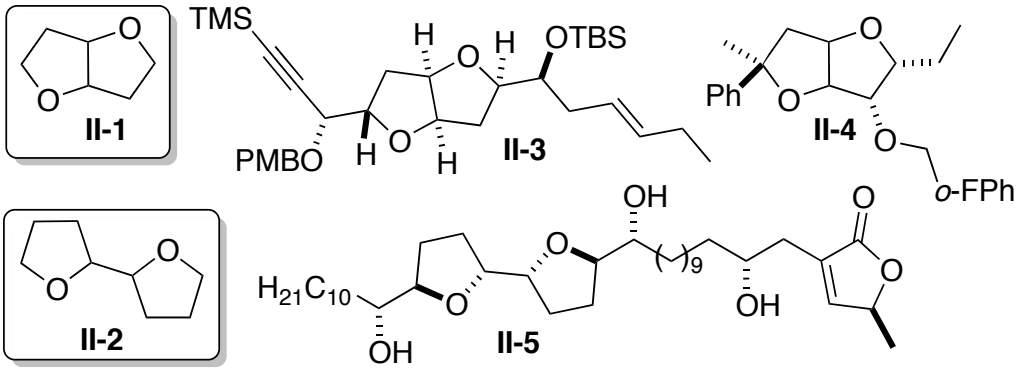
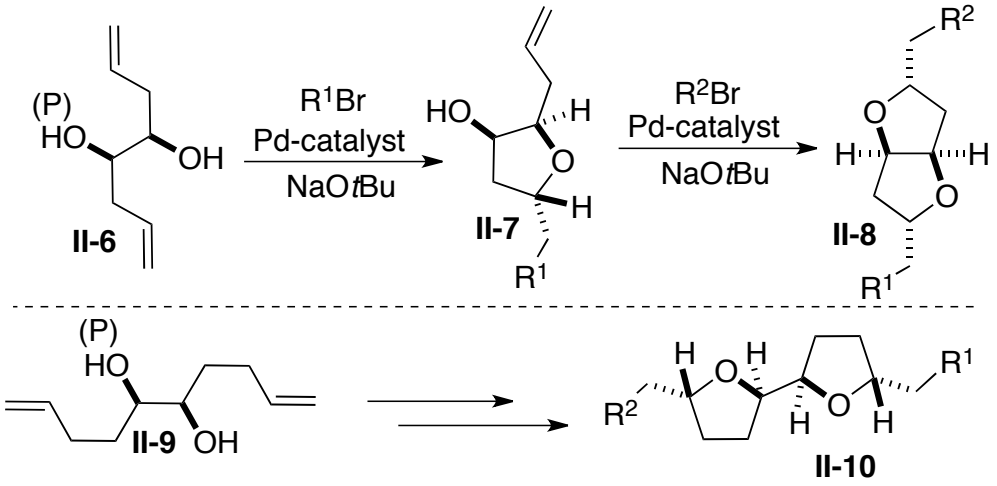


Figure 2.1. Examples of Biologically Active *Bis*-Tetrahydrofurans.

A variety of different approaches have been developed for the construction of these useful compounds.[5] Many of these strategies involve generation of the bis-tetrahydrofuran framework via sequential (or tandem) ring-closing reactions of 1,2-diols bearing pendant functional groups such as alkenes, epoxides, alcohols, or allylic acetates/halides.[6] Although these methods effectively form the heterocyclic ring, they do not allow the simultaneous construction of a C-C bond. Thus, substituents attached to the tetrahydrofuran C-2 position, such as the side

chains present in **II-3**-**II-5**, must be installed in separate steps either prior to or following ring-closure.



Scheme 2.1. Synthetic Strategy

We felt that an alternative approach to the construction of substituted fused-ring tetrahydrofurans with general structure **II-8** could be developed using sequential Pd-catalyzed carboetherification reactions[7,8] of unsaturated 1,2-diols such as **II-6**. As shown in Scheme 2-1, treatment of **II-6** with an aryl or alkenyl halide in the presence of NaO*t*Bu and a palladium catalyst should provide **II-7**, which could be converted to **II-8** in a second catalytic transformation. This strategy could also be applied to the synthesis of attached-ring tetrahydrofurans (e.g., **II-9** to **II-10**) by simply extending the tether between the alcohols and the alkenes by one methylene unit. Importantly, each carboetherification reaction would generate both a C-O bond (to form the heterocylic ring) and a C-C bond, thus providing a more concise approach to substituted bis-tetrahydrofurans compared to currently available methods.

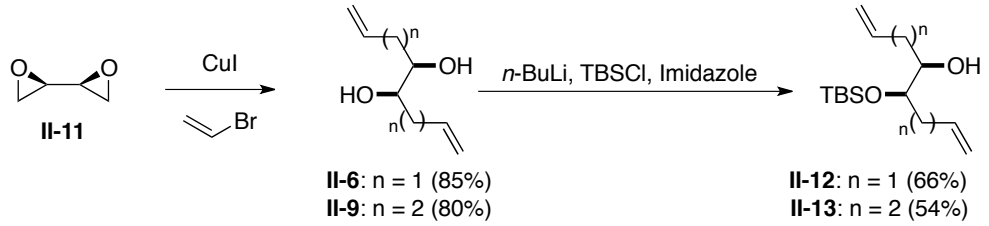


Figure 2.2. Protection of 1,2-diols

2.2 Efforts Toward a One-pot Synthesis

To examine the feasibility of the strategy outlined above, we elected to examine the selective monocyclization of known diols **II-6** and **II-9**[9] which can be generated by Cu-catalyzed addition of vinylmagnesium bromide or allylmagnesium bromide to commercially available butadiene diepoxide. We also prepared mono-TBS-protected[10] derivatives **II-12** and **II-13** (Figure 2-2), as our prior studies indicated that carboetherification reactions of mono-protected 1,2-diols are often more efficient than transformations of the corresponding unprotected diols.

Preliminary attempts to effect selective monocyclization of unprotected diols **II-6** and **II-9** provided unsatisfactory results (Figure 2-3). Treatment of **II-6** with one equivalent of bromobenzene under our standard carboetherification conditions (NaO*t*Bu, cat. $Pd_2(dba)_3$/Dpe-Phos)[11] afforded mixtures of bis-cyclized product **II-14** and unreacted starting material. Treatment of **II-6** with four equivalents of bromobenzene led to complete consumption of starting material and the formation of **II-14** with >20:1 dr, albeit in only 30% yield. Efforts to achieve monocyclization of **II-9** did lead to the formation of desired tetrahydrofuran **II-15**, but yields were low and isomerization of the second alkene was problematic. Use of excess aryl halide in this reaction failed to generate significant amounts of the bis-tetrahydrofuran target, and instead provided an 81% combined yield of **II-15** and inseparable alkene isomers.

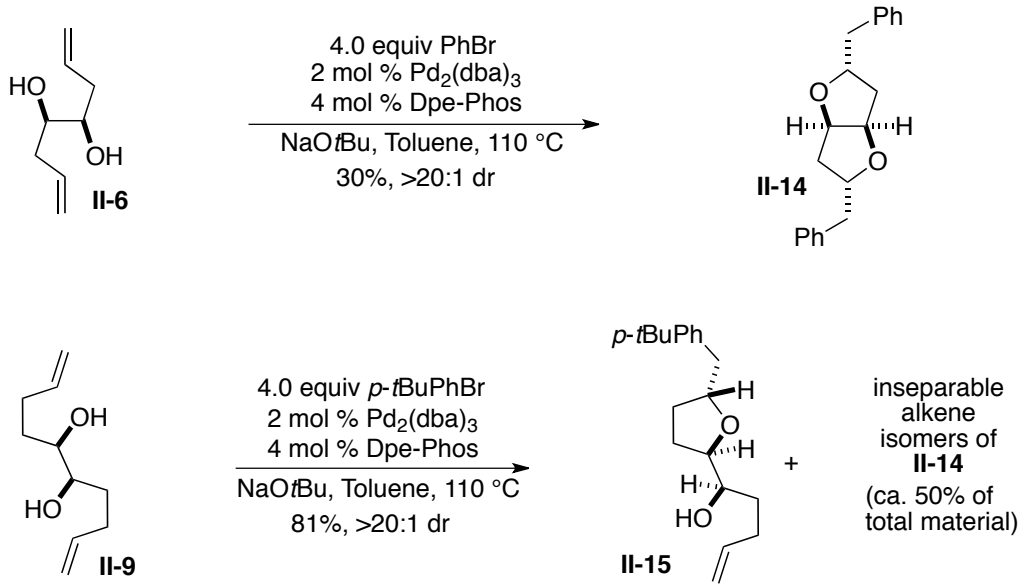


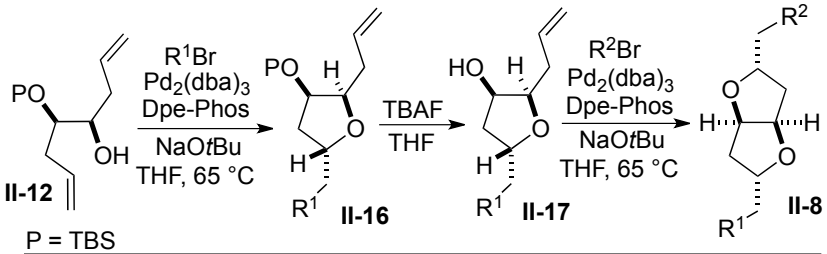
Figure 2.3. Attempted Monocyclization of 1,2-Diols.

2.3 Carboetherification Reactions of TBS-Protected Substrates

Although carboetherification reactions of **II-6** and **II-9** were generally ineffective, transformations of TBS-protected substrates **II-12** and **II-13** proceeded smoothly. As shown in Table 2-1, treatment of **II-12** with an aryl bromide in the presence of NaO*t*Bu and a catalyst composed of $Pd_2(dba)_3$ and Dpe-Phos provided tetrahydrofurans **II-16** in good yields with excellent diastereoselectivities. Cleavage of the silyl ether protecting group was achieved under standard conditions, and carboetherification of the resulting alcohols **II-17** provided fused tetrahydrofurans (**II-8**) as single stereoisomers (>20:1 dr). Both cyclizations led to products that are *trans*-2,5-disubstituted around the tetrahydrofuran ring(s), which is consistent with our previously reported observations and stereochemical models for the conversion of γ-hydroxy alkenes to tetrahydrofurans.

The first carboetherification reaction in this sequence (**II-12** to **II-16**) was sensitive to the electronic properties of the aryl bromide, and the best yields were obtained with electron-neutral substrates (entries 1-6 of Table 2-1). However, the scope of the second carboetherification reaction (entries 16 to 8 of Table 2-1)

was much broader, and a number of different aryl bromides were effectively coupled. In addition, use of β-bromostyrene in the second transformation was also successful (entry 7 of Table 2-1). Diastereoselectivities were uniformly high in all of the carboetherification reactions (>20:1 dr), and in many cases the overall yield of **II-8** exceeded 50% over the three-step sequence.



P = TBS

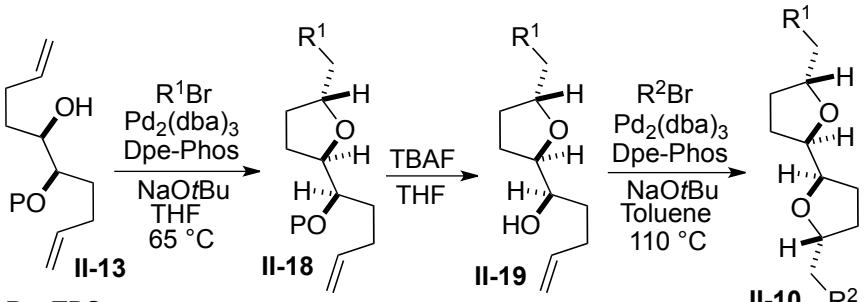
entry	R^1	yield **II-16** (%)[b]	yield **II-17** (%)[b]	R^2	yield **II-8** (%)[b]	overall yield (%)[c]
1	Ph	86	92	*p*-F_3CPh	86	68
2				*p*-PhC(O)Ph	94	74
3	*p*-Tol	91	91	3-pyridyl	91	75
4				*m*-MeOPh	81	67
5	*p*-*t*BuPh	71	90	*p*-PhPh	87	43
6				2-naphthyl	85	54
7	*p*-PhC(O)Ph	44	92	(*E*)-β-styryl	67	27
8				6-MeO-2-naphthyl	89	36

[a] Conditions: Steps 1 and 3: 1.0 equiv **II-12** or **II-17**, 2.0 equiv ArBr, 2.0 equiv NaO*t*Bu, 2 mol % $Pd_2(dba)_3$, 4 mol % Dpe-Phos, THF, 65 °C. Step 2: 1.0 equiv **II-16**, 10 equiv TBAF, THF, rt. [b] Isolated yields (average of two or more experiments). All products were obtained with >20:1 dr. [c] Yield obtained over the three step sequence from **II-12** to **II-8**.

Table 2.1. Stepwise Synthesis of Fused Tetrahydrofurans[a]

The synthesis of attached-ring bis-tetrahydrofurans was achieved by subjecting protected diol **II-13** to an analogous sequence of carboetherification (**II-13** to **II-18**), deprotection (**II-18** to **II-19**), and carboetherification (**II-19** to **II-10**). As observed in the transformations of **II-12**, the scope of the second carboetherification step is considerably broader than the first (with respect to the aryl bromide component). Yields of attached-ring tetrahydrofurans were slightly lower than the corresponding fused-ring products described above. However,

diastereoselectivities were excellent, and all products were obtained with >20:1 dr favoring 2,5-*trans*-stereochemistry around both tetrahydrofuran rings.



P = TBS

entry	R^1	yield **18** (%)[b]	yield **19** (%)[b]	R^2	yield **10** (%)[b]	overall yield (%)[c]
1	*p*-*t*BuPh	73	89	*p*-Tol	64	42
2				*p*-PhPh	63	41
3	Ph	72	91	3-pyridyl	54	35
4				2-naphthyl	61	40
5	*m*-MeOPh	64	91	*p*-F_3CPh	75	44
6				*p*-PhC(O)Ph	72	42
7	*p*-MeOPh	55	96	3,5-Cl_2Ph	71	37
8				6-MeO-2-naphthyl	53	28

[a] Conditions: Steps 1 and 3: 1.0 equiv **II-13** or **II-19**, 2.0 equiv ArBr, 2.0 equiv NaO*t*Bu, 2 mol % $Pd_2(dba)_3$, 4 mol % Dpe-Phos, Toluene or THF, 65 or 110 °C. Step 2: 1.0 equiv **II-18**, 10 equiv TBAF, THF, rt. [b] Isolated yields (average of two or more experiments). All products were obtained with >20:1 dr. [c] Yield obtained over the three step sequence from **II-13** to **II-10**.

Table 2.2. Stepwise Synthesis of Attached Tetrahydrofurans[a]

To further probe the synthetic utility of these transformations, we sought to determine if nonracemic starting materials could be converted to bis-tetrahydrofuran products without loss of enantiomeric purity. To this end, (-)-**II-13** was prepared in 96% ee via asymmetric dihydroxylation of commercially available *trans*-1,5,9-decatriene (**II-20**)[12] followed by mono-TBS-protection of the resulting diol. This substrate was converted to (-)-**II-10h** using a sequence of reactions identical to that shown in Table 2-2, entry 8, and the product was obtained with >20:1 dr and 95% ee (Figure 2-4).

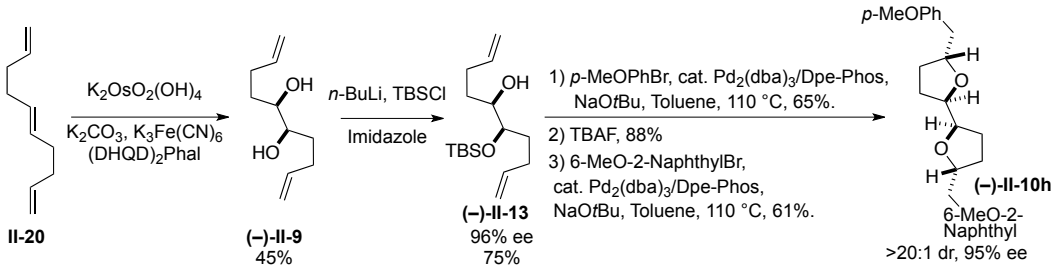
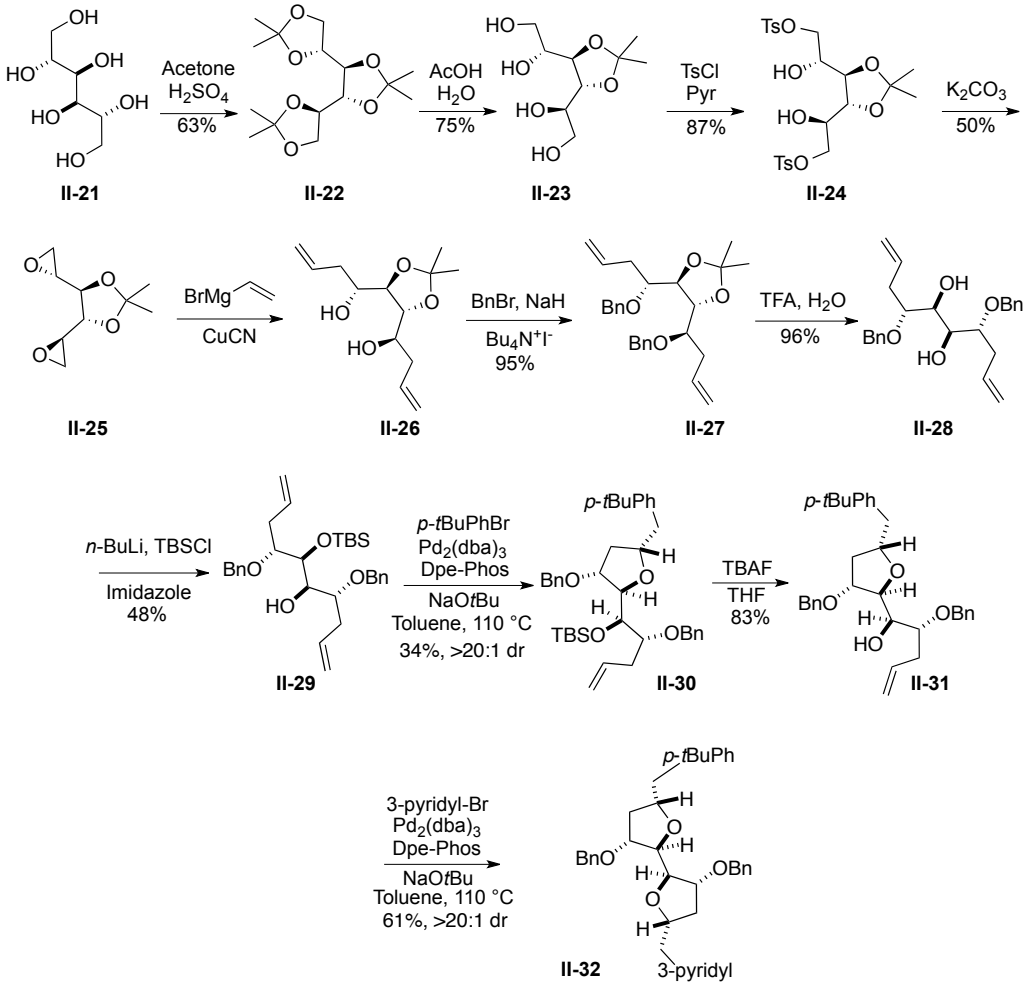


Figure 2.4. Synthesis of an Enantioenriched *Bis*-Tetrahydrofuran.

The synthesis of more elaborate tetrahydrofuran products is also feasible using this method. For example, protected tetraol derivative **II-29** was generated from D-mannitol using standard transformations.[13] Namely, D-mannitol was converted to triacetonide **II-22**, which was selectively cleaved to monoacetonide **II-23** using an aqueous solution of acetic acid. Subsequent tosylation of the primary alcohol followed by base-catalyzed epoxide formation and Grignard addition afforded **II-26** in 41% overall yield. Next, benzyl protection, cleavage of the acetonide using TFA, and selective mono-TBS-protection of the resulting diol was performed to yield **II-29.** This substrate was converted to bis-tetrahydrofuran **II-32** with >20:1 dr using the same reaction sequence described above (Scheme 2-2).



Scheme 2.2. Synthesis of a Highly Substituted *Bis*-Tetrahydrofuran

2.4 Conclusions

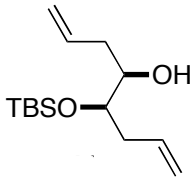
In conclusion, we have developed a concise approach to the construction of both attached-ring and fused-ring bis-tetrahydrofurans using sequential Pd-catalyzed carboetherification reactions. This strategy allows for preparation of derivatives bearing different substituents at the 2-position of each tetrahydrofuran ring, and provides access to derivatives that could not be easily generated with existing methods.

2.5 Experimental

General. All reactions were carried out under a nitrogen atmosphere in oven or flame dried glassware. Tris(dibenzylideneacetone)dipalladium (0) and all

phosphine ligands were purchased from Strem Chemical Co. and used without further purification. All aryl bromides and 1,3 butadiene diepoxide were obtained from commercial sources (Aldrich Chemical CO or Acros Chemical CO) and were used as obtained. (4*R*,5*S*,6*S*,7*R*)-4,7-bis(benzyloxy)deca-1,9-diene-5,6-diol,[14,15] (5*R**,6*R**)-deca-1,9-diene-5,6-diol,[16] (+)-(5*R*,6*R*)-deca-1,9-diene-5,6-diol, and (4*R**,5*R**)-octa-1,7-diene-4,5-diol were prepared according to literature procedures. Toluene and THF were purified using a GlassContour solvent purification system. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR. The yields reported in the supporting information describe the result of a single experiment, whereas the yields reported in Tables 2-1 and 2-2 are average yields of two or more experiments. Thus, the yields reported in the supporting information may differ from those shown in Tables 2-1 and 2-2.

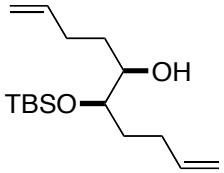
Preparation of Substrates



II-12

(±)-(4*R,5*R**)-5-(*tert*-Butyldimethylsiloxy)octa-1,7-dien-4-ol II-12).** A flame-dried flask was cooled under a stream of nitrogen and charged with (4*R**,5*R**)-octa-1,7-diene-4,5-diol (1.5 g, 10.6 mmol). THF (10.6 mL) was added, the resulting solution was cooled to –78 °C, and *n*-BuLi (5.6 ml, 10.6 mmol, 1.9 M in hexanes) was added dropwise with stirring. The reaction mixture was allowed to warm to rt over 1 h and then a solution of TBSCl (1.59 g, 10.6 mmol) in THF (10.6 mL) was added slowly. The resulting mixture was stirred at rt for 30 min, then imidazole (36 mg, 0.53 mmol) was added and the mixture was stirred overnight at rt. A solution of saturated aqueous $NaHCO_3$ (5 mL) was added, and

the resulting mixture was diluted with ethyl acetate (5 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 X 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel to afford the title compound as a pale yellow oil (1.8 g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91–5.72 (m, 2 H), 5.13–5.04 (m, 4 H), 3.65–3.59 (m, 2 H), 2.49–2.39 (m, 1 H), 2.26–2.15 (m, 4 H), 0.9 (s, 9 H), 0.01 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.1, 134.1, 117.5, 116.9, 73.7, 71.7, 38.3, 25.7, 17.9, –4.2, –4.8; IR (film, cm^{-1}) 3450, 2930; MS(ESI): 279.1756 (279.1756 calcd for $C_{13}H_{28}SiO_2$, M + Na^+).

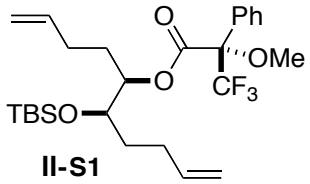


II-13

(±)-(5*R,6*R**)-6-(*tert*-Butyldimethylsiloxy)deca-1,9-dien-5-ol (II-13).** The conversion of (5*R**,6*R**)-deca-1,9-diene-5,6-diol (2.93 g, 17.24 mmol) to the title compound was achieved using a procedure analogous to that described above for the preparation of **II-12**. This procedure afforded 2.65 g (54%) of the title compound as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90–5.74 (m, 2 H), 5.07–4.94 (m, 4 H), 3.58–3.53 (m, 1 H), 3.51–3.45 (m, 1 H), 2.30–2.20 (m, 1 H), 2.18–2.00 (m, 4 H), 1.80–1.69 (m, 1 H), 1.59–1.45 (m, 3 H), 0.90 (s, 9 H), 0.04 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 138.3, 114.7, 114.6, 74.4, 71.8, 33.2, 32.8, 30.1, 29.2, 18.1, –4.2, –4.6; IR (film, cm^{-1}): 3459, 2953; MS(ESI): 307.2063 (307.2069 calcd for $C_{15}H_{32}SiO_2$, M + Na^+).

(–)-(5*R*,6*R*)-6-(*tert*-Butyldimethylsiloxy)deca-1,9-dien-5-ol (II-13). The conversion of (+)-(5*R*,6*R*)-deca-1,9-diene-5,6-diol (1.19 g, 7.0 mmol) to the title compound was achieved using a procedure analogous to that described above

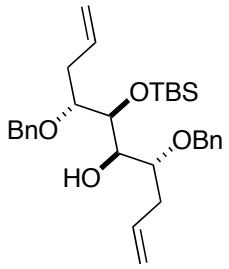
for the preparation of **II-12**. This procedure afforded 1.29 g (44%) of the title compound as a pale yellow oil, $[\alpha]_D^{23}$ = –3.3° (*c* 0.42, CH_2Cl_2). The enantiopurity of this compound was judged to be 96% ee through ^{19}F NMR analysis of the corresponding Mosher ester derivative (**II-S1**).



II-S1

(–)-(2*S*,4*R*,5*R*)-5-[(*tert*-Butyldimethylsilyloxy)nona-1,8-dien-4-yl]-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (II-S1). A flame-dried flask was cooled under a stream of nitrogen and charged with dimethylaminopyridine (4 mg, 0.035 mmol), DCC (40 mg, 0.193 mmol), (*S*)-α-methoxytrifluorophenylacetic acid (45 mg, 0.193 mmol) and THF (1 mL). A solution of (5*R*,6*R*)-6-(*tert*-butyldimethylsiloxy)deca-1,9-dien-5-ol (50 mg, 0.18 mmol) in THF (0.35 mL) was added dropwise, and the resulting mixture was stirred at rt until the starting material was consumed as judged by GC analysis. The reaction was diluted with cold pentane, filtered, and washed with brine. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 X 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel to afford the title compound as a clear oil (77 mg, 87%), $[\alpha]_D^{23}$ = –7.3° (*c* 0.70, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.53–7.46 (m, 2 H), 7.39–7.34 (m, 3 H), 5.79–5.66 (m, 1 H), 5.65–5.53 (m, 1 H), 5.00–4.84 (m, 5 H), 3.70–3.64 (m, 1 H), 3.54–3.51 (s, 3 H), 2.14–1.90 (m, 3 H), 1.87–1.74 (m, 2 H), 1.70–1.59 (m, 1 H), 1.39–1.27 (m, 1 H), 1.26–1.16 (m, 1 H), 0.85 (s, 9 H), 0.10 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 138.0, 137.2, 132.1, 129.6, 128.4, 127.2, 119.4 (q, *J* = 186 Hz) 115.6, 114.8, 70.6, 55.7, 55.6, 34.9, 30.4, 30.1, 26.6, 25.8 (q, *J* = 49.6 Hz), 17.9, -4.4, –4.7 (one signal is missing due to incidental equivalence); ^{19}F NMR (376 MHz, $CDCl_3$) –71.4; IR

(film, cm^{-1}) 2930, 1746, 1170; MS(ESI): 523.2457 (523.2467 calcd for $C_{26}H_{39}SiO_4F_3$, M + Na^+)



II-29

(–)-(4*R*,5*R*,6*S*,7*R*)-4,7-Bis(benzyloxy)-6-(*tert*-butyldimethylsiloxy)deca-1,9-dien-5-ol (II-29). The conversion of (4*R*,5*S*,6*S*,7*R*)-4,7-bis(benzyloxy)deca-1,9-diene-5,6-diol (1.76 g, 4.7 mmol) to the title compound was achieved using a procedure analogous to that described above for the preparation of **II-12**. This procedure afforded 0.9 g (50%) of the title compound as a colorless oil, $[\alpha]_D^{23}$ = –4.2° (*c* 0.63, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.28 (m, 5 H), 7.27–7.24 (m, 4 H), 7.24–7.20 (m, 1 H), 5.99–5.87 (m, 1 H), 5.86–5.74 (m, 1 H), 5.19–4.95 (m, 4 H), 4.68 (d, *J* = 11.4 Hz, 1 H), 4.56 (d, *J* = 11.4 Hz, 1 H), 4.47 (d, *J* = 11.7 Hz, 1 H), 4.36 (d, *J* = 11.4 Hz, 1 H), 4.16 (t, *J* = 2.0 Hz, 1 H), 3.59–3.54 (m, 1 H), 3.48–3.40 (m, 2 H), 3.07 (d, *J* = 6.3 Hz, 1 H), 2.67–2.58 (m, 1 H), 2.54–2.45 (m, 1 H), 2.41–2.25 (m, 2 H), 0.88 (s, 9 H), 0.05 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 138.4, 135.4, 128.3, 128.2, 127.7, 127.6, 127.57, 125.5, 117.5, 117.0, 83.4, 78.9, 72.6, 71.4, 70.8, 70.4, 34.9, 33.6, 26.0, 18.3, –3.7, –4.9; IR (film, cm^{-1}) 3516, 3067; MS(ESI) 519.2907 (519.2921 calcd for $C_{30}H_{44}SiO_4$, M + Na^+).

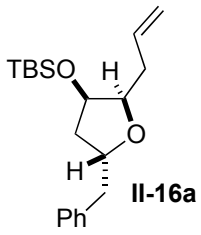
Synthesis of Bis-Tetrahydrofurans via Pd-Catalyzed Alkene Carboetherification

General Procedure 1: Palladium-Catalyzed Carboetherification Reactions for the Formation of Tetrahydrofuran Derivatives. An oven or flame-dried

Schlenk tube was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (2 mol% complex, 4 mol % Pd), Dpe-phos (4 mol %), NaOtBu (2.0 equiv), and the aryl bromide (2.0 equiv). The tube was purged with nitrogen and the alcohol substrate (1.0 equiv), and THF or Toluene (0.25 M in substrate) were added. The mixture was heated to 65 °C or 110 °C with stirring until the starting material had been consumed as judged by GC or ^{1}H NMR analysis. The mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl (2 mL), and diluted with ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was then purified by flash chromatography on silica gel.

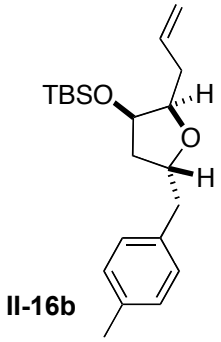
General Procedure 2: Cleavage of TBS Protecting Groups. An oven or flame-dried round-bottomed flask was cooled under a stream of nitrogen and charged with the protected alcohol (1.0 equiv). The tube was purged with nitrogen, THF (0.1 M in protected alcohol) was added, and the reaction was cooled to 0 $^{\circ}$C. TBAF (10 equiv, 1 M in THF) was added dropwise and the reaction was warmed to rt. The mixture was stirred at rt until the starting material had been consumed as judged by GC analysis. The mixture was then quenched with 1 M HCl (5 mL) and diluted with ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was then purified by flash chromatography on silica gel.

Synthesis of Fused-Ring Bis-Tetrahydrofurans (Table 2-1)



II-16a

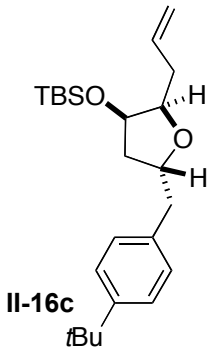
(±)-(2*R,3*R**,5*R**)-(2-Allyl-5-benzyltetrahydrofuran-3-yloxy)(*tert*-butyl)dimethylsilane (II-16a, Table 2-1, Entries 1–2).** The coupling of (±)-**II-12** (400 mg, 1.56 mmol) with bromobenzene (330 µL, 3.13 mmol) was achieved following general procedure 1 using THF as solvent and a reaction temperature of 65 °C. This procedure afforded 385 mg (74%) of the title compound as an orange oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.21 (m, 5 H), 5.95–5.83 (m, 1 H), 5.19–5.06 (m, 2 H), 4.55–4.46 (m, 1 H), 4.24–4.20 (m, 1 H), 3.90–3.85 (m, 1 H), 3.04–2.94 (dd, *J* = 5.5, 13.3 Hz, 1 H), 2.83–2.76 (dd, *J* = 7.1, 13.7 Hz, 1 H), 1.92–1.85 (m, 2 H), 1.79–1.71 (m, 1 H), 1.68–1.62, (m, 1 H), 0.91 (s, 9 H), 0.01 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 135.7, 129.4, 128.2, 126.1, 116.3, 82.4, 73.3, 42.0, 41.0, 34.2, 25.7, 18.0, –4.5, –5.0; IR (film, cm^{-1}) 3030, 1472; MS(ESI): 355.2060 (355.2069 calcd for $C_{20}H_{32}SiO_2$, M + Na^+).



II-16b

(±)-(2*R,3*R**,5*R**)-[2-Allyl-5-(4-methylbenzyl)tetrahydrofuran-3-yloxy](*tert*-butyl)dimethylsilane (II-16b, Table 2-1, Entries 3–4).** The coupling of (±)-**II-12** (200 mg, 0.78 mmol) with 4-bromotoluene (190 µL, 1.56 mmol) was achieved

following general procedure 1 using THF as solvent and a reaction temperature of 65 °C. This procedure afforded 230 mg (85%) of the title compound as a red oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13–7.07 (m, 4 H), 5.92–5.81 (m, 1 H), 5.17–5.03 (m, 2 H), 4.50–4.43 (m, 1 H), 4.21–4.17 (m, 1 H), 3.87–3.82 (m, 1 H), 2.94 (dd, *J* = 5.5, 8.1 Hz, 1 H), 2.74 (dd, *J* = 7.0, 13.7 Hz, 1 H), 2.76–2.69 (m, 2 H), 2.33 (s, 3 H), 1.89–1.82 (m, 1 H), 1.76–1.67 (m, 1 H), 0.88 (s, 9 H), 0.01 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 135.5, 129.3, 128.9, 116.2, 82.3, 77.7, 73.3, 41.6, 41.0, 34.2, 25.7, 21.0, 18.0, –4.5, –5.1; IR (film, cm^{-1}) 2930, 1463. MS(ESI): 369.2213 (369.2226 calcd for $C_{21}H_{34}SiO_2$, M + Na^+).

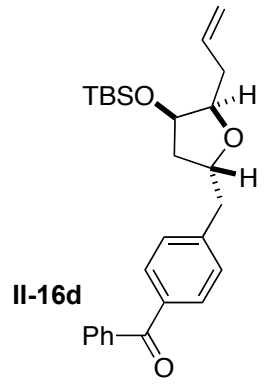


II-16c

*t*Bu

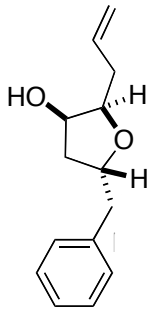
(±)-(2*R,3*R**,5*R**)-[2-Allyl-5-(4-*tert*-butylbenzyl)tetrahydrofuran-3-yloxy](*tert*-butyl)dimethylsilane (II-16c, Table 2-1, Entries 5–6).** The coupling of (±)-**II-12** (400 mg, 1.56 mmol) with 1-bromo-4-*tert*-butylbenzene (0.55 mL, 3.13 mmol) was achieved following general procedure 1 using THF as solvent and a reaction temperature of 65 °C. This procedure afforded 450 mg (74%) of the title compound as a red oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.2 Hz, 2 H), 7.17 (d, *J* = 8.2 Hz, 2 H), 5.94–5.83 (m, 1 H), 5.18–5.05 (m, 2 H), 4.53–4.45 (m, 1 H), 4.22–4.19 (m, 1 H), 3.90–3.85 (m, 1 H), 2.93 (dd, *J* = 5.5, 16.0 Hz, 1 H), 2.75 (dd, *J* = 6.7, 12.0 Hz, 1 H), 2.45–2.29 (m, 2 H), 1.94–1.85 (m, 1 H), 1.80–1.71 (m, 1 H) 1.33 (s, 9 H), 0.89 (s, 9 H), 0.01 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 140.4, 134.1, 130.1, 121.3, 87.3, 78.3,

46.6, 46.1, 39.4, 39.2, 36.4, 30.8, 23.1, 6.0, 0.5, 0.0; IR (film, cm^{-1}) 2957, 1471. MS(ESI): 411.2687 (411.2695 calc for $C_{24}H_{40}SiO_2$, M + Na^+).



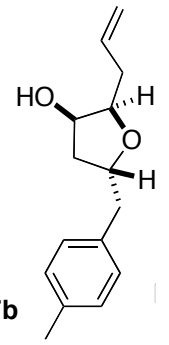
II-16d

(±)-(2*R,4*R**,5*R**)-4-[5-Allyl-4-(*tert*-butyldimethylsilyloxy)tetrahydrofuran-2-ylmethyl]phenyl(phenyl)methanone (II-16d, Table 2-1, Entries 7–8).** The coupling of (±)-**II-12** (500 mg, 1.95 mmol) with 4-bromobenzophenone (1.02 g, 3.9 mmol) was achieved following general procedure 1 using THF as solvent and a reaction temperature of 65 °C. This procedure afforded 300 mg (42%) of the title compound as an amber oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.15 (m, 9 H); 5.91–5.79 (m, 1 H), 5.15–5.03 (m, 2 H), 4.56–4.46 (m, 1 H), 4.23–4.19 (m, 1 H), 3.87–3.22 (m, 1 H), 2.99 (dd, *J* = 6.3, 13.7 Hz, 1 H), 2.88 (dd, *J* = 6.3, 13.7 Hz, 1 H), 2.44–2.27 (m, 1 H), 1.89 (dd, *J* = 1.6, 5.9 Hz, 1 H), 1.85 (dd, *J* = 5.9, 7.0 Hz, 1 H), 1.77–1.69 (m, 1 H), 0.88 (s, 9 H), 0.05 (s, 3 H), (0.01 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 143.7, 137.8, 135.6, 132.2, 130.2, 129.9, 129.4, 128.2, 116.4, 82.5, 73.2, 42.0, 41.3, 34.1, 25.7, 18.0, –4.5, –5.0 (one carbon signal is absent due to incidental equivalence); IR (film, cm^{-1}) 2928, 1700, 1278. MS(ESI): 459.2330 (459.2331 calcd for $C_{27}H_{36}SiO_3$, M + Na^+).



II-17a

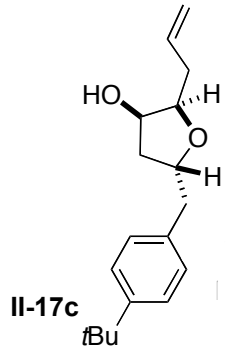
(±)-(2*R,3*R**,5*R**)-2-Allyl-5-benzyltetrahydrofuran-3-ol (II-17a, Table 2-1, Entries 1–2)**. Removal of the TBS protecting group from **II-17a** (198 mg, 0.593 mmol) with TBAF (5.93 mL, 5.93 mmol) was achieved following general procedure 2. This procedure afforded 127 mg (97%) of the title compound as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.19 (m, 5 H), 5.92–5.81 (m, 1 H), 5.21–5.07 (m, 2 H), 4.54–4.45 (m, 1 H), 4.25–4.20 (m, 1 H), 3.87 (dt, *J* = 2.7, 7.0 Hz, 1 H), 2.97 (dd, *J* = 5.9, 13.7 Hz, 1 H), 2.78–2.63 (m, 1 H), 2.51–2.35 (m, 2 H), 1.98 (dd, *J* = 6.3, 13.3 Hz, 1 H), 1.85–1.77 (m, 1 H), 1.68 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 134.8, 129.4, 128.3, 126.3, 117.0, 81.4, 77.8, 73.1, 42.0, 40.8, 33.8; IR (film, cm^{-1}) 3411, 2925, 1454. MS(ESI): 241.1201 (241.1204 calcd for $C_{14}H_{18}O_2$, M + Na^+).



II-17b

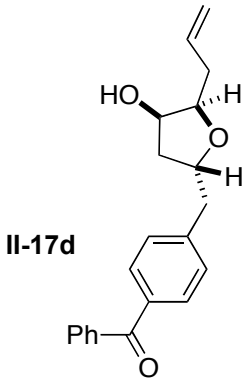
(±)-(2*R,3*R**,5*R**)-2-Allyl-5-(4-methylbenzyl)tetrahydrofuran-3-ol (II-17b, Table 2-1, Entries 3–4).** Removal of the TBS protecting group from **II-16b** (181 mg, 0.52 mmol) with TBAF (5.2 mL, 5.2 mmol) was achieved following general procedure 2. This procedure afforded 113 mg (93%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (s, 4 H), 5.92–5.81 (m, 1 H), 5.21–

5.06 (m, 2 H), 4.51–4.43 (m, 1 H), 4.26–4.20 (m, 1 H), 3.86 (dt, *J* = 2.7, 7.1 Hz, 1 H), 2.93 (dd, *J* = 5.9, 13.7 Hz, 1 H), 2.71 (dd, *J* = 7.0, 13.7 Hz, 1 H), 2.51–2.34 (m, 2 H), 2.31 (s, 3 H), 2.01–1.95 (m, 1 H), 1.85–1.77 (m, 1 H), 1.61–1.53 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 135.0, 134.9, 129.3, 129.0, 117.0, 81.5, 77.9, 72.9, 41.6, 40.7, 33.8, 21.0; IR (film, cm^{-1}) 3451, 2985, 1422. MS(ESI): 255.1352 (255.1361 calcd for $C_{15}H_{20}O_2$, M + Na^+).



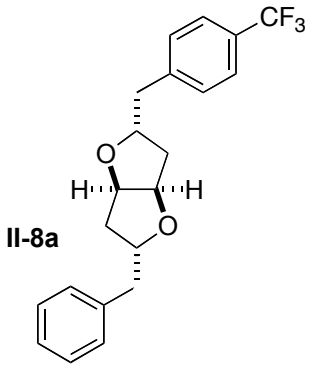
II-17c

(±)-(2*R,3*R**,5*R**)-2-Allyl-5-(4-*tert*-butylbenzyl)tetrahydrofuran-3-ol (II-17c, Table 2-1, Entries 5–6).** Removal of the TBS protecting group from **II-16b** (100 mg, 0.287 mmol) with TBAF (2.87 mL, 2.87 mmol) was achieved following general procedure 2. This procedure afforded 65 mg (92%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.32 (m, 2 H), 7.17–7.12 (m, 2 H), 5.93–5.82 (m, 1 H), 5.22–5.07 (m, 2 H), 4.53–4.44 (m, 1 H), 4.24 (t, *J* = 3.5 Hz, 1 H), 3.90 (dt, *J* = 6.7, 7.0 Hz, 1 H), 2.95 (dd, *J* = 5.9, 13.7 Hz, 1 H), 2.71 (dd, *J* = 7.0, 13.7 Hz, 1 H), 2.39–2.06 (m, 2 H), 2.05–1.97 (m, 1 H), 1.87–1.78, (m, 1 H), 1.67 (s, 1 H), 1.31 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 135.1, 134.9, 129.0, 125.2, 117.0, 81.5, 77.9, 72.9, 41.6, 41.0, 34.4, 33.8, 31.4; IR (film, cm^{-1}) 3418, 2963, 1363. MS(ESI): 297.1826 (297.1830 calcd for $C_{18}H_{26}O_2$, M + Na^+).



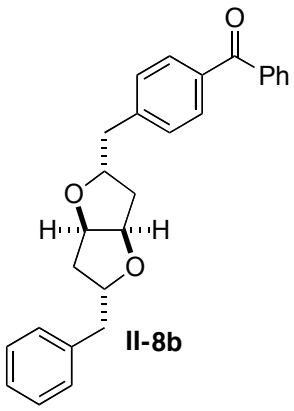
II-17d

(±)-(2*R,4*R**,5*R**)-4-(5-Allyl-4-hydroxytetrahydrofuran-2-ylmethyl)phenyl(phenyl)methanone (II-16d, Table 2-1, Entries 7–8).** Removal of the TBS protecting group from **II-156** (30 mg, 0.077 mmol) with TBAF (77 μL, 0.77 mmol) was achieved following general procedure 2. This procedure afforded 23 mg (92%) of the title compound as an amber oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79–7.71 (m, 4 H), 7.60–7.54 (m, 1 H), 7.49–7.43 (m, 2 H), 7.35–7.30 (m, 2 H), 5.91–5.79 (m, 1 H), 5.19–5.05 (m, 2 H), 4.57–4.48 (m, 1 H), 4.24 (s, 1 H), 3.87 (dt, *J* = 2.7, 7.0 Hz, 1 H), 2.99 (dd, *J* = 6.3, 13.7 Hz, 1 H), 2.85 (dd, *J* = 6.3, 13.7 Hz, 1 H), 2.50–2.34 (m, 2 H), 2.02 (dd, *J* = 6.3, 13.7 Hz, 2 H), 1.85–1.77 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6; 143.5, 137.7, 135.6, 134.8, 132.3, 130.3, 130.0, 129.4, 128.2, 117.1, 81.6, 72.9, 42.0, 40.9, 33.8 (one carbon signal is absent due to incidental equivalence; IR (film, cm^{-1}) 3474, 2932, 1265. MS(ESI): 345.1468 (345.1467 calcd for $C_{21}H_{22}O_3$, M + Na^+).



II-8a

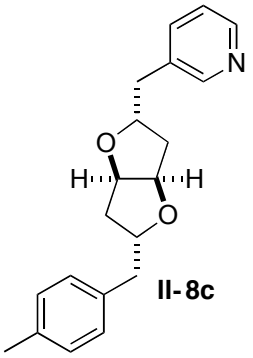
(±)-(2*R,3a*R**,5*R**,6a*R**)-2-Benzyl-5-[4-(trifluoromethyl)benzyl]hexahydrofuro[3,2-b]furan (II-8a, Table 2-1, Entry 1).** The coupling of **II-17a** (31 mg, 0.14 mmol) with 4-bromobenzotrifluoride (60 µL, 0.28 mmol) was achieved following general procedure 1 using THF as solvent and a reaction temperature of 65 °C. This procedure afforded 45 mg (87%) of the title compound as a yellow oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.34 (d, *J* = 7.8 Hz, 2 H), 7.17–7.08 (m, 4 H), 7.06–7.01 (m, 3 H), 4.55–4.50 (m, 2 H), 4.14–4.05 (m, 2 H), 2.77–2.70 (m, 2 H), 2.66 (dd, *J* = 5.5, 13.7 Hz, 1 H), 2.57 (dd, *J* = 6.3, 13.7 Hz, 1 H), 1.94 (dt, *J* = 1.5, 12.5 Hz, 2 H), 1.54–1.40 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 138.2, 129.3 (q, *J* = 183 Hz, 1 C), 128.3, 128.2, 125.2 (q, *J* = 60 Hz), 83.8, 83.7, 83.68, 83.52, 77.3, 41.7, 41.4, 40.7, 40.66 (one signal is absent due to incidental equivalence); IR (film, cm^{-1}) 2936, 1325, 1113. MS(ESI): 385.1406 (385.1391 calcd for $C_{21}H_{21}F_3O_2$, M + Na^+).



II-8b

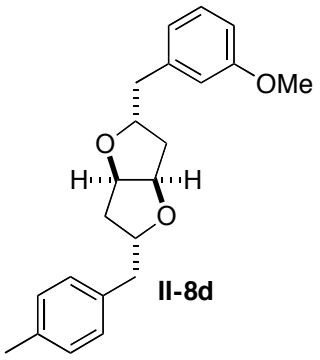
(±)-(2*R,3a*R**,5*R**,6a*R**)-4-(5-Benzylhexahydrofuro[3,2-b]furan-2-ylmethyl)phenyl(phenyl)methanone (II-8b, Table 2-1, Entry 2).** The coupling of **II-17a** (31 mg, 0.14 mmol) with 4-bromobenzophenone (74 mg, 0.28 mmol) was achieved following general procedure 1 using THF as solvent and a reaction temperature of 65 °C. This procedure afforded 55 mg (96%) of the title compound as a yellow oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.60 (m, 2 H), 7.59–7.55 (m, 2 H), 7.44–7.38 (m, 1 H), 7.34–7.28 (m, 2 H),

7.19–7.01 (m, 7 H), 4.56–4.51 (m, 2 H), 4.17–4.06 (m, 2 H), 2.81–2.71 (m, 2 H), 2.67 (dd, *J* = 5.9, 7.8 Hz, 1 H), 2.57 (dd, *J* = 6.7, 13.7 Hz, 1 H), 2.01–1.90 (m, 2 H), 1.55–1.46 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 143.4, 138.1, 137.7, 135.6, 132.2, 130.2, 130.0, 129.2, 129.1, 128.3, 128.2, 126.2, 83.7, 83.5, 80.6, 80.0, 41.7, 41.6, 40.7, 40.6; IR (film, cm^{-1}) 2993, 1759, 1246. MS(ESI): 421.1771 (421.1780 calcd for $C_{27}H_{26}O_3$, M + Na^+).



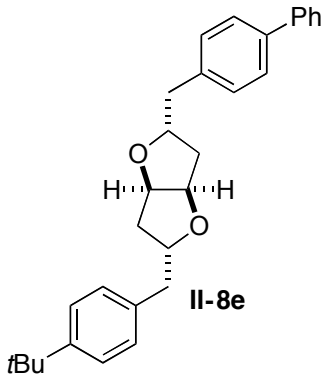
II-8c

(±)-(2*R,3a*R**,5*R**,6a*R**)-3-[5-(4-Methylbenzyl)hexahydrofuro[3,2-b]furan-2-ylmethyl]pyridine (II-8c, Table 2-1, Entry 3).** The coupling of **II-17b** (56 mg, 0.24 mmol) with 3-bromopyridine (47 µL, 0.48 mmol) was achieved following general procedure 1 using THF as solvent and a reaction temperature of 65 °C. This procedure afforded 75 mg (92%) of the title compound as a yellow oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47–8.40 (m, 2 H), 7.55–7.51 (m, 1 H), 7.22–7.17 (m, 1 H), 7.08 (s, 4 H), 4.69–4.64 (m, 2 H), 4.28–4.18 (m, 2 H), 2.89–2.74 (m, 3 H), 2.68 (dd, *J* = 6.4, 7.0 Hz, 1 H), 2.30 (s, 3 H), 2.14–2.03 (m, 2 H), 1.69–1.58 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 147.7, 136.7, 137.7, 135.6, 134.9, 129.0, 128.9, 123.1, 83.7, 83.4, 80.7, 79.6, 41.2, 40.52, 40.5, 38.5, 20.9; IR (film, cm^{-1}) 3053, 1265. MS(ESI): 310.1810 (310.1807 calcd for $C_{20}H_{23}O_2N$, M + H^+).



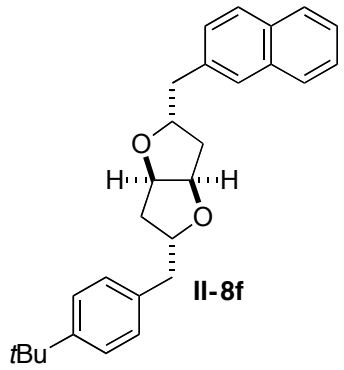
II-8d

(±)-(2*R,3a*R**,5*R**,6a*R**)-2-(3-Methoxybenzyl)-5-(4-methylbenzyl)hexahydrofuro[3,2-b]furan (II-8d, Table 2-1, Entry 4).** The coupling of **II-17b** (40 mg, 0.34 mmol) with 3-bromoanisole (43 µL, 0.34 mmol) was achieved following general procedure 1 using THF as solvent and a reaction temperature of 65 °C. This procedure afforded 48 mg (82%) of the title compound as a yellow oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.18 (m, 1 H), 7.10 (s, 4 H), 6.82–6.75 (m, 3 H), 4.72–4.68 (m, 2 H), 4.32–4.22 (m, 2 H), 3.80 (s, 3 H), 2.94–2.85 (m, 2 H), 2.74–2.67 (m, 2 H), 2.33 (s, 3 H), 2.13 (q, *J* = 2.4 Hz, 1 H), 2.09 (q, *J* = 2.3 Hz, 1 H), 1.71–1.62 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 139.9, 135.7, 135.1, 129.3, 129.1, 129.0, 121.7, 115.1, 111.5, 83.7, 83.6, 80.7, 80.4, 55.1, 41.8, 41.3, 40.8, 40.7, 21.0; IR (film, cm^{-1}) 2920, 1259. MS(ESI): 361.1788 (361.1780 calcd for $C_{22}H_{26}O_3$, M + Na^+).



II-8e

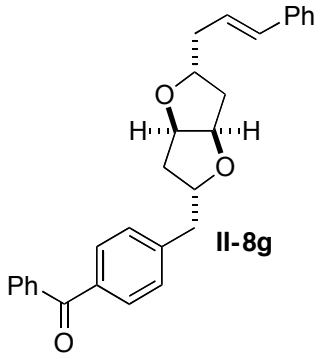
(±)-(2*R,3a*R**,5*R**,6a*R**)-2-(Biphenyl-4-ylmethyl)-5-(4-*tert*-butylbenzyl)hexahydrofuro[3,2-b]furan (II-8e, Table 2-1, Entry 5).** The coupling of **II-17c** (46 mg, 0.2 mmol) with 4-bromobiphenyl (46 mg, 0.2 mmol) was achieved following general procedure 1 using THF as solvent and a reaction temperature of 65 °C. This procedure afforded 35 mg (83%) of the title compound as a yellow oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.58 (m, 2 H), 7.56–7.52, (m, 2 H), 7.49–7.43 (m, 2 H), 7.38–7.28 (m, 5 H), 7.16 (d, *J* = 8.2 Hz, 2 H), 4.75 (d, *J* = 4.9 Hz, 2 H), 4.37–4.26 (m, 2 H), 2.94 (dt, *J* = 6.3, 14.0 Hz, 2 H), 2.81 (dd, *J* = 6.3, 13.9 Hz, 1 H), 2.72 (dd, *J* = 6.4, 13.7 Hz, 1 H), 2.20–2.12 (m, 2 H), 1.77–1.64 (m, 2 H), 1.34 (s, 9 H);^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 141.0, 139.2, 137.4, 135.2, 129.7, 129.0, 128.7, 127.1, 127.0, 125.2, 83.7, 83.6, 80.7, 80.5, 41.4, 41.3, 40.9, 40.8, 34.4, 31.4 (one carbon signal is missing due to incidental equivalence); IR (film, cm^{-1}) 2900, 1091. MS(ESI): 427.2628 (427.2637 calcd for $C_{30}H_{34}O_2$, M + H^+).



II-8f

(±)-(2*R,3a*R**,5*R**,6a*R**)-2-(4-*tert*-Butylbenzyl)-5-(naphthalen-2-ylmethyl)hexahydrofuro[3,2-b]furan (II-8f, Table 2-1, Entry 6).** The coupling of **II-17c** (41 mg, 0.2 mmol) with 2-bromonapthalene (41 mg, 0.2 mmol) was achieved following the general procedure 1 using THF as solvent and a reaction temperature of 65 °C. This procedure afforded 36 mg (90%) of the title compound as a yellow oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.76 (m, 3 H),

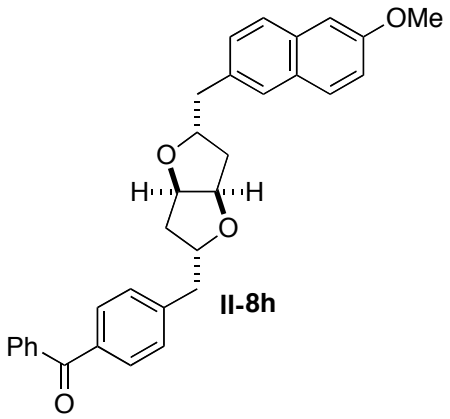
7.66 (s, 1 H), 7.50–7.41 (m, 2 H), 7.38–7.34 (m, 1 H), 7.33–7.29 (m, 2 H), 7.17–7.12 (m, 2 H), 4.74–4.71 (m, 2 H), 4.43–4.34 (m, 1 H), 4.33–4.24 (m, 1 H), 3.07 (dd, *J* = 5.9, 13.7 Hz, 1 H), 2.96–2.87 (m, 2 H), 2.17–2.09 (m, 2 H), 1.77–1.64 (m, 3 H), 1.32 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 135.9, 135.2, 133.5, 132.2, 128.8, 127.9, 127.8, 127.6, 127.6, 127.5, 125.9, 125.3, 125.2, 83.7, 83.6, 80.7, 80.5, 41.8, 41.3, 40.9, 40.8, 34.4, 31.4 (two carbon signals are missing due to incidental equivalence; IR (film, cm^{-1}) 2960, 1091. MS(ESI): 423.2292 (423.2300 calcd for $C_{28}H_{32}O_2$, M + Na^+).



II-8g

(±)-4-(2*R,3a*R**,5*R**,6a*R**)-4-(5-Cinnamylhexahydrofuro[3,2-b]furan-2-ylmethyl)phenyl(phenyl)methanone (II-8g, Table 2-1, Entry 7).** The coupling of **II-17d** (70 mg, 0.23 mmol) with β-bromostyrene (58 μL, 0.45 mmol) was achieved following general procedure 1 using THF as solvent and a reaction temperature of 65 °C. This procedure afforded 68 mg (70%) of the title compound as a yellow oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis^{1}H NMR (400 MHz, $CDCl_3$) 7.79–7.21 (m, 3 H), 7.59–7.54 (m, 1 H), 7.49–7.43 (m, 2 H), 7.34–7.30 (m, 4 H), 7.29–7.24 (m, 2 H), 7.24–7.16 (m, 2 H), 6.43 (d, *J* = 16.0 Hz, 1 H), 6.22–6.13 (m, 1 H), 4.74–4.69 (m, 2 H), 4.36–4.29 (m, 1 H), 4.19–4.12 (m, 1 H), 2.95 (dd, *J* = 6.3, 13.7 Hz, 1 H), 2.85 (dd, *J* = 5.9, 7.8 Hz, 1 H), 2.51–2.35 (m, 2 H), 2.20–2.11 (m, 2 H), 1.73–1.64 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 143.4, 137.7, 137.3, 135.6, 132.2, 132.1, 130.2, 130.0, 129.1, 128.4, 128.1, 127.0, 126.0, 83.8, 83.5, 80.0, 79.5, 41.6, 40.7, 40.5, 38.8 (one signal is absent due to incidental

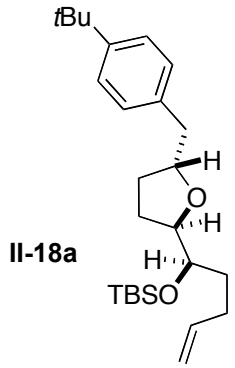
equivalence); IR (film, cm^{-1}) 2920, 1700, 1278. MS(ESI): 447.1938 (447.193 calcd for $C_{29}H_{28}O_3$, M + Na^+).



II-8h

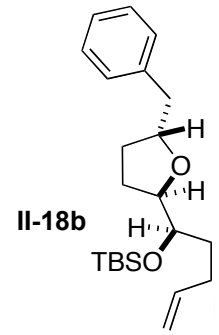
(±)-(2*R,3a*R**,5*R**,6a*R**)-4-[5-(6-Methoxynaphthalen-2-ylmethyl)hexahydrofuro[3,2-b]furan-2-ylmethyl]phenyl(phenyl)methanone (II-8h, Table 2-1, Entry 8).** The coupling of **II-17d** (50 mg, 0.16 mmol) with 2-bromo-6-methoxynaphthalene (70 mg, 0.32 mmol) was achieved following general procedure 1 using THF as solvent and a reaction temperature of 65 °C. This procedure afforded 70 mg (91%) of the title compound as an orange oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.77 (m, 3 H), 7.75–7.71 (m, 3 H), 7.67 (q, *J* = 5.5 Hz, 2 H), 7.50–7.44 (m, 2 H), 7.31 (d, *J* = 8.2 Hz, 3 H), 7.14–7.09 (m, 2 H), 4.73–4.68 (m, 2 H), 4.39–4.27 (m, 2 H), 3.90 (s, 3 H), 3.03 (dd, *J* = 5.9, 13.7 Hz, 1 H), 2.98–2.81 (m, 3 H), 2.17–2.08 (m, 2 H), 1.76–1.63 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 157.2, 143.4, 137.7, 135.6, 133.3, 133.1, 132.1, 130.2, 129.9, 129.1, 129.0, 128.2, 128.1, 127.3, 126.6, 118.6, 105.4, 83.7, 83.5, 80.7, 79.9, 55.2, 41.6, 40.7, 40.6 (two carbons signals are absent due to incidental equivalence); IR (film, cm^{-1}) 2935, 1657, 1278. MS(ESI): 501.2053 (501.2042 calcd for $C_{32}H_{30}O_4$, M + Na^+).

Synthesis of Attached-Ring Bis-Tetrahydrofurans (Table 2)



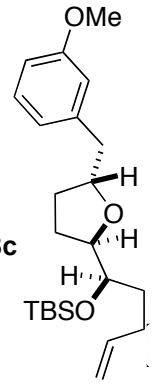
II-18a

(±)-(1*R,2*R**,5*R**)-*tert*-Butyl 1-[5-(4-*tert*-butylbenzyl)tetrahydrofuran-2-yl]pent-4-enyloxy)dimethylsilane (II-18a, Table 2-2, Entries 1–2)**. The coupling of (±)-**II-13** (400 mg, 1.4 mmol) with 1-bromo-4-*tert*-butylbenzene (0.5 mL, 2.8 mmol) was achieved following general procedure 1 using THF as solvent and a reaction temperature of 65 °C. This procedure afforded 460 mg (79%) of the title compound as an amber oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.27 (m, 2 H), 7.17–7.13 (m, 2 H), 5.88–5.76 (m, 1 H), 5.05–4.92 (m, 2 H), 4.17–4.09 (m, 1 H), 3.96 (dd, *J* = 6.3, 18.0 Hz, 1 H), 3.63–3.57 (m, 1 H), 2.91 (dd, *J* = 6.1, 13.7 Hz, 1 H), 2.69 (dd, *J* = 7.0, 13.5 Hz, 1 H), 2.26–2.15 (m, 1 H), 2.13–2.02 (m, 1 H), 1.95–1.84 (m, 2 H), 1.70–1.49 (m, 3 H) 1.46–1.39 (m, 1 H), 1.31 (s, 9 H), 0.88 (s, 9 H), 0.05 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 139.0, 129.0, 125.1, 114.3, 81.5, 80.1, 74.4, 41.4, 34.3, 32.0, 31.9, 31.4, 30.0, 27.4, 26.0, 25.9, –4.2, –4.7; IR (film, cm^{-1}) 2930, 1089. MS(ESI): 439.3005 (439.3008 calcd for $C_{26}H_{44}SiO_2$, M + Na^+).



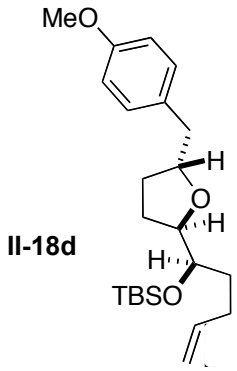
II-18b

(±)-(1*R,2*R**,5*R**)-1-[(5-Benzyltetrahydrofuran-2-yl)pent-4-enyloxy](*tert*-butyl)dimethylsilane (II-18b, Table 2-2, Entries 3–4),** The coupling of (±)-**II-13** (400 mg, 1.4 mmol) with bromobenzene (0.3 mL, 2.8 mmol) was achieved following general procedure 1 using THF as solvent and a reaction temperature of 65 °C. This procedure afforded 350 mg (68%) of the title compound as a yellow oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.15 (m, 5 H), 5.86–5.75 (m, 1 H), 5.03–4.90 (m, 2 H), 3.94 (q, *J* = 13.9 Hz, 1 H), 3.61–3.55 (m, 1 H), 2.92 (dd, *J* = 5.9, 13.5 Hz, 1 H), 2.69 (dd, *J* = 7.0, 13.5 Hz, 1 H), 2.24–2.13 (m, 1 H), 2.11–2.00 (m, 1 H), 1.91–1.77 (m, 2 H), 1.68–1.48 (m, 4 H), 1.46–1.36 (m, 1 H), 0.87 (s, 9 H), 0.04 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 138.8, 129.2, 128.1, 126.0, 114.3, 81.5, 80.0, 74.4, 41.9, 32.1, 31.7, 29.9, 27.4, 26.0, –4.2, –4.7; IR (film, cm^{-1}) 2930, 1078. MS(ESI): 383.2373 (383.2382 calcd for $C_{22}H_{36}SiO_2$, M + Na^+).



II-18c

(±)-(1*R,2*R**,5*R**)-*tert*-Butyl 1-{[5-(3-methoxybenzyl)tetrahydrofuran-2-yl]pent-4-enyloxy}dimethylsilane (II-18c, Table 2-2, Entries 5–6).** The coupling of (±)-**II-13** (400 mg, 1.4 mmol) with 3-bromoanisole (0.36 mL, 2.8 mmol) was achieved following the general procedure 1 using THF solvent and a reaction temperature of 65 °C. This procedure afforded 360 mg (65%) of the title compound as an orange oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, *J* = 7.8 Hz, 1 H), 6.82–6.73 (m, 3 H), 5.88–5.76 (m, 1 H), 5.05–4.92 (m, 2 H), 4.19–4.11 (m, 1 H), 3.96 (q, *J* = 6.2 Hz, 1 H), 3.79 (s, 3 H), 3.63–3.57 (m, 1 H), 2.81 (dd, *J* = 5.9, 13.5 Hz, 1 H), 2.70 (dd, *J* = 7.0, 13.5 Hz, 1 H), 2.25–2.14 (m, 1 H), 1.94–1.83 (m, 2 H) 1.71–1.49 (m, 4 H), 1.49–1.37 (m, 1 H), 0.88 (s, 9 H), 0.05 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 140.4, 139.0, 129.1, 121.8, 115.0, 114.4, 111.5, 81.6, 80.0, 74.4, 55.1, 42.0, 32.1, 31.8, 30.0, 27.4, 26.0, –4.2, –4.7; IR (film, cm^{-1}) 2928, 1062. MS(ESI): 413.2482 (413.2488 calcd for $C_{23}H_{38}SiO_3$, M + Na^+).

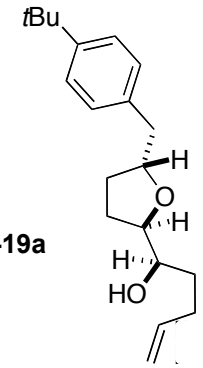


II-18d

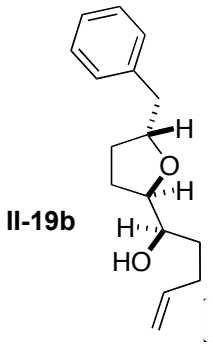
(±)-(1*R,2*R**,5*R**)-1-{[5-(4-Methoxybenzyl)tetrahydrofuran-2-yl]pent-4-enyloxy}dimethylsilane (II-18d, Table 2-2, Entries 7–8).** The coupling of (±)-**II-13** (400 mg, 1.4 mmol) with 4-bromoanisole (0.36 mL, 2.8 mmol) was achieved following general procedure 1 using THF as solvent and a reaction temperature of 65 °C. This procedure afforded 310 mg (56%) of the title compound as an orange oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.10 (m, 2 H),

6.84–6.79 (m, 2 H), 5.88–5.75 (m, 1 H), 5.05–4.89 (m, 2 H), 4.14–4.05 (m, 1 H), 3.98–3.90 (m, 1 H), 3.78 (d, *J* = 4.1 Hz, 1 H), 3.58 (s, 3 H), 3.48–3.39 (m, 1 H), 2.91–2.84 (m, 1 H), 2.69–2.61 (m, 1 H), 2.12–2.00 (m, 1 H), 1.92–1.81 (m, 2 H), 1.70–1.49 (m, 3 H), 1.49–1.33 (m, 1 H), 0.88 (s, 9 H), 0.05 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 138.9, 130.8, 130.2, 114.3, 113.6, 81.4, 80.1, 74.3, 55.1, 40.9, 32.0, 31.6, 30.0, 27.3, 25.9, –4.2, –4.8; IR (film, cm^{-1}) 2929, 1040. MS(ESI): 413.2474 (413.2488 calcd for $C_{23}H_{38}SiO_3$, M + Na^+).

II-19a

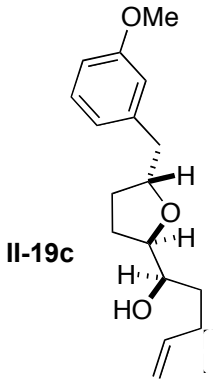


(±)-(1*R,2*R**,5*R**)-1-[5-(4-*tert*-Butylbenzyl)tetrahydrofuran-2-yl]pent-4-en-1-ol (II-19a, Table 2-2, Entries 1–2).** Removal of the TBS protecting group from **II-18a** (26 mg, 0.067 mmol) with TBAF (0.67 mL, 0.67 mmol) was achieved following general procedure 2. This procedure afforded 18 mg (96%) of the title compound as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.29 (m, 2 H), 7.17–7.13, (m, 2 H), 5.90–5.73 (m, 1 H), 5.09–4.94 (m, 2 H), 4.19–4.10 (m, 1 H), 3.89–3.82 (q, *J* = 7.0 Hz, 1 H), 3.44–3.36 (m, 1 H), 2.93 (dd, *J* = 6.3, 13.7 Hz, 1 H), 2.69, (dd, *J* = 8.0, 13.7 Hz, 1 H), 2.40–2.34 (d, *J* = 3.7 Hz, 1 H), 2.31–2.20 (m, 1 H), 2.18–2.06 (m, 1 H), 1.99–1.87 (m, 2 H), 1.65–1.40 (m, 4 H), 1.27 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 138.5, 135.5, 128.9, 114.7, 82.1, 80.0, 77.3, 73.4, 41.3, 34.3, 32.5, 32.0, 31.3, 29.8, 28.2; IR (film, cm^{-1}) 3436, 2964, 1060. MS(ESI): 325.2141 (325.2144 calcd for $C_{20}H_{30}O_2$, M + Na^+).



II-19b

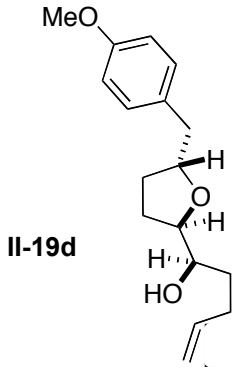
(±)-(1*R,2*R**,5*R**)-1-(5-Benzyltetrahydrofuran-2-yl)pent-4-en-1-ol (II-19b, Table 2-2, Entries 3–4).** Removal of the TBS protecting group from **II-18a** (36 mg, 0.1 mmol) with TBAF (1.0 mL, 1.0 mmol) was achieved following general procedure 2. This procedure afforded 22 mg (92%) of the title compound as an amber oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.31 (m, 3 H), 7.29–7.24 (m, 2 H), 5.95–5.83 (m, 1 H), 5.14–5.00 (m, 2 H), 4.25–4.17 (m, 1 H), 3.90 (q, *J* = 7.0 Hz, 1 H), 3.49–3.43 (m, 1 H), 3.01 (dd, *J* = 6.3, 13.7 Hz, 1 H), 2.78 (dd, *J* = 7.0, 13.7 Hz 1 H), 2.45 (s, 1 H), 2.40–2.30 (m, 1 H), 2.27–2.16 (m, 1 H), 2.07–1.95 (m, 2 H), 1.74–1.62 (m, 2 H), 1.59–1.51 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 138.5, 129.3, 128.3, 126.2, 114.7, 82.2, 79.9, 73.4, 41.8, 32.5, 31.9, 29.8, 28.2; IR (film, cm^{-1}) 3449, 2964, 1073. MS(ESI): 269.1514 (269.1517 calcd for $C_{16}H_{22}O_2$, M + Na^+).



II-19c

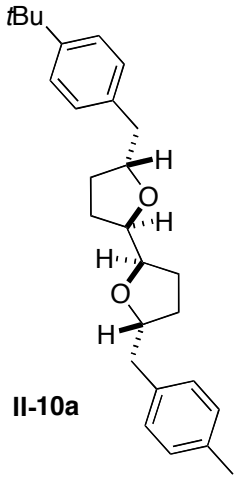
(±)-(1*R,2*R**,5*R**)-1-[5-(3-Methoxybenzyl)tetrahydrofuran-2-yl]pent-4-en-1-ol (II-19c, Table 2-2, Entries 5–6).** Removal of the TBS protecting group from **II-18c** (250 mg, 0.64 mmol) with TBAF (6.4 mL, 6.4 mmol) was achieved following

general procedure 2. This procedure afforded 170 mg (97%) of the title compound as an amber oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.17 (m, 2 H), 6.82–6.74 (m, 2 H), 5.89–5.77 (m, 1 H), 5.08–4.94 (m, 2 H), 4.19–4.10 (m, 1 H), 3.87–3.80 (m, 1 H), 3.79 (s, 3 H), 3.43–3.38 (m, 1 H), 2.93 (dd, *J* = 6.3, 13.7 Hz, 1 H), 2.70 (dd, *J* = 6.7, 13.7 Hz, 1 H), 2.35–2.24 (m, 1 H), 2.21–2.10 (m, 1 H), 2.02–1.90 (m, 2 H), 1.68–1.57 (m, 2 H), 1.54–1.45 (m, 2 H) (the OH proton signal was not detected due to broadening); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 140.2, 138.5, 129.2, 121.7, 115.0, 114.7, 111.5, 82.2, 79.9, 73.4, 55.1, 41.9, 32.6, 32.0, 30.0, 28.2; IR (film, cm^{-1}) 3453, 2937, 1046. MS(ESI): 299.1617 (299.1623 calcd for $C_{17}H_{24}O_3$, M + Na^+).



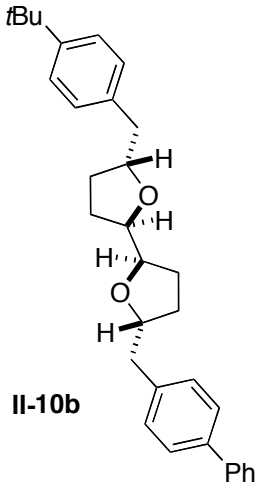
II-19d

(±)-(1*R,2*R**,5*R**)-1-[5-(4-Methoxybenzyl)tetrahydrofuran-2-yl]pent-4-en-1-ol (II-19d, Table 2-2, Entries 7–8).** Removal of the TBS protecting group from **II-18d** (290 mg, 0.74 mmol) with TBAF (7.4 mL, 7.4 mmol) was achieved following general procedure 2. This procedure afforded 190 mg (94%) of the title compound as an amber oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15–7.11 (m, 2 H), 6.85–6.81 (m, 2 H), 5.89–5.77 (m, 1 H), 5.08–4.94 (m, 2 H), 4.15–4.07 (m, 1 H), 3.86–3.80 (m, 1 H), 3,79 (s, 3 H), 3.43–3.36 (m, 1 H), 2.88 (dd, *J* = 5.9, 13.7 Hz, 1 H), 2.67 (dd, *J* = 6.7, 13.7 Hz, 1 H), 2.37 (s, 1 H), 2.36–2.24 (m, 1 H), 2.21–2.12 (m, 1 H), 2.00–1.89 (m, 2 H), 1.66–1.56 (m, 2 H), 1.54–1.46 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 138.4, 130.6, 130.2, 114.7, 113.7, 82.1, 80.1, 73.4, 55.1, 40.8, 32.5, 31.7, 29.8, 28.2; IR (film, cm^{-1}) 3469, 2918, 1036. MS(ESI): 299.1622 (299.1623 calcd for $C_{17}H_{24}O_3$, M + Na^+).



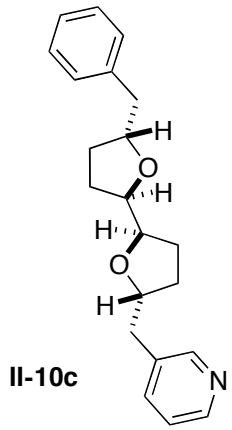
II-10a

(±)-(2*R,2'*R**,5*R**,5'*R**)-5-(4-*tert*-Butylbenzyl)-5'-(4-methylbenzyl)octahydro-2,2'-bifuran (II-10a, Table 2-2, Entry 1).** The coupling of **II-19a** (30 mg, 0.11 mmol) with 4-bromotoluene (28 µL, 0.22 mmol) was achieved following general procedure 1 using toluene as solvent and a reaction temperature of 110 °C. This procedure afforded 30 mg (67%) of the title compound as an amber oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.20 (m, 2 H), 7.19 (s, 1 H), 7.08–7.04 (m, 2 H), 7.01 (s, 3 H), 4.16–4.08 (m, 2 H), 3.90–3.84 (m, 2 H), 3.02–2.95 (m, 2 H), 2.56 (dd, *J* = 8.2, 13.3 Hz, 2 H), 2.24 (s, 3 H), 1.90–1.78 (m, 4 H), 1.56–1.44 (m, 4 H), 1.23 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 135.7, 135.6, 135.5, 129.2, 129.0, 128.9, 125.1, 81.7, 81.6, 80.5, 80.4, 41.5, 41.5, 34.3, 31.6, 31.4, 31.39, 29.8, 28.3, 21.0; IR (film, cm^{-1}) 2900, 1051. MS(ESI): 415.2594 (415.2613 calcd for $C_{27}H_{36}O_2$, M + Na^+).



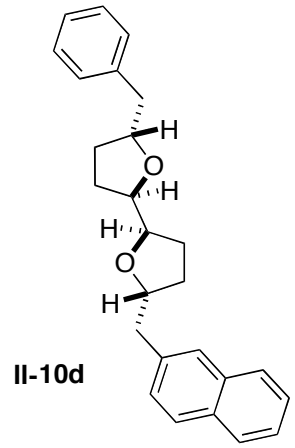
II-10b

(±)-(2*R,2'*R**,5*R**,5'*R**)-5-(Biphenyl-4-ylmethyl)-5'-(4-*tert*-butylbenzyl)octahydro-2,2'-bifuran** (**II-10b, Table 2-2, Entry 2**). The coupling of **II-19a** (50 mg, 0.17 mmol) with 4-bromobiphenyl (80 mg, 0.34 mmol) was achieved following general procedure 1 using toluene as solvent and a reaction temperature of 110 °C. This procedure afforded 46 mg (61%) of the title compound as a yellow oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.58 (m, 2 H), 7.55–7.50 (m, 2 H), 7.44 (t, *J* = 7.4 Hz, 2 H), 7.37–7.28, (m, 5 H), 7.15 (d, *J* = 8.2 Hz, 2 H), 4.31–4.17 (m, 2 H), 4.02–3.94 (m, 2 H), 3.11 (dt, *J* = 5.1, 13.9 Hz, 2 H), 2.75 (dd, *J* = 8.0, 13.5 Hz, 1 H), 2.65 (dd, *J* = 8.4, 13.3 Hz, 1 H), 2.00–1.89 (m, 4 H), 1.69–1.55 (m, 4 H), 1.32 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 141.0, 139.0, 137.9, 135.6, 129.7, 128.9, 128.7, 127.0, 126.9, 125.1, 81.7, 81.6, 80.5, 80.3, 41.6, 41.4, 34.3, 31.5, 29.8, 28.3 (three carbon signals are absent due to incidental equivalence); IR (film, cm^{-1}) 2910, 1049. MS(ESI): 477.2776 (477.2770 calcd for $C_{32}H_{38}O_2$, M + Na^+).



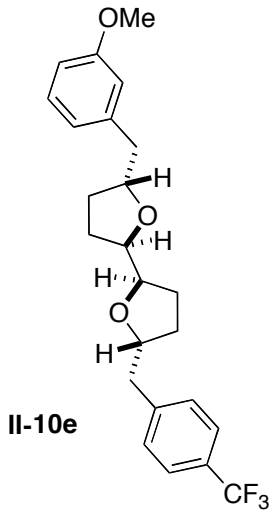
II-10c

(±)-(2*R,2'*R**,5*R**,5'*R**)-3-[5'-Benzyloctahydro-2,2'-bifuran-5-yl)methyl]pyridine (II-10c, Table 2-2, Entry 3).** The coupling of **II-19b** (25 mg, 0.1 mmol) with 3-bromopyridine (20 μL, 0.2 mmol) was achieved following general procedure 1 using toluene as solvent and a reaction temperature of 110 °C. This procedure afforded 20 mg (61%) of the title compound as an amber oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 2 H), 7.55 (d, *J* = 7.6, 1 H), 7.26–7.13 (m, 6 H), 4.19–4.08 (m, 2 H), 3.92–3.84 (m, 2 H), 3.01 (dd, *J* = 5.1, 13.0 Hz, 2 H), 2.93 (dd, *J* = 5.7, 13.9 Hz, 2 H), 1.94–1.81 (m, 4 H), 1.64–1.44 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 147.6, 138.7, 136.9, 134.2, 129.3, 128.2, 126.1, 123.2, 81.8, 81.5, 80.5, 79.6, 41.9, 38.9, 31.4, 31.3, 29.7, 28.3; IR (film, cm^{-1}) 2917, 1068. MS(ESI): 324.1960 (324.1964 calcd for $C_{21}H_{25}O_2N$, M + H^+).



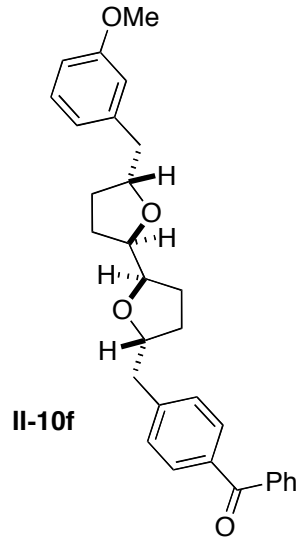
II-10d

(±)-(2*R,2'*R**,5*R**,5'*R**)-5-Benzyl-5'-(naphthalen-2-ylmethyl)octahydro-2,2'-bifuran (II-10d, Table 2-2, Entry 4).** The coupling of **II-19b** (50 mg, 0.17 mmol) with 2-bromonaphthalene (36 mg, 0.34 mmol) was achieved following general procedure 1 using toluene as solvent and a reaction temperature of 110 °C. This procedure afforded 40 mg (65%) of the title compound as an orange oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, CD_3CF_2OD) δ 8.48–8.39 (m, 3 H), 8.33–8.27 (m, 1 H), 8.15–8.04 (m, 2 H), 8.04–7.82 (m, 6 H), 5.01–4.83 (m, 2 H), 4.69–4.60 (m, 2 H), 3.86–3.83 (m, 1 H), 3.69–3.60 (m, 1 H), 3.48–3.38 (m, 1 H), 3.31–3.23 (m, 1 H), 2.70–2.45 (m, 4 H), 2.35–2.20 (m, 2 H), 2.18–2.05 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 136.3, 133.4, 132.0, 129.2, 128.2, 128.0, 127.7, 127.5, 127.48, 127.4, 126.0, 125.8, 125.2, 81.7, 81.68, 80.4, 80.3, 42.0, 41.9, 31.4, 31.39, 28.3, 28.26; IR (film, cm^{-1}) 3057, 1058. MS(ESI): 395.1994 (395.1987 calcd for $C_{26}H_{28}O_2$, M + Na^+).



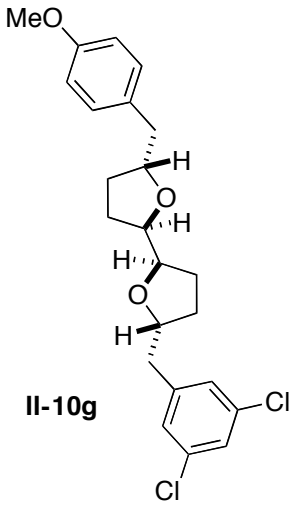
II-10e

(±)-(2*R,2'*R**,5*R**,5'*R**)-5-(3-Methoxybenzyl)-5'-[4-(trifluoromethyl)benzyl]octahydro-2,2'-bifuran (II-10e, Table 2-2, Entry 5).** The coupling of **II-19c** (40 mg, 0.15 mmol) with 4-brombenzotrifluoride (40 µL, 0.30 mmol) was achieved following general procedure 1 using toluene as solvent and a reaction temperature of 110 °C. This procedure afforded 40 mg (67%) of the title compound as an orange oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.44 (m, 2 H), 7.43–7.35 (m, 2 H), 7.18 (t, *J* = 7.4 Hz, 1 H), 6.81–6.73 (m, 3 H), 4.24–4.15 (m, 2 H), 3.97–3.89 (m, 2 H), 3.78 (s, 3 H), 3.09–3.00 (m, 2 H), 2.78 (dd, *J* = 7.1, 13.7 Hz, 1 H), 2.65 (dd, *J* = 8.2, 13.3 Hz, 1 H), 1.96–1.85 (m, 4 H), 1.68–1.49 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 140.3, 139.7, 132.7, 129.2, 126.2 (q, *J* = 222.8 Hz), 125.9, 123.0, 121.7, 115.0, 111.4, 81.7, 81.5, 80.3, 79.8, 55.1, 42.0, 41.6, 31.5, 31.4, 28.3, 28.26; IR (film, cm^{-1}) 2918, 1331, 1125. MS(ESI): 443.1815 (443.1810 calcd for $C_{24}H_{27}O_3F_3$, M + Na^+).



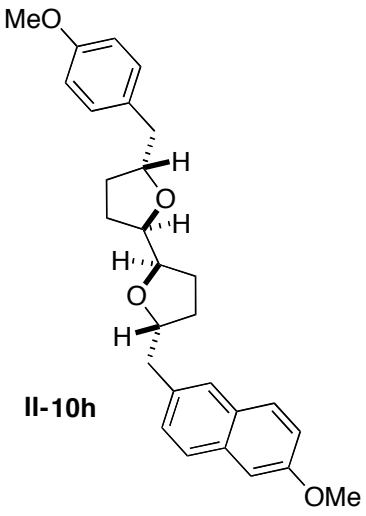
II-10f

(±)-(2*R,2'*R**,5*R**,5'*R**)-4-[5'-(3-Methoxybenzyl)octahydro-2,2'-bifuran-5-ylmethyl]phenyl(phenyl)methanone (II-10f, Table 2-2, Entry 6).** The coupling of **II-19c** (40 mg, 0.15 mmol) with 4-bromobenzophenone (80 mg, 0.30 mmol) was achieved following general procedure 1 using toluene as solvent and a reaction temperature of 110 °C. This procedure afforded 46 mg (65%) of the title compound as an amber oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.77 (m, 2 H), 7.61–7.55 (m, 2 H), 7.51–7.45 (m, 2 H), 7.32 (d, *J* = 8.2 Hz, 2 H), 7.18 (t, *J* = 7.8 Hz, 2 H), 6.81–6.72 (m, 3 H), 4.29–4.16 (m, 2 H), 3.98–3.92 (m, 2 H), 3.78 (s, 3 H), 3.14–3.02 (m, 2 H), 2.81 (dd, *J* = 7.0, 13.3 Hz, 1 H), 2.66 (dd, *J* = 5.1, 8.2 Hz, 1 H), 1.97–1.86 (m, 4 H), 1.68–1.52 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 159.5, 144.0, 140.3, 137.8, 135.5, 132.2, 130.2, 130.0, 129.3, 129.2, 128.2, 121.7, 115.0, 111.4, 81.8, 81.6, 80.4, 79.9, 55.1, 42.0, 41.9, 31.6, 31.5, 28.3, 28.3; IR (film, cm^{-1}) 2918, 1603, 1315. MS(ESI): 479.2190 (479.2198 calcd for $C_{30}H_{32}O_4$, M + Na^+).



II-10g

(±)-(2*R,2'*R**,5*R**,5'*R**)-5-(3,5-Dichlorobenzyl)-5'-(4-methoxybenzyl)octahydro-2,2'-bifuran (II-10g, Table 2-2, Entry 7).** The coupling of **II-19d** (30 mg, 0.10 mmol) with 1-bromo-3,5-dichlorobenzene (47 mg, 0.20 mmol) was achieved following general procedure 1 using toluene as solvent and a reaction temperature of 110 °C. This procedure afforded 30 mg (69%) of the title compound as an amber oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.19 (m, 1 H), 7.14–7.08 (m, 4 H), 6.85–6.79 (m, 2 H), 4.20–4.10 (m, 2 H), 3.95–3.88 (m, 2 H), 3.78 (s, 3 H), 3.01–2.90 (m, 2 H), 2.71–2.59 (m, 2 H), 1.98–1.85 (m, 4 H), 1.69–1.45 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 142.3, 134.6, 130.8, 130.2, 127.8, 126.3, 113.7, 81.8, 81.5, 80.6, 79.4, 55.2, 41.2, 41.0, 31.5, 31.4, 28.3, 28.2; IR (film, cm^{-1}) 2931, 1038, 795. MS(ESI): 443.1162 (443.1157 calcd for $C_{22}H_{26}O_3Cl_2$, M + Na^+).

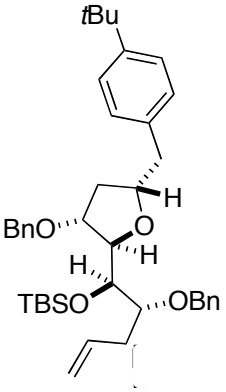


II-10h

(±)-(2*R,2'*R**,5*R**,5'*R**)-5-(4-Methoxybenzyl)-5'-(6-methoxynaphthalen-2-ylmethyl)octahydro-2,2'-bifuran (II-10h, Table 2-2, Entry 8).** The coupling of **II-19d** (30 mg, 0.10 mmol) with 2-bromo-6-methoxynaphthalene (48 mg, 0.20 mmol) was achieved following general procedure 1 using toluene as solvent and a reaction temperature of 110 °C. This procedure afforded 21 mg (52%) of the title compound as an amber oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, ($(CF_3)_2CDOD$) δ 8.32 (t, *J* = 8.4 Hz, 2 H), 8.21 (s, 1 H), 7.95 (d, *J* = 8.4 Hz, 1 H), 7.85 (s, 2 H), 7.79–7.72 (m, 2 H), 7.50 (d, *J* = 8.2 Hz, 2 H), 4.98–4.89 (m, 1 H), 4.87–4.78 (m, 1 H), 4.64–4.56 (m, 2 H), 4.45 (s, 3 H), 4.41 (s, 3 H), 3.75 (dd, *J* = 5.5, 13.1 Hz, 1 H), 3.57 (dd, *J* = 5.5, 13.3 Hz, 1 H), 3.38 (dd, *J* = 8.0, 13.1 Hz, 1 H), 3.21 (dd, *J* = 8.0, 13.3 Hz, 1 H), 2.66–2.46 (m, 4 H), 2.35–2.16 (m, 2 H), 2.15–2.05 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 157.1, 133.9, 133.0, 130.7, 130.1, 128.9, 128.4, 127.3, 126.5, 118.5, 113.5, 105.5, 81.6, 81.58, 80.5, 80.3, 55.2, 55.1, 41.7, 40.9, 31.4, 31.3, 28.2 (two carbon signals are absent due to incidental equivalence); IR (film, cm^{-1}) 2933, 1035. MS(ESI): 592.3429 (593.3427 calcd for $C_{28}H_{32}O_4$, M + Na^+).

(–)-(2*R*,2'*R*,5*R*,5'*R*)-5-(4-Methoxybenzyl)-5'-(6-methoxynaphthalen-2-ylmethyl)octahydro-2,2'-bifuran (II-10h, eq 2-4). The title compound was prepared from (–)-**II-13** using a sequence identical to that described above for the conversion of (±)-**II-13** to (±)-**II-18d**, (±)-**II-18d** to (±)-**II-19d**, and (±)-**II-19d** to (±)-**II-10h**. The yield of (+)-**II-18d** was 65%; $[\alpha]_D^{23}$ = +0.6° (*c* 0.43, CH_2Cl_2). The yield of (–)-**II-19d** was 88%; $[\alpha]_D^{23}$ = –3.3° (*c* 0.11, CH_2Cl_2). The yield of (–)-**II-10h** was 61%; $[\alpha]_D^{23}$ = –14.2° (*c* 0.12, CH_2Cl_2). NMR data for these compounds were identical to those reported above.

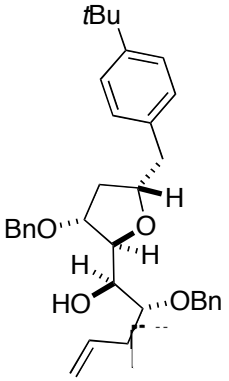
II-30



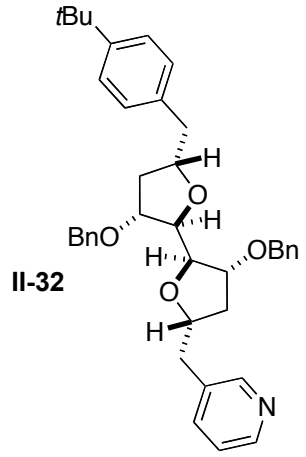
(–)-(1'*R*,2'*S*,2*R*,3*R*,5*S*)-2'-(Benzyloxy)-1'-[3-(benzyloxy)-5-(4-*tert*-butylbenzyl)tetrahydrofuran-2-yl]pent-4-enyloxy(*tert*-butyl)dimethylsilane (II-30). The coupling of **II-29** (40 mg, 0.8 mmol) with 4-bromo-*tert*-butylbenzene (280 µL, 1.6 mmol) was achieved following general procedure 1 using THF as solvent and a reaction temperature of 65 °C. This procedure afforded 170 mg (35%) of the title compound as an orange oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis, $[\alpha]_D^{23}$ = –12.2° (*c* 0.37, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.26 (m, 12 H), 7.21–7.16 (m, 2 H), 6.00–5.89 (m, 1 H), 5.12–5.02 (m, 2 H), 4.61–4.54 (m, 2 H), 4.44 (d, *J* = 11.0 Hz, 1 H), 4.37 (d, *J* = 11.7 Hz, 1 H), 4.34–4.25 (m, 1 H), 4.08–4.01 (m, 2 H), 3.85 (q, *J* = 2.7 Hz, 1 H), 3.39–3.32 (m, 1 H), 3.03 (dd, *J* = 6.3, 13.3 Hz, 1 H), 2.85 (dd, *J* = 7.0, 13.7 Hz, 1 H), 2.45–2.39 (m, 2 H), 2.29–2.21 (m, 1 H), 1.84–1.74 (m, 1 H), 1.36 (s, 9 H), 0.92 (s, 9 H), 0.08 (s, 3 H), 0.01 (s, 3 H);^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 138.7, 137.9, 136.5, 135.5, 128.9, 128.3, 128.1, 127.8, 127.6,

127.3, 125.1, 116.1, 84.2, 80.6, 80.3, 79.3, 74.6, 71.9, 71.4, 41.5, 37.6, 35.1, 34.3, 31.3, 26.0, 18.3, –4.3, –4.7; IR (film, cm^{-1}) 2955, 1092. MS(ESI): 651.3848 (651.3846 calcd for $C_{40}H_{56}SiO_4$, M + Na^+).

II-31



(–)-(1'*R*,2'*S*,2*S*,3*R*,5*S*)-2'-(Benzyloxy)-1'-[3-(benzyloxy)-5-(4-*tert*-butylbenzyl)tetrahydrofuran-2-yl]pent-4-en-1-ol (II-31). Removal of the TBS protecting group from **II-30** (160 mg, 0.25 mmol) with TBAF (2.5 mL, 2.5 mmol) was achieved following general procedure 2. This procedure afforded 106 mg (81%) of the title compound as an orange oil, $[\alpha]_D^{23}$ = –70.4° (*c* 0.1, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.26 (m, 12 H), 7.17–7.13 (m, 2 H), 6.01–5.88 (m, 1 H), 5.20–5.07 (m, 2 H), 4.66–4.44 (m, 4 H), 4.40–4.29 (m, 2 H), 4.21–4.15 (m, 1 H), 3.64–3.56 (m, 1 H), 3.51–3.45 (m, 1 H), 3.06 (dd, *J* = 6.6, 13.5 Hz, 1 H), 2.83 (dd, *J* = 6.5, 13.5 Hz, 1 H), 2.61–2.54 (m, 1 H), 2.48–2.39 (m, 1 H), 2.23–2.14 (m, 2 H), 1.91–1.84 (m, 1 H), 1.32 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 138.4, 138.1, 135.5, 134.9, 129.0, 128.4, 128.3, 127.9, 127.7, 127.6, 127.59, 125.3, 117.3, 82.0, 80.9, 80.4, 79.4, 72.4, 72.2, 71.8, 41.7, 37.3, 35.2, 34.4, 31.4; IR (film, cm^{-1}) 3468, 2961, 1100. MS(ESI): 537.2988 (537.2981 calcd for $C_{34}H_{42}O_4$, M + Na^+).



II-32

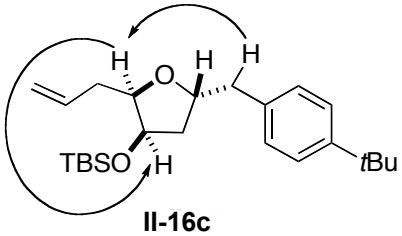
(–)-(2*R*,2'*R*,3*R*,3'*R*,5*S*,5'*S*)-3-[3,3'-Bis(benzyloxy)-5'-(4-*tert*-butylbenzyl)octahydro-2,2'-bifuran-5-ylmethyl]pyridine (II-32). The coupling of **II-31** (110 mg, 0.20 mmol) with 3-bromopyridine (40 µL, 0.40 mmol) was achieved following general procedure 1 using toluene as solvent and a reaction temperature of 110 °C. This procedure afforded 120 mg (57%) of the title compound as an amber oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis, $[\alpha]_D^{23} = -43.7^o$ (*c* 0.83, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43–8.36 (m, 1 H), 7.46–7.41 (m, 1 H), 7.31–7.20 (m, 11 H). 7.15–7.09 (m, 2 H), 7.07–7.02 (m, 3 H), 4.50–4.34 (m, 4 H), 4.20–4.09 (m, 3 H), 4.07–4.00 (m, 3 H), 3.00–2.89 (m, 2 H), 2.80–2.66 (m, 2 H), 2.19–2.04 (m, 2 H), 1.78–1.64 (m, 2 H), 1.25 (s, 9 H);^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 148.9, 147.6, 138.1, 138.0, 136.8, 135.5, 134.3, 128.9, 128.44, 128.4, 127.7, 127.67, 127.6, 125.2, 123.2, 84.4, 84.2, 81.0, 80.9, 80.3, 79.6, 71.7, 41.7, 39.3, 37.3, 37.2, 34.4, 31.4 (two signals are absent due to incidental equivalence); IR (film, cm^{-1}) 2918, 1648, 1185. MS(ESI): 592.3429 (593.3427 calcd for $C_{39}H_{45}NO_4$, M + Na^+).

Assignment of Stereochemistry

2,3,5 Substituted Tetrahydrofurans (Table 2-1)

The relative stereochemistry of **II-16c** was assigned on the basis of signals observed in ^{1}H NMR nOe experiments. Relevant nOe data is shown below.

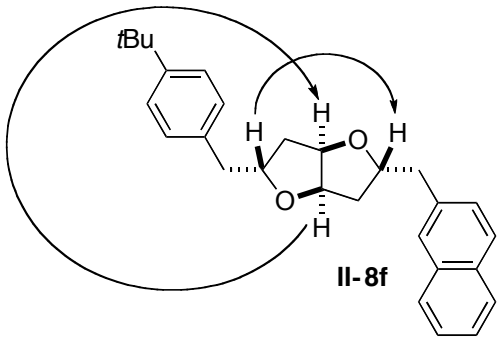
The stereochemistry of the related compounds **II-16a**, **II-16b**, and **II-16d** was assigned based on analogy to **II-16c**.



II-16c

Fused Bis-Tetrahydrofurans (Table 2-1)

The relative stereochemistry of **II-8f** was assigned on the basis of signals observed in ^{1}H NMR nOe experiments. Relevant nOe data is shown below.

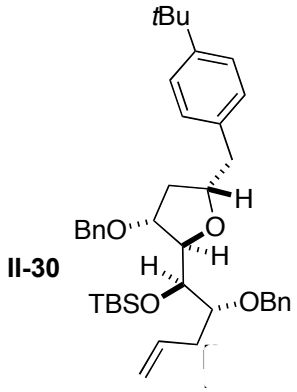


II-8f

The stereochemistry of the related compounds **II-8a–e** and **II-8g–h** was assigned based on analogy to **II-8f**.

2,5 Substituted Tetrahydrofurans (Table 2-2 and Scheme 2-2)

The relative stereochemistry of **II-30** was assigned on the basis of signals observed in ^{1}H NMR nOe experiments. Relevant nOe data is shown below.

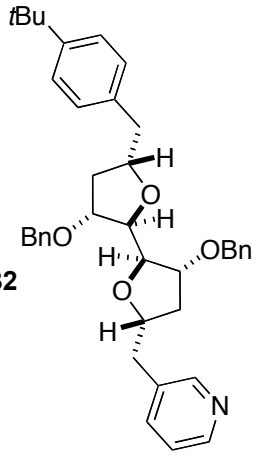


II-30

The stereochemistry of the related compounds **II-19a–d** and was assigned based on analogy to **II-30**.

Attached-Ring Bis-Tetrahydrofurans

The relative stereochemistry of **II-32** was assigned on the basis of signals observed in ^{1}H NMR nOe experiments. Relevant nOe data is shown below.



II-32

The stereochemistry of the related compounds **II-10a–h** was assigned based on analogy to **II-32**.

2.6 References

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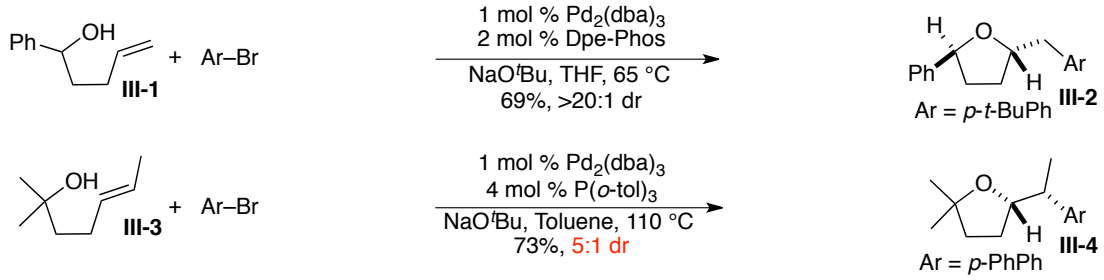
Chapter 3: Palladium-Catalyzed Carboetherification Reactions of Internal Alkene Substrates

3.1 Introduction

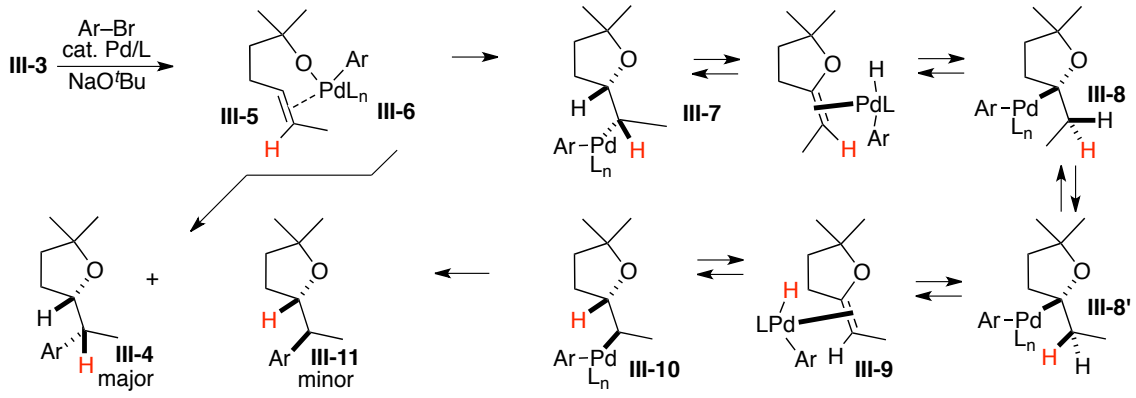
The prevalence of tetrahydrofuran units in natural products and other biologically active molecules has inspired the invention of numerous methods for the construction of these heterocycles.[1] For the past several years, our group has investigated a new approach to the stereoselective synthesis of tetrahydrofurans via Pd-catalyzed cross-coupling reactions between γ-hydroxy alkenes and aryl or alkenyl halides.[2] These reactions exhibit several attractive, synthetically useful features: simple starting materials are employed, both a C-O and a C-C bond are generated, and control of relative stereochemistry around the tetrahydrofuran ring is generally high. For example, the coupling of **III-1** with 1-bromo-4-*tert*-butylbenzene afforded **III-2** in 69% yield with >20:1 dr (Scheme 3-1).[3] Although Pd-catalyzed carboetherifications have considerable utility, at the time I joined the group, the method suffered from a significant limitation: transformations of substrates such as **III-3** that contain acyclic internal alkenes afford products bearing stereocenters adjacent to the ring (e.g., **III-4**) with only modest stereoselectivity (ca. 3-5:1 dr).



Scheme 3-1. Prior Studies

3.2 Mechanism of Diastereomer Formation

Through a series of deuterium labeling experiments, Dr. Mike Hay found that both diastereomers (e.g., **III-4** and **III-11**) formed in carboetherification reactions of substrates such as **III-3** arise from a common intermediate (**III-6**) (Scheme 3-2).[4,5] The mechanism of these transformations involves oxidative addition of the aryl halide to Pd(0) followed by substitution of alkoxide for bromide to provide **III-5**. A key syn-oxypalladation of **III-5** generates intermediate **III-6**, which can undergo C-C bond-forming reductive elimination to afford tetrahydrofuran product **III-4**. However, the reductive elimination from complex **III-6** is not fast enough to avoid competing β-hydride elimination. Thus, partial isomerization of **III-6** occurs via β-hydride elimination/hydridopalladation to provide **III-8**, which undergoes σ-bond rotation followed by a second β-hydride elimination/hydridopalladation to yield **III-10**. Reductive elimination from **III-10** affords the minor stereoisomer **III-11**, leading to the modest diastereoselectivity observed with substrates such as **III-3**.

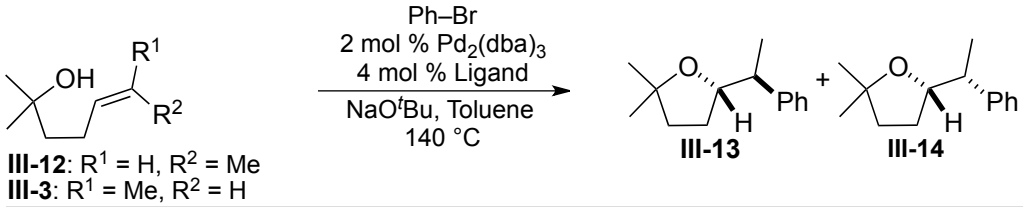


Scheme 3-2. Mechanism

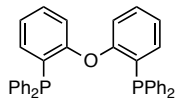
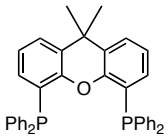
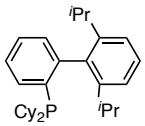
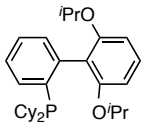
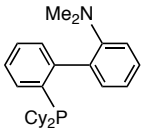
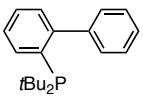
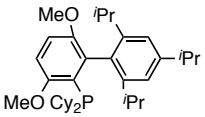
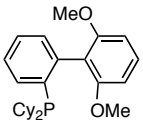
3.3 Ligand Optimization

In recent years, a number of new phosphine ligands have been developed for Pd-catalyzed carbon-carbon and carbon-heteroatom bond-forming reactions that accelerate reductive elimination.[6] It seemed that one of these ligands could potentially improve the diastereoselectivity in Pd-catalyzed carboetherifications of

internal alkenes by increasing the rate of reductive elimination from intermediate **III-6**. In order to probe this hypothesis, we investigated the Pd-catalyzed coupling of (*Z*)-2-methylhept-5-en-2-ol (**III-12**) with bromobenzene using a number of different ligands known to promote rapid reductive elimination.[7] As shown in Table 3-1, P(*o*-tol)$_3$, which was employed in our initial studies, provided **III-13** in good yield but only 4:1 dr. Chelating ligands with wide bite angles, such as Dpe-Phos and xantphos, failed to provide satisfactory results. However, considerably improved diastereoselectivity was obtained using Buchwald's S-Phos ligand (entry 9, 9:1 dr). In addition, the Pd/S-Phos catalyst transformed *E*-alcohol stereoisomer **III-3** to tetrahydrofuran **III-14** in good yield and excellent diastereoselectivity (entry 10, 20:1 dr).[8,9]



III-12: R^1 = H, R^2 = Me
III-3: R^1 = Me, R^2 = H

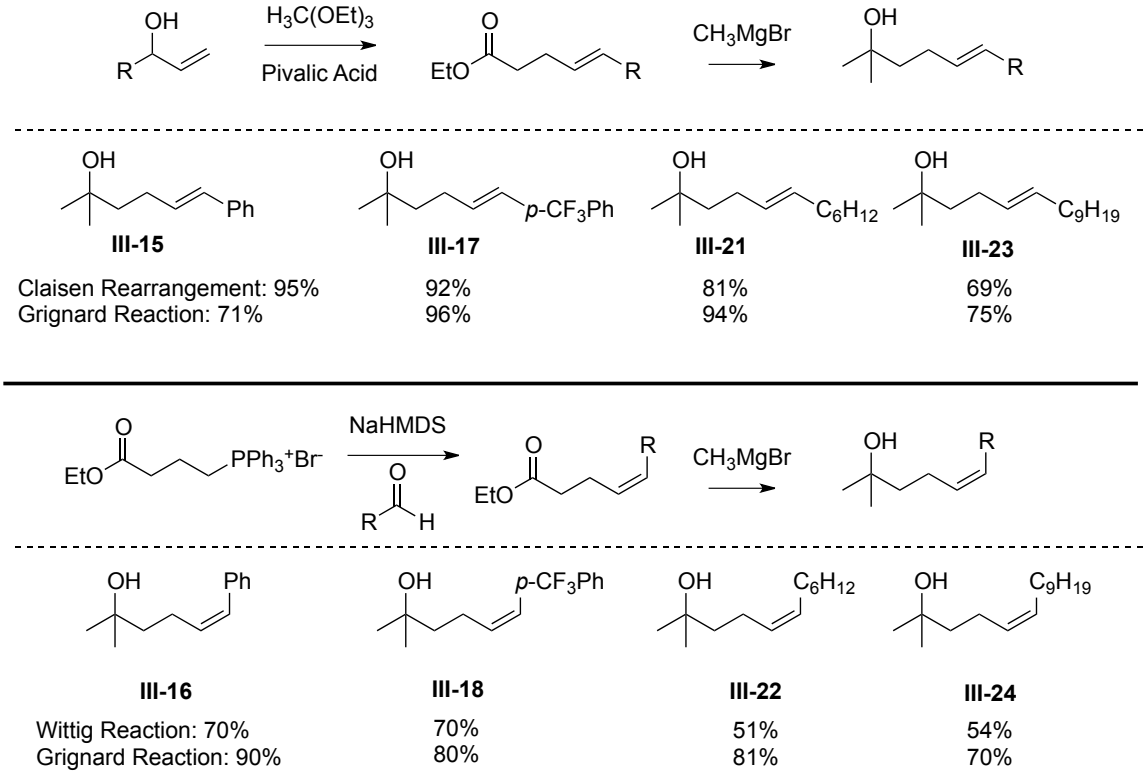
entry	substrate	ligand		III-13:III-14	yield (%)[b]
1	**III-12**	P(*o*-tol)$_3$		4:1	76
2	**III-12**	Dpe-Phos		1:1	55
3	**III-12**	Xantphos		2:1	17
4	**III-12**	X-Phos		3:1	40
5	**III-12**	RuPhos		9:1	68
6	**III-12**	Dave-phos		2:1	49
7	**III-12**	John-phos		2:1	18
8	**III-12**	Brett-phos		–	0
9	**III-12**	S-Phos		9:1	84
10	**III-3**	S-Phos		1:20	86

[a] Conditions: 1.0 equiv of alcohol, 2.0 equiv of ArBr, 2.0 equiv of NaO$_t$Bu, 2 mol % of Pd$_2$(dba)$_3$, 4 mol % of ligand, xylenes, 140 °C. [b] Isolated yields (average of two or more experiments).

Table 3-1. Ligand Optimization[a]

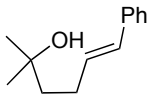
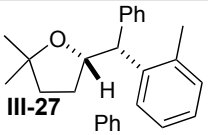
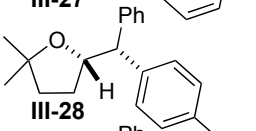
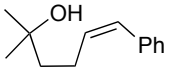
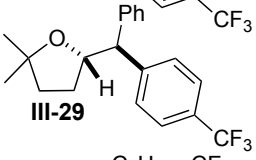
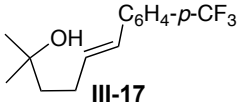
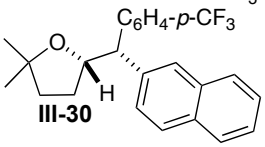
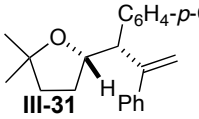
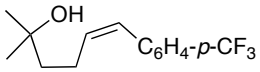
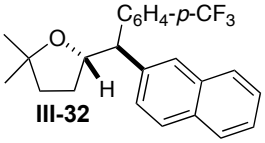
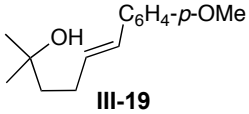
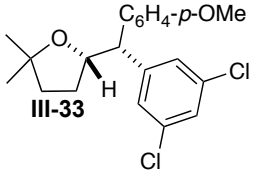
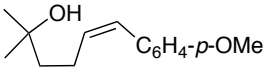
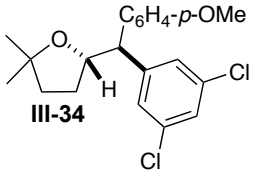
3.3 Substrate Scope

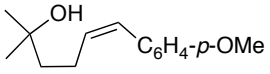
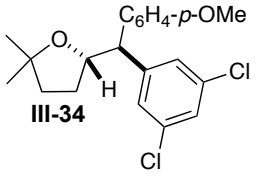
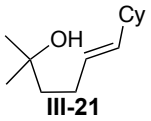
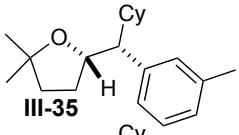
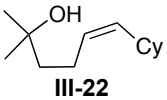
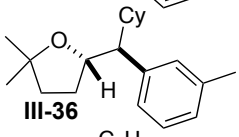
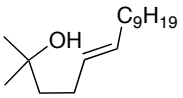
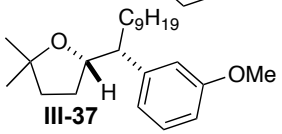
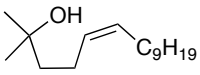
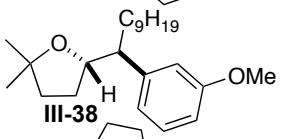
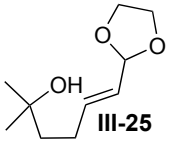
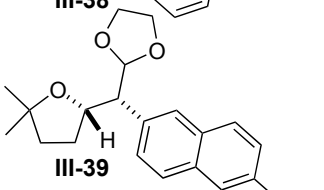
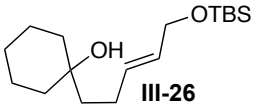
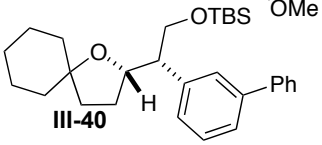
With a much more effective catalyst system in hand, we investigated Pd-catalyzed carboetherification reactions between a range of aryl or alkenyl bromides and several different γ-hydroxyalkene substrates, which were synthesized according to the general route shown in Scheme **3-3**.[10]



Scheme 3-3. General Method for the Synthesis of Various Substrates

As shown in Table 3-2, both electron-donating and electron-withdrawing groups on the aryl bromide were tolerated. In all cases examined, the major diastereomer resulted from *syn*-addition of the arene and the oxygen atom across the double bond, which is consistent with our prior results.

entry	substrate	product	dr	yield (%)[b]
1	 **III-15**	 **III-27**	>20:1	82
2	**III-15**	 **III-28**	>20:1	87
3	 **III-16**	 **III-29**	9:1	74
4	 **III-17**	 **III-30**	>20:1	89
5	**III-17**	 **III-31**	>20:1	55
6	 **III-18**	 **III-32**	>20:1	96
7	 **III-19**	 **III-33**	>20:1	51
8	 **III-20**	 **III-34**	>20:1	60

8	 **III-20**	 **III-34**	>20:1	60
9	 **III-21**	 **III-35**	>20:1	90
10	 **III-22**	 **III-36**	2:1	23[c,d]
11	 **III-23**	 **III-37**	>20:1	94
12	 **III-24**	 **III-38**	4:1	43[d]
13	 **III-25**	 **III-39**	>20:1	42
14	 **III-26** 18:1 *E*:*Z*	 **III-40**	12:1	86

a Conditions: 1.0 equiv of alcohol, 2.0 equiv of ArBr, 2.0 equiv of NaOtBu, 2 mol % of Pd2(dba)3, 4 mol % of S-Phos, xylenes, 140 °C. *b* Isolated yields (average of two or more experiments). *c* NMR yield. This material was contaminated with ca. 15% of an inseparable unidentified side product. *d* Formation of a side product tentatively assigned as a regioisomer was also observed.

Table 3-2. Synthesis of Tetrahydrofurans[a]

In most instances, *E*-alkene substrates bearing aryl or alkyl substituents were converted to the desired products with high diastereoselectivities (entries 1, 2, 4, 5, 7, and 11). In addition, the coupling reaction of a sterically hindered cyclohexyl-substituted alkene was also efficient (entry 9). An *E*-alkene bearing an acetal was transformed into the desired tetrahydrofuran **III-39** with good diastereoselectivity, but only modest yield (entry 13). In contrast, the conversion

of cyclohexanol derivative **III-26** to spirocyclic tetrahydrofuran **III-40** proceeded with good yield (entry 14), but slightly lower stereoselectivity (12:1).

Although reactions of *Z*-alkenes substituted with methyl or phenyl groups proceeded with only 9:1 dr (Table 3-1, entry 9, and Table 3-2, entry 3), substrates bearing either electron-rich or electron-poor aryl substituents on the alkene were converted to products with excellent diastereoselectivity (Table 3-2, entries 6 and 8). However, chemical yields were lower with the electron-donating aryl substituent (entry 8). Unfortunately, *Z*-alkene substrates bearing either a long alkyl chain (entry 12) or a bulky substituent (entry 10) were transformed with poor diastereoselectivity, and the formation of side products tentatively assigned as regioisomers was also observed.[11]

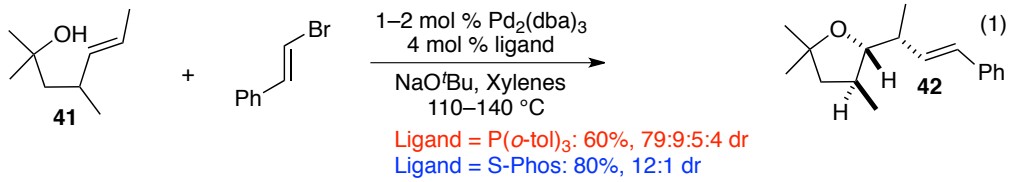
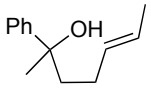
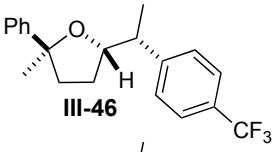
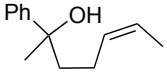
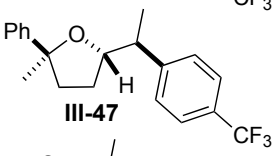
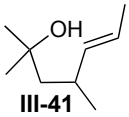
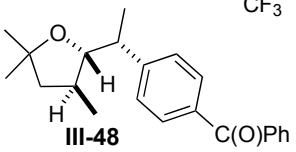
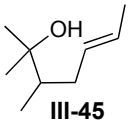
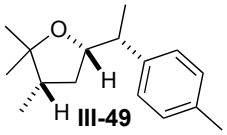


Figure 3.1. Improvement in dr with S-phos.

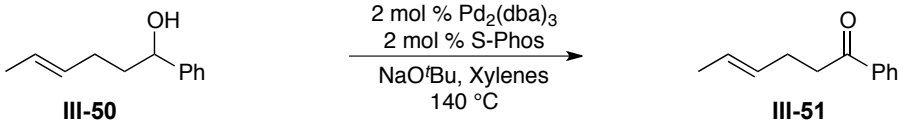
Prior efforts to effect carboetherification reactions of internal alkene substrates bearing stereocenters led to the formation of complicated mixtures of stereoisomers. For example, Dr. Mike Hay had previously shown the Pd/P(*o*-tol)$_3$-catalyzed coupling of **III-41** with β-bromostyrene proceeded in 60% yield and afforded an inseparable mixture of four diastereomers (eq 1). However, I found that the use of the S-Phos ligand provided **III-42** in 80% yield with 12:1 dr.[12] As shown in Table 3-3, *E*-alkene substrates bearing stereocenters at C1 (entry 1) or C3 (entry 3) were efficiently converted to polysubstituted tetrahydrofurans with good to excellent stereocontrol. The conversion of *Z*-alkene **III-44** to tetrahydrofuran **III-47** proceeded with 7:1 *syn*/*anti* addition selectivity, which is similar to results obtained for carboetherification of (*Z*)-2-methylhept-5-en-2-ol **III-12** (Table 3-1, entry 9).[13] Although the coupling of **III-45** with 4-bromotoluene provided a 4:1 mixture of tetrahydrofuran diastereomers epimeric at C4,

complete selectivity for *syn*-addition was observed.[14] Nonetheless, all four transformations illustrated in Table 3-3 afforded products with significantly better diastereoselectivities than were obtained in related transformations with P(*o*-tol)$_3$ as ligand. Although this method is very effective with tertiary alcohol substrates bearing internal alkenes, efforts to employ secondary alcohols failed to generate tetrahydrofuran products. Instead, oxidation of the secondary alcohol to the corresponding ketone was observed, as shown in Figure 3-2.[15]

entry	substrate	product	dr	yield (%)[b]
1	 **III-43**	 **III-46**	>20:1	83
2	 **III-44**	 **III-47**	7:1[c]	87
3	 **III-41**	 **III-48**	20:1	83
4	 **III-45**	 **III-49**	4:1[d]	84

[a] Conditions: 1.0 equiv of alcohol, 2.0 equiv of ArBr, 2.0 equiv of NaO^{t}Bu, 2 mol % of $Pd_2(dba)_3$, 4 mol % of S-Phos, Xylenes, 140 °C. [b] Isolated yields (average of two or more experiments). [c] The two diaster- eomers are epimeric at C1′. [d] The two diastereomers are epimeric at C4.

Table 3-3. Synthesis of Polysubstituted Tetrahydrofurans[a]

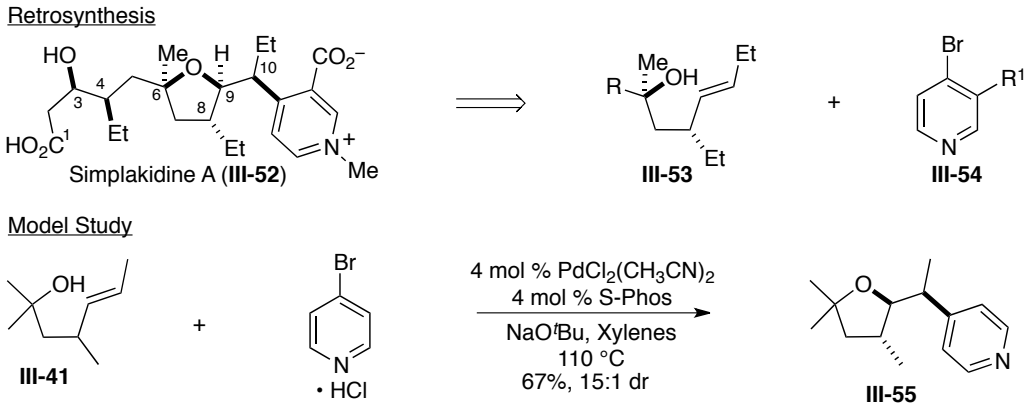


III-50 **III-51**

Figure 3.2. Attempted Pd-Catalyzed Carboetherification Reactions of Secondary Alcohols.

3.4 A Model System of Simplakidine A

The results illustrated in Table 3-3 prompted us to model the feasibility of applying our method to the synthesis of simplakidine A (**III-52**).[16] This polysubstituted tetrahydrofuran natural product exhibits cytotoxic activity and has not previously been synthesized. As shown in Scheme 3-3, the tetrahydrofuran core of this molecule could potentially be generated through a Pd-catalyzed carboetherification between a tertiary alcohol bearing a pendant *E*-alkene (**III-53**) and a suitably substituted 4-bromopyridine derivative (**III-54**). The ring-closing reaction would form the C9 and C10 stereo-centers with concomitant installation of the heteroaryl group.

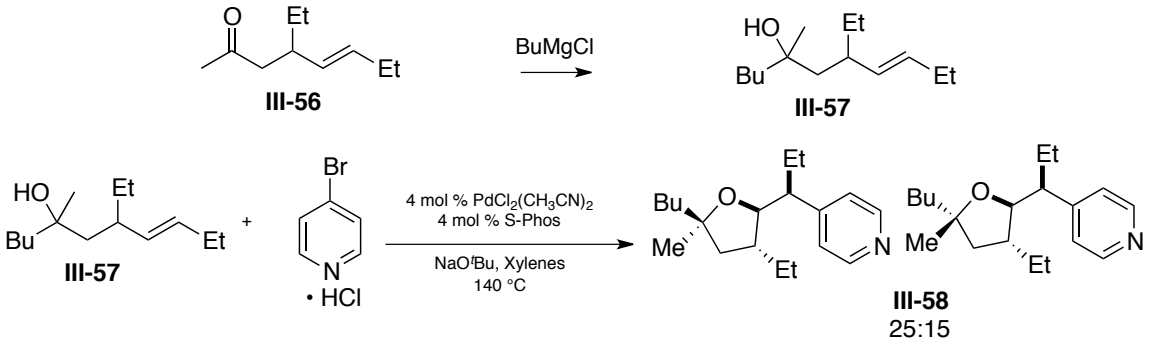


Scheme 3-4. Strategy for the Synthesis of Simplakidine A

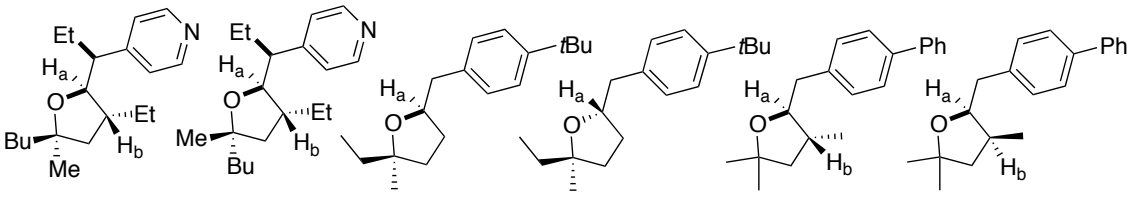
The two substituents on C6 of the natural product are fairly close in size (approximately Me vs *i*-Bu), which suggests the diastereotopic face selectivity of the alkene carboetherification reaction will likely be controlled by the stereochemical configuration at C8 of substrate **III-53** rather than C6. Thus, the simple tertiary alcohol **III-41** seemed to be a reasonable approximation to **III-53** for an initial model study. As such, we examined the Pd/S-Phos-catalyzed coupling of **III-41** with 4-bromopyridine hydrochloride. We were gratified to find that this transformation provided **III-55** with 15:1 dr in 67% yield.

To determine if the assumption that tertiary alcohol **III-41** could be used to approximate **III-53** was reasonable, **III-56** was synthesized according to a

literature procedure[17] and was transformed into substrate **III-57** in 2:1 dr via Grignard addition. Subsequently, **III-57** was coupled under the optimized conditions to 4-bromopyridine, and the desired product **III-58** was obtained as a mixture of 4 diastereomers in a 25:15:6:2 ratio (Scheme 3-5). Based on analogy to known compounds **III-60** and **III-61,** in which the proton at the 2 position of the tetrahydrofuran ring of the minor 2,5-*cis* isomer is shifted upfield with respect to the 2,5-*trans* isomer, and **III-62** and **III-63,** in which the proton at the 3 position of the tetrahydrofuran ring of the 2,3-*cis* isomer is shifted upfield with respect to the 2,3-*trans* isomer, we tentatively assigned the major isomer (**III-58)** as the 2,3-*trans*, 2,5-*cis* product and the minor isomer (**III-59**) as the 2,3-*trans*, 2,5-*trans* product. Thus, the stereocenter at C4 of **III-57** likely controlled the diastereoselectivity of the reaction, indicating that simplakidine, which possesses a 2,3-*trans*, 2,5-*cis* configuration, may be accessed using our methodology. However, in order to more accurately determine the diastereoselectivity of the reaction, **III-57** must be synthesized as a single diastereomer and subjected to the optimized conditions, and nOe analysis must be performed on the final product.



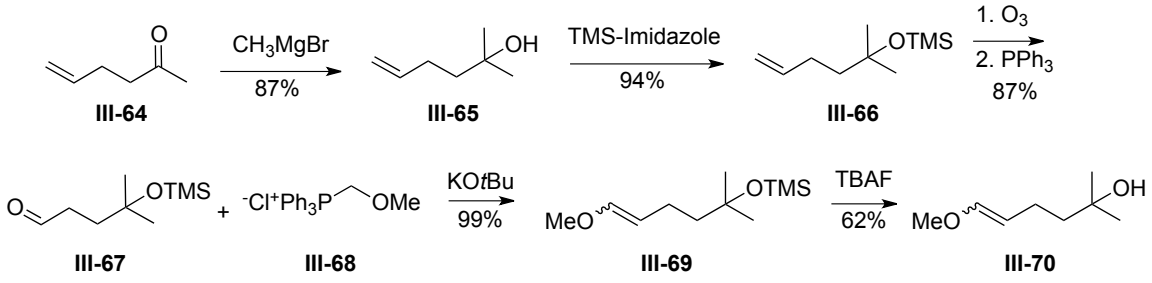
Scheme 3-5. Pd-Catalyzed Carboetherification Reactions of a Model System Containing a Stereocenter at the Cyclizing Alcohol



	III-58 Major	III-59 Minor	III-60	III-61	III-62	III-63
Chemical Shift of H_a	3.77–3.73	3.73–3.69	4.24–4.17	4.16–4.01	3.82–3.77	4.29–4.20
Chemical Shift of H_b	1.96–1.92	1.92–1.89	NA	NA	2.08–1.92	2.48–2.39

Figure 3-3. Known Compounds Used to Assign the Stereochemistry of **III-58** and **III-59**

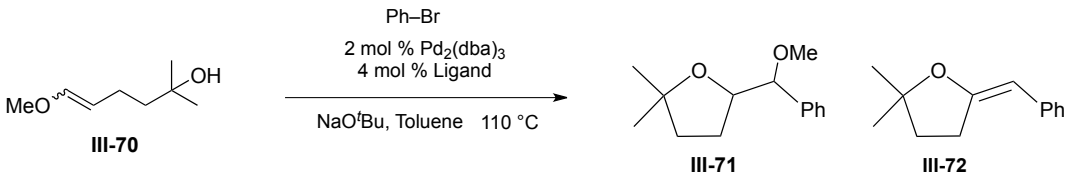
Although we had demonstrated that polysubstituted natural products such as simplakidine could be accessed with our methodology, we desired to develop a general strategy for biologically active tetrahydrofurans, especially the annoaceous acetogenins, which possess a hydroxyl substituent at the 1' position. To this end, we evaluated the carboetherification of enol ether substrate **III-70.** This substrate was synthesized from commercially available hex-5-en-2-one (**III-64**) via methyl Grignard addition, TMS protection of the resulting alcohol, and ozonolysis to afford aldehyde **III-67**. Subsequently, **III-67** was transformed to **III-70** using the corresponding Wittig reagent followed by removal of the TMS group.



Scheme 3-6. Synthesis of Enol Ether Substrate **III-70**

Using a catalyst system composed of S-phos and Pd_2dba_3, a complex mixture of starting material and various unidentified products were obtained. In contrast, when chelating ligand xantphos was employed, **III-72**, a compound derived from alkoxy elimination, was detected in the crude HNMR spectrum. A variety of other

ligands were also used to effect the desired transformation; however, in all cases, the reaction conditions failed to produce polysubstituted tetrahydrofurans in appreciable yield. Thus, further optimization is necessary in order to access these biologically relevant motifs.



III-70 **III-71** **III-72**

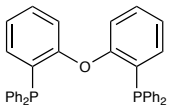
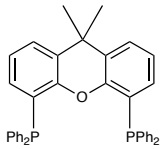
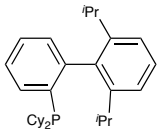
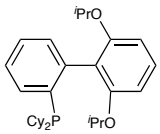
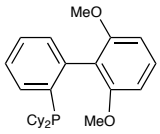
entry	ligand		Result
1	P(*o*-tol)$_3$		**III-70** Recollected
2	Dpe-Phos		**III-72** Yield not obtained
3	Xantphos		**III-72** Yield not obtained
4	X-Phos		**III-70** Recollected, complex mixture
5	RuPhos		**III-70** Recollected, complex mixture
6	S-Phos		**III-70** Recollected, complex mixture

Table 3-4. Attempted Pd-Catalyzed Carboetherification of **III-70**

3.5 Conclusions

In conclusion, we have developed significantly improved conditions for the synthesis of tetrahydrofurans bearing stereocenters at C2 and C1′ via Pd-

catalyzed carboetherification. The Pd/S-Phos catalyst system minimizes isomerization after the key *syn*-oxypalladation event in the catalytic cycle by facilitating rapid C-C bond-forming reductive elimination. This significantly expands the range of tetrahydrofuran products that can be generated efficiently by coupling aryl or alkenyl halides with unsaturated alcohol substrates. In addition, the experiments illustrated in Table 3-1 provide a measure of the relative facility of sp^3C-CAr bond-forming reductive elimination with a series of different ligands, which may be useful in the development of other metal-catalyzed reactions.

3.6 Experimental

General. All reactions were carried out under a nitrogen atmosphere in oven or flame dried glassware. Tris(dibenzylideneacetone)dipalladium (0) and all phosphine ligands were purchased from Strem Chemical Co. and used without further purification. All aryl bromides were obtained from commercial sources (Aldrich Chemical CO or Acros Chemical CO) and were used as obtained. [3-(Ethoxycarbonyl)propyl]triphenylphosphonium bromide,[18] (*E*)-ethyl 5-phenylpent-4- enoate,[19] (*Z*)-ethyl 5-phenylpent-4-enoate,[20] **(***E*)-ethyl 5-(4-methoxyphenyl)pent-4-enoate,[21] 1-[4-(trifluoromethyl)phenyl]prop-2-en-1-ol,[22] 1-cyclohexylprop-2-en-1-ol,6 dodec-1-en-3-ol,[23] 1-(but- 3-enyl)cyclohexanol,8 (*E*)-2-methylhept-5-en-2-ol,[24] (*Z*)-2-methylhept-5-en-2-ol,[25] and (*E*)-2,4-dimethylhept-5-en-2-ol[26] were prepared according to literature procedures. Stereochemistry of tetrahydrofuran products was assigned by analogy to related compounds previously reported by our group through comparison of NMR spectra.[27] Toluene and THF were purified using a GlassContour solvent purification system. Yields refer to isolated yields of compounds estimated to be 95% pure as determined by ^{1}H NMR. The yields reported in the supporting information describe the result of a single experiment, whereas the yields reported in Tables 3-1–3-2 and eq 3-3–3-5 are average yields of two or more experiments. Thus, the yields reported in the supporting information may differ from those shown in Tables 3-1–3-2 and eq 3-3–3-5.

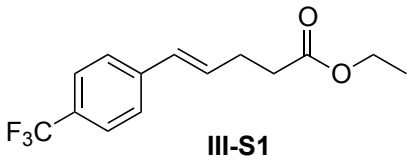
Preparation of Substrates

General Procedure 1: Synthesis of (*E*)-!,"-Unsaturated Esters via Johnson Orthoester

Claisen Rearrangements of Allylic Alcohols.[28] A round bottom flask equipped with a short path distillation head and a recovery flask was charged with an appropriate allylic alcohol (1.0 equiv), triethyl orthoacetate (5 equiv), and pivalic acid (0.05 equiv). The mixture was heated to 140 °C with stirring until the starting material had been completely consumed as judged by GC analysis. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (1:1 v:v). A solution of 1 M HCl (1:1 v:v) was slowly added and the resulting biphasic mixture was stirred for 1 h at rt. The layers were separated and the organic layer was washed with water (2 x 50 mL) and saturated $NaHCO_3$ (1 x 50 mL). The organic layer was then dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel.

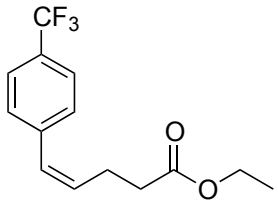
General Procedure 2: Synthesis of (*Z*)-γ,δ-Unsaturated Esters via Wittig Olefinations of Aldehydes With [3-(Ethoxycarbonyl)propyl]triphenylphosphonium Bromide.[29] An oven-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with [3-(ethoxycarbonyl)propyl]triphenylphosphonium bromide (1 equiv) and THF (1 M). The resulting suspension was cooled to –78 °C then a solution of NaHMDS (1 equiv) in THF (1 M) was added dropwise. The resulting mixture was stirred at –78 °C for one h, then a solution of the appropriate aldehyde (1 equiv) in THF (3 M) was added dropwise. The reaction mixture was stirred at –78 °C for 2 h then was warmed to rt, and stirred overnight (ca 12 h). A solution of brine (5 mL) was added, followed by with EtOAc (5 mL), and the mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were then dried

over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel.



III-S1

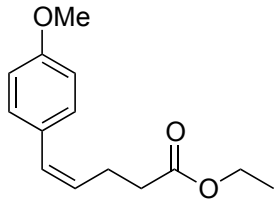
(*E*)-Ethyl 5-[4-(trifluoromethyl)phenyl]pent-4-enoate (III-S1). General procedure 1 was used for conversion of 1-[4-(trifluoromethyl)phenyl]prop-2-en-1-ol (1.74 g, 0.86 mmol) to the title compound. This procedure afforded 2.6 g (92%) of the title compound as a colorless oil. This material was obtained with >20:1 *E*:*Z* selectivity as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.2 Hz, 2 H), 7.34 (d, *J* = 8.2 Hz, 2 H), 6.40 (d, *J* = 15.8 Hz, 1 H), 6.26 (dt, *J* =6.2, 15.8 Hz, 1 H), 4.10 (q, *J* = 7.0 Hz, 2 H), 2.54–2.47 (m, 2 H), 2.46–2.41 (m, 2 H), 1.20 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 140.8, 131.33 (q, *J* = 234.2 Hz), 129.0 (q, *J* = 32.1 Hz), 128.8, 125.3 (q, *J* = 3.8 Hz), 122.9, 60.3, 33.6, 28.2, 14.1; IR (film, cm^{-1}) 2984, 1734, 1327; MS(ESI): 272.1026 (272.1024 calcd for $C_{14}H_{15}F_3O_2$, M^+).



III-S2

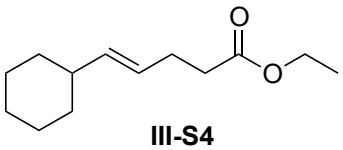
(*Z*)-Ethyl 5-[4-(trifluoromethyl)phenyl]pent-4-enoate (III-S2). General Procedure 2 was used for conversion of 4-(trifluoromethyl)benzaldehyde (0.35 mL, 3.28 mmol) to the title compound. This procedure to afforded 0.70 g (70%) of the title compound as a colorless oil. This material was obtained as a 20:1 mixture of *Z*:*E* isomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.3 Hz, 2 H), 7.34 (d, *J* = 8.3 Hz, 2 H), 6.44 (d, *J* = 11.7 Hz, 1 H), 5.72 (dt, *J* = 7.3, 11.7 Hz, 1 H), 4.10 (q, *J* =

7.1 Hz, 2 H), 2.65–2.59 (m, 2 H), 2.43–2.38 (m, 2 H), 1.20 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 140.9, 131.4 (q, *J* = 218.9), 129.0 (q, *J* = 47.2 Hz), 128.9, 125.1 (q, *J* = 3.7 Hz), 123.2, 60.3, 34.0, 23.9, 14.0; IR (film, cm^{-1}) 2984, 1734; MS(ESI): 272.1026 (272.1024 calcd for $C_{14}H_{17}F_3O$, M^+).



III-S3

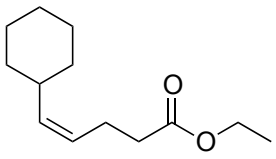
(*Z*)-Ethyl 5-(4-methoxyphenyl)pent-4-enoate (III-S3). General Procedure 2 was used for the conversion of 4-methoxybenzaldehyde (0.4 g, 3.28 mmol) to the title compound. This procedure afforded 0.46 g (59%) of the title compound as a colorless oil. This material was obtained as a 10:1 mixture of *Z*:*E* isomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.22 (m, 2 H), 6.90–6.87 (m, 2 H), 6.41 (d, *J* = 11.7 Hz, 1 H), 5.54 (dt, *J* = 7.1, 11.7 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 2.70–2.64 (m, 2H), 2.46–2.42 (m, 2 H), 1.25 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 158.4, 129.9, 129.5, 128.8, 113.6, 60.4, 55.2, 34.5, 24.1, 14.2 (one carbon signal is absent due to incidental equivalence); IR (film, cm^{-1}) 2981, 1732; MS(ESI): 257.1152 (257.1154 calcd for $C_{14}H_{18}O_3$, M + Na^+).



III-S4

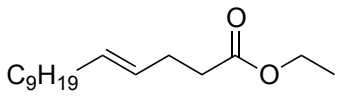
(*E*)-Ethyl 5-cyclohexylpent-4-enoate (III-S4). General Procedure 1 was used for the conversion of 1- cyclohexylprop-2-en-1-ol (1.28 g, 9.13 mmol) to the title compound. This procedure afforded 1.92 g (81%) of the title compound as a colorless oil. This material was obtained with >20:1 *E*:*Z* selectivity as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.45–5.32 (m, 2 H), 4.13 (q, *J* =

7.3 Hz, 2 H), 2.38–2.26 (m, 4 H), 1.94–1.85 (m, 1 H), 1.74–1.60 (m, 5 H), 1.30–1.21 (m, 5 H), 1.19–1.10 (m, 1 H), 1.09–0.98 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 137.6,125.3, 60.1, 40.5, 34.4, 33.0, 28.0, 26.1, 25.9, 14.2; IR (film, cm^{-1}) 2924, 1738; MS(ESI): 233.1520 (233.1517 calcd for $C_{14}H_{18}O_2$, M + Na^+).



III-S5

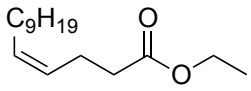
(*Z*)-Ethyl 5-cyclohexylpent-4-enoate (III-S5). General Procedure 2 was used for the conversion of 1-cyclohexylprop-2-en-1-ol (1.70 g, 3.70 mmol) to the title compound. This procedure afforded 0.65 g (51%) of the title compound as a colorless oil. This material was obtained with 20:1 *E*:*Z* selectivity as judged by 1H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21–5.12 (m, 2 H), 4.06 (q, *J* = 7.0 Hz, 2 H), 2.34–2.24 (m, 4 H), 2.23–2.17 (m, 1 H), 1.66–1.50 (m, 5 H), 1.27–1.17 (m, 5 H), 1.13–1.05 (m, 1 H), 1.03–0.94 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 137.3, 125.4, 60.1, 36.2, 34.6, 33.2, 26.0, 25.8, 23.0, 14.2; IR (film, cm^{-1}) 2923, 1739; MS(ESI): 233.1521 (233.152 calcd for $C_{14}H_{18}O_2$, M + Na^+).



III-S6

(*E*)-Ethyl tetradec-4-enoate (III-S6). General Procedure 1 was used for the conversion of dodec-1-en-3-ol (1.3 g, 7.06 mmol) to the title compound. This procedure afforded 1.17 g (69%) of the title compound as a colorless oil. This material was obtained with >20:1 *E*:*Z* selectivity as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50–5.35 (m, 2 H), 4.12 (q, *J* = 6.8 Hz, 2 H), 2.37–2.26 (m, 4 H), 1.96 (q, *J* = 6.6 Hz, 2H), 1.35–1.19 (m, 17 H), 0.88 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 131.8, 127.9, 60.2, 34.4, 32.5, 32.0,

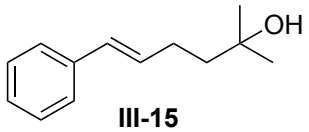
29.6, 29.5, 29.4, 29.3, 29.1, 27.9, 22.7, 14.2, 14.1; IR (film, cm^{-1}) 2924, 1739; MS(ESI): 277.2140 (277.2144 calcd for $C_{16}H_{30}O_2$, M + Na^+).



III-S7

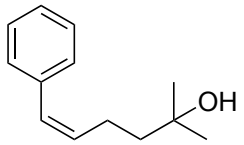
(*Z*)-Ethyl tetradec-4-enoate (III-S7). General Procedure 2 was used for the conversion of dodec-1-en-3-ol (1.50 g, 3.28 mmol) to the title compound. This procedure afforded 0.83 g (54%) of the title compound as a colorless oil. This material was obtained with 20:1 *E*:*Z* selectivity as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40–5.20 (m, 2 H), 4.05 (q, *J* = 7.0 Hz, 2 H), 2.33–2.20 (m, 4 H), 2.00–1.92 (m, 2 H), 1.29–1.15 (m, 17 H), 0.80 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 131.4, 127.2, 60.1, 34.3, 31.8, 29.6, 29.5, 29.4, 29.3, 29.2, 27.1, 22.7, 22.6, 14.1, 14.0; IR (film, cm^{-1}) 2924, 1739; MS(ESI): 277.2135 (277.2144 calcd for $C_{16}H_{30}O_2$, M + Na^+).

General Procedure 3: **Addition of MeMgBr to Esters.** An oven or flame dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with MeMgBr (3 equiv, 3.0 M in diethyl ether). Additional ether was added to provide a 1.0 M solution of MeMgBr, which was then cooled to 0 °C. The appropriate ester (1.0 equiv) was added dropwise via syringe and the resulting mixture was warmed to rt and stirred for 2–4 h until the starting material was completely consumed as judged by TLC analysis. A saturated solution of aqueous NH_4Cl (1:1 by volume with the reaction mixture) was added dropwise and the resulting mixture was then diluted with ethyl acetate (40 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.



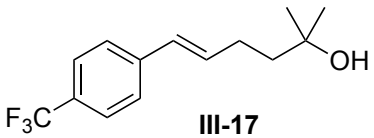
III-15

(*E*)-2-Methyl-6-phenylhex-5-en-2-ol (III-15). General Procedure 3 was used for the conversion of (*E*)-ethyl 5-phenylpent-4-enoate (1.16 g, 5.6 mmol) to the title compound. This procedure afforded 0.76 g (71%) of the title compound as a white solid, m.p. 42 °C. This material was obtained as a >20:1 mixture of *E*:*Z* isomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.22 (m, 4 H), 7.18–7.13 (m, 1 H), 6.38 (d, *J* = 15.8 Hz, 1 H), 6.21 (dt, *J* = 6.8 Hz, 15.8 Hz, 1 H), 2.31–2.24 (m, 2 H), 1.65–1.59 (m, 3 H), 1.21 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 130.8, 129.8, 128.4, 126.9, 125.9, 70.9, 43.2, 29.2, 28.0; IR (film, cm^{-1}) 3362, 2970; MS(ESI): 190.1355 (190.1358 calcd for $C_{13}H_{18}O$, M^+).



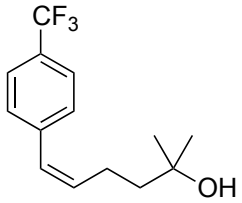
III-16

(*Z*)-2-Methyl-6-phenylhex-5-en-2-ol (III-16). General Procedure 3 was used for the conversion of (*Z*)-ethyl 5-phenylpent-4-enoate (0.47 g, 2.3 mmol) to the title compound. This procedure afforded 0.39 g (90%) of the title compound as a colorless oil. This material was obtained as a >20:1 mixture of *Z*:*E* isomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.26 (m, 4 H), 7.23–7.17 (m, 1 H), 6.44–6.40 (m, 1 H), 5.65 (dt, *J* = 7.2, 11.7 Hz, 1 H), 2.44–2.37 (m, 2 H), 1.64–1.58 (m, 3 H), 1.20 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 132.8, 129.0, 128.7, 128.2, 126.6, 70.8, 43.8, 29.2, 23.7; IR (film, cm^{-1}) 3370, 2970; MS(ESI): 190.1360 (190.1358 calcd for $C_{13}H_{18}O$, M^+).



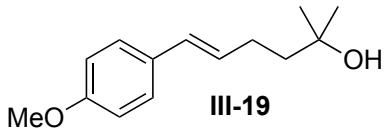
III-17

(*E*)-2-Methyl-6-[4-(trifluoromethyl)phenyl]hex-5-en-2-ol (III-17). General Procedure 3 was used for the conversion of (*E*)-ethyl5-[4-(trifluoromethyl)phenyl]pent-4-enoate (0.75 g, 2.75 mmol) to the title compound. This procedure afforded 0.71 g (96%) of the title compound as a white solid m.p. 58°C. This material was obtained as a >20:1 mixture of *E*:*Z* isomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.1 Hz, 2 H), 7.34 (d, *J* = 8.1 Hz, 2 H), 6.40 (d, *J* = 11.5 Hz, 1 H), 5.74 (dt, *J* = 7.4, 11.5 Hz, 1 H), 2.41–2.32 (m, 2 H), 1.62–1.56 (m, 3 H), 1.18 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 134.9, 128.8, 128.6 (q, *J* = 32.0 Hz), 127.7 (q, *J* = 225.2 Hz), 125.1 (q, *J* = 3.8 Hz), 70.8, 43.4, 29.2, 23.6; IR (film, cm^{-1}) 3370, 2972, 1327). MS(EI): 240.1132 (240.1126 calcd for $C_{14}H_{17}F_3O$, M – H_2O).



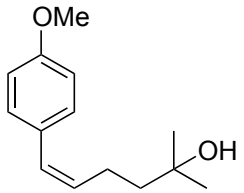
III-18

(*Z*)-2-Methyl-6-[4-(trifluoromethyl)phenyl]hex-5-en-2-ol (III-18). General Procedure 3 was used for the conversion of (*Z*)-ethyl 5-[4-(trifluoromethyl)phenyl]pent-4-enoate (0.52 g, 1.91 mmol) to the title compound. This procedure afforded 0.49 g (80%) of the title compound as a colorless oil. This material was obtained as a >20:1 mixture of *Z*:*E* isomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.1 Hz, 2 H), 7.43 (d, *J* = 8.1 Hz, 2 H), 6.46 (d, *J* = 15.9 Hz, 1 H), 6.36 (dt, *J* = 6.6, 15.9 Hz, 1 H), 2.39–2.33 (m, 2 H), 1.70–1.66 (m, 3 H), 1.28 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 133.8, 128.8, 128.7 (q, *J* = 32.5 Hz), 126.0 (q, *J* = 220.2 Hz), 125.4 (q, *J* = 3.7 Hz), 70.8, 42.9, 29.3, 28.1 (one signal is missing due to incidental equivalence); IR (film, cm^{-1}) 3470, 2972; MS(EI): 240.1134 (240.1126 calcd for $C_{14}H_{17}F_3O$, M – H_2O).



III-19

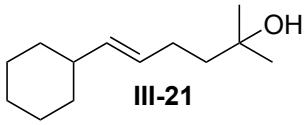
(*E*)-6-(4-Methoxyphenyl)-2-methylhex-5-en-2-ol (III-19). General Procedure 3 was used for the conversion of **(***E*)-ethyl 5-(4-methoxyphenyl)pent-4-enoate (0.095 g, 0.04 mmol) to the title compound. This procedure afforded 0.059 g (66%) of the title compound as a white solid, m.p. 48 °C. This material was obtained as a >20:1 mixture of *E*:*Z* isomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.21 (m, 2 H), 6.81–6.78 (m, 2 H), 6.32 (d, *J* = 15.8 Hz, 1 H), 6.06 (dt, *J* = 6.8, 15.8 Hz, 1 H), 3.76 (s, 3 H), 2.29–2.21 (m, 2 H), 1.63–1.57 (m, 2 H), 1.35 (s, 1 H), 1.22 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 130.5, 129.2, 128.6, 126.9, 113.9, 70.9, 55.2, 43.3, 29.3, 27.9; IR (film, cm^{-1}) 3297, 2966, 1250; MS(ESI): 243.1372 (243.1361 calcd for $C_{14}H_{20}O_2$, M + Na^+).



III-20

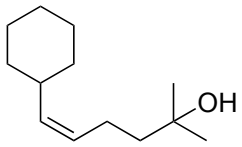
(*Z*)-6-(4-Methoxyphenyl)-2-methylhex-5-en-2-ol (III-20). General Procedure 3 was used for the conversion of (*Z*)-ethyl 5-(4-methoxyphenyl)pent-4-enoate (0.45 g, 1.92 mmol) to the title compound. A second chromoatographic purification using silver impregnated silica gel provided the product as a >20:1 mixture of *Z*:*E* isomers as judged by ^{1}H NMR analysis. This procedure afforded 0.42 g (86%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.17 (m, 2 H), 6.85–6.82 (m, 2 H), 6.34–6.30 (m, 1 H), 5.53 (dt, *J* = 7.2, 11.5 Hz, 1 H), 3.77 (s, 3 H), 2.42–2.34 (m, 2 H), 1.64–1.57 (m, 2 H), 1.41 (s, 1 H), 1.19 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 131.0, 130.2, 129.8, 128.4, 113.6, 70.9,

55.2, 43.8, 29.2, 23.7; IR (film, cm^{-1}) 3364, 2968, 1250; MS(ESI): 243.1361 (243.1361 calcd for $C_{14}H_{20}O_2$, M + Na^+).



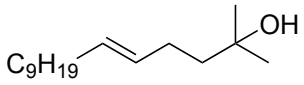
III-21

(*E*)-6-Cyclohexyl-2-methylhex-5-en-2-ol (III-21). General Procedure 3 was used for the conversion of (*E*)-ethyl 5-cyclohexylpent-4-enoate (0.26 g, 1.25 mmol) to the title compound. This procedure afforded 0.25 g (93%) of the title compound as a colorless oil. This material was obtained as a 20:1 mixture of *E*:*Z* isomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.30–5.19 (m, 2 H), 2.32–2.24 (m, 1 H), 2.17–2.11 (m, 2 H), 1.74–1.59 (m, 6 H), 1.56– 1.51 (m, 2 H), 1.35–1.12 (m, 9 H), 1.11–1.03 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 127.7, 71.1, 44.0, 36.3, 33.3, 29.2, 26.0, 25.9, 22.5, 19.2; IR (film, cm^{-1}) 3362, 2923; MS(EI): 178.1729 (178.1722 calcd for $C_{13}H_{24}O$, M – H_2O).



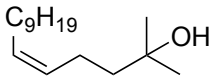
III-22

(*Z*)-6-Cyclohexyl-2-methylhex-5-en-2-ol (III-22). General Procedure 3 was used for the conversion of (*Z*)-ethyl 5-cyclohexylpent-4-enoate (1.46 g, 6.94 mmol) to the title compound. This procedure afforded 1.36 g (81%) of the title compound as a colorless oil. This material was obtained as a >20:1 mixture of *E*:*Z* isomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz $CDCl_3$) δ 5.37–5.34 (m, 2 H), 2.07–2.00 (m, 2 H), 1.90–1.80 (m, 1 H), 1.71–1.59 (m, 5 H), 1.59–1.55 (m, 1 H), 1.52 (s, 1 H), 1.51–1.47 (m, 2 H), 1.28 (s, 1 H), 1.27–0.91 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 127.5, 71.1, 43.4, 40.6, 33.1, 29.2, 27.6, 27.5 26.2, 26.0; IR (film, cm^{-1}) 3358, 2924; MS(ESI): 197.1903 (197.1905 calcd for $C_{13}H_{24}O$, M + H^+).



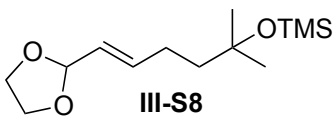
III-23

(*E*)-2-Methylpentadec-5-en-2-ol (III-23). General Procedure 3 was used for the conversion of (*E*)-ethyl tetradec-4-enoate (0.63 g, 2.46 mmol) to the title compound. This procedure afforded 0.44 g (75%) of the title compound as a colorless oil. This material was obtained as a >20:1 mixture of *E*:*Z* isomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41–5.37 (m, 2 H), 2.08–2.01 (m, 2 H), 1.97–1.90 (m, 2 H), 1.66 (s, 1 H), 1.53–1.47 (m, 2 H), 1.34–1.20 (m, 14 H), 1.17 (s, 6 H), 0.85 (t, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.6, 130.1, 70.9, 43.5, 32.5, 31.9, 29.6, 29.5, 29.3, 29.2, 29.1, 27.6, 22.6, 14.1 (one signal is missing due to incidental equivalence); IR (film, cm^{-1}) 3364, 2960; MS(ESI): 241.2521 (241.2531 calcd for $C_{16}H_{32}O$, M + H$^+$).



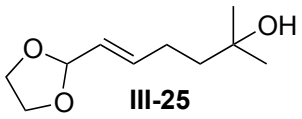
III-24

(*Z*)-2-Methylpentadec-5-en-2-ol (III-24). General Procedure 3 was used for the conversion of (*Z*)-ethyl tetradec-4-enoate (0.29 g, 1.12 mmol) to the title compound. This procedure afforded 0.27 g (70%) of the title compound as a colorless oil. This material was obtained as a 20:1 mixture of *E*:*Z* isomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36–5.28 (m, 2 H), 2.11–2.04 (m, 2 H), 2.03–1.94 (m, 2 H), 1.66 (s, br, 1 H), 1.50–1.44 (m, 2 H), 1.33–1.20 (m, 14 H), 1.18 (s, 6 H), 0.83 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.3, 129.4, 71.0, 43.6, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 27.1, 22.6, 22.3, 14.0; IR (film, cm^{-1}) 3367, 2924; MS(EI): 222.2344 (222.2348 calcd for $C_{16}H_{32}O$, M – H_2O).



III-S8

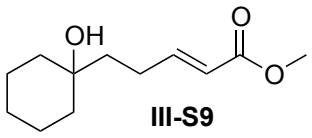
(*E*)-[6-(1,3-Dioxolan-2-yl)-2-methylhex-5-en-2-yloxy]trimethylsilane (III-S8). An oven-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with 2-vinyl-1,3-dioxolane (0.1 mL, 0.99 mmol), trimethyl(2-methylhex-5-en-2-yloxy)silane (0.186 g, 0.99 mmol), and CH_2Cl_2 (2.5 mL) was added. Solid 1,3-Bis(2,4,6-trimethylphenyl)-2-(imidazolidinylidene)(dichlorophenylmethylene)(tricyclohexylphosphine)ruthenium (Grubbs 2nd generation catalyst) (0.042 g, 0.05 mmol) was added and the mixture was heated to reflux overnight. The mixture was then cooled to rt and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 0.23 g (90%) of a yellow oil. This material was obtained as a 15:1 mixture of *E*:*Z*. isomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (dt, *J* = 6.7, 15.5 Hz, 1 H), 5.45 (tq, *J* = 1.6, 6.7 Hz, 1 H), 5.14 (d, *J* = 6.7 Hz, 1 H), 4.00–3.91 (m, 2 H), 3.89–3.83 (m, 2 H), 2.15–2.07 (m, 2 H), 1.52–1.45 (m, 2 H), 1.18 (s, 6 H), 0.05 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 125.8, 104.2, 73.5, 64.9, 43.4, 30.0, 27.0, 2.5; IR (film, cm^{-1}) 2970, 1249; MS(ESI): 281.1535 (281.1549 calcd for $C_{13}H_{26}O_3Si$, M + Na^+).



III-25

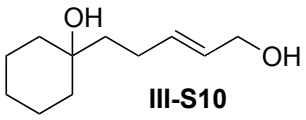
(*E*)-6-(1,3-Dioxolan-2-yl)-2-methylhex-5-en-2-ol (III-25). A flask equipped with a magnetic stirbar was purged with nitrogen and charged with (*E*)-[6-(1,3-dioxolan-2-yl)-2-methylhex-5-en-2- yloxy]trimethylsilane (0.27 g, 1 mmol) and THF (1 mL). The resulting solution was cooled to 0 °C then TBAF (3.18 mL, 3.18 mmol, 1 M in THF) was added dropwise. The mixture was warmed to rt and stirred until the starting material had been completely consumed as judged by TLC analysis. The mixture was diluted with water (x mL) then extracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on basic alumina to afford 0.197 g (81%) of the title

compound as a colorless oil. This material was obtained as a 15:1 mixture of *E*:*Z* isomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (dt, *J* = 6.7, 13.3 Hz, 1 H), 5.43 (tq, *J* = 0.4, 6.7 Hz, 1 H), 5.11 (d, *J* = 6.7 Hz, 1 H), 3.95–3.89 (m, 2 H), 3.85–3.77 (m, 2 H), 2.14–2.07 (m, 2 H), 1.54–1.47 (m, 4 H), 1.14 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 126.1, 104.0, 70.5, 64.8, 42.4, 29.2, 26.9; IR (film, cm^{-1}) 3391, 22968; MS(ESI): 209.1149 (209.1154 calcd for $C_{10}H_{18}O_3$, M + Na^+).



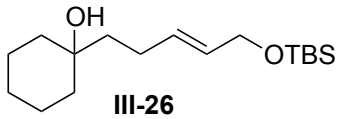
III-S9

(*E*)-Methyl 5-(1-hydroxycyclohexyl)pent-2-enoate (III-S9). An oven-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with methyl acrylate (0.29 mL, 3.24 mmol), 1-(but-3-enyl)cyclohexanol8 (0.1 g, 0.65 mmol), and CH_2Cl_2 (3.25 mL). Solid 1,3-Bis(2,4,6-trimethylphenyl)-2-(imidazolidinylidene)(dichlorophenylmethylene) (tricyclohexylphosphine)ruthenium (Grubbs 2nd generation catalyst) (28 mg, 0.032 mmol) was added and the reaction mixture was heated to reflux for 4 hours. The mixture was then cooled to rt and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 0.11 g (78%) of the title compound as a tan oil. This material was obtained as a 15:1 mixture of *E*:*Z* isomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (dt, *J* = 6.9, 15.7 Hz, 1 H), 5.76 (dt, *J* = 1.6, 15.7 Hz, 1 H), 3.64 (s, 3 H), 2.27–2.20 (m, 2 H), 1.69–1.10 (m, 13 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 150.1, 120.5, 51.3, 40.3, 37.3, 26.0, 25.9, 25.7, 22.1; IR (film, cm^{-1}) 3482, 2931, 1725; MS(ESI): 235.1303 (235.1310 calcd for $C_{12}H_{20}O_3$, M + Na^+).



III-S10

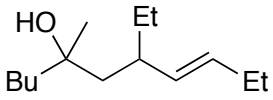
(*E*)-1-(5-Hydroxypent-3-en-1yl)cyclohexanol (III-S10). An oven-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with (*E*)-methyl 4-(1-hydroxycyclohexyl)pent-2-enoate (100 mg, 0.47 mmol) and THF (0.5 mL). The resulting solution was cooled to –78 °C, then DIBAL-H (1.97 mL, 1.97 mmol, 1 M in THF) was added dropwise. The reaction mixture was stirred at –78 °C for one h, at which time TLC analysis indicated the starting material had been completely consumed. The reaction was quenched with 1M NaOH, and the solid precipitate was washed with EtOAc. The organic solutions were combined and washed with brine (1 x 5 mL), then dried over anhydrous Na2SO4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to yield 86 mg (73%) of the title compound as a colorless oil. This material was obtained as a 15:1 mixture of *E*:*Z* isomers. Data are for the major isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72–5.52 (m, 2 H), 4.02 (d, *J* = 5.5 Hz, 2 H), 2.14–2.05 (m, 2 H), 1.60–1.29 (m, 13 H), 1.27–1.15 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.4, 128.9, 71.3, 63.6, 41.5, 37.4, 25.8, 25.7, 22.1; IR (film, cm^{-1}) 3350, 1456; MS(ESI): 207.1352 (207.1361 calcd for $C_{11}H_{20}O_2$, M + Na^+).



III-26

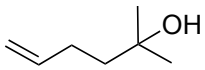
(*E*)-1-[5-(*tert*-Butyldimethylsilyloxy)pent-3-en-1yl]cyclohexanol (III-26). An oven-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with (*E*)-1-(4-hydroxybut-2-enyl)cyclohexanol (56 mg, 0.3 mmol) and DMF (0.3 mL). The solution was cooled to 0 °C then imidazole was added (25 mg, 0.3 mmol), followed by a solution of TBSCl (40 mg, 0.3 mmol) in DMF (0.3 mL). The mixture was warmed to rt and stirred overnight (ca 12 h). Water (x mL) was added to the reaction mixture, which was then extracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The product was then purified by flash chromatography on silica gel to yield 69 mg (79%) of the title

compound as a colorless oil. This material was obtained as an 18:1 mixture of *E*:*Z*. isomers. Data are for the major isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66–5.57 (m, 1 H), 5.56–5.44 (m, 1 H), 4.09–4.05 (m, 2 H), 2.12–2.04 (m, 2 H), 1.60–1.33 (m, 11 H), 1.28–1.15 (m, 2 H), 0.85 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.4, 129.2, 71.3, 63.9, 42.6, 37.4, 25.9, 25.8, 22.2, 18.4, –5.1, (one signal is missing due to incidental equivalence); IR (film, cm^{-1}) 3392, 2930; MS(ESI): 321.2213 (321.2226 calcd for $C_{17}H_{34}O_2Si$, M + Na^+).



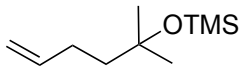
III-57

(E)-7-ethyl-5-methylundec-8-en-5-ol An oven or flame dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen, charged with BuMgBr (3 equiv, 3.0 M in diethyl ether, 3.25 mL) and cooled to 0 °C. (E)-4-ethyloct-5-en-2-one (1.0 equiv, 0.5 mL) was added dropwise via syringe and the resulting mixture was warmed to rt and stirred for 2–4 h until the starting material was completely consumed as judged by TLC analysis. A saturated solution of aqueous NH_4Cl (1:1 by volume with the reaction mixture) was added dropwise and the resulting mixture was then diluted with ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel to obtain 0.63 g of the product as a clear oil in 98% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46–5.36 (m, 1 H), 5.18–5.09 (m, 1 H), 2.06–1.86 (m, 4 H), 1.46–1.33 (m, 3 H), 1.32–1.15 (m, 4 H), 1.13–1.07 (m, 2 H), 1.00 (s, 3 H), 0.87 (t, *J* = 7.4 Hz, 3 H), 0.83-0.77 (m, 2 H), 0.72 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.0, 132.9, 73.2, 46.4, 41.6, 40.8, 29.7, 27.6, 26.4, 25.4, 23.2, 13.9, 13.7.



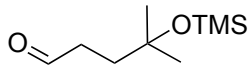
III-65

2-methylhex-5-en-2-ol An oven or flame dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen, charged with a 3 M solution of methylgrignard in THF (2 equiv, 68 mL) and cooled to 0 °C. A 1 M solution of hex-5-en-2-one in THF (1.0 equiv, 10 g) was added dropwise via syringe and the resulting mixture was warmed to rt and stirred for 5 h until the starting material was completely consumed as judged by TLC analysis. A 1 M solution of HCl (1:1 by volume with the reaction mixture) was added and the resulting mixture was diluted with ethyl acetate. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel to obtain 10.12 g of the product as a clear oil in 87% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80-5.91 (m, 1 H), 5.05 (dq, J=17.39, 1.53 Hz, 1 H), 4.96 (dq, J=11.29, 1.83, 1.22 Hz, 1 H), 2.11-2.19 (m, 2 H), 1.54-1.62 (m, 2H), 1.23 (s, 6H).



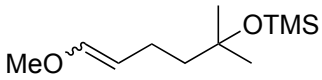
III-66

trimethyl((2-methylhex-5-en-2-yl)oxy)silane An oven or flame dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with 2-methylhex-5-en-2-ol (1 equiv, 3.23 g) and trimethylsilylimidazole (1.5 equiv, 5.95 mL) and the resulting neat mixture was heated to 60 ^{o}C until the starting material was completely consumed as judged by TLC analysis. The crude product was then purified by flash chromatography on silica gel to obtain 4.95 g of the product as a clear oil in 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90-5.78 (m, 1 H), 5.04-4.89 (m, 2 H), 2.15-2.07 (m, 2 H), 1.55-1.48 (m, 3 H), 1.21 (s, 6 H), 0.08 (s, 9 H).



III-67

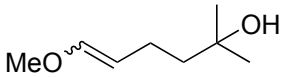
4-methyl-4-((trimethylsilyl)oxy)pentanal An oven or flame dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen, charged with a solution of trimethyl((2-methylhex-5-en-2-yl)oxy)silane in CH_2Cl_2 (1 equiv, 1.0 M, 0.68 g) and cooled to -78 °C. Ozone was bubbled through the solution until the reaction mixture turned a pale blue color. Next, triphenylphosphine was added (2 equiv, 1.78 g), and the reaction was warmed to rt and stirred overnight. Upon completion, a saturated solution of aqueous NaCl (1:1 by volume with the reaction mixture) was added and the resulting mixture was diluted with ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel to obtain 0.46 g of the product as a clear oil in 67% yield.



III-69

((6-methoxy-2-methylhex-5-en-2-yl)oxy)trimethylsilane An oven or flame dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen, charged with a solution of (methoxymethyl)-triphenylphosphonium chloride in THF (1.2 equiv, 0.1 M, 1.71 g) and cooled to -78 °C. Potassium *tert*-butoxide was added portionwise (1.2 equiv, 0.59 g), and the reaction was allowed to stir for 1 hr at -78 °C. Next, a 1 M solution of 4-methyl-4-((trimethylsilyl)oxy)pentanal in THF (1 equiv, 0.84 g) was added dropwise, and the reaction was warmed to rt and stirred until the starting material was consumed, as indicated by GC analysis. A saturated solution of aqueous NaCl (1:1 by volume with the reaction mixture) was added and the resulting mixture was diluted with ethyl acetate (10 mL). The layers were separated and the

aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel to obtain 0.90 g of the product as a clear oil in 99% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22-6.20 (m, 1 H), 4.69-4.62 (m, 1 H), 3.40 (s, 1 H), 2.00-1.86 (m, 2 H), 1.51-1.44 (m, 3 H), 1.09 (s, 6 H), 0.08 (s, 9 H).

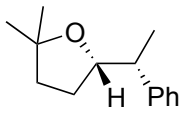


III-70

6-methoxy-2-methylhex-5-en-2-ol An oven or flame dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen, charged with ((6-methoxy-2-methylhex-5-en-2-yl)oxy)trimethylsilane (1 equiv, 1.0 M in THF, 0.86 g) and cooled to 0 °C. A 1 M solution of TBAF in THF (3.0 equiv, 12 mL) was added dropwise via syringe and the resulting mixture was warmed to rt and stirred for 3 h until the starting material was completely consumed as judged by TLC analysis. A saturated solution of aqueous NH_4Cl (1:1 by volume with the reaction mixture) was added and the resulting mixture was diluted with ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel to obtain 0.58 g of the product as a clear oil in 62% yield and 2.4:1 dr. Data are for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32-6.25 (m, 1 H), 4.76-4.66 (m, 1 H), 3.47 (s, 1 H), 2.03-1.94 (m, 2 H), 1.55-1.47 (m, 3 H), 1.19 (s, 6 H).

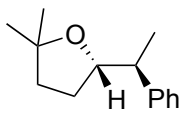
Synthesis of Tetrahydrofurans via Pd-Catalyzed Alkene Carboetherification General Procedure 4: Palladium-Catalyzed Carboetherification Reactions for the Formation of Tetrahydrofurans. An oven or flame-dried Schlenk tube was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (2 mol% complex, 4 mol % Pd), S-Phos (4 mol %),

NaO*t*Bu (2.0 equiv), and the aryl bromide (2.0 equiv). The tube was purged with nitrogen and the alcohol substrate (1.0 equiv), and xylenes (0.25 M in substrate) were added. The mixture was heated to 140 °C with stirring until the starting material had been consumed as judged by GC or 1H NMR analysis. The mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl (2 mL), and diluted with ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.



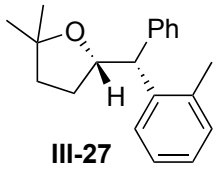
III-13

(1'*S,5*S**)-2,2-Dimethyl-5-(1-phenylethyl)tetrahydrofuran** (**III-13**). The coupling of (*Z*)-2-methylhept-5-en-2-ol (0.025 g, 0.20 mmol) with bromobenzene (0.041 mL, 0.4 mmol) was conducted following General Procedure 4. This procedure afforded 0.033 g (84%) of the title compound as an orange oil. This material was obtained as a 9:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.27 (m, 3 H), 7.23–7.20 (m, 2 H), 4.08–4.02 (m, 1 H), 2.74 (p, *J* = 7.1 Hz, 1 H), 1.76–1.69 (m, 1 H), 1.66–1.54 (m, 3 H), 1.35 (d, *J* = 7.2 Hz, 3 H), 1.25 (s, 3 H), 1.22 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 128.1, 128.0, 126.2, 83.4, 80.6, 46.0, 38.2, 30.0, 29.1, 28.2, 18.8; IR (film, cm^{-1}) 2968, 1063; MS(ESI): 227.1408 (227.1412 calcd for $C_{14}H_{20}O$, M + Na^+).



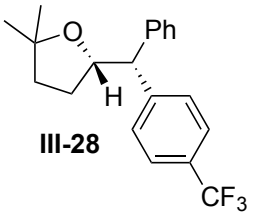
III-14

(1'*R,5*S**)-2,2-Dimethyl-5-(1-phenylethyl)tetrahydrofuran** (**III-14**). The coupling of (*E*)-2-methylhept-5-en-2-ol (0.05 g, 0.39 mmol) with bromobenzene (0.082 mL, 0.78 mmol) was conducted following General Procedure 4. This procedure afforded 0.079 g (86%) of the title compound as an orange oil. This material was obtained as a 20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.25 (m, 4 H), 7.24–7.17 (m, 1 H), 4.19–4.13 (m, 1 H), 2.96–2.88 (m, 1 H), 1.90–1.81 (m, 1 H), 1.78–1.71 (m, 1 H), 1.70–1.61 (m, 1 H), 1.69–1.51 (m, 1 H), 1.30 (d, *J* = 7.2 Hz, 3 H), 1.25 (s, 3 H), 1.21 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 128.2, 128.0, 126.1, 82.6, 80.5, 44.0, 38.5, 28.7, 28.3, 28.0, 19.2; IR (film, cm^{-1}) 2968, 1046; MS(ESI): 227.1408 (227.1412 calcd for $C_{14}H_{20}O$, M + Na^+).



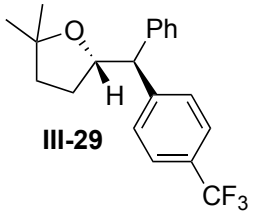
III-27

(1'*R,5*S**)-2,2-Dimethyl-5-phenyl[(*o*-tolyl)methyl]tetrahydrofuran (III-27)**. The coupling of (*E*)-2-methyl-6-phenylhex-5-en-2-ol (0.025 g, 0.13 mmol) with 1-bromo-2-methylbenzene (0.031 mL, 0.26 mmol) was conducted following General Procedure 4. This procedure afforded 0.037 g (95%) of the title compound as a yellow oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.6 Hz, 1 H), 7.27–7.16 (m, 6 H), 7.15–7.07 (m, 2 H), 4.72–4.66 (m, 1 H), 4.18 (d, *J* = 7.6 Hz, 1 H), 2.20 (s, 3 H), 1.91–1.81 (m, 1 H), 1.79–1.73 (m, 1 H), 1.72–1.63 (m, 1 H), 1.57–1.49 (m, 1 H), 1.25 (s, 3 H), 1.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 140.8, 136.8, 130.5, 129.2, 128.0, 127.3, 126.1, 126.0, 125.7, 80.7, 80.3, 53.0, 38.4, 30.9, 29.0, 28.1, 20.1; IR (film, cm^{-1}) 2967, 1489; MS(ESI): 303.1722 (303.1725 calcd for $C_{20}H_{24}O$, M + Na^+).



III-28

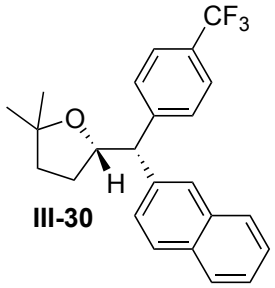
(1'*R,5*S**)-2,2-Dimethyl-5-{phenyl[4-(trifluoromethyl)phenyl]methyl}tetrahydrofuran** (**III-28**). The coupling of (*E*)-2-methyl-6-phenylhex-5-en-2-ol (0.05 g, 0.26 mmol) with 1-bromo-4-(trifluoromethyl)benzene (0.074 mL, 0.52 mmol) was conducted following General Procedure 4. This procedure afforded 0.077 g (87%) of the title compound as a clear oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.3 Hz, 2 H), 7.50 (d, *J* = 8.3 Hz, 2 H), 7.34-7.22 (m, 5 H), 4.77– 4.71 (m, 1 H), 4.02 (d, *J* = 8.2 Hz, 1 H), 1.95–1.88 (m, 1 H), 1.78–1.64 (m, 3 H), 1.30 (s, 3 H), 1.24 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.0, 142.4, 129.3, (q, *J* = 241.5 Hz), 128.6, 128.45 (q, *J* = 32.5 Hz), 128.2, 126.7, 125.1 (q, *J* = 3.9 Hz), 81.5, 80.1, 57.3, 38.2, 31.3, 29.1, 28.3; IR (film, cm^{-1}) 2969, 1325; MS(ESI): 357.1438 (357.1442 calcd for $C_{20}H_{21}F_3O$, M + Na^+).



III-29

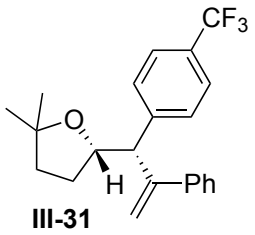
(1'*S,5*S**)-2,2-Dimethyl-5-{phenyl[4-(trifluoromethyl)phenyl]methyl}tetrahydrofuran** (**III-29**). The coupling of (*Z*)-2-methyl-6-phenylhex-5-en-2-ol (0.025 g, 0.13 mmol) with 1-bromo-4-(trifluoromethyl)benzene (0.037 mL, 0.26 mmol) was conducted following General Procedure 4. This procedure afforded 0.035 g (80%) of the title compound as a clear oil. This material was obtained as a 9:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50

(d, *J* = 8.4 Hz, 2 H), 7.38 (d, *J* = 8.4 Hz, 2 H), 7.31–7.23 (m, 4 H), 7.21–7.16 (m, 4.68 (q, *J* = 7.2 Hz, 1 H), 4.02 (d, *J* = 7.2 Hz, 1 H), 1.92–1.84 (m, 1 H), 1.70–1.59 (m, 2 H), 1.56–1.46 (m, 1 H), 1.24 (s, 3 H), 1.14 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 141.5, 129.1 (q, *J* = 262.7 Hz), 128.6, 128.3 (q, *J* = 36.0 Hz), 128.2, 126.5, 125.2 (q, *J* = 3.8 Hz), 81.3, 79.7, 56.6, 38.2, 30.9, 29.1, 28.9, 28.2, 28.1; IR (film, cm^{-1}) 2973, 1328; MS(ESI): 357.1431 (357.1442 calcd for $C_{20}H_{21}F_3O$, M + Na^+).



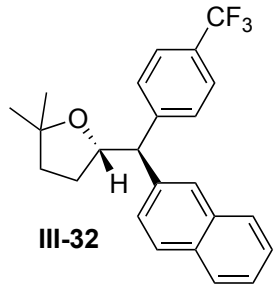
III-30

(1'*R,5*S**)-2,2-Dimethyl-5-{naphthalen-2-yl[4-(trifluoromethyl)phenyl]methyl} tetrahydrofuran** (**III-30**). The coupling of (*E*)-2-methyl-6-[4-(trifluoromethyl)phenyl]hex-5-en-2-ol (0.03 g, 0.12 mmol) with 2-bromonaphthalene (0.048 g, 0.23 mmol) was conducted following General Procedure 4. This procedure afforded 0.037 g (84%) of the title compound as a clear oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis, but contained ca 2% of an unidentified impurity. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.78 (m, 3 H), 7.75 (d, *J* = 8.5 Hz, 1 H), 7.54 (d, *J* = 8.5 Hz, 2 H), 7.49–7.39 (m, 5 H), 4.83 (q, *J* = 6.3 Hz, 1 H), 4.22 (d, *J* = 6.3 Hz, 1 H), 2.01–1.93 (m, 1 H), 1.78–1.67 (m, 2 H), 1.59–1.52 (m, 1 H), 1.29 (s, 3 H), 1.18 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.0, 139.0, 133.4, 132.3, 130.1, 129.2 (q, *J* = 52.0 Hz), 127.9, 127.8 (q, *J* = 225.2), 127.7, 127.6, 127.5, 125.9, 125.6, 125.2 (q, *J* = 3.8 Hz), 81.4, 79.7, 56.7, 38.2, 31.0, 28.9, 28.1; IR (film, cm^{-1}) 2969, 1325; MS(ESI): 407.1600 (407.1599 calcd for $C_{24}H_{23}F_3O$, M + Na^+).



III-31

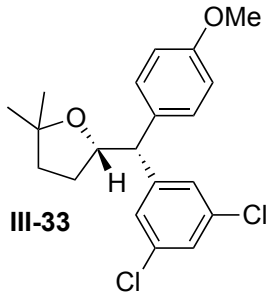
(1'*S,5*R**)-2,2-Dimethyl-5-{2-phenyl-1-[4-(trifluoromethyl)phenyl]allyl}tetrahydrofuran** (**III-31**). The coupling of (*E*)-2-methyl-6-[4-(trifluoromethyl)phenyl]hex-5-en-2-ol (0.03 g, 0.12 mmol) with α-bromostyrene (0.035 mL, 0.23 mmol) was conducted following General Procedure 4. This procedure afforded 0.025 g (62%) of the title compound as an amber oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.1 Hz, 2 H), 7.35 (d, *J* = 8.1 Hz, 2 H), 7.29–7.27 (m, 2 H), 7.24– 7.18 (m, 3 H), 5.55 (s, 1 H), 5.45 (s, 1 H), 4.55 (q, *J* = 7.3 Hz, 1 H), 4.02 (d, *J* = 7.3 Hz, 1 H), 1.81–1.74 (m, 1 H), 1.69–1.60 (m, 2 H), 1.50–1.44 (m, 1 H), 1.28 (s, 3 H), 1.23 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 133.9, 129.3, 128.1 (q, *J* = 253.1 Hz), 128.9, 127.4, 127.2 (q, *J* = 65 Hz), 126.8, 124.9 (q, *J* = 3.8 Hz), 114.7, 79.7, 69.0, 55.7, 38.3, 30.3, 28.9, 28.0, 19.3; IR (film, cm^{-1}) 2968, 1324; MS(EI): 360.1709 (360.1701 calcd for $C_{22}H_{23}F_3O$, M^+).



III-32

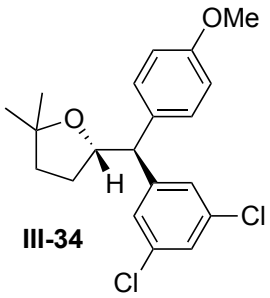
(1'*S,5*S**)-2,2-Dimethyl-5-{naphthalen-2-yl[4-(trifluoromethyl)phenyl]methyl} tetrahydrofuran** (**III-32**). The coupling of (*Z*)-2-methyl-6-[4-(trifluoromethyl)phenyl]hex-5-en-2-ol (0.03 g, 0.12 mmol) with 2-bromonaphthalene (0.048 g, 0.23 mmol) was conducted following General

Procedure 4. This procedure afforded 0.042 g (94%) of the title compound as a clear oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.77 (m, 2 H), 7.76 (d, *J* = 8.3 Hz, 2 H), 7.55–7.50 (m, 3 H), 7.50–7.43 (m, 3 H), 7.31 (dd, *J* = 1.9, 8.3 Hz, 1 H), 4.85–4.80 (m, 1 H), 4.15 (d, *J* = 8.1 Hz, 1 H), 1.94–1.86 (m, 1 H), 1.80–1.62 (m, 3 H), 1.30 (s, 3 H), 1.24 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 139.9, 133.4, 132.3, 129.3 (q, *J* = 49.6 Hz), 128.3, 127.8 (q, *J* = 230.1 Hz), 127.6, 127.1, 126.9, 126.2, 125.8, 125.1 (q, *J* = 3.7 Hz), 81.6, 80.0, 57.3, 38.3, 31.4, 29.2, 19.0, 18.9 (one carbon signal is absent due to incidental equivalence; IR (film, cm^{-1}) 2969, 1326; MS(ESI): 407.1597 (407.1599 calcd for $C_{24}H_{23}F_3O$, M + Na^+).



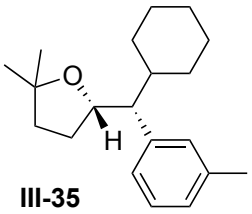
III-33

(1'*R,5*S**)-5-(3,5-Dichlorophenyl)(4-methoxyphenyl)methyl-2,2-dimethyltetrahydrofuran** (**III-33**). The coupling of (*E*)-6-(4-methoxyphenyl)-2-methylhex-5-en-2-ol (0.02 g, 0.09 mmol) with 1-bromo-3,5 dichlorobenzene (0.041 g, 0.18 mmol) was conducted following General Procedure 4. This procedure afforded 0.017 g (52%) of the title compound as a clear oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 1.7 Hz, 2 H), 7.12 (t, *J* = 2.4 Hz, 1 H), 7.11–7.07 (m, 2 H), 6.81– 6.76 (m, 2 H), 4.53 (q, *J* = 7.2 Hz, 1 H), 3.77–3.73 (m, 4 H), 1.88–1.76 (m, 1 H), 1.67–1.52 (m, 3 H), 1.21 (s, 3 H), 1.15 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 146.4, 134.3, 134.0, 129.4,127.5, 126.2, 113.9, 81.5, 80.0, 56.0, 55.2, 38.1, 31.2, 29.0, 28.1; IR (film, cm^{-1}) 2968, 1511; MS(ESI): 387.0906 (387.0895 calcd for $C_{20}H_{22}Cl_2O_2$ M + Na^+).



III-34

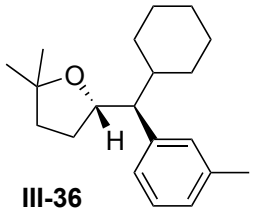
(1'*S,5*S**)-5-(3,5-Dichlorophenyl)(4-methoxyphenyl)methyl-2,2-dimethyltetrahydrofuran** (**III-34**). The coupling of (*Z*)-6-(4-methoxyphenyl)-2-methylhex-5-en-2-ol (0.027 g, 0.123 mmol) with 1-bromo-3,5 dichlorobenzene (0.055 g, 0.24 mmol) was conducted following General Procedure 4. This procedure afforded 0.037 g (69%) of the title compound as a clear oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–7.11 (m, 5 H), 6.82–6.78 (m, 2 H), 4.53 (q, *J* = 7.4 Hz, 1 H), 3.83 (d, *J* = 7.4 Hz, 1 H), 3.74 (s, 3 H), 1.93–1.82 (m, 1 H), 1.67–1.54 (m, 2 H), 1.49–1.38 (m, 1 H), 1.20 (s, 3 H), 1.11 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 147.0, 134.5, 132.8, 130.0, 127.2, 126.3, 113.6, 81.3, 79.6, 55.3, 55.1, 38.1, 30.7, 28.8, 28.0; IR (film, cm^{-1}) 2969, 1512; MS(ESI): 387.1600 (387.0901 calcd for $C_{20}H_{22}Cl_2O_2$, M + Na^+).



III-35

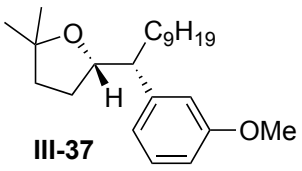
(1'*R,5*S**)-5-[Cyclohexyl(*m*-tolyl)methyl]-2,2-dimethyltetrahydrofuran** (**III-35**). The coupling of (*E*)-6-cyclohexyl-2-methylhex-5-en-2-ol (0.025 g, 0.127 mmol) with 3-bromotoluene (0.031 mL, 0.26 mmol) was conducted following General Procedure 4. This procedure afforded 0.034 g (94%) of the title compound as a clear oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (t, *J* = 7.4 Hz, 1 H), 7.05–7.03 (m, 1 H), 7.00–6.93 (m, 2 H), 4.42–4.36 (m, 1 H),

2.28 (s, 3 H), 2.18–2.12 (m, 1 H), 2.11–2.03 (m, 1 H), 1.85–1.66 (m, 3 H), 1.60–1.42 (m, 4 H), 1.38–1.26 (m, 3 H), 1.17–1.04 (m, 8 H), 0.98–0.87 (m, 1 H), 0.72–0.60 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 136.5, 131.1, 127.5, 127.0, 126.5, 80.2, 77.3, 56.3, 39.3, 38.1, 32.2, 31.4, 29.8, 28.4, 27.8, 26.7, 26.3, 26.2, 21.5; IR (film, cm^{-1}) 2923, 1738; MS(ESI): 309.2193 (309.2194 calcd for $C_{20}H_{30}O$, M + Na^+).



III-36

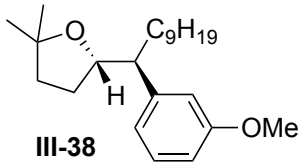
(1'*S,5*S**)-5-[Cyclohexyl(*m*-tolyl)methyl]-2,2-dimethyltetrahydrofuran (III-36**). The coupling of (*Z*)-6-cyclohexyl-2-methylhex-5-en-2-ol (0.05 g, 0.26 mmol) with 3-bromotoluene (0.062 mL, 0.5o mmol) was conducted following General Procedure 4. This procedure afforded 0.016 g (22%) of the title compound as an amber oil. This material was obtained as a 2:1 mixture of diastereomers as judged by ^{1}H NMR analysis, and was contaminated with ca. 15% of an unidentified side product. Carbon NMR data are not reported due to the complexity of the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15–7.00 (m, 2 H), 6.96–6.85 (m, 2 H), 4.38–4.33 (m, 1 H), 2.88–2.79 (m, 1 H), 2.24 (s, 3 H), 2.20–2.14 (m, 2 H), 2.14–2.05 (m, 2 H), 1.74–1.59 (m, 3 H), 1.59–1.45 (m, 2 H), 1.31–1.21 (m, 6 H), 1.14–1.00 (m, 6 H); IR (film, cm^{-1}) 2921, 1446; MS(ESI): 309.2196 (309.2194 calcd for $C_{20}H_{30}O$, M + Na^+).



III-37

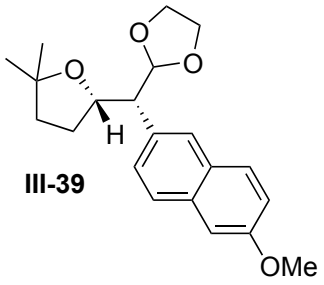
(1'*R,5*S**)-5-[1-(3-Methoxyphenyl)decyl]-2,2-dimethyltetrahydrofuran** (**III-37**). The coupling of (*E*)-2-methylpentadec-5-en-2-ol (0.025 g, 0.104 mmol) with 3-bromoanisole (0.026 mL, 0.21 mmol) was conducted following General

Procedure 4. This procedure afforded 0.036 g (92%) of the title compound as a clear oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (t, *J* = 8.3 Hz, 1 H), 6.85–6.81 (m, 2 H), 6.77–6.74 (m, 1 H), 4.18–4.13 (m, 1 H), 3.81 (s, 3 H), 2.68–2.62 (m, 1 H), 1.90–1.82 (m, 1 H), 1.76–1.64 (m, 3 H), 1.63–1.56 (m, 1 H), 1.47–1.41 (m, 1 H), 1.34–1.10 (m, 20 H), 0.88 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 114.1, 128.7, 121.8, 115.0, 111.2, 82.0, 80.4, 55.1, 50.5, 38.4, 31.9, 31.3, 29.8, 29.6, 29.5, 29.3, 28.9, 28.7, 28.0, 27.7, 22.7, 14.1; IR (film, cm^{-1}) 2968, 1512; MS(ESI): 369.2757 (369.2770 calcd for $C_{23}H_{38}O_2$, M + Na^+).



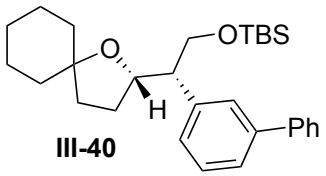
III-38

(1'*S,5*S**)-5-[1-(3-Methoxyphenyl)decyl]-2,2-dimethyltetrahydrofuran** (**III-38**). The coupling of (*Z*)-2-methylpentadec-5-en-2-ol (0.029 g, 0.120 mmol) with 3-bromoanisole (0.030 mL, 0.24 mmol) was conducted following General Procedure 4. This procedure afforded 0.018 g (43%) of the title compound as an orange oil. This material was obtained as a 4:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.8 Hz, 1 H), 6.76–6.68 (m, 3 H), 4.05–3.97 (m, 1 H), 3.81–3.76 (m, 4 H), 2.52–2.44 (m, 1 H), 2.03–1.91 (m, 1 H), 1.70–1.45 (m, 6 H), 1.26–1.15 (m, 18 H), 0.89–0.83 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 144.6, 128.9, 121.0, 114.5, 111.0, 82.8, 80.8, 55.1, 52.6, 38.2, 32.8, 31.9, 30.3, 29.7, 29.6, 29.5, 29.3, 29.2, 28.3, 27.5, 22.6, 14.1; IR (film, cm^{-1}) 2924, 1456; MS(ESI): 369.2769 (369.2770 calcd for $C_{23}H_{38}O_2$, M + Na^+).



III-39

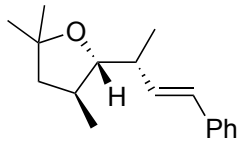
(1'*R,5*S**)-2-[(5,5-Dimethyltetrahydrofuran-2-yl)(6-methoxynaphthalen-2-yl)methyl]-1,3-dioxolane** (**III-39**). The coupling of (*E*)-6-(1,3-dioxolan-2-yl)-2-methylhex-5-en-2-ol (0.025 g, 0.13 mmol) with 2-bromo-6-methoxy-naphthalene (0.064 g, 0.27 mmol) was conducted following General Procedure 4. This procedure afforded 0.023 g (50%) of the title compound as an orange solid. m.p. 92 °C. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73–7.64 (m, 3 H), 7.47 (dd, *J* = 2.2, 8.3 Hz, 1 H), 7.11–7.07 (m, 2 H), 5.40 (d, *J* = 8.6 Hz, 1 H), 4.62–4.56 (m, 1 H), 3.98–3.84 (m, 6 H), 3.82–3.72 (m, 1 H), 2.88 (dd, *J* = 2.2, 8.3 Hz, 1 H), 2.04–1.92 (m, 1 H), 1.65–1.56 (m, 1 H), 1.55–1.46 (m, 1 H), 1.18 (s, 3 H), 1.171–1.10 (m, 1 H), 1.06 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 133.7, 132.7, 129.4, 129.2, 129.0, 128.7, 126.0, 118.5, 105.5, 105.2, 81.2, 77.8, 65.1, 55.3, 54.6, 38.0, 29.7, 28.4, 27.8, 19.1; IR (film, cm^{-1}) 2965, 1646, 1540; MS(ES): 365.1718 (365.1729 calcd for $C_{21}H_{26}O_4$, M + Na^+).



III-40

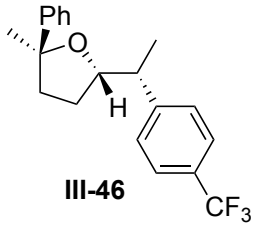
(1'*R,2*S**)-2-[(Biphenyl-3-yl)-2-(-1-oxaspiro[4.5]decan-2-yl)ethoxy](*tert*-butyl) dimethylsilane** (**III-40**). The coupling of (*E*)-1-(4-(tert-butyldimethylsilyloxy)but-2-enyl)cyclohexanol (0.028 g, 0.10 mmol) with 3-bromo-biphenyl (0.046 mL, 0.20 mmol) was conducted following General Procedure 4. This procedure afforded 0.040 g (90%) of the title compound as a clear oil. This material was obtained as a 12:1 mixture of diastereomers as judged by ^{1}H NMR

analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.55 (m, 2 H), 7.53–7.50 (m, 1 H), 7.44–7.37 (m, 3 H), 7.33–7.24 (m, 3 H), 4.40–4.34 (m, 1 H), 4.03 (dd, *J* = 7.8, 9.8 Hz, 1 H), 3.83 (dd, *J* = 6.1, 12.2 Hz, 1 H), 2.89–2.78 (m, 1 H), 1.88–1.80 (m, 1 H), 1.66–1.50 (m, 6 H), 1.46–1.35 (m, 3 H), 1.34–1.20 (m, 4 H), 0.83 (s, 9 H), 0.00 (s, 3 H), -0.05 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 140.8, 140.3, 128.8, 128.6, 128.5, 127.9, 127.1, 126.9, 125.1, 82.0, 77.3, 65.2, 52.8, 38.1, 37.4, 29.1, 25.9, 25.8, 24.0, 23.7, 18.3, –5.4, –5.5; IR (film, cm^{-1}) 2928, 1093; MS(ESI): 473.2862 (473.2852 calcd for $C_{29}H_{42}O_2Si$, M + Na^+).



III-42

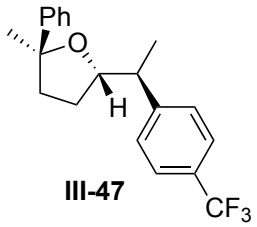
(*E*)-(1'*R,4*S**,5*S**)-2,2,4-Trimethyl-5-(-4-phenylbut-3-en-2-yl)tetrahydrofuran** (**III-42**). The coupling of (*E*)-2,4-dimethylhept-5-en-2-ol10 (0.025 g, 0.18 mmol) with β-bromostyrene (0.045 mL, 0.35 mmol) was conducted following General Procedure 4. This procedure afforded 0.043 g (92%) of the title compound as an orange oil. This was obtained as a 12:1 mixture of diastereomers, as judged by ^{1}H NMR analysis. Characterization data were identical to those previously reported in the literature.



III-46

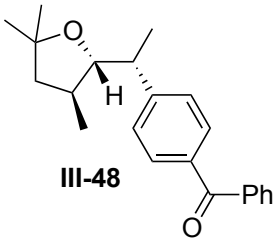
(1'*R,2*S**,5*S**)-2-Methyl-2-phenyl-5-{1-[4-(trifluoromethyl)phenyl]ethyl}tetrahydrofuran (III-46).** The coupling of (*E*)-2-phenylhept-5-en-2-ol (0.03 g, 0.16 mmol) with 4-bromobenzotriflouride (0.044 mL, 0.32 mmol) was conducted following General Procedure 4. This procedure afforded 0.05 g (93%) of the title compound as a clear oil. This material was

obtained as a 20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1 H), 7.47 (d, *J* = 7.2 Hz, 2 H), 7.42–7.37 (m, 1 H), 7.31–7.24 (m, 4 H), 7.20– 7.14 (m, 1 H), 4.14–4.07 (m, 1 H), 3.00–2.91 (m, 1 H), 2.18–2.09 (m, 1 H), 1.85–1.74 (m, 2 H), 1.70–1.58 (m, 1 H), 1.38 (s, 3 H), 1.35 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 145.1, 132.0 (q, *J* = 32.6 Hz), 128.3, 128.1 (q, *J* = 252.4 Hz), 125.0 (q, *J* = 3.7 Hz), 124.6, 123.0, 84.4, 82.3, 67.0, 44.5, 39.1, 29.3, 18.0; IR (film) 2957, 1327; MS(ESI): 357.1434 (357.1442 calcd for $C_{20}H_{21}F_3O$, M + Na^+).



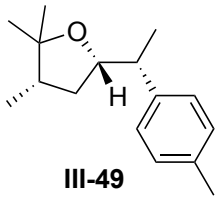
III-47

(1'*S,2*S**,5*S**)-2-methyl-2-phenyl-5-{1-[4-(trifluoromethyl)phenyl]ethyl}tetrahydrofuran (III-47).** The coupling of (*Z*)-2-phenylhept-5-en-2-ol (0.03 g, 0.16 mmol) with 4-bromo-benzotriflouride (0.044 mL, 0.32 mmol) was conducted following General Procedure 4. This procedure afforded 0.05 g (94%) of the title compound as a clear oil. This material was obtained as a 7:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1 H), 7.54–7.47 (m, 2 H), 7.46–7.41 (m, 3 H), 7.38–7.33, (m, 2 H), 7.28–7.22 (m, 1 H), 4.13 (q, *J* = 6.8 Hz, 1 H), 3.03 (p, *J* = 7.1 Hz, 1 H), 2.17–2.11 (m, 1 H), 1.86–1.79 (m, 1 H), 1.70–1.59 (m, 2 H), 1.48 (s, 3 H), 1.47 (d, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 145.2, 131.4 (q, *J* = 31.5 Hz), 128.7, 128.8 (q, *J* = 225.0 Hz), 125.0 (q, *J* = 3.9 Hz), 124.7, 123.1, 84.7, 82.9, 45.0, 39.1, 30.6, 29.3, 18.1; IR (film, cm^{-1}) 2971, 1326; MS(ESI): 357.1456 (357.1442 calcd for $C_{20}H_{21}F_3O$, M + Na^+).



III-48

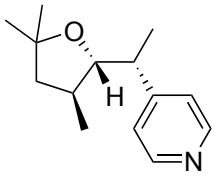
(1'*R,3*S**,2*S**)-Phenyl-{4-[1-(3,5,5-trimethyltetrahydrofuran-2-yl)ethyl]phenyl}methanone** (**III-48**). The coupling of (*E*)-2,4-dimethylhept-5-en-2-ol (0.03 g, 0.21 mmol) with 4-bromo-benzophenone (0.11 g, 0.42 mmol) was conducted following General Procedure 4. This procedure afforded 0.059 g (86%) of the title compound as a clear oil. This material was obtained as a 20:1 mixture of diastereomers as judged by ^{1}H NMR analysis material. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79–7.75 (m, 2 H), 7.74–7.70 (m, 2 H), 7.58–7.52 (m, 1 H), 7.48–7.42 (m, 2 H), 7.40–7.36 (m, 2 H), 3.66–3.62 (m, 1 H), 2.99–2.91 (m, 1 H), 1.80–1.72 (m, 2 H), 1.42–1.36 (m, 4 H), 1.24 (s, 3 H), 0.95 (s, 3 H), 0.91 (d, *J* = 6.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 137.9, 135.4, 132.0, 129.9, 129.7, 128.9, 128.1, 88.8, 79.2, 48.1, 48.0, 42.2, 36.2, 29.4, 29.2, 18.5, 16.8; IR (film, cm^{-1}) 2930, 1653; MS(ESI): 345.1826 (345.1830 calcd for $C_{22}H_{26}O_2$, M + Na^+).



III-49

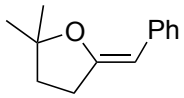
(1'*R,3*S**,5*S**)-2,2,3-Trimethyl-5-(1-*p*-tolylethyl)tetrahydrofuran** (**III-49**). The coupling of (*E*)-2,4-dimethylhept-5-en-2-ol (0.025 g, 0.18 mmol) with 4-bromotoluene (0.043 mL, 0.35 mmol) was conducted following General Procedure 4. This procedure afforded 0.033 g (85%) of the title compound as a clear oil. This material was obtained as a 4:1 mixture of diastereomers (epimeric at C3) as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13–7.04 (m, 4 H), 3.98 (p, *J* = 5.9 Hz, 1 H), 2.86–2.76 (m, 1 H), 2.28 (s, 3 H), 1.98–1.89 (m, 1 H), 1.58–1.50 (m, 1H), 1.46–1.36 (m, 1 H), 1.19 (d, *J* = 7.0 Hz, 3 H), 1.16

(s, 3 H), 0.93 (s, 3 H), 0.87 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 135.4, 129.5, 128.7, 85.4, 79.3, 48.2, 40.2, 38.6, 29.6, 29.4, 21.0, 18.9, 16.7; IR (film, cm^{-1}) 2967, 1064; MS(ESI): 241.1565 (241.1568 calcd for $C_{16}H_{24}O$, M + Na^+).



III-50

(1'*R,3*S**,5*S**)-3,5,5-Trimethyltetrahydrofuran-2-yl(ethyl)pyridine** (**III-50**). The coupling of (*E*)-2,4-dimethylhept-5-en-2-ol (0.02 g, 0.14 mmol) with 4-bromopyridine HCl (0.55 g, 0.28 mmol) was conducted following General Procedure 4 except using 4 equiv of NaO*t*Bu. This procedure afforded 22 mg (71%) of the title compound as an amber oil. This was obtained as a 15:1 mixture of diastereomers (epimeric at C3) as judged by ^{1}H NMR analysis material. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 5.3 Hz, 2 H), 7.17–7.15 (m, 2 H), 3.57 (dd, *J* = 3.7, 9.0 Hz, 1 H), 2.84–2.76 (m, 1 H), 1.77–1.63 (m, 2 H), 1.40–1.35 (m, 1 H), 1.32 (d, *J* = 7.3 Hz, 3 H), 1.20 (s, 3 H), 0.91 (s, 3 H), 0.88 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 149.0, 124.4, 88.2, 79.2, 47.9, 41.8, 36.3, 29.3, 29.2, 18.1, 16.7; IR (film, cm–1) 2965, 1598; MS(ESI): 220.1707 (220.1701 calcd for $C_{14}H_{21}NO$, M + H^+).



III-72

(Z)-5-benzylidene-2,2-dimethyltetrahydrofuran (**III-72**). The coupling of 6-methoxy-2-methylhex-5-en-2-ol (0.02 g, 0.14 mmol) with bromobenze (0.029 mL, 0.28 mmol) was conducted following General Procedure 4. The yield of the reaction was not determined. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.51 (m, 2 H),

7.44 (m, 1 H), 7.32-7.24 (m, 1 H), 5.24 (t, J = 3.9 Hz, 1 H), 2.21-2.15 (m, 2 H), 1.65 (t, J = 6.6 Hz, 2 H), 1.31 (s, 6 H).

3.7 References

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[4] For related reactions of hydroxy dienes, see: Yeh, M. -C. P.; Tsao, W -C.; Tu, L. -H. *Organometallics* **2005**, *24*, 5909–5915. For related reactions of allylic alcohols that generate oxiranes, see: (b) Hayashi, S.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2009**, *131*, 2052–2053.

[5] For recent, complementary alkene difunctionalization reactions of unsaturated alcohols that generate disubstituted tetrahydrofurans with formation of both a C-C and a C-O bond, see: (a) Zhang, G.; Cui, L.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 1474–1475. (b) Nicolai, S.; Erard, S.; Gonzalez, D. F.; Waser, J. *Org. Lett.* **2010**, *12*, 384–387. (c) Protti, S.; Dondi, D.; Fagnoni, M.; Albini, A. *Eur. J. Org. Chem.* **2008**, 2240–2247. (d) Yang, X.; Fang, X.; Yang, X.; Zhao, M.; Han, Y.; Shen, Y.; Wu, F. *Tetrahedron* **2008**, *64*, 2259–2269.

[6] (a) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338–6361. (b) Van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741–2770.

[7] Ligand definitions: Dpe-Phos = bis(2-diphenylphosphinophenyl) ether; Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; X-Phos = 2-(dicyclohexylphosphino)-2′,4′,6′-triisopropyl-1,1′-biphenyl; Ru-Phos = 2-dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl; Dave-phos = 2-dicyclohexylphosphino-2′(N,N-dimethylamino)biphenyl; John-phos = 2-(di-tert-butylphosphino)biphenyl; Brett-phos) 2-(dicyclohexylphos- phino)-3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl; S-Phos = 2-dicy- clohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl.

[8] Diastereomeric ratios observed in crude reaction mixtures were identical to those obtained upon isolation.

[9] The precise origin of the efficacy of S-Phos in these transformations is not entirely clear but is likely related to features that have been ascribed to its utility in Suzuki coupling reactions. See: Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871–1876.

[10] Reaction temperatures of 140°C were employed to ensure transformations proceeded to completion. Use of lower reaction temperatures did not have a significant influence on diastereoselectivity.

[11] For a discussion of the mechanism for regioisomer formation, see ref 3a.

[12] The two diastereomers are epimeric at C3.

[13] A reaction that was halted at 30% conversion showed no evidence for Z to E isomerization of the alkene starting material.

[14] Use of P(o-tol)3 for the coupling of β-bromostyrene with **III-45** afforded a 65:17:14:4 mixture of diastereomers. See ref 3c.

[15] Analogous reactions of secondary alcohol substrates bearing terminal alkenes (e.g., **III-1**) provide trans-2,5-disubstituted products in good yield with >20:1 dr. See refs 3b, 3d and 3e.

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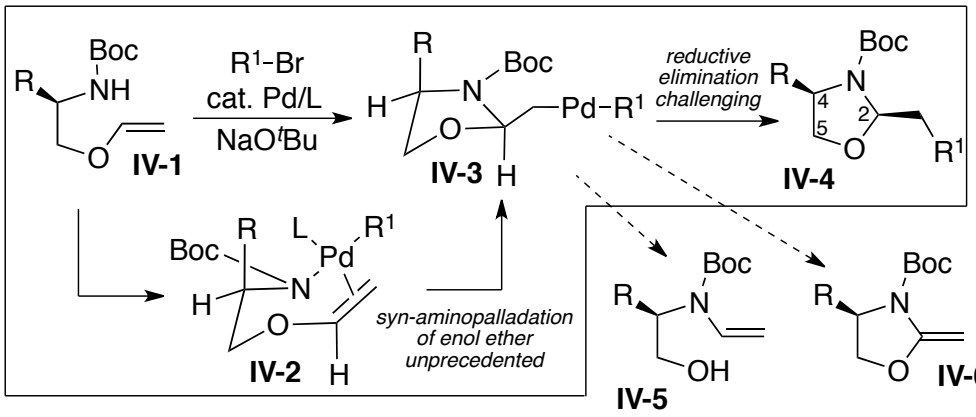
Chapter 4: Stereoselective Synthesis of Substituted 1,3-Oxazolidines via Pd-Catalyzed Carboamination Reactions of O-Vinyl-1, 2-Amino Alcohols

4.1 Introduction

Substituted 1,3-oxazolidines are displayed in many biologically active compounds[1] and are also broadly employed in asymmetric synthesis as chiral auxiliaries, or as chiral ligands for transition metal catalysts.[2] The classical approach to 2,4- and 2,5-disubstituted 1,3-oxazolidines involves condensation of an aldehyde with an amino alcohol, and alternative routes that involve carbon-heteroatom bond-forming cycloaddition,[3] conjugate addition,[4] or aza-Wacker type reactions[5] have also been explored. However, most methods for the preparation of 1,3-oxazolidines effect the construction of the C-N and the C-O bond during the ring-forming event. Transformations that generate both a carbon-heteroatom bond and a carbon-carbon bond during oxazolidine formation are relatively rare and are typically not amenable to the stereo-controlled preparation of 2,4- or 2,5-disubstituted products.[6]

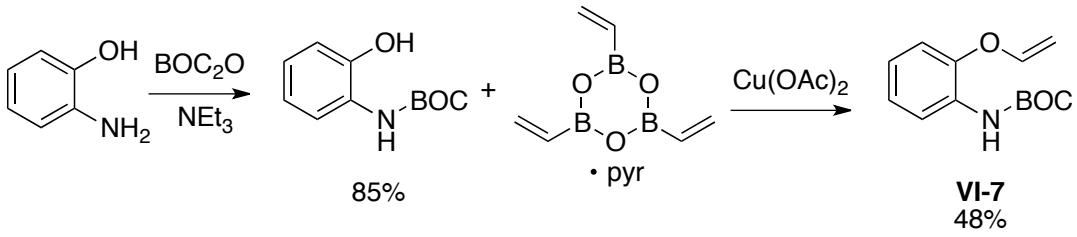


Scheme 4-1. Carboamination Strategy for Stereoselective Oxazolidine Synthesis

We sought to develop a new method for the preparation of 1,3-oxazolidines (e.g., **IV-4**) via Pd-catalyzed carboamination reactions between aryl or alkenyl bromides and enol ethers (**IV-1**) derived from readily available 1,2-amino alcohols (Scheme 4-1). This approach has significant potential utility, as the reactions should proceed with kinetic control of stereochemistry and provide enantiomerically pure products with good levels of diastereoselectivity.[7,8] However, in order to accomplish this goal, it was necessary to overcome two key obstacles. The transformations were expected to proceed via intramolecular syn-aminopalladation of intermediate **IV-2**,[9] but enol ethers (or similarly electron-rich alkenes) have not previously been employed in Pd-catalyzed carboaminations between unsaturated amines and aryl/alkenyl halides.[10] No studies have demonstrated that such highly electron-rich alkenes can undergo syn-migratory insertion into Pd-N bonds of LnPd(R1)(NR2) complexes.[11] Moreover, mechanistic experiments by Stahl indicate that the transition state for syn-aminopalladation exhibits characteristics of a N-nucleophile/alkene electrophile combination,[12] which suggests that insertions of electron-rich alkenes could have relatively high barriers.[13] In addition to the challenges associated with syn-amino-palladation of an electron-rich alkene, the reductive elimination of intermediate **IV-3** was also expected to be difficult. The two inductively electron-withdrawing heteroatoms on the carbon beta to Pd will slow the rate of C-C bond formation from **IV-3**[14]. Thus, competing β-hydride elimination[15] to generate **IV-6** or β-alkoxide elimination[16] to form **IV-5** could be problematic.

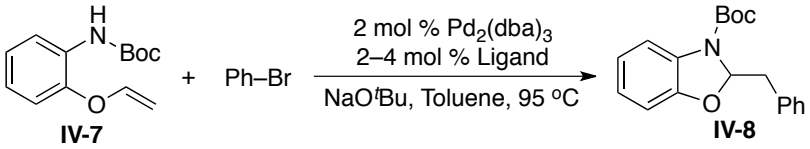
4.2 Optimization of the Reaction Conditions

In preliminary feasibility studies, we elected to examine the reactivity of bromobenzene with the simple, geometrically constrained enol ether **IV-7**, which was synthesized by boc-protecting the amino group of 2-aminophenol and subsequent conversion of the phenol to the vinyl ether using 2,4,6-trivinylcyclotriboroxane-pyridine complex and a stoichiometric amount of copper acetate, as shown in Scheme 4-2.



Scheme 4-2. Synthesis of the Substrate Used in Optimization Studies

Given the anticipated challenges described above, we focused our catalyst optimization studies on two classes of ligands: (a) bis-phosphine ligands with relatively wide bite angles; and (b) bulky monodentate phosphine ligands (Table 4-1). These classes of ligands have been shown to promote rapid C-C bond-forming reductive elimination,[17] and prior studies suggested they could also potentially facilitate the key amino-palladation step.[18] A preliminary survey of catalysts composed of $Pd_2(dba)_3$ and a wide bite angle ligand indicated that the yield of **IV-8** increased with increasing bite angle, and promising results were obtained with Xantphos (58% yield).[19] However, our experiments with monodentate phosphines showed the monodentate S-Phos ligand was superior to Xantphos,[20] as the 1, 3-oxazolidine product **IV-8** was isolated in 70% yield when this phosphine was employed.



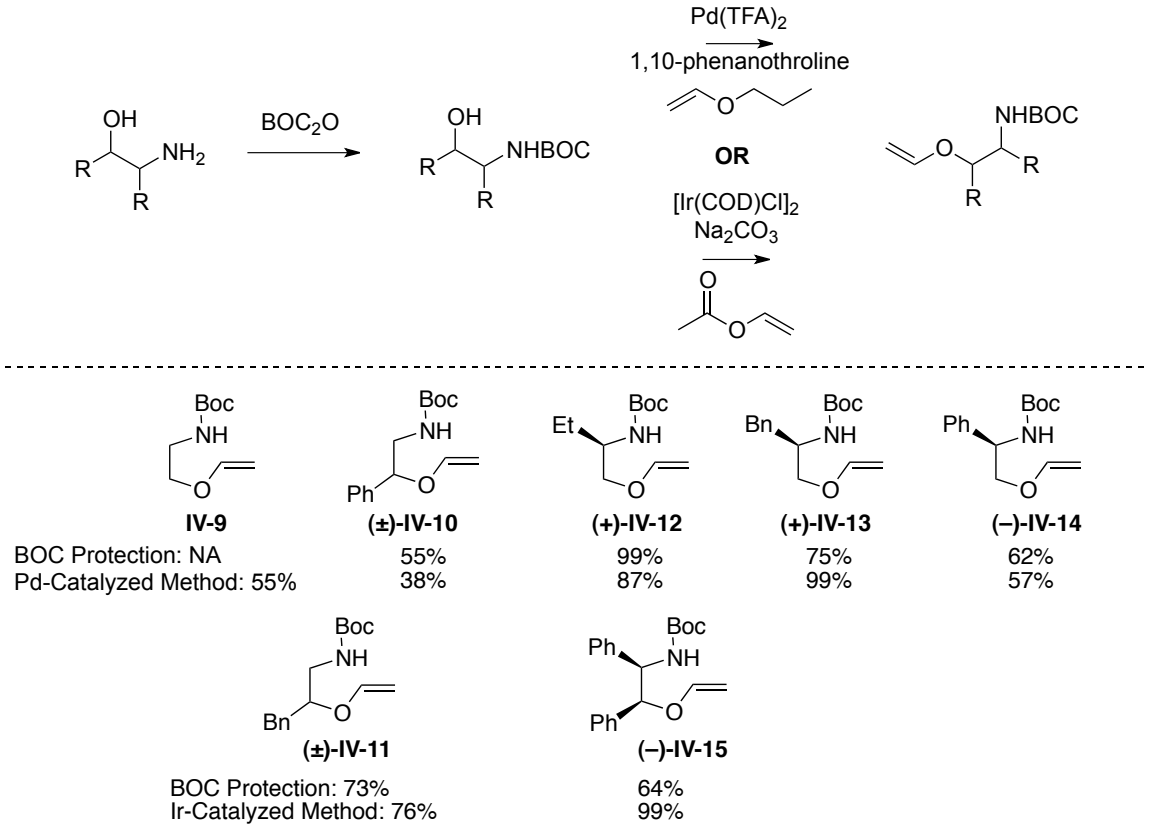
entry	ligand	yield[b]
1	dppb	0%
2	Dpe-Phos	13%
3	Xantphos	58%
4	P(*o*-tol)$_3$	0%
5	Ru-Phos	20%
6	S-Phos	70%[c]

[a] Conditions: 1.0 equiv of 7, 2.0 equiv of PhBr, 2.0 equiv of NaO^{t}Bu, 2 mol % $Pd_2(dba)_3$, 2-4 mol % ligand, Toluene, 95 C. [b] Yields were determined by ^{1}H NMR analysis of crude reaction mixtures using phenanthrene as an internal standard. [c] Isolated yield (average of two experiments).

Table 4-1. Catalyst Optimization Studies[a]

4.3 Exploration of Substrate Scope

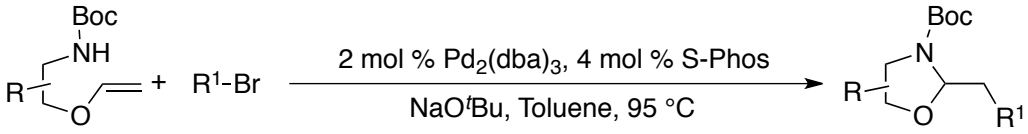
Having discovered a suitable catalyst system for enol ether carboamination, we sought to probe the scope of this new method. A variety of substrates were synthesized via O-vinylation of the corresponding amino alcohols via Pd- or Ir-catalyzed vinyl transfer, as shown in Scheme 4-3.[21]

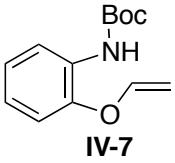
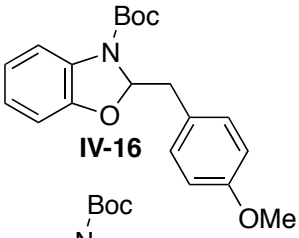
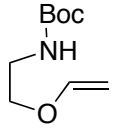
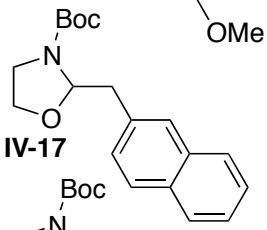
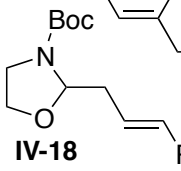
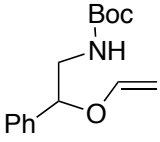
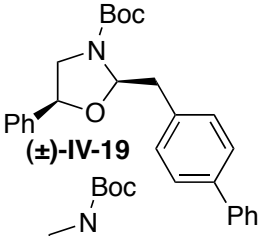
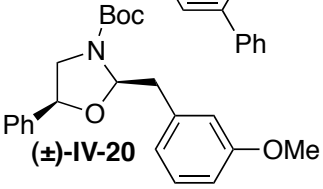
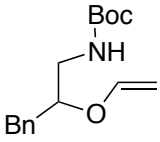
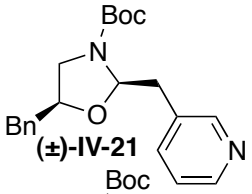
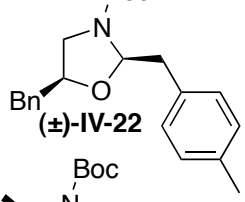
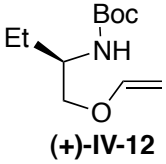
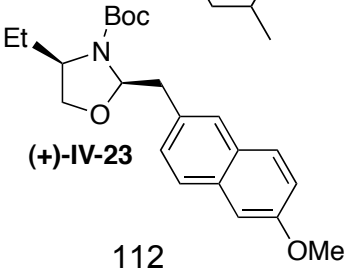


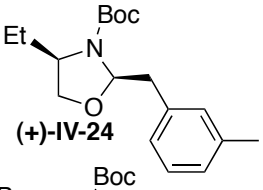
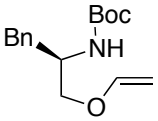
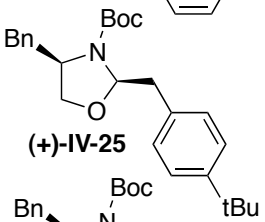
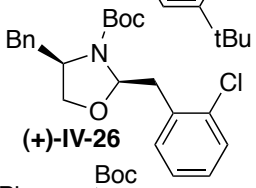
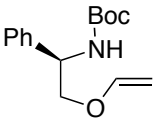
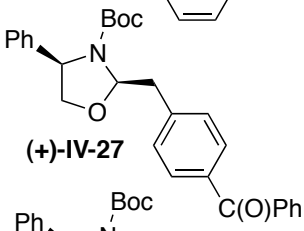
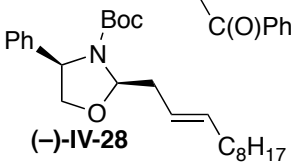
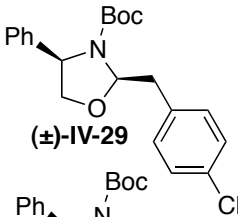
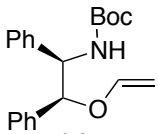
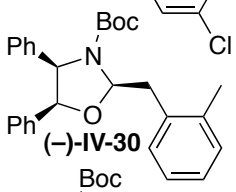
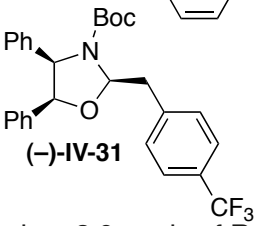
Scheme 4-3. Substrate Synthesis

As shown in Table 4-2, substrates bearing substituents adjacent to the oxygen or nitrogen atom were transformed to 2,5-*cis*- or 2,4-*cis*-disubstituted-1,3-oxazolidines in good yield (entries 4-14). The products were typically generated with 8-17:1 dr (crude). Additionally, in many cases diastereomers could be partially separated by chromatography, and upon isolation the desired products were obtained with up to >20:1 dr. Disubstituted substrate **IV-(–)-15** was converted to trisubstituted products **IV-(–)-30** and **IV-(–)-31** with good

stereocontrol (entries 15-16).[22] The transformations were effective with a wide range of aryl bromides, and alkenyl halides were also successfully used as coupling partners (entries 3 and 13).



entry	substrate	product	dr[b]	yield[c]
1	 **IV-7**	 **IV-16**	—	69%
2	 **IV-9**	 **IV-17**	—	63%
3	**IV-9**	 **IV-18**	—	57%
4	 **(±)-IV-10**	 **(±)-IV-19**	12:1 (9:1)	83%
5	**(±)-IV-10**	 **(±)-IV-20**	>20:1 (14:1)	89%
6	 **(±)-IV-11**	 **(±)-IV-21**	12:1 (12:1)	69%
7	**(±)-IV-11**	 **(±)-IV-22**	>20:1 (9:1)	83%
8	 **(+)-IV-12**	 **(+)-IV-23**	15:1 (15:1)	58%

entry	substrate	product	dr[b]	yield[c]
9	**(+)-IV-12**	 **(+)-IV-24**	19:1 (9:1)	63%
10	 **(+)-IV-13**	 **(+)-IV-25**	>20:1 (8:1)	67%
11	**(+)-IV-13**	 **(+)-IV-26**	17:1 (17:1)	62%
12	 **(–)-IV-14**	 **(+)-IV-27**	11:1 (8:1)	72%
13	**(–)-IV-14**	 **(–)-IV-28**	9:1 (9:1)	58%
14	**(±)-IV-14**	 **(±)-IV-29**	18:1 (9:1)	53%
15	 **(–)-IV-15**	 **(–)-IV-30**	16:1 (16:1)	76%
16	**(–)-IV-15**	 **(–)-IV-31**	17:1 (15:1)	70%

a Conditions: 1.0 equiv of amine, 2.0 equiv of R_1Br, 2.0 equiv of NaO_tBu, 2 mol % $Pd_2(dba)_3$, 4 mol % S-Phos, Toluene, 95 C. b Diastereomeric ratios were determined by $_1H$ NMR analysis of the pure, isolated material. Numbers in parentheses are diastereomeric ratios observed by NMR analysis of crude reaction mixtures. c Isolated yields (average of two or more experiments).

Table 4-2. Stereoselective Synthesis of Substituted Oxazolidines[a]

4.4 Stereochemical Model

A model that accounts for the relative stereochemistry of the products is illustrated in Figure 4-1. Transformations of substrates **IV-12-IV-14** proceed via transition state **IV-32**, in which the substituent adjacent to the nitrogen atom is oriented in an axial position to minimize $A^{1,3}$ strain in alternative transition state **IV-33**. Reactions of **IV-10-IV-11** undergo cyclization via transition state **IV-34**, in which the substituent adjacent to the oxygen atom is equatorial to avoid 1,3-diaxial interactions that would be present in transition state **IV-35**. The nature of the aryl or alkenyl halide appears to have a small effect on diastereoselectivity, but no clear trend is apparent.

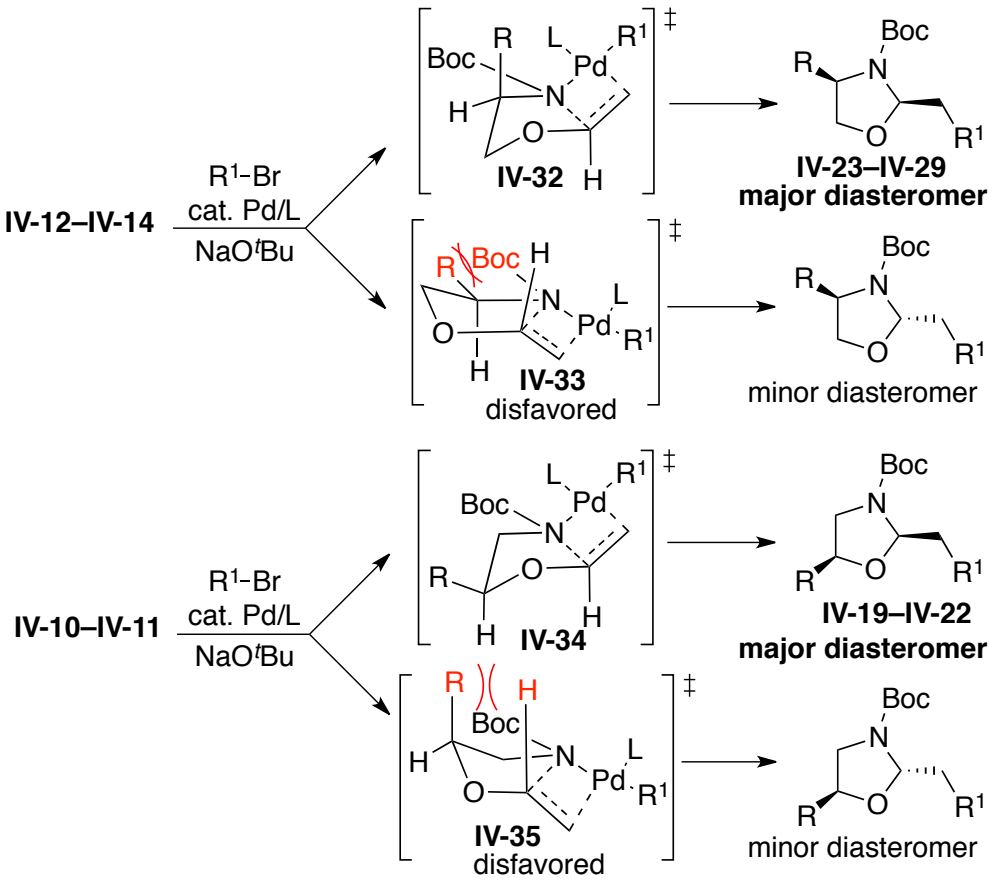


Figure 4-1. Stereochemical Model

4.5 Conclusions

In summary, we have developed a concise approach to the synthesis of enantiomerically pure 2,4- and 2,5-disubstituted 1,3-oxazolidines. The heterocyclic products are generated in only three steps from commercially available amino alcohols in good yield and diastereoselectivity. This transformation provides access to compounds that are difficult to prepare in a stereocontrolled manner with existing methods. These transformations also illustrate the viability of enol ethers as participants in alkene carboamination processes and highlight the efficacy of S-Phos in promoting challenging sp3-sp3 C-C bond-forming reductive elimination from Pd(II).

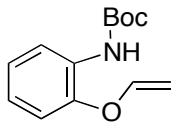
4.6 Experimental

Preparation of Substrates

General Procedure 1: Synthesis of vinyl ethers via Pd-catalyzed vinylation.[23] An oven-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with the appropriate Boc-protected amino alcohol (1 equiv), palladium trifluoroacetate (1 mol %), 1,10 phenanthroline (1 mol %), triethylamine (0.1 equiv) and *n*-butyl vinyl ether (0.25 M). The resulting solution was heated to 75 $^{\circ}$C for 12 h, then was cooled to rt. Brine (5 mL) and EtOAc (5 mL) were added, and the mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel using 10:1 hexanes:ethyl acetate that contained 1% triethylamine (by volume) as the eluent.

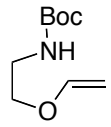
General Procedure 2: Iridium-catalyzed synthesis of vinyl ethers.[24] A flame-dried round-bottomed flask equipped with a magnetic stirbar, a reflux condenser, and a rubber septum was cooled under a stream of nitrogen and charged with di-μ-chloro-bis(1,5-cyclooctadiene)diiridium (I), $[Ir(cod)Cl]_2$, (0.01 equiv) and sodium carbonate (0.6 equiv). The appropriate Boc-protected amino

alcohol (1 equiv), vinyl acetate (2 equiv), and toluene (1 M) were added, and the resulting mixture was heated to reflux for 12 h. The mixture was cooled to rt, brine (5 mL) and EtOAc (5 mL) were added, and the mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel using 10:1 hexanes:ethyl acetate that contained 1% triethylamine (by volume) as the eluent.



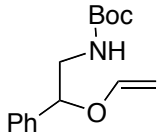
IV-7

***tert*-Butyl [2-(vinyloxy)phenyl]carbamate (IV-7).**[25] An oven-dried flask was cooled under a stream of nitrogen and charged with $Cu(OAc)_2$ (1 equiv) and CH_2Cl_2 (0.1 M). The resulting mixture was stirred at rt for 10 min then 2,4,6-trivinylcyclotriboroxane-pyridine (1 equiv), *tert*-butyl (2-hydroxyphenyl)carbamate (1 equiv), and pyridine (10 equiv) were added. The resulting mixture was stirred at rt for 24 h, then was passed through an alumina column eluting with CH_2Cl_2. The resulting solution was concentrated *in vacuo* to afford the title compound as an orange oil that was used without additional purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.6 Hz, 1 H), 7.09–7.02 (m, 1 H), 6.99–6.90 (m, 2 H), 6.56 (dd, *J* = 6.1, 13.7 Hz, 1 H), 4.79 (dd, *J* = 1.8, 15.3 Hz, 1 H), 4.49 (dd, *J* = 1.8, 6.1 Hz, 1 H), 1.52 (s, 9 H) [missing NH peak]; ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 148.0, 144.6, 129.2, 123.9, 122.4, 118.9, 115.9, 95.9, 80.6, 28.3; IR (film, cm^{-1}) 3442, 2978, 1733; MS(EI): 235.1208 (235.1214 calcd for $C_{13}H_{17}NO_3$, M^+).



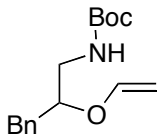
IV-9

***tert*-Butyl [2-(vinyloxy)ethyl]carbamate (IV-9).** General Procedure 1 was used for conversion of *tert*-butyl (2-hydroxyethyl)carbamate (0.2 mL, 1.23 mmol) to the title compound. This procedure afforded 0.64 g (55%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.40 (dd, *J* = 6.7, 14.3 Hz, 1 H), 4.87 (s, br, 1 H), 4.16 (dd, *J* = 2.4, 14.5 Hz, 1 H), 3.99 (dd, *J* = 2.4, 6.9 Hz, 1 H), 3.70 (t, *J*= 6.4 Hz, 2 H), 3.41–3.34 (m, 2 H), 1.41 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 151.4, 87.0, 79.4, 67.0, 39.8, 28.3; IR (film, cm^{-1}) 3341, 2976, 1699; MS(ESI): 210.1095 (210.1101 calcd for $C_9H_{17}NO_3$, M + H^+).



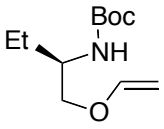
IV-10

(±)-*tert*-Butyl [2-phenyl-2-(vinyloxy)ethyl]carbamate (IV-10). General Procedure 1 was used for the conversion of *tert*-butyl (2-hydroxy-2-phenylethyl)carbamate (0.5 g, 2.1 mmol) to the title compound. This procedure afforded 0.20 g (38%) of the title compound as a white solid, mp = 76 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.24 (m, 5 H), 6.31 (dd, *J* = 6.7, 14.2 Hz, 1 H), 4.97–4.80 (m, 2 H), 4.24 (d, *J* = 14.2 Hz, 1 H), 4.00 (dd, *J* = 1.6, 6.6 Hz, 1 H), 3.60–3.46 (m, 1 H), 3.32–3.23 (m, 1 H), 1.45 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 150.4, 138.6, 128.6, 128.0, 126.2, 90.0, 80.3, 79.5, 46.7, 28.4; IR (film, cm^{-1}) 3392, 2978, 1683; MS(ESI): MS(ESI): 286.1410 (286.1414 calcd for $C_{16}H_{23}NO_3$ M + Na^+).



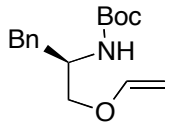
IV-11

(±)-*tert*-Butyl [3-phenyl-2-(vinyloxy)propyl]carbamate (IV-11). General Procedure 2 was used for the conversion of *tert*-butyl (2-hydroxy-3-phenylpropyl)carbamate (0.4 g, 1.5 mmol) to the title compound. This procedure afforded 0.32 g (76%) of the title compound as a white solid, mp = 62 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.24 (m, 2 H), 7.23–7.16 (m, 3 H), 6.47 (dd, *J* = 6.8, 14.5 Hz, 1 H), 4.80 (s, br, 1 H), 4.13 (dd, *J* = 2.2, 14.3 Hz, 1 H), 4.08–3.98 (m, 2 H), 3.63–3.54 (m, 2 H), 2.96–2.80 (m, 2 H), 1.41 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.22, 151.4, 137.8, 129.4, 128.5, 126.5, 87.0, 79.4, 67.6, 51.0, 37.7, 28.5; IR (film, cm^{-1}) 3395, 1686, 1164; MS(ESI): 300.1573 (300.1570 calcd for $C_{16}H_{23}NO_3$ M + Na^+).



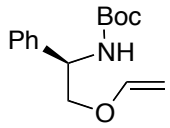
IV-12

(+)-(*R*)-*tert*-Butyl [1-(vinyloxy)butan-2-yl]carbamate (IV-12). General Procedure 1 was used for the conversion of (*R*)-*tert*-butyl (1-hydroxybutan-2-yl)carbamate (1.0 g, 5.28 mmol) to the title compound. This procedure afforded 0.99 g (87%) of the title compound as a colorless oil $[a]_D^{23}$ = +28.5 (*c* 18.53, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.47 (dd, *J* = 6.8, 14.4 Hz, 1 H), 4.67 (s, br, 1 H), 4.18 (dd, *J* = 2.0, 14.2 Hz, 1 H), 4.0 (dd, *J* = 2.2, 6.8 Hz, 1 H), 3.76–3.63 (m, 3 H), 1.66–1.58 (m, 1 H), 1.56–1.48 (m, 1 H), 1.45 (s, 9 H), 0.94 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 151.7, 86.7, 69.1, 51.2, 28.4, 24.9, 10.5 (one carbon signal is missing due to incidental equivalence); IR (film, cm^{-1}) 3440, 2970, 1686; MS(ESI): 238.1412 (238.1414 calcd for $C_{11}H_{21}NO_3$, M + Na^+).



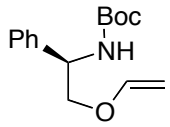
IV-13

(+)-(*R*)-*tert*-Butyl [1-phenyl-3-(vinyloxy)propan-2-yl]carbamate (IV-13). General Procedure 1 was used for the conversion of (*R*)-*tert*-butyl (1-hydroxy-3-phenylpropan-2-yl)carbamate (0.5 g, 1.99 mmol) to the title compound. This procedure afforded 0.54 g (99%) of the title compound as a white solid, mp = 62 ^{o}C, $[a]_D^{23}$ = +20.7 (*c* 18.06, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.24 (m, 2 H), 7.22–7.15 (m, 3 H), 6.47 (dd, *J* = 6.8, 14.2 Hz, 1 H), 4.86 (s, br, 1 H), 4.13 (dd, *J* = 2.1, 14.2 Hz, 1 H), 4.08–3.96 (m, 2 H), 3.63–3.54 (m, 2 H), 2.93–2.80 (m, 2 H), 1.41 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 151.4, 137.8, 129.4, 128.4, 126.4, 87.0, 79.3, 67.7, 51.0, 37.7, 28.3.; IR (film, cm^{-1}) 3359, 2922, 1687; MS(ESI): 300.1567 (300.1570 calcd for $C_{16}H_{23}NO_3$, M + Na^+).



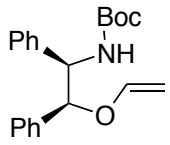
IV-14

(–)-(*R*)-*tert*-Butyl [1-phenyl-2-(vinyloxy)ethyl]carbamate (IV-14). General Procedure 1 was used for the conversion of (*R*)-*tert*-butyl (2-hydroxy-1-phenylethyl)carbamate (0.4 g, 1.68 mmol) to the title compound. This procedure afforded 0.23 g (52%) of the title compound as a white solid, mp = 72 ^{o}C, $[a]_D^{23}$ = –18.1 (*c* 2.02, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.32 (m, 3 H), 7.31–7.27 (m, 2 H), 6.46 (dd, *J* = 6.8, 14.2 Hz, 1 H), 5.20 (s, 1 H), 4.96 (s, 1H), 4.21 (dd, *J* = 2.2, 14.4 Hz, 1 H), 4.04 (dd, *J* = 2.2, 6.8 Hz, 1 H), 3.98–3.92 (m, 1 H), 3.91–3.85 (m, 1 H), 1.45 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 151.3, 139.8, 128.5, 127.6, 126.7, 87.2, 79.8, 70.3, 53.7, 28.4; IR (film, cm^{-1}) 3390, 2978, 1682; MS(ESI): 286.1414 (286.1414 calcd for $C_{16}H_{23}NO_3$ M + Na^+).



IV-14

(±)-*tert*-Butyl [1-phenyl-2-(vinyloxy)ethyl]carbamate (IV-14). General Procedure 1 was used for the conversion of *tert*-butyl (2-hydroxy-1-phenylethyl)carbamate (1.5 g, 6.32 mmol) to the title compound. This procedure afforded 0.95 g (57%) of the title compound as a white solid, mp = 72 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.32 (m, 3 H), 7.31–7.27 (m, 2 H), 6.46 (dd, *J* = 6.8, 14.2 Hz, 1 H), 5.20 (s, 1 H), 4.96 (s, 1H), 4.21 (dd, *J* = 2.2, 14.4 Hz, 1 H), 4.04 (dd, *J* = 2.2, 6.8 Hz, 1 H), 3.98–3.92 (m, 1 H), 3.91–3.85 (m, 1 H), 1.45 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 151.3, 139.8, 128.5, 127.6, 126.7, 87.2, 79.8, 70.3, 53.7, 28.4; IR (film, cm^{-1}) 3390, 2978, 1682; MS(ESI): 286.1412 (286.1414 calcd for $C_{16}H_{23}NO_3$ M + Na^+).

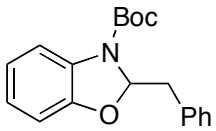


IV-15

(–)-(1*R*,2*S*)-*tert*-Butyl [1,2-diphenyl-2-(vinyloxy)ethyl]carbamate (IV-15). General Procedure 2 was used for the conversion of (1*R*,2*S*)-*tert*-butyl (2-hydroxy-1,2-diphenylethyl)carbamate (0.5 g, 1.99 mmol) to the title compound. This procedure afforded 0.54 g (99%) of the title compound as a white solid, mp = 62 ^{o}C, $[a]_D^{23}$ = –32.3 (*c* 2.33, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.16 (m, 6 H), 7.03–6.98 (m, 2 H), 6.97–6.92 (m, 2 H), 6.35 (dd, *J* = 6.6, 14.2 Hz, 1 H), 5.40 (s, br, 1 H), 5.19 (s, br, 1 H), 4.96 (s, br, 1 H), 4.24 (d, *J* = 14.2 Hz, 1 H), 4.03 (dd, *J* = 1.7, 6.6 Hz. 1 H), 1.42 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 150.4, 137.1, 128.2, 128.0, 127.7, 127.5, 127.4, 126.8, 126.6, 90.1, 83.0, 79.7, 59.4, 28.4; IR (film, cm^{-1}) 3388, 2979, 1681, 1171; MS(ESI): 362.1727 (362.1727 calcd for $C_{21}H_{25}NO_3$, M + Na^+).

Synthesis of Substituted 1,3-Oxazolidines via Pd-Catalyzed Alkene Carboamination

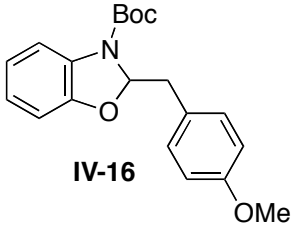
General Procedure 4: Palladium-Catalyzed Carboamination Reactions for the Formation of Oxazolidines. An oven or flame-dried Schlenk tube was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (2 mol% complex, 4 mol % Pd), S-Phos (4 mol %), NaO^tBu (2.0 equiv), and the aryl bromide (2.0 equiv). The tube was purged with nitrogen and the amine substrate (1.0 equiv), and toluene (0.25 M in substrate) were added. The mixture was heated to 98 °C with stirring until the starting material had been consumed as judged by GC or ^1H NMR analysis. The mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl (2 mL), and diluted with ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was then purified by flash chromatography on silica gel.



IV-8

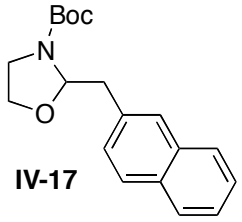
(±)-*tert*-Butyl 2-benzylbenzo[d]oxazole-3(2H)-carboxylate (**IV-8**). The coupling of *tert*-butyl [2-(vinyloxy)phenyl]carbamate (20 mg, 0.09 mmol) with bromobenzene (0.27 µL, 0.17 mmol) was conducted following General Procedure 4. This procedure afforded 19.5 mg (74%) of the title compound as an orange oil. ^1H NMR (400 MHz, C_7D_8, 100 ^oC) δ 7.45 (s, 1 H), 7.17–7.13 (m, 2 H), 7.07–7.02 (m, 3 H), 7.00–6.94 (m, 2 H), 6.70–6.62 (m, 1 H), 6.59–6.55 (m, 1 H), 3.11 (dd, *J* = 2.7, 14.1 Hz, 1 H), 2.99 (dd, *J* = 6.4, 14.1 Hz, 1 H), 1.40 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 135.0, 131.6, 131.5, 129.9, 128.6, 128.4, 128.3, 127.0, 126.8, 123.3, 120.9, 114.1, 113.8, 108.7, 94.7, 82.4, 41.4, 40.6, 28.3 (doubling of 5 peaks was observed due to the interconversion of rotamers);

IR (film, cm^{-1}) 2978, 1702, 1480; MS(ESI): 334.1416 (334.1414 calcd for $C_{20}H_{23}NO_4$, M + Na^+).



IV-16

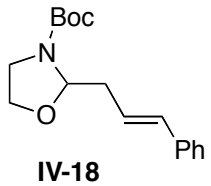
(±)-*tert*-Butyl 2-(4-methoxybenzyl)benzo[*d*]oxazole-3(2*H*)-carboxylate (IV-16). The coupling of *tert*-butyl [2-(vinyloxy)phenyl]carbamate (20 mg, 0.09 mmol) with 4-bromoanisole (21 µL, 0.17 mmol) was conducted following General Procedure 4. This procedure afforded 20 mg (71%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, C_7D_8, 90 ^{o}C) δ 7.49 (s, 1 H), 7.10–7.05 (m, 1 H), 6.99–6.95 (m, 1 H), 6.67–6.64 (m, 5 H), 6.14–6.08 (m, 1 H), 3.33 (s, 3 H), 3.13–3.06 (s, 1 H), 2.02–1.93 (s, 1 H), 1.40 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 150.1, 130.9, 127.0, 126.5, 123.2, 121.0, 114.0, 113.8, 108.7, 94.8, 82.4, 55.2, 40.4, 39.6, 29.7, 28.3 (doubling of 1 peak was observed due to the interconversion of rotamers); IR (film, cm^{-1}) 2974, 1702, 1480, 1248, 1063; MS(ESI): 364.1519 (364.1519 calcd for $C_{19}H_{21}NO_3$, M + Na^+).



IV-17

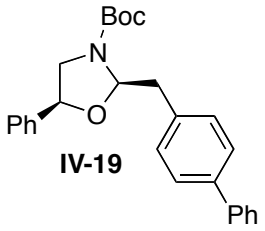
(±)-*tert*-Butyl 2-(naphthalen-2-ylmethyl)oxazolidine-3-carboxylate (IV-17). The coupling of *tert*-butyl [2-(vinyloxy)ethyl]carbamate (30 mg, 0.16 mmol) with 2-bromonaphthalene (66 mg, 0.32 mmol) was conducted following General Procedure 4. This procedure afforded 50 mg (70%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, C_7D_8, 100 ^{o}C) δ 7.67–7.64 (m, 1 H), 7.63–7.54 (m, 2 H), 7.39–7.33 (m, 1 H), 7.25–7.17 (m, 1 H), 7.09–7.05 (m, 1 H), 7.00–6.95 (m,

1 H), 4.39–4.33 (m, 1 H), 3.55–3.45 (m, 1 H), 3.41–3.28 (m, 2 H), 3.25–3.17 (m, 1 H), 3.16–3.07 (m, 1 H), 2.79–2.69 (m, 1 H), 1.41 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 134.2, 133.5, 132.3, 128.6, 127.6, 127.5, 125.8, 125.4, 89.3, 80.4, 65.6, 44.5, 40.8, 28.4 (2 carbon signals are missing due to incidental equivalence); IR (film, cm^{-1}) 2967, 2928, 1699; MS(ESI): 336.1568 (336.1570 calcd for $C_{19}H_{23}NO_3$, M + Na^+).



IV-18

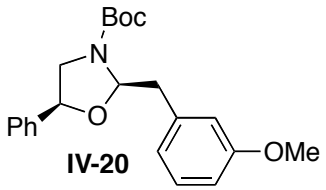
(±)-(*E*)-*tert*-Butyl 2-cinnamyloxazolidine-3-carboxylate (**IV-18**). The coupling of *tert*-butyl [2-(vinyloxy)ethyl]carbamate (20 mg, 0.11 mmol) with (*E*)-b-bromostyrene (28 µL, 0.22 mmol) was conducted following General Procedure 4. This procedure afforded 20 mg (65%) of the title compound as an orange oil. ^{1}H NMR (400 MHz, C_7D_8, 100 ^{o}C) δ 7.22–7.18 (m, 1 H), 7.10–7.04 (m, 3 H). 7.01–7.94 (m, 1 H), 6.44 (d, *J* = 15.9 Hz, 1 H), 6.23–6.14 (m, 1 H), 5.20–5.14 (m, 1 H), 3.68–3.60 (m, 1 H), 3.47–3.35 (m, 2 H), 3.10–3.00 (m, 1 H), 2.71–2.64 (m, 1 H), 2.62–2.55 (m, 1 H), 1.40 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 137.9, 137.4, 133.2, 131.5, 128.9, 128.7, 128.5, 128.1, 127.1, 126.7, 126.1, 124.2, 123.9, 88.5, 80.2, 65.7, 44.7, 38.0, 28.4 (doubling of 7 peaks was observed due to the interconversion of rotamers); IR (film, cm^{-1}) 2976, 1699, 1457; MS(EI): 290.1761 (290.1756 calcd for $C_{17}H_{23}NO_3$, M + H^+).



IV-19

(±)-(*2R*,5S)-*tert*-Butyl 2-([1,1'-biphenyl]-4-ylmethyl)-5-phenyloxazolidine-3-carboxylate** (**IV-19**). The coupling of (±)-*tert*-butyl [2-phenyl-2-

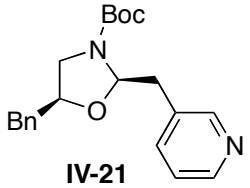
(vinyloxy)ethyl]carbamate (20 mg, 0.08 mmol) with 2-bromobiphenyl (35 mg, 0.15 mmol) was conducted following General Procedure 4. This procedure afforded 21 mg (68%) of the title compound as an orange oil. This material was formed as a 9:1 mixture of diastereomers as judged by ^{1}H NMR analysis of the crude product; the isolated product was obtained in 12:1 dr following purification. Data are for the major isomer. ^{1}H NMR (400 MHz, C_6D_6, 70 ^{o}C) δ 7.43–7.38 (m, 4 H), 7.37–7.33 (m, 2 H), 7.18–7.12 (m, 2 H), 7.07–7.03 (m, 4 H), 7.02–6.97 (m, 2 H), 5.48–5.42 (m, 1 H), 4.46–4.40 (m, 1 H), 3.92–3.80 (m, 1 H), 3.30–3.16 (m, 2 H), 2.74 (t, *J* = 10.2 Hz, 1 H), 1.45–1.42 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 141.1, 139.5, 137.4, 135.4, 130.9, 129.7, 129.0, 128.7, 128.6, 128.4, 128.3, 128.1, 127.4, 127.3, 127.1, 127.0, 126.9, 126.6, 126.4, 126.2, 90.0, 89.3, 80.3, 78.9, 52.3, 40.6, 39.2, 28.5, 28.4, 28.0, 27.9 (doubling of 13 peaks was observed due to the interconversion of rotamers); IR (film, cm^{-1}) 2918, 1699, 1366; MS(ESI): 416.2214 (416.2220 calcd for $C_{27}H_{29}NO_3$, M + H$^+$).



IV-20

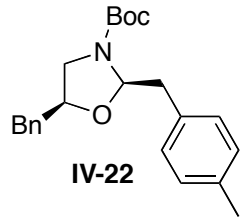
(±)-(2*R,5*S**)-*tert*-Butyl 2-(3-methoxybenzyl)-5-phenyloxazolidine-3-carboxylate** (**IV-20**). The coupling of (±)-*tert*-butyl [2-phenyl-2-(vinyloxy)ethyl]carbamate (20 mg, 0.07 mmol) with 3-bromo-anisole (28 μL, 0.15 mmol) was conducted following General Procedure 4. This procedure afforded 025 mg (89%) of the title compound as an amber oil. This material was formed as a 14:1 mixture of diastereomers as judged by ^{1}H NMR analysis of the crude product; the isolated product was obtained in >20:1 dr following purification. Data are for the major isomer. ^{1}H NMR (400 MHz, C_6D_6, 70 ^{o}C) δ 7.07–6.88 (m, 8 H), 6.68 (d, *J* = 8.2 Hz, 1 H), 5.45–5.40 (m, 1 H), 4.44–4.37 (m, 1 H), 3.83 (s, 1 H), 3.35 (s, 3 H), 3.25–3.16 (m, 2 H), 2.68 (t, *J* = 10.0 Hz, 1 H), 1.42 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 152.6, 137.7, 137.4, 129.0, 128.4, 128.3, 126.6,

122.8, 115.9, 112.3, 89.2, 80.1, 78.7, 55.1, 40.9, 39.8, 28.4; IR (film, cm^{-1}) 2930, 1696, 1367; MS(ESI): 370.2016 (370.2013 calcd for $C_{23}H_{29}NO_3$ M + H^+).



IV-21

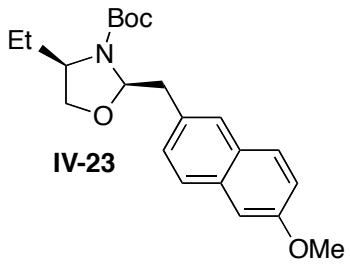
(±)-(2*R,5*S**)-*tert*-Butyl 5-benzyl-2-(pyridin-3-ylmethyl)oxazolidine-3-carboxylate** (**IV-21**). The coupling of (±)-*tert*-butyl [3-phenyl-2-(vinyloxy)propyl]carbamate (20 mg, 0.07 mmol) with 3-bromopyridine (15 mg, 0.14 mmol) was conducted following General Procedure 4. This procedure afforded 25 mg (63%) of the title compound as an orange oil. This material was formed as a 12:1 mixture of diastereomers as judged by ^{1}H NMR analysis of the crude product; the isolated product was obtained in 12:1 dr following purification. Data are for the major isomer. ^{1}H NMR (400 MHz, C_7D_8, 90 ^{o}C) δ 8.65 (s, 1 H), 8.42 (d, *J* = 3.6 Hz, 1 H), 7.35 (d, *J* = 7.4 Hz, 1 H), 7.11–7.04 (m, 2 H), 7.02–7.91 (m, 3 H), 6.85–6.79 (m, 1 H), 5.11–5.06 (m, 1 H), 3.87 (s, 1 H), 3.54 (d, *J* = 8.8 Hz, 1 H), 3.34–3.26 (m, 1 H), 3.07–2.99 (m, 1 H), 2.97–2.89 (m, 1 H), 2.74 (d, *J* = 12.9 Hz, 1 H), 1.96 (t, *J* = 11.6 Hz, 1 H), 1.40 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 151.6, 148.0, 138.0, 131.9, 129.2, 128.5, 128.4, 126.5, 123.0, 80.1, 69.2, 58.4, 39.3, 28.6, 28.4 (one carbon signal is missing due to incidental equivalence); IR (film, cm^{-1}) 3028, 2929, 1699, 1367; MS(ESI): 355.2019 (355.2016 calcd for $C_{21}H_{26}N_2O_3$,M+H^+).



IV-22

(±)-(2*R,5*S**)-*tert*-Butyl 5-benzyl-2-(4-methylbenzyl)oxazolidine-3-carboxylate (IV-22**). The coupling of (±)-*tert*-butyl [3-phenyl-2-

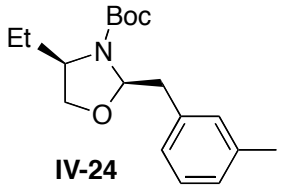
(vinyloxy)propyl]carbamate (20 mg, 0.07 mmol) with 4-bromotoluene (24 μL, 0.14 mmol) was conducted following General Procedure 4. This procedure afforded 20 mg (74%) of the title compound as an amber oil. This material was formed as a 9:1 mixture of diastereomers as judged by ^{1}H NMR analysis of the crude product; the isolated product was obtained in >20:1 dr following purification. Data are for the major isomer. ^{1}H NMR (400 MHz, C_7D_8, 90 ^{o}C) δ 7.21–7.16 (m, 2 H), 7.07–7.00 (m, 4 H), 6.98–6.92 (m, 3 H), 5.20–5.15 (m, 1 H), 3.90 (s, 1 H), 3.59–3.53 (m, 1 H), 3.36–3.30 (m, 1 H), 3.15 (d, *J* = 14.1 Hz, 1 H), 3.02–2.92 (m, 1 H), 2.82 (d, *J* = 12.9 Hz, 1 H), 2.12–2.09 (m, 3 H), 2.08–2.02 (m, 1 H), 1.39 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 138.3, 136.1, 133.5, 130.2, 129.4, 128.8, 128.5, 127.3, 126.4, 126.3, 91.1, 90.5, 69.3, 69.0, 58.4, 39.4, 29.7, 28.4, 21.1 (doubling of 3 peaks was observed due to the interconversion of rotamers); IR (film, cm^{-1}) 2973, 1699, 1366; MS(EI): 390.2037 (390.2040 calcd for $C_{23}H_{29}NO_3$, M + Na$^+$).



IV-23

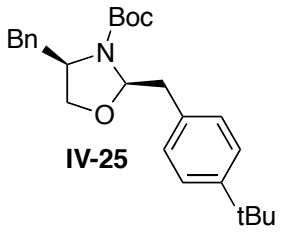
(+)-(2*R*,4*R*)-*tert*-Butyl 4-ethyl-2-[(6-methoxynaphthalen-2-yl)methyl]oxazolidine-3-carboxylate (**IV-23**). The coupling of (*R*)-*tert*-butyl [1-(vinyloxy)butan-2-yl]carbamate (20 mg, 0.09 mmol) with 2-bromo-6-methoxynaphthalene (44 mg, 0.18 mmol) was conducted following General Procedure 4. This procedure afforded 20 mg (58%) of the title compound as an amber oil, $[a]_D^{23}$ = +48.5 (*c* 1.59, CH_2Cl_2). This material was formed as a 15:1 mixture of diastereomers as judged by ^{1}H NMR analysis of the crude product; the isolated product was obtained in 15:1 dr following purification. Data are for the major isomer. ^{1}H NMR (400 MHz, C_7D_8, 100 ^{o}C) δ 7.64 (s, 1 H), 7.55–7.47 (m, 2 H), 7.41 (d, *J* = 8.6 Hz, 1 H), 7.07–7.02 (m, 1 H), 6.99–6.93 (m, 1 H), 5.31–5.26

(m, 1 H), 3.67–3.68 (m, 1 H), 3.53–3.44 (m, 5 H), 3.33 (d, *J* = 14.1 Hz, 1 H), 3.15 (dd, *J* = 6.1, 13.7 Hz, 1 H), 1.47–1.31 (m, 10 H), 1.12–0.99 (m, 1 H), 0.67–0.61 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 153.6, 133.4, 132.0, 129.1, 128.9, 128.4, 126.4, 118.6, 105.6, 90.5, 70.1, 58.2, 55.2, 28.4, 28.3, 26.8, 10.6 (2 carbon signals are missing due to incidental equivalence); IR (film, cm^{-1}) 3368, 2976, 1699; MS(ESI): 372.2173 (372.2169 calcd for $C_{22}H_{29}NO_4$, M + H^+).



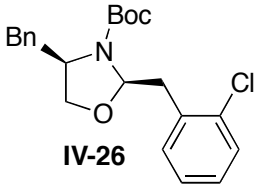
IV-24

(+)-(2*R*,4*R*)-*tert*-Butyl 4-ethyl-2-(3-methylbenzyl)oxazolidine-3-carboxylate (**IV-24**). The coupling of (*R*)-*tert*-butyl [1-(vinyloxy)butan-2-yl]carbamate (20 mg, 0.09 mmol) with 3-bromotoluene (31 µL, 0.18 mmol) was conducted following General Procedure 4. This procedure afforded 21 mg (74%) of the title compound as a yellow oil, $[a]_D^{23}$ = +45.0 (*c* 3.65, CH_2Cl_2). This material was formed as a 9:1 mixture of diastereomers as judged by ^{1}H NMR analysis of the crude product; the isolated product was obtained in 19:1 dr following purification. Data are for the major isomer. ^{1}H NMR (400 MHz, C_7D_8, 100 ^{o}C) δ 7.12–7.02 (m, 2 H), 6.99–6.94 (m, 1 H), 6.91–6.85 (m, 1 H), 5.24–5.18 (m, 1 H), 3.61 (s, 1 H), 3.50–3.38 (m, 2 H), 3.17 (d, *J* = 13.3 Hz, 1 H), 2.97 (dd, *J* = 5.9, 13.3 Hz, 1 H), 2.16 (s, 3 H), 2.09 (s, 1 H), 1.40 (s, 9 H), 1.14–1.02 (s, 1 H), 0.68 (t, *J* = 7.2 Hz, 3 H);^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 137.6, 136.7, 130.8, 128.0, 127.2, 90.4, 80.0, 70.0, 58.1, 41.5, 28.5, 26.8, 21.3, 10.6, (1 carbon signal is missing due to incidental equivalence); IR (film, cm^{-1}) 2972, 1699, 1366; MS(ESI): 328.1883 (328.1883 calcd for $C_{18}H_{27}NO_3$, M + Na^+).



IV-25

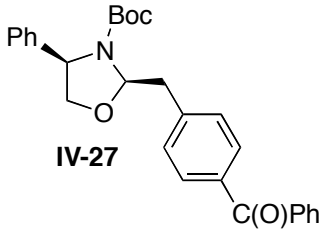
(+)-(2*R*,4*R*)-*tert*-Butyl 4-benzyl-2-[4-(*tert*-butyl)benzyl]oxazolidine-3-carboxylate (**IV-25**). The coupling of (*R*)-*tert*-butyl [1-phenyl-3-(vinyloxy)propan-2-yl]carbamate (25 mg, 0.12 mmol) with 4-bromo-*tert*-butylbenzene (49 µL, 0.23 mmol) was conducted following General Procedure 4. This procedure afforded 25 mg (89%) of the title compound as a yellow oil, $[a]_D^{23}$ = +26.5 (*c* 4.69, CH_2Cl_2). This material was formed as an 8:1 mixture of diastereomers as judged by ^1H NMR analysis of the crude product; the isolated product was obtained in >20:1 dr following purification. Data are for the major isomer. ^1H NMR (400 MHz, C_6D_6, 70 ^oC) δ 7.32–7.28 (m, 2 H), 7.27–7.22 (m, 2 H), 7.07–7.00 (m, 2 H), 6.99–6.92 (m, 3 H), 5.27–5.22 (m, 1 H), 3.98–3.86 (m, 1 H), 3.57–3.51 (m, 1 H), 3.31–3.16 (m, 2 H), 3.11–2.96 (m, 1 H), 2.89–2.78 (m, 1 H), 2.00 (t, *J* = 10.8 Hz, 1 H), 1.40 (s, 9 H), 1.16 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 149.4, 138.3, 133.6, 130.0, 129.3, 128.5, 126.4, 125.0, 106.1, 90.5, 80.2, 69.4, 58.1, 47.4, 39.2, 34.4, 31.4, 31.2, 28.5, doubling of 2 peaks was observed due to the interconversion of rotamers; IR (film, cm^{-1}) 2966, 1696, 1367; MS(EI): 410.2695 (410.2695 calcd for $C_{26}H_{35}NO_3$, M + H^+).



IV-26

(+)-(2*R*,4*R*)-*tert*-Butyl 4-benzyl-2-(2-chlorobenzyl)oxazolidine-3-carboxylate (**IV-26**). The coupling of (*R*)-*tert*-butyl [1-phenyl-3-(vinyloxy)propan-2-yl]carbamate (25 mg, 0.12 mmol) with 2-bromochlorobenzene (44 µL, 0.23 mmol) was conducted following General Procedure 4. This procedure afforded

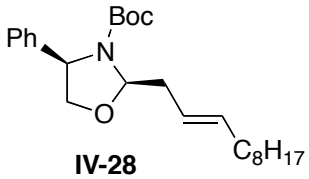
22 mg (75%) of the title compound as a yellow oil, $[a]_D^{23}$ = +30.0 (*c* 4.68, CH_2Cl_2). This material was formed as a 17:1 mixture of diastereomers as judged by ^1H NMR analysis of the crude product; the isolated product was obtained in 17:1 dr following purification. Data are for the major isomer. ^1H NMR (400 MHz, C_6D_6, 70 ^oC) δ 7.22 (d, *J* = 6.7 Hz, 1 H), 7.17 (d, *J* = 7.6 Hz, 1 H), 7.07–6.95 (m, 5 H), 6.90–6.82 (m, 1 H), 6.78–6.71 (m, 1 H), 5.41–5.35 (m, 1 H), 3.98 (s, 1 H), 3.61–3.54 (m, 1 H), 3.45–3.36 (m, 1 H), 3.35–3.26 (m, 1 H), 3.10–2.92 (m, 2 H), 2.36–2.25 (m, 1 H), 1.37 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 138.1, 134.6, 132.5, 129.4, 128.5, 128.1, 127.7, 126.5, 88.9, 80.1, 69.2, 58.2, 39.6, 38.6, 37.5, 28.6, 28.5 (2 peaks are missing due to incidental equivalence, and doubling of 2 peaks was observed due to the interconversion of rotamers); IR (film, cm^{-1}) 3062, 2977, 1699, 1397; MS(ESI): 410.1487 (410.1493 calcd for $C_{22}H_{26}ClNO_3$, M + Na^+).



IV-27

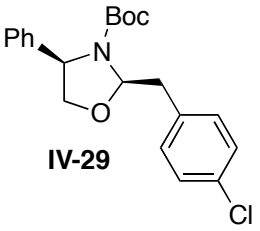
(+)-(2*R*,4*R*)-*tert*-Butyl 2-(4-benzoylbenzyl)-4-phenyloxazolidine-3-carboxylate (**IV-27**). The coupling of (*R*)-*tert*-butyl [1-phenyl-2-(vinyloxy)ethyl]carbamate (20 mg, 0.08 mmol) with 4-bromobenzophenone (40 mg, 0.12 mmol) was conducted following General Procedure 4. This procedure afforded 27 mg (80%) of the title compound as a yellow oil, $[a]_D^{23}$ = +27.1 (*c* 2.06, CH_2Cl_2).This material was formed as an 8:1 mixture of diastereomers as judged by ^1H NMR analysis of the crude product; the isolated product was obtained in 11:1 dr following purification. The enantiopurity was judged to be >99% ee by chiral HPLC analysis (chiralcel AD column, 1% isopropanol/hexanes, 0.5% triethylamine, 1.0 mL/min, RT = 17.39 min and 23.48 min). Data are for the major isomer. ^1H NMR (400 MHz, C_6D_6, 70 ^oC) δ 7.71–7.75 (m, 4 H), 7.28–7.23 (m, 2 H), 7.08–6.95 (m, 8 H), 5.35–5.30 (m, 1 H), 4.62 (s, br, 1 H), 3.70–3.64 (m,

2 H), 3.40 (d, *J* = 13.6 Hz, 1 H), 3.10 (dd, *J* = 7.3, 13.5 Hz, 1 H), 1.34–1.24 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.2, 153.6, 141.9, 137.8, 136.0, 132.2, 128.7, 128.4, 128.3, 128.2, 127.8, 127.4, 126.5, 126.3, 91.0, 73.1, 66.6, 60.5, 46.2, 40.6, 28.3 (doubling of 1 peak was observed due to the interconversion of rotamers); IR (film, cm^{-1}) 2928, 1696, 1366; MS(ESI): 444.2168 (444.2169 calcd for $C_{28}H_{29}NO_4$, M + H$^+$).



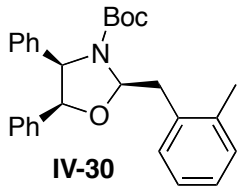
IV-28

(–)-(*E*)-(2*R*,4*R*)-tert-butyl 4-phenyl-2-(undec-2-en-1-yl)oxazolidine-3-carboxylate (**IV-28**). The coupling of (*R*)-*tert*-butyl (1-phenyl-2-(vinyloxy)ethyl)carbamate (0.025 g, 0.095 mmol) with (*E*)-1-bromodec-1-ene (0.042, 0.19 mmol) was conducted following General Procedure 4. This procedure afforded 0.021 g (58%) of the title compound as a yellow oil. This material was obtained as a 9:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. $[a]_D^{23}$ = –10.0 (*c* 1.94, CH_2Cl_2). ^{1}H NMR (400 MHz, C_7D_8, 100 ^{o}C) δ 7.38–7.34 (m, 2 H), 7.26–7.19 (m, 1 H), 7.17–7.11 (m, 1 H), 7.09–7.04 (m, 1 H), 5.73–5.45 (m, 2 H), 5.37–5.32 (m, 1 H), 4.84–4.78 (m, 1 H), 3.97–3.85 (m, 2 H), 2.97–2.88 (m, 1 H), 2.71–2.62 (m, 1 H), 2.21–2.16 (m, 2 H), 1.40–1.21 (m, 23 H), 1.11–0.99 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 143.9, 134.8, 134.4, 130.3, 128.3, 127.3, 126.4, 124.2, 110.8, 90.8, 72.9, 60.5, 55.4, 37.9, 33.2, 32.7, 31.9, 29.5, 29.3, 29.2, 29.1, 28.2, 14.1, 3.9 (doubling of 4 peaks was observed due to the interconversion of rotamers); IR (film, cm^{-1}) 2926, 1704, 1451; MS(ESI): 402.3010 (402.3003 calcd for $C_{25}H_{39}NO_3$, M + H$^+$).



IV-29

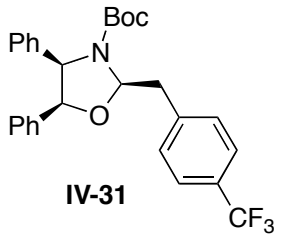
(±)-(2*R,4*R**)-*tert*-Butyl 2-(4-chlorobenzyl)-4-phenyloxazolidine-3-carboxylate** (**IV-29**). The coupling of (±)-*tert*-butyl [1-phenyl-2-(vinyloxy)ethyl]carbamate (20 mg, 0.08 mmol) with 1-bromo-4-chlorobenzene (29 mg, 0.15 mmol) was conducted following General Procedure 4. This procedure afforded 15 mg (53%) of the title compound as an orange oil. This material was formed as a 9:1 mixture of diastereomers as judged by ^{1}H NMR analysis of the crude product; the isolated product was obtained in 18:1 dr following purification. Data are for the major isomer. ^{1}H NMR (400 MHz, C_7D_8, 100 ^{o}C) δ 7.13–7.96 (m, 9 H), 5.22 (d, *J* = 6.8 Hz, 1 H), 4.66–4.59 (m, 1 H), 3.75–3.68 (m, 2 H), 3.25 (d, *J* = 14.1 Hz, 1 H), 3.03 (dd, *J* = 7.1, 13.9 Hz, 1 H), 1.29 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 140.8, 135.3, 131.3, 128.8, 128.4, 127.8, 127.4, 127.3, 126.6, 126.3, 113.7, 91.1, 80.7, 73.2, 60.5, 39.7, 28.3, 27.9 (doubling of 4 peaks was observed due to the interconversion of rotamers); IR (film, cm^{-1}) 2976, 2930, 1699, 1396; MS(ESI): 396.1322 (396.1337 calcd for $C_{21}H_{24}ClNO_3$, M + Na^+).



IV-30

(–)-(4*R*,5*S*)-*tert*-Butyl 2-(2-methylbenzyl)-4,5-diphenyloxazolidine-3-carboxylate (**IV-30**). The coupling of (–)-(1*R*,2*S*)-*tert*-butyl [1,2-diphenyl-2-(vinyloxy)ethyl]carbamate (25 mg, 0.07 mmol) with 2-bromotoluene (25 µL, 0.14 mmol) was conducted following General Procedure 4. This procedure afforded 25 mg (74%) of the title compound as an orange oil, m.p. = 51 ^{o}C, $[a]_D^{23}$ = –88.4 (*c* 1.69, CH_2Cl_2). This material was formed as a 16:1 mixture of diastereomers as judged by ^{1}H NMR analysis of the crude product; the isolated product was obtained in 18:1 dr following purification. Data are for the major isomer. ^{1}H NMR (400 MHz, C_6D_6, 70 ^{o}C) δ 7.56 (d, *J* = 6.4 Hz, 1 H), 7.10–7.02 (m, 3 H), 6.93–6.84 (m, 8 H), 6.83–6.78 (m, 2 H), 5.39–5.34 (m, 1 H), 4.98 (s, 1 H), 4.79–4.74 (m, 1 H), 3.96 (d, *J* = 15.2 Hz, 1 H), 3.43–3.36 (m, 1 H), 2.49 (s, 3 H), 1.34 (s, 9

H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 138.3, 137.4, 135.6, 135.4, 131.2, 130.3, 127.7, 127.6, 127.5, 126.9, 126.8, 126.7, 126.6, 125.9, 90.4, 82.7, 80.1, 65.3, 39.6, 28.4, 20.2; IR (film, cm^{-1}) 2977, 1697, 1367; MS(ESI): 428.2217 (428.2220 calcd for $C_{28}H_{30}NO_3$, M^+).

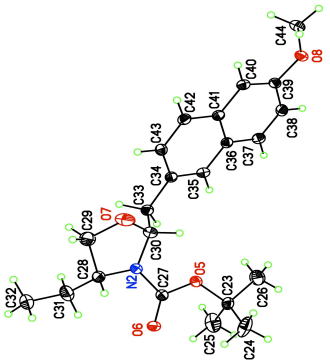


IV-31

(–)-(4*R*,5*S*)-*tert*-Butyl 4,5-diphenyl-2-[4-(trifluoromethyl)benzyl]oxazolidine-3-carboxylate (**IV-31**). The coupling of (1*R*,2*S*)-*tert*-butyl [1,2-diphenyl-2-(vinyloxy)ethyl]carbamate (25 mg, 0.07 mmol) with 1-bromo-4-(trifluoromethyl)benzene (33 mg, 0.14 mmol) was conducted following General Procedure 4. This procedure afforded 23 mg (64%) of the title compound as an orange oil, $[a]_D^{23}$ = –42.1 (*c* 2.23, CH_2Cl_2). This material was formed as a 15:1 mixture of diastereomers as judged by ^{1}H NMR analysis of the crude product; the isolated product was obtained in 17:1 dr following purification. Data are for the major isomer. ^{1}H NMR (400 MHz, C_6D_6, 70 ^{o}C) δ 7.36 (s, 3 H), 6.90–6.74 (m, 9 H), 6.20 (d, *J* = 6.7 Hz, 2 H), 5.21 (d, *J* = 6.8 Hz, 1 H), 4.87 (d, *J* = 5.1 Hz, 1 H), 4.76 (d, *J* = 6.7 Hz, 1 H), 3.67 (d, *J* = 13.9 Hz, 1 H), 3.38 (dd, *J* = 6.7, 13.7 Hz, 1 H), 1.29 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 140.8, 137.9, 135.3, 130.8 (q, *J* = 276.3 Hz), 129.3 (q, *J* = 31.8 Hz), 127.7, 127.6, 127.3, 126.8, 126.6, 126.4, 125.7, 125.2, 123.0, 89.7, 82.8, 82.7, 81.3, 80.6, 65.1, 39.8, 28.3, 28.8 (doubling of 3 peaks was observed due to the interconversion of rotamers); IR (film, cm^{-1}) 2979, 1700, 1324; MS(ES): 428.1456 (428.1468 calcd for $C_{24}H_{20}F_3NO_3$, M + H^+).

Assignment of Stereochemistry

The relative stereochemistry of (+)-**IV-23** was assigned by single crystal x-ray analysis as shown below. The relative stereochemistry of other 2,4-disbustituted products was assigned based on analogy to **(+)-IV-23**.



The stereochemistry of **(±)-IV-19** was assigned by single crystal x-ray analysis as shown below. The relative stereochemistry of other 2,5-disbustituted products was assigned based on analogy to **(±)-IV-19**.

4.7 References

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[11] Stahl has reported the Pd(II)-catalyzed transfer of vinyl groups from enol ethers to nitrogen nucleophiles. These reactions proceed via aminopalladation of a cationic Pd(II) alkene complex followed by α-alkoxide elimination. See: (a) Brice, J. L.; Meerdink, J. E.; Stahl, S. S. *Org. Lett.* **2004**, *6*, 1845. The stereochemistry of the aminopalladation step in the vinyl exchange reactions is not entirely clear, but subsequent studies suggest these reactions may occur through an outer-sphere anti-aminopalladation pathway rather than an inner-sphere (migratory insertion) syn-aminopalladation mechanism. See:(b) Maleckis, A.; Jaun- zeme, I.; Jirgensons, A. *Eur. J. Org. Chem.* **2009**, *36*, 6407.

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[18] Mechanistic studies suggest that the insertion of alkenes into Pd-N bonds occurs via intermediate palladium complexes that contain a single bound phosphine. For further discussion, see ref 9.

[19] Enamide and ketene aminal side products with structures similar to **IV-5** and **IV-6** were not isolated and could not be unambiguously identified through 1H NMR analysis of crude reaction mixtures. However, these side products may be prone to hydrolysis during workup.

[20] Ligand definitions: Dpe-Phos = bis(diphenylphosphinophenyl) ether; dppb = 1,4-bis(diphenylphosphino)butane; Xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene; Ru-Phos = 2-dicyclo-hexylphosphino-20'6'-di-isopropoxy-1,10 -biphenyl, S-Phos = 2-dicyclo-hexylphosphino-2',6' -dimethoxy-1,10-biphenyl.

[21] (a) McKinley, N. F.; O'Shea, D. F. *J. Org. Chem.* **2004**, *69*, 5087. (b) Bosch, M.; Schlaf, M. *J. Org. Chem.* **2003**, *68*, 5225. (c) Okimoto, Y.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2002**, *124*, 1590.

[22] For a representative case, chiral HPLC analysis indicated complete retention of enantiomeric purity (99% ee) during the three-step conversion of (R)-phenylglycinol to **(+)-IV-27**.

[23] Bosch, M.; Schlaf, M.; *J. Org. Chem*, **2003**, *68*, 5225–5227.

[24] Okimoto, Y.; Sakaguchi, S.; Ishii, Y.; *J. Am. Chem. Soc.*, **2002**, *124*, 1590–1591.

[25] McKinley, N.F.; O'Shea, D.F.; *J. Org. Chem.* **2004**, *69*, 5087–5092.

Chapter 5: Synthesis of Chromans via Palladium-Catalyzed Carboetherification

5.1 Introduction

Chromans and other benzo-fused oxygen heterocycles are displayed in a number of biologically active natural products,[1] including α-tocopherol[2] and polyalthidin. In addition, 2-benzylchroman derivatives such as englitazone (**V-1**, antidiabetic activity) and molecules with general structure **V-2** (beta-secretase inhibitory activities)[3] have been explored as pharmaceutical leads (Figure 5-1).

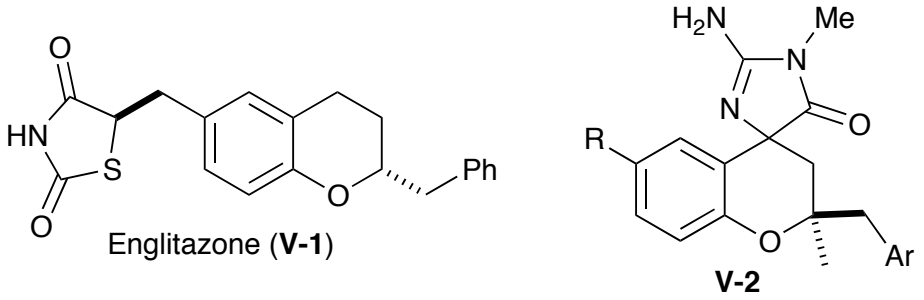
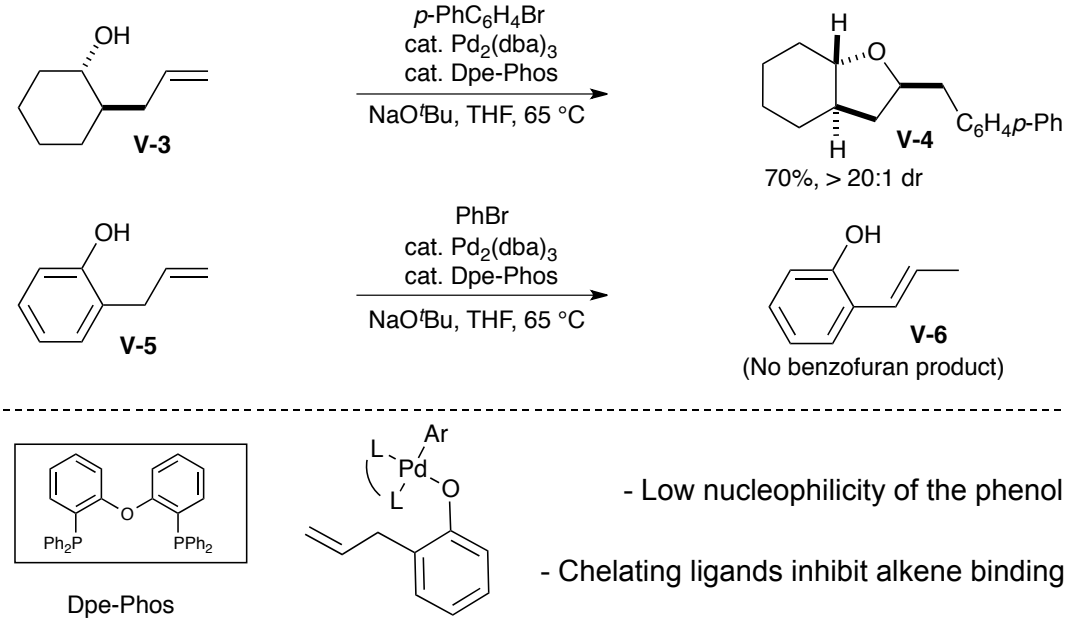


Figure 5-1. Biologically Active 2-Benzylchroman Derivatives

Over the past several years we have developed a new approach to the construction of substituted tetrahydrofurans via palladium-catalyzed carboetherification reactions between aryl or alkenyl halides and alcohols bearing pendant alkenes.[4,5,6] For example, treatment of alcohol **V-3** with 4-bromobiphenyl, NaO*t*Bu, and a catalyst composed of $Pd_2(dba)_3$/Dpe-Phos provided **V-4** in 70% yield with >20:1 dr (Scheme 5-1). We envisioned this method could provide a concise and convergent approach to benzofurans or chromans[7,8] from simple starting materials (phenols bearing pendant alkenes)[9]. However, although the Pd-catalyzed carboetherification reactions were quite effective for the generation of tetrahydrofurans, our efforts to employ Pd-

catalyzed carboetherification reactions for the synthesis of 6-membered heterocycles (e.g., tetrahydropyrans) failed to afford satisfactory results.[10] In addition, the scope of our carboetherification method appeared to be limited to aliphatic alcohol substrates, as efforts to couple 2-allylphenol **V-5** with bromobenzene failed to generate the desired substituted benzofuran product.[11] Instead, the formation of 2-(prop-1-en-1-yl)phenol **V-6** via double bond isomerization was observed.



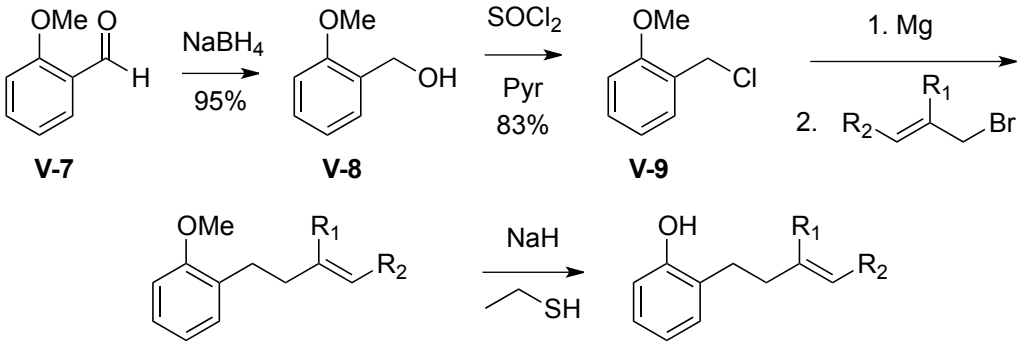
Scheme 5-1. Palladium-Catalyzed Carboetherification Reactions of Alcohols vs. Phenols

We have previously illustrated that the mechanism of Pd-catalyzed carboetherification reactions, such as those shown in Scheme 5-1, involves suprafacial insertion of the substrate alkene into the Pd–O bond of an intermediate palladium alkoxide complex. Recent mechanistic studies conducted by our group and others have shown that the rate of alkene insertion into Pd-heteroatom bonds is highly dependent on the nucleophilicity of the heteroatom, and the insertion likely occurs from an intermediate Pd-complex that bears a single phosphine ligand.[12] These results suggest that two factors may be

responsible for the poor reactivity of phenols such as **V-5** in Pd/Dpe-Phos-catalyzed carboetherifications: (a) the relatively low nucleophilicity of phenols as compared to aliphatic alcohols; and (b) use of the chelating bis-phosphine Dpe-Phos, which may disfavor generation of the reactive monophosphine intermediate. These factors apparently slow the catalytic reaction to the point that alkene isomerization of **V-5** to **V-6** occurs more rapidly than the desired transformation.

5.2 Optimization Studies

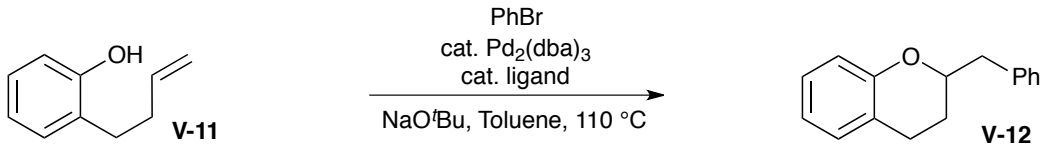
The hypothesis outlined above suggests that use of catalysts bearing monodentate phosphine ligands may provide improved results in carboetherification reactions of phenol derivatives, as these ligands could potentially facilitate the key alkene insertion step. In addition, we also anticipated that the conversion of 2-(but-3-en-1-yl)phenol (**V-11**) to chroman **V-12** (Table 5-1) may be more straightforward than the analogous transformation of 2-allylphenol (**V-5**) to a benzofuran derivative, as **V-11** should be much less prone to base-mediated alkene isomerization than **V-5**. Thus, we synthesized **V-11** from p-anisaldehyde using the literature procedure[16] shown in Scheme 5-2 and examined the coupling of **V-11** with bromobenzene using the biaryl monophosphine ligand S-Phos. We had previously found this ligand provided good results in other challenging carboetherification reactions, and we were gratified to discover these conditions afforded the desired product **V-12** in 86% isolated yield. A quick survey of related biaryl phosphines did not lead to any further improvement (entries 2-5), and Dpe-Phos produced **V-12** in only 30% yield (entry 6).

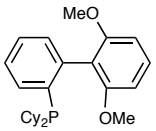
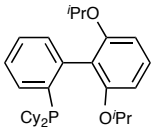
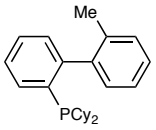
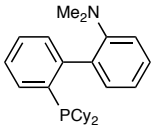
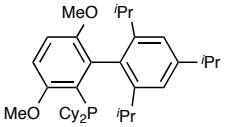
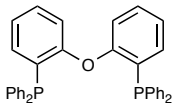


V-10 R_1 = H, R_2 = H, 56%
V-13 R_1 = CH_3, R_2 = H, 74%
V-46 R_1 = H, R_2 = H, 62%

V-11 R_1 = H, R_2 = H, 76%
V-14 R_1 = CH_3, R_2 = H, 76%
V-47 R_1 = H, R_2 = H, 70%

Scheme 5-2. Synthesis of Substrate **V-11**, **V-14**, and **V-47**



Entry	Ligand	Yield[b]
1	 S-Phos	84% (75%)
2	 RuPhos	76%
3	 Me-Phos	31%
4	 Dave-Phos	12%
5	 Brett-Phos	47%
6	 Dpe-Phos	30%

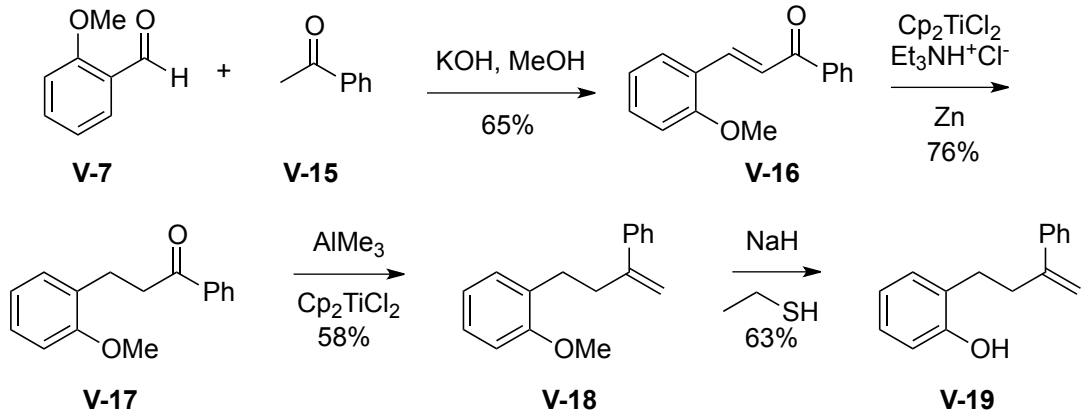
[a] Conditions: 1.0 equiv **V-11**, 2.0 equiv PhBr, 2.0 equiv NaO^{t}Bu, 2 mol % $Pd_2(dba)_3$, 4 mol % ligand, toluene (0.25 M), 110 °C. [b] Yields were determined by ^{1}H NMR analysis of crude reaction mixtures using phenanthrene as an internal standard. The yield in parentheses is an isolated yield of pure product.

Table 5-1. Optimization of Ligand for the Coupling of **V-11** with Bromobenzene[a]

5.3 Substrate Scope

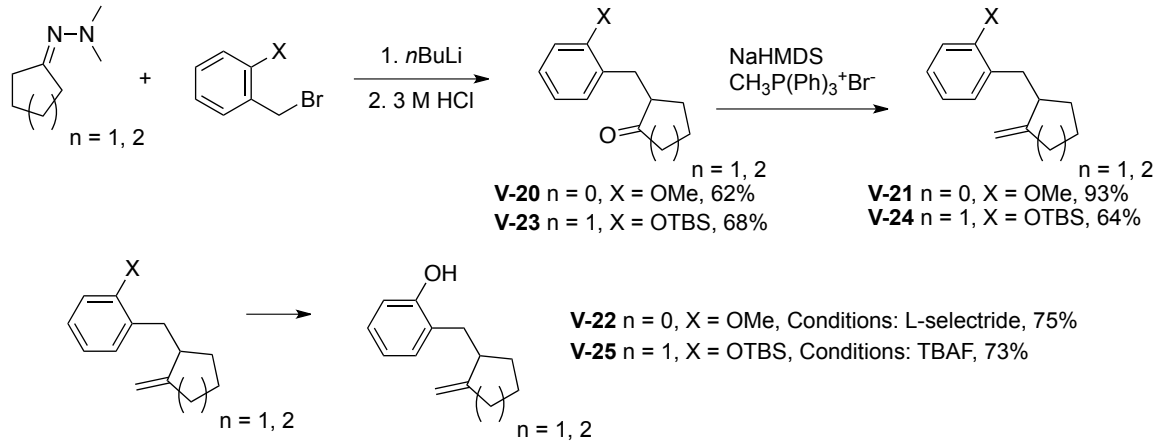
In order to examine the scope of the phenol carboetherification reactions, a number of substrates that differed in their substitution patterns were synthesized and subjected to the optimized reaction conditions. Namely, **V-14** was synthesized according to a literature procedure analogous to that shown in Scheme 5-2,[17] and **V-19** was prepared through an aldol reaction, selective reduction of the alkene, conversion of the ketone to the corresponding alkene via

addition of Tebbe's Reagent and subsequent cleavage of the arylmethyl ether to the phenol, as shown in Scheme 5-3.



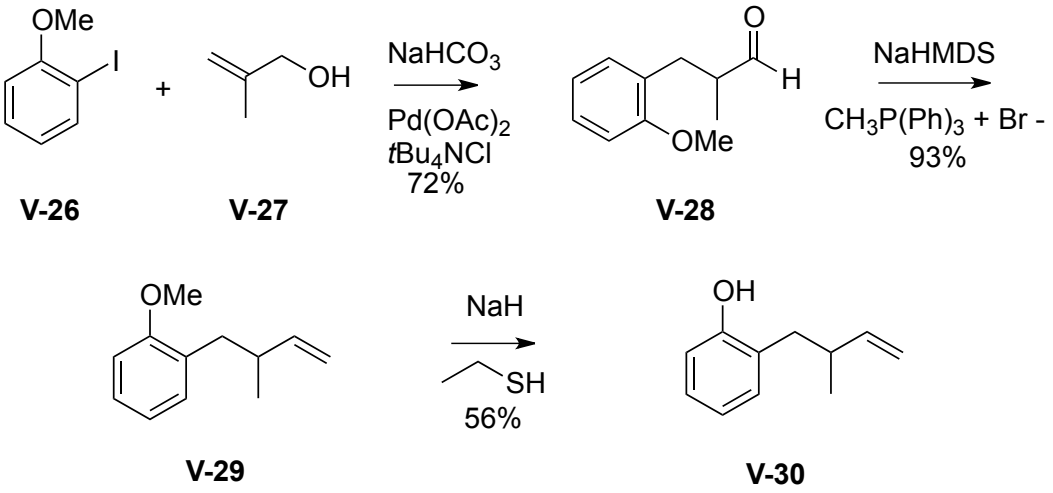
Scheme 5-3. Synthesis of Substrate **V-19**

As shown in Table 5-2, substrates **V-11**, **V-14**, and **V-19** were converted to 2-substituted- or 2,2-disubstituted chromans in moderate to good yield (entries 1–9). In addition, cyclopentane- and cyclohexane-derived substrates **V-22**–**V-25** were prepared in accordance with the method shown in Scheme 5-4, which features a hydrazone alkylation, Wittig reaction and arylmethyl ether cleavage, and were transformed to tricyclic products **V-39**–**V-41** with high diastereoselectivity (entries 10–12).



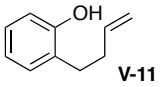
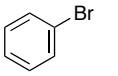
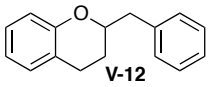
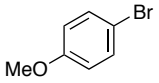
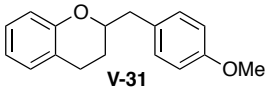
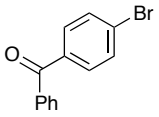
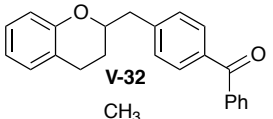
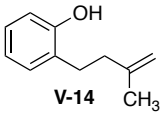
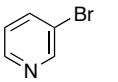
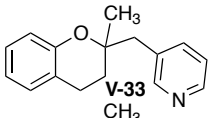
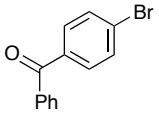
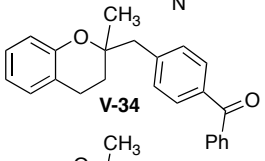
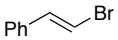
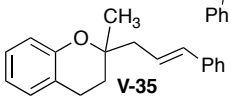
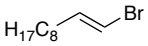
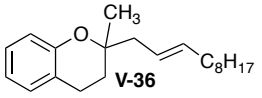
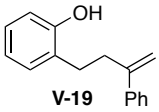
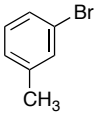
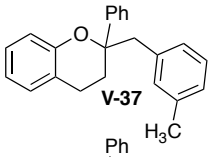
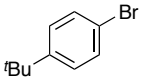
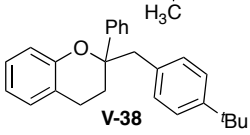
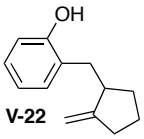
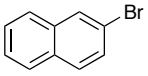
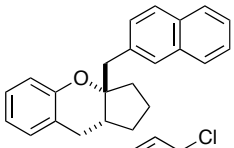
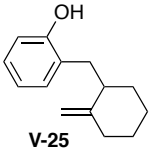
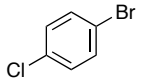
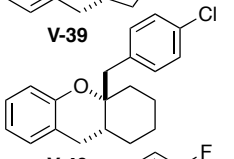
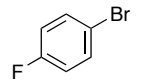
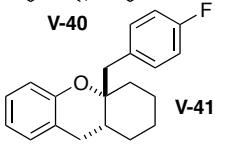
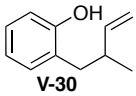
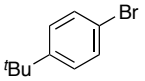
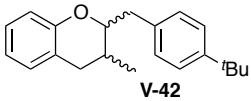
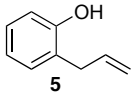
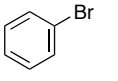
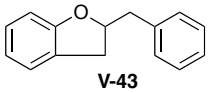
Scheme 5-4. Synthesis of Substrate **V-22** and **V-25**

However, stereocontrol was poor in the reaction of 4-bromo-tert-butylbenzene and **V-30**, which was synthesized via Heck reaction, Wittig olefination and arylmethyl ether cleavage (Scheme 5-5). **V-42** was produced in 2:1 dr, and a significant amount (ca. 25%) of an inseparable unidentified low molecular weight side product was also formed (entry 13). Although these new reaction conditions were generally effective for the preparation of chromans, efforts to transform **V-5** to substituted benzofuran **V-43** were still only modestly successful; the desired product was generated in 37% yield (entry 14).



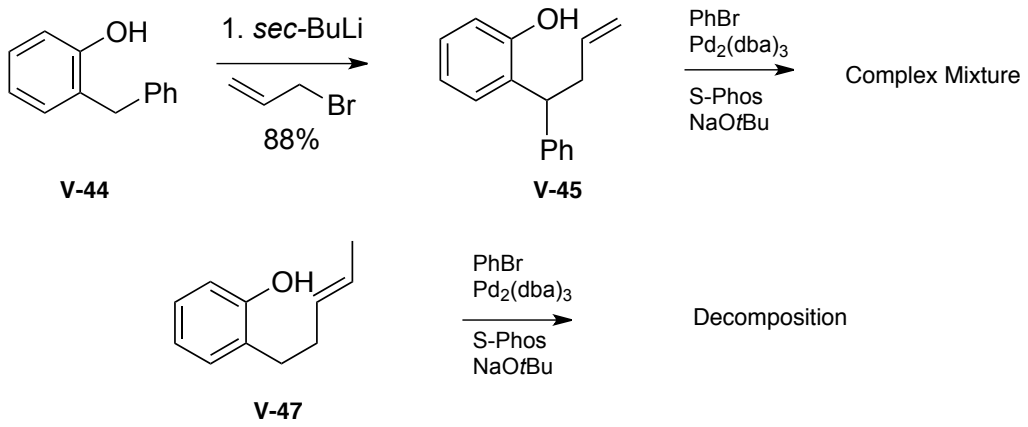
Scheme 5-5. Synthesis of Substrate **V-30**

A range of different electrophiles were examined in the carboetherification reactions of **V-11**, **V-14**, and **V-19**. As shown in Table 5-2, aryl halides bearing chloride, fluoride, methoxy and diaryl ketone functionality were successfully converted to the desired products. Alkenyl halides were also effective coupling partners in these reactions (entries 6–7), and the coupling of **V-14** with the heteroaryl halide 3-bromopyridine also proceeded smoothly (entry 4). However, the scope of carboetherification reactions involving **V-22** and **V-25** was not as broad, and use of aryl halides that were relatively electron rich or electron deficient led to poor reactivity or low yields.

Entry	Substrate	RBr	Product	Yield[b]
1	 **V-11**		 **V-12**	75%
2	**V-11**		 **V-31**	57%
3	**V-11**		 **V-32**	51%
4	 **V-14**		 **V-33**	87%
5	**V-14**		 **V-34**	71%
6	**V-14**		 **V-35**	83%
7	**V-14**		 **V-36**	68%
8	 **V-19**		 **V-37**	54%
9	**V-19**		 **V-38**	56%
10	 **V-22**		 **V-39**	59% >20:1 dr
11	 **V-25**		 **V-40**	71% >20:1 dr
12	**V-25**		 **V-41**	63% >20:1 dr
13	 **V-30**		 **V-42**	ca. 47%[c] 2:1 dr
14	 **5**		 **V-43**	37%

[a] Conditions: 1.0 equiv phenol substrate, 2.0 equiv R–Br, 2.0 equiv NaO^{t}Bu, 2 mol % $Pd_2(dba)_3$, 4 mol % S-Phos, toluene (0.25 M), 110 °C. [b] Isolated yield (average of two experiments). [c] The two inseparable stereoisomeric products were isolated in 63% yield and ca. 75% purity. The remaining 25% of the mixture was primarily composed of an unidentifed low molecular weight side product that appears to be derived from the phenol substrate.

Table 5-2. Pd-Catalyzed Carboetherification Reactions of Phenols Bearing Pendant Alkenes[a]



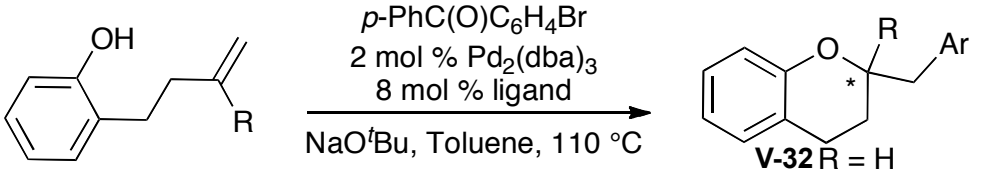
Scheme 5-6. Palladium-Catalyzed Carboetherification Reactions of Substituted Phenols

Substrates **V-45** and **V-47**, which possess an additional substituent and an internal alkene, respectively, were synthesized according to literature procedures and were subjected to the optimized conditions. However, complex mixtures of regio- and stereoisomers were obtained with substrate **V-45**, and decomposition occurred with substrate **V-47**, as shown in Scheme 5-6.

5.4 Progress Towards the Development of Enantioselective Conditions

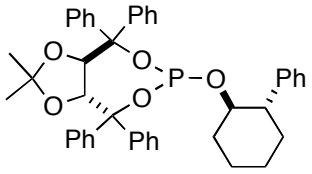
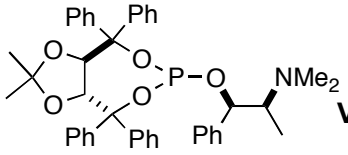
Having successfully developed a new synthesis of racemic chroman derivatives, we sought to explore the enantioselective construction of these compounds through the use of chiral ligands for the palladium catalyst. In prior studies we found that the chiral phosphoramidite Siphos-PE[13] provides satisfactory results in asymmetric carboamination reactions that afford pyrrolidine derivatives.[14] Unfortunately, this ligand gave poor results (37% yield, 13% ee) in the reaction of **V-11** with 4-bromobenzophenone. Although we have not yet developed an efficient asymmetric variant of these transformations, after further exploration we have discovered two promising leads. As shown in Table 5-3, ligand **V-48** provides good yield and moderate enantioselectivity for the conversion of **V-11** to **V-32**, whereas ligand **V-49**[15] provides **V-32** in 76% ee

(although the chemical yield is low). Asymmetric transformations of methyl substituted substrate **V-14** are more challenging, as use of ligand **V-48** led to formation of **V-34** in only 7% ee, and use of ligand **V-49** failed to generate the desired product. Nonetheless, this collection of results illustrates the potential feasibility of enantioselective construction of chroman derivatives via Pd-catalyzed carboetherification reactions, although further optimization is obviously needed.



V-11 R = H
V-14 R = Me

V-32 R = H
V-34 R = Me
Ar = *p*-$C_6H_4C(O)Ph$

Ligand	R	Yield[b]	ee[c]
 **V-48**	H	70%	30%
	CH_3	30%	7%
 **V-49**	H	14%	76%
	CH_3	0%	—

[a] Conditions: 1.0 equiv **V-11** or **V-14,** 2.0 equiv ArBr, 2.0 equiv NaO*t*Bu, 2 mol % $Pd_2(dba)_3$, 8 mol % ligand, toluene (0.25 M), 110 °C. [b] Isolated yield (average of two experiments). [C] Determined by chiral HPLC analysis.

Table 5-3. Efforts Toward the Development of Enantioselective Conditions

5.5 Conclusions

In conclusion, we have developed a new method for the construction of 2-substituted chroman derivatives via Pd-catalyzed carboetherification reactions. These transformations employ simple substrates, and provide access to a number of different derivatives in a straightforward manner. In addition these are the first examples of Pd-catalyzed alkene carboetherification reactions between aryl bromides and alkenyl phenols, and are also rare cases in which six-

membered oxygen heterocycles are generated via 1,2-alkene carboheterofunctionalization processes. Future studies will be directed towards the development of improved catalysts for enantioselective variants of these transformations.

5.6 Experimental

General. All reactions were carried out under a nitrogen atmosphere in oven or flame dried glassware. Tris(dibenzylideneacetone)dipalladium (0) and all phosphine ligands were purchased from Strem Chemical Co. and used without further purification. All aryl bromides were obtained from commercial sources (Aldrich Chemical Co. or Acros Chemical Co.) and were used as obtained. 2-(But-3-en-1-yl)phenol,[16] 2-(3-methylbut-3-en-1-yl)phenol,1 2-allylphenol, 3-(2-methoxyphenyl)-1-phenylpropan-1-one,[17] 2-cyclopentylidene-1,1-dimethylhydrazine,[18] 1-(bromomethyl)-2-methoxybenzene,[19] 2-cyclohexylidene-1,1-dimethylhydrazine, and [2-(bromomethyl)phenoxy](tert-butyl)dimethylsilane,[20] were prepared according to literature procedures. Toluene and THF were purified using a GlassContour solvent purification system. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by 1H NMR. The yields reported in the supporting information describe the result of a single experiment, whereas the yields reported in Tables 5-2–5-3 are average yields of two or more experiments. Thus, the yields reported in the supporting information may differ from those shown in Tables 5-2–5-3.

Synthesis of Substrates

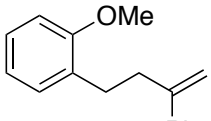
General Procedure 1: Alkylation of hydrazones.[21] An oven-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with the appropriate hydrazone (1 equiv) and THF (1 M). The resulting solution was cooled to 0 °C and a solution of n-BuLi (1 equiv, 1.6 M in hexanes) was added dropwise. The reaction mixture was stirred at 0 °C for 1 hr, then the alkyl halide (1 equiv) was added dropwise as a 1 M solution in THF, and the

reaction mixture was warmed to rt. The mixture was stirred at rt until GC analysis indicated that the starting materials were fully consumed, then 1 M HCl was added (10 mL), and the reaction was stirred for 4 hr at rt. Brine (5 mL) and EtOAc (5 mL) were added, and the mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over anhydrous MgSO4, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel.

General Procedure 2: Methylenation of ketones.[22] A flame-dried round-bottomed flask equipped with a magnetic stirbar and a rubber septum was cooled under a stream of nitrogen and charged with methyltriphenylphosphonium bromide (1 equiv) and THF (1 M). The reaction mixture was cooled to –78 ^{o}C and a solution of NaHMDS was added dropwise (1 equiv, 2 M in THF). The resulting mixture was stirred at –78 ^{o}C for 2 h then the ketone substrate (1 equiv) was added dropwise as a 1 M solution in THF and the reaction mixture was heated to 40 ^{o}C until the starting material had been completely consumed as judged by tlc analysis. The mixture was cooled to rt, brine (5 mL) and EtOAc (5 mL) were added, and the mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over anhydrous MgSO4, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel.

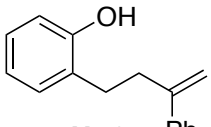
General Procedure 3: Deprotection of aryl(methyl)ethers. A flame-dried round-bottomed flask equipped with a magnetic stirbar, reflux condenser and a rubber septum was cooled under a stream of nitrogen and charged with NaH (4 equiv) and DMF (2 M). The reaction mixture was cooled to 0 ^{o}C and a 2 M solution of ethanethiol (2.6 equiv) in DMF was added dropwise. The resulting mixture was stirred at rt for 30 min, then the methyl ether substrate (1 equiv) was added and the reaction mixture was heated to 160 ^{o}C until the starting material

had been completely consumed as judged by tlc analysis. The reaction mixture was then cooled to rt and 1 M HCl (5 mL) and EtOAc (5 mL) were added. The mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 20 mL), and the combined organic layers were dried over anhydrous MgSO4, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel.



V-18

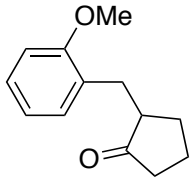
1-Methoxy-2-(3-phenylbut-3-en-1-yl)benzene (**V-18**). General Procedure 2 was used for the conversion of 3-(2-methoxyphenyl)-1-phenylpropan-1-one (1.77 g, 7.36 mmol) to the title compound. This procedure afforded 0.98 g (56%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.0 Hz, 2 H), 7.33 (t, *J* = 7.0 Hz, 2 H), 7.26 (d, *J* = 7.0 Hz, 1 H), 7.20–7.14 (m, 1 H), 7.09 (dd, *J* = 1.6, 7.2 Hz, 1 H), 6.89–6.81 (m, 1 H), 5.30 (s, 1 H), 5.06 (s, 1 H), 3.81 (s, 3 H), 2.76 (s, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 148.3, 141.2, 130.4, 129.9, 128.3, 127.3, 127.1, 126.1, 120.3, 112.2, 110.2, 55.2, 35.5, 29.7; IR (film, cm^{-1}) 2929, 1495, 1243; MS(ESI): 241.1228 (241.1223 calcd for $C_{17}H_{18}O$, M + H^+).



V-19

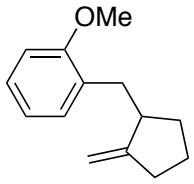
2-(3-Phenylbut-3-en-1-yl)phenol (**V-19**). General Procedure 3 was used for the conversion of 1-methoxy-2-(3-phenylbut-3-en-1-yl)benzene (1.1 g, 4.6 mmol) to the title compound. This procedure afforded 0.66 g (63%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.8 Hz, 2 H), 7.43 (t, *J* = 7.3 Hz, 2 H), 7.40–7.34 (m, 1 H), 7.20–7.14 (m, 2 H), 6.96 (t, *J* = 7.6 Hz, 1 H), 6.79 (d, *J* = 7.8 Hz, 1 H), 5.42 (s, 1 H), 5.18 (s, 1 H), 4.86 (s, 1 H), 2.94–2.84 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 148.0, 141.0, 130.4,

128.5, 128.0, 127.6, 127.4, 126.2, 120.9, 115.4, 112.8, 35.5, 29.3; IR (film, cm^{-1}) 3411, 3030, 1454; MS(EI): 224.1208 (224.1201 calcd for $C_{16}H_{16}O$, M^+).



V-20

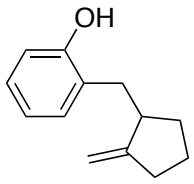
2-(2-Methoxybenzyl)cyclopentanone (**V-20**). General Procedure 1 was used for the conversion of 2-cyclopentylidene-1,1-dimethylhydrazine (1.0 g, 7.9 mmol) and 1-(bromomethyl)-2-methoxybenzene (1.24 g, 7.9 mmol) to the title compound. This procedure afforded 1.0 g (62%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, *J* = 1.7, 7.8 Hz, 1 H), 7.12 (dd, *J* = 1.7, 7.3 Hz, 1 H), 6.88 (t, *J* = 7.6 Hz, 1 H), 6.85 (d, *J* = 8.0 Hz, 1 H), 3.82 (s, 3 H), 3.28–3.20 (m, 1 H), 2.51–2.42 (m, 2 H), 2.37–2.29 (m, 1 H), 2.19–2.10 (m, 1 H), 2.04–1.92 (m, 2 H), 1.79–1.66 (m, 1 H), 1.60–1.50 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.7, 157.6, 130.5, 128.5, 127.4, 120.3, 110.2, 55.2, 49.6, 38.1, 30.2, 29.3, 20.6; IR (film, cm^{-1}) 2928, 1699, 1456; MS(EI): 204.1148 (204.1150 calcd for $C_{13}H_{16}O_2$, M^+).



V-21

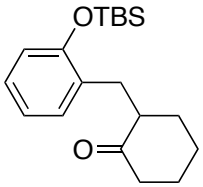
1-Methoxy-2-[(2-methylenecyclopentyl)methyl]benzene (**V-21**). General Procedure 2 was used for the conversion of 2-(2-methoxybenzyl)cyclopentanone (0.7 g, 3.5 mmol) to the title compound. This procedure afforded 0.64 g (93%) of the title compound as a colorless oil. 1H NMR (400 MHz, CDCl3) δ 7.32–7.23 (m, 2 H), 6.99 (t, J = 7.3 Hz, 1 H), 6.94 (d, J = 8.3 Hz, 1 H), 5.05 (s, 1 H), 4.97 (s, 1 H), 3.91 (s, 3 H), 3.12 (dd, J = 5.1, 13.2 Hz, 1 H), 2.87–2.80 (m, 1 H), 2.60 (dd, J = 9.8, 13.2 Hz, 1 H), 2.53–2.47 (m, 2 H), 1.88–1.76 (m, 2 H), 1.68–1.56 (m, 1 H), 1.51–1.43 (m, 1 H); 13C NMR (100 MHz, CDCl3) δ 157.7, 156.7, 130.7, 130.0,

127.1, 120.3, 110.2, 104.6, 55.2, 44.2, 35.3, 33.3, 32.8, 24.1; IR (film, cm^{-1}) 2928, 1490, 1261; MS(EI): 302.0274 (302.2066 calcd for $C_{14}H_{18}O$, M^+).



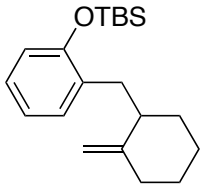
V-22

2-[(2-Methylenecyclopentyl)methyl]phenol (**V-22**). An oven-dried flask equipped with a magnetic stirbar and a reflux condenser was cooled under a stream of nitrogen and charged with 1-methoxy-2-[(2-methylenecyclopentyl)methyl]benzene (0.1 g, 0.46 mmol). L-selectride (3 equiv, 1 M in THF) was added, and the reaction mixture was stirred at rt for 3 d. After the starting material had been completely consumed, 1 M HCl (5 mL) and EtOAc (5 mL) were added, and the mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over anhydrous MgSO4, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel to afford 0.75 g (75%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15–7.07 (m, 2 H), 6.88 (t, J = 7.4 Hz, 1 H), 6.78 (d, J = 7.8 Hz, 1 H), 4.97 (s, 1 H), 4.91 (s, 1 H), 2.95 (dd, J = 5.4, 13.6 Hz, 1 H), 2.78–2.70 (m, 1 H), 2.57 (dd, J = 8.9, 13.6 Hz, 1 H), 2.41–2.34 (m, 2 H), 1.79–1.65 (m, 3 H), 1.57–1.49 (m, 1 H), 1.45–1.30 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 153.7, 131.2, 127.3, 120.6, 115.5, 105.0, 44.0, 35.1, 33.3, 32.4, 24.1, one peak is missing due to incidental equivalence; IR (film, cm^{-1}) 3435, 2928, 1456; MS(EI): 188.1201 (188.1197 calcd for $C_{13}H_{16}O$, M^+).



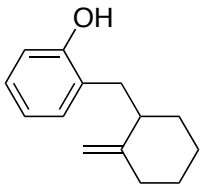
V-23

2-[2-(tert-Butyldimethylsiloxy)benzyl]cyclohexanone. General Procedure 1 was used for the conversion of 2-cyclohexylidene-1,1-dimethylhydrazine (0.23 g, 1.66 mmol) and 2-(bromomethylphenoxy)(tert-butyl)dimethylsilane (0.5 g, 1.66 mmol) to the title compound. This procedure afforded 0.36 g (68%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13–7.04 (m, 2 H), 6.86 (dt, J = 1.2, 7.4 Hz, 1 H), 6.77 (dd, J = 0.2, 8.0 Hz, 1 H), 3.21 (dd, J = 4.5, 9.2 Hz, 1 H), 2.71–2.61 (m, 1 H), 2.45–2.23 (m, 3 H), 2.10–1.94 (m, 2 H), 1.85–1.77 (m, 1 H), 1.73–1.49 (m, 3 H), 1.41–1.21 (m, 2 H), 0.98 (s, 9 H), 0.24 (s, 3 H), 0.21 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.9, 153.8, 131.6, 130.8, 127.0, 120.8, 118.3, 50.7, 42.2, 33.6, 30.7, 28.2, 25.7, 25.2, 18.2, 0.2, 0.0; IR (film, cm^{-1}) 2931, 1711, 1253; MS(ESI): 319.2088 (319.2088 calcd for $C_{19}H_{30}O_2Si$, M + H^+).



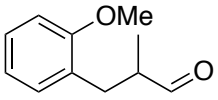
V-24

tert-Butyldimethyl{2-[(2-methylenecyclohexyl)methyl]phenoxy}silane (**V-24**). General Procedure 2 was used for the conversion of 2-[2-(tert-butyldimethylsiloxy)benzyl]cyclohexanone (1.4 g, 4.41 mmol) to the title compound. This procedure afforded 0.86 g (64%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90–6.84 (m, 2 H), 6.68–6.62 (m, 1 H), 6.59 (d, *J* = 7.8 Hz, 1 H), 4.48 (s, 1 H), 4.41 (s, 1 H), 2.78 (dd, *J* = 5.4, 13.4 Hz, 1 H), 2.32 (dd, *J* = 6.2, 13.2 Hz, 1 H), 2.21–2.10 (m, 2 H), 1.86–1.78 (m, 1 H), 1.55–1.41 (m, 3 H), 1.30–1.22 (m, 1 H), 1.17–1.05 (m, 1 H), 1.00–0.92 (m, 1 H), 0.81 (s, 9 H), 0.05 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 157.0, 135.6, 135.1, 130.6, 124.6, 122.3, 109.2, 46.7, 39.6, 37.4, 35.5, 29.7, 29.6, 28.9, 22.1, 0.2, 0.0; IR (film, cm^{-1}) 2930, 1598, 1252; MS(EI): 316.2225 (316.2222 calcd for $C_{20}H_{32}OSi$, M^+).



V-25

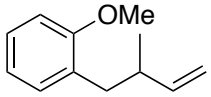
2-[(2-Methylenecyclohexyl)methyl]phenol (**V-25**). An oven-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with tert-butyldimethyl{2-[(2-methylenecyclohexyl)methyl]phenoxy}silane (0.57 g, 1.8 mmol). The flask was cooled to 0 ^{o}C and TBAF (3 equiv, 1 M in THF) was added. The resulting mixture was warmed to rt and was stirred for 2 h until the starting material had been completely consumed as judged by tlc analysis. A solution of 1 M HCl (5 mL) and EtOAc (5 mL) were added, and the resulting mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over anhydrous MgSO4, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel 0.37 g (73%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10–7.05 (m, 2 H), 6.85 (dt, J = 1.0, 8.2 Hz, 1 H), 6.79–6.76 (m, 1 H), 5.51 (s, 1 H), 4.70 (s, 1 H), 4.64 (s, 1 H), 2.97 (dd, J = 5.3, 13.4 Hz, 1 H), 2.58 (dd, J = 9.3, 13.7 Hz, 1 H), 2.42–2.31 (m, 2 H), 2.10–2.05 (m, 1 H), 1.75–1.61 (m, 3 H), 1.54–1.34 (m, 2 H), 1.28–1.17 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 153.1, 131.2, 127.2, 127.1, 120.4, 115.3, 105.6, 43.0, 35.4, 33.1, 33.0, 28.7, 24.7.; IR (film, cm^{-1}) 3435, 1507, 1229; MS(ESI): 203.1427 (203.1430 calcd for $C_{14}H_{18}O$, $M + H^{+}$).



V-28

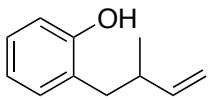
3-(2-Methoxyphenyl)butanal (**V-28**). An oven-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with sodium bicarbonate (0.89 g, 10.7 mmol), palladium acetate (0.0192 g, 0.09 mmol) and tetrabutylammonium chloride (1.19 g, 4.3 mmol). DMF (10 mL), 2-iodoanisole

(1.0 g, 4.27 mmol), and 2-methylprop-2-en-1-ol (0.46 mL, 6.4 mmol) were added, and the reaction mixture was heated to 85 ^{o}C. Palladium acetate was added again (0.0192 g, 0.09 mmol) after 12 h, and the reaction was stirred for another 12 h. When the reaction was complete, sat'd NH_4Cl (5 mL) and ether (5 mL) were added, and the resulting mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with ether (2 x 20 mL). The combined organic layers were dried over anhydrous MgSO4, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel 0.61 g (85%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (s, 1 H), 7.20 (dt, *J* = 1.8, 8.9 Hz, 1 H), 7.10 (dd, *J* = 1.4, 7.4 Hz, 1 H), 6.88 (dt, *J* = 1.0, 7.4 Hz, 1 H), 6.84 (d, *J* = 6.8 Hz, 1 H), 3.78 (s, 3 H), 3.07 (dd, *J* = 6.4, 13.1 Hz, 1 H), 2.71 (ds, *J* = 1.6, 7.0 Hz, 1 H), 2.63 (dd, *J* = 7.4, 13.1 Hz, 1 H), 1.04 (d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.8, 157.4, 130.9, 127.8, 127.0, 120.4, 110.3, 55.1, 46.4, 31.7, 13.3; IR (film, cm^{-1}) 2963, 1718, 1245; MS(EI): 178.0994 (178.0994 calcd for $C_{11}H_{14}O_2$, M^+).



V-29

1-Methoxy-2-(pent-4-en-2-yl)benzene (**V-29**). General Procedure 2 was used for the conversion of 3-(2-methoxyphenyl)butanal (0.47 g, 2.62 mmol) to the title compound. This procedure afforded 0.43 g (93%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.41 (m, 1 H), 7.20 (dt, J = 1.8, 8.0 Hz, 1 H), 7.19 (dd, J = 1.6, 7.2 Hz, 1 H), 7.00–6.91 (m, 1 H), 5.98–5.88 (m, 1 H), 5.07–4.98 (m, 2 H), 3.88 (s, 3 H), 2.84–2.76 (m, 1 H), 2.70–2.58 (m, 2 H), 1.10 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 144.6, 131.0, 129.3, 128.6, 127.1, 120.2, 112.2, 55.2, 37.8, 37.5, 19.6.; IR (film, cm^{-1}) 2962, 1495, 1243; MS(EI): 176.1201 (176.1201 calcd for $C_{12}H_{16}O$, M^+).

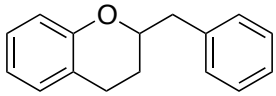


V-30

2-(Pent-4-en-2-yl)phenol (**V-13**). General Procedure 3 was used for the conversion of 1-methoxy-2-(pent-4-en-2-yl)benzene (**V-30**) (0.16 g, 0.91 mmol) to the title compound. This procedure afforded 0.10 g (75%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10–7.04 (m, 2 H), 6.87–6.82 (m, 1 H), 6.74 (d, *J* = 8.7 Hz, 1 H), 5.89–5.75 (m, 1 H), 5.00–4.90 (m, 2 H), 4.78 (s, 1 H), 2.69–2.60 (m, 1 H), 2.59–2.48 (m, 2 H), 1.02 (d, *J* = 6.4 Hz, 3 H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 144.2, 131.5, 127.3, 127.1, 120.6, 115.6, 113.0, 38.0, 37.4, 19.6.; IR (film, cm^{-1}) 3367, 2974, 1456; MS(EI): 162.1042 (162.1045 calcd for $C_{11}H_{14}O$, M^+).

Synthesis of Benzopyrans via Pd-Catalyzed Alkene Carboetherification

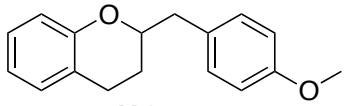
General Procedure 4: Palladium-Catalyzed Carboetherification Reactions. An oven or flame-dried Schlenk tube was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (2 mol% complex, 4 mol % Pd), S-Phos (4 mol %), NaO*t*Bu (2.0 equiv), and the aryl bromide (2.0 equiv). The tube was purged with nitrogen and the alcohol substrate (1.0 equiv), and toluene (0.25 M substrate concentration) were added. The mixture was heated to 110 °C with stirring until the starting material had been consumed as judged by GC or 1H NMR analysis. The mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl (2 mL), and diluted with ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.



V-12

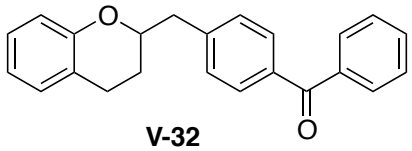
(±)-2-Benzylchroman (**V-12**). The coupling of 2-(but-3-en-1-yl)phenol (30 mg, 0.20 mmol) with bromobenzene (0.43 µL, 0.40 mmol) was conducted following General Procedure 4. This procedure afforded 37.4 mg (83%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.19 (m, 5 H),

7.09–6.97 (m, 2 H), 6.83–6.75 (m, 2 H), 4.23–4.15 (m, 1 H), 3.12 (dd, *J* = 7.6, 13.6 Hz, 1 H), 2.85 (dd, *J* = 7.0, 13.6 Hz, 1 H), 2.78–2.68 (m, 2 H), 2.00–1.91 (m, 1 H), 1.74–1.62 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 137.8, 129.6, 129.5, 128.3, 127.1, 126.4, 121.9, 120.0, 116.7, 76.5, 41.8, 26.5, 24.5; IR (film, cm^{-1}) 2924, 1456, 1236; MS(EI): 224.1207 (224.1201 calcd for $C_{16}H_{16}O$, M^+).



V-31

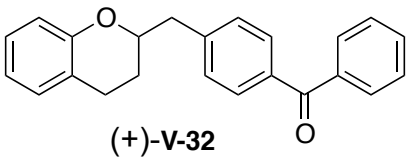
(±)-2-(4-Methoxybenzyl)chroman (**V-31**). The coupling of 2-(but-3-en-1-yl)phenol (25 mg, 0.17 mmol) with 4-bromoanisole (40 µL, 0.34 mmol) was conducted following General Procedure 4. This procedure afforded 28 mg (66%) of the title compound as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.15 (m, 2 H), 7.06 (t, *J* = 7.4 Hz, 1 H), 7.01 (d, *J* = 7.0 Hz, 1 H), 6.86–6.75 (m, 4 H), 4.19–4.11 (m, 1 H), 3.78 (s, 3 H), 3.07 (dd, *J* = 6.1, 13.9 Hz, 1 H), 2.83–2.70 (m, 3 H), 2.00–1.92 (m, 1 H), 1.73–1.63 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.2, 130.5, 129.9, 129.5, 127.2, 120.0, 116.7, 115.7, 113.8, 76.7, 55.4, 55.2, 40.9, 26.4, 24.6; IR (film, cm^{-1}) 2929, 1488, 1247; MS(EI): 254.1307 (254.1313 calcd for $C_{16}H_{16}O$, M^+).



V-32

(±)-[4-(Chroman-2-ylmethyl)phenyl](phenyl)methanone (**V-32**). The coupling of 2-(but-3-en-1-yl)phenol (20 mg, 0.13 mmol) with 4-bromobenzophenone (70 mg, 0.26 mmol) was conducted following General Procedure 4. This procedure afforded 24.7 mg (56%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.78 (m, 4 H), 7.63–7.58 (m, 1 H), 7.51 (t, *J* = 7.8 Hz, 2 H), 7.42 (d, *J* = 8.0 Hz, 2 H), 7.11 (t, *J* = 7.3 Hz, 1 H), 7.06 (d, *J* = 7.6 Hz, 1 H), 6.88–6.81 (m, 2 H), 4.33–4.27 (m, 1 H), 3.21 (dd, *J* = 6.6, 13.9 Hz, 1 H), 3.01 (dd, *J* = 6.1, 13.7 Hz, 1 H), 2.90–2.75 (m, 2 H), 2.07–2.00 (m, 1 H), 1.83–1.73 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 154.6, 143.0,

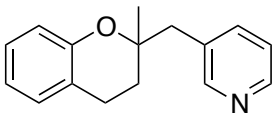
137.8, 135.8, 132.3, 130.2, 130.0, 129.5, 128.3, 127.3, 121.8, 120.2, 116.8, 76.0, 41.8, 26.8, 24.5, 18.5; IR (film, cm^{-1}) 2918, 1616, 1457; MS(ESI): 329.1537 (329.1536 calcd for $C_{23}H_{20}O_2$, $[M+H]^+$).



(+)-**V-32**

(+)-[4-(Chroman-2-ylmethyl)phenyl](phenyl)methanone ((+)-**V-32**). The coupling of 2-(but-3-en-1-yl)phenol (25 mg, 0.17 mmol) with 4-bromobenzophenone (88 mg, 0.33 mmol) was conducted following General Procedure 4 except using **V-48** as a ligand. This procedure afforded 0.044 mg (70%) of the title compound as a yellow oil, [α]D23 = +4.2 (c 0.40, CH_2Cl_2). The enantiopurity was determined to be 30% ee by chiral HPLC analysis [OJH 0.46 cm x 25 cm, 10% isopropanol/hexanes, 2 mL/min, RT = 11.5 and 13.1 min]. Spectroscopic data were identical to those above for (±)-**V-32**.

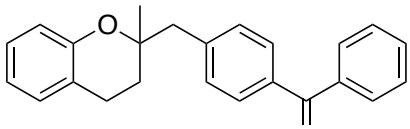
(+)-[4-(Chroman-2-ylmethyl)phenyl](phenyl)methanone (**(+)-V-32**). The coupling of 2-(but-3-en-1-yl)phenol (20 mg, 0.13 mmol) with 4-bromobenzophenone (70 mg, 0.026 mmol) was conducted following General Procedure 4 except using **V**-**49** as ligand. This procedure afforded 0.06 mg (14%) of the title compound as a yellow oil, [α]D23 = +11.2 (c 0.02, CH2Cl2). The enantiopurity was determined to be 76% ee by chiral HPLC analysis [OJH 0.46 cm x 25 cm, 10% isopropanol/hexanes, 2 mL/min, RT = 11.5 and 13.1 min]. Spectroscopic data were identical to those above for (±)-**V-32**.



V-33

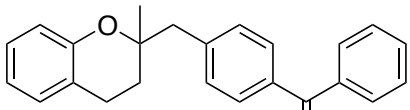
(±)-3-[(2-Methylchroman-2-yl)methyl]pyridine (**V-33**). The coupling of 2-(3-methylbut-3-en-1-yl)phenol (20 mg, 0.12 mmol) with 3-bromopyridine (23.7 μL, 0.24 mmol) was conducted following General Procedure 4. This procedure

afforded 24 mg (81%) of the title compound as an amber oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16–7.07 (m, 4 H), 6.88–6.84 (m, 2 H), 6.80–6.77 (m, 2 H), 2.94 (d, J = 13.6 Hz, 1 H), 2.89–2.78 (m, 3 H), 1.87–1.74 (m, 2 H), 1.24 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 131.5, 129.9, 129.5, 127.3, 119.7, 119.5, 117.4, 76.3, 45.1, 30.8, 25.7, 24.3, 22.1, 18.4, 18.2; IR (film, cm^{-1}) 2928, 1581, 1455, 1243; MS(ESI): 240.1386 (240.1383 calcd for $C_{16}H_{17}NO$, M + H^+).



V-34

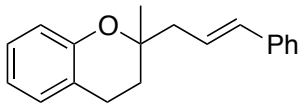
(±)-{4-[(2-Methylchroman-2-yl)methyl]phenyl}(phenyl)methanone (**V-34**). The coupling of 2-(3-methylbut-3-en-1-yl)phenol (20.0 mg, 0.12 mmol) with 4-bromobenzophenone (70.0 mg, 0.24 mmol) was conducted following General Procedure 4. This procedure afforded 35.0 mg (83%) of the title compound as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.77 (m, 2 H), 7.75–7.71 (m, 2 H), 7.60–7.53 (m, 1 H), 7.49–7.44 (m, 2 H), 7.36–7.32 (m, 2 H), 7.13–7.04 (m, 2 H), 6.86-6.81 (m, 2 H), 3.07 (d, *J* = 13.3 Hz, 1 H), 2.90 (d, *J* = 13.5 Hz, 1 H), 2.82 (t, *J* = 6.6 Hz, 2 H), 1.83 (t, *J* = 6.8 Hz, 2 H), 1.26 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 153.6, 142.4, 137.8, 135.7, 132.3, 130.6, 130.0, 129.9, 129.6, 128.2, 127.4, 120.8, 119.9, 117.3, 75.9, 45.7, 31.2, 24.5, 22.1; IR (film, cm^{-1}) 2927, 1653, 1278; MS(EI): 343.1697 (343.1693 calcd for $C_{24}H_{22}O_2$, $[M+H]^+$).



(–)-**V-34**

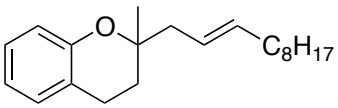
(–)-{4-[(2-Methylchroman-2-yl)methyl]phenyl}(phenyl)methanone (**–**)-**V-34**). The coupling of 2-(3-methylbut-3-en-1-yl)phenol (20 mg, 0.12 mmol) with 4-bromobenzophenone (64 mg, 0.24 mmol) was conducted following General Procedure 4 except using **V-48** as ligand. This procedure afforded 13 mg (30%) of the title compound as an orange oil. [α]D23 = –4.1 (c 0.11, CH_2Cl_2). The enantiopurity was determined to be 7% ee by chiral HPLC analysis [OJH 0.46 cm

x 25 cm, 10% isopropanol/hexanes, 1 mL/min, RT = 13.2 and 15.2 min]. Spectroscopic data were identical to those above for (±)-**V-34**.



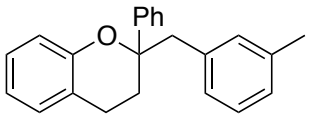
V-35

(±)-2-Cinnamyl-2-methylchroman (**V-35**). The coupling of 2-(3-methylbut-3-en-1-yl)phenol (20 mg, 0.12 mmol) with (E)-β-bromostyrene (30 µL, 0.24 mmol) was conducted following General Procedure 4. This procedure afforded 28 mg (88%) of the title compound as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.27 (m, 4 H), 7.26–7.18 (m, 2 H), 7.13–7.02 (m, 2 H), 6.86–6.79 (m, 1 H), 6.45 (d, *J* = 15.8 Hz, 1 H), 6.33–6.24 (m, 1 H), 2.79 (t, *J* = 6.8 Hz, 2 H), 2.56–2.50 (m, 2 H), 1.94–1.85 (m, 1 H), 1.83–1.74 (m, 1 H), 1.33 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 137.4, 133.2, 129.4, 128.5, 127.3, 127.2, 126.1, 125.2, 121.0, 119.8, 117.3, 76.1, 43.4, 30.8, 24.6, 22.1.); IR (film, cm^{-1}) 2929, 1581, 1453; MS(EI): 264.1512 (264.1514 calcd for $C_{19}H_{20}O$, M^+).



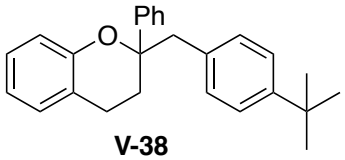
V-36

(±)-(E)-2-Methyl-2-(undec-2-en-1-yl)chroman (**V-36**). The coupling of 2-(3-methylbut-3-en-1-yl)phenol (20 mg, 0.12 mmol) with (E)-1-bromodec-1-ene (30 µL, 0.54 mmol) was conducted following General Procedure 4. This procedure afforded 37.0 mg (80%) of the title compound as an amber oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09–6.99 (m, 2 H), 6.81–6.73 (m, 2 H), 5.56–5.36 (m, 2 H), 2.76–2.68 (m, 2 H), 2.37–2.25 (m, 2 H), 1.99 (p, J = 6.9 Hz, 2 H), 1.87–1.64 (m, 2 H), 1.35–1.17 (m, 16 H), 0.85 (t, J = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 134.5, 133.0, 129.4, 127.2, 123.7, 121.1, 117.2, 76.0, 42.8, 37.3, 32.6, 31.8, 30.6, 30.4, 29.4, 29.3, 27.4, 24.4, 22.6, 14.1; IR (film, cm^{-1}) 2926, 1653, 1456; MS(EI): 300.2453 (300.2453 calcd for $C_{21}H_{32}O$, M^+).



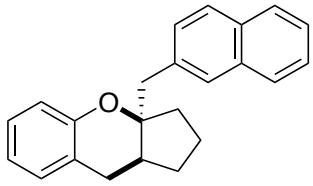
V-37

(±)-2-(3-Methylbenzyl)-2-phenylchroman (**V-37**). The coupling of 2-(3-phenylbut-3-en-1-yl)phenol (25 mg, 0.11 mmol) with *m*-bromotoluene (24 µL, 0.22 mmol) was conducted following General Procedure 4. This procedure afforded 35 mg (57%) of the title compound as an amber oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.23 (m, 4 H), 7.17–7.08 (m, 3 H), 7.04–6.98 (m, 2 H), 6.92–6.88 (m, 3 H), 6.79 (dt, *J* = 1.2, 7.3 Hz, 1 H), 3.22 (d, J = 13.4 Hz, 1 H), 3.10 (d, *J* = 13.4 Hz, 1 H), 2.63–2.56 (m, 1 H), 2.49–2.38 (m, 2 H), 2.28 (s, 3 H), 2.08-2.00 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 143.8, 137.0, 136.3, 131.8, 129.3, 128.3, 128.1, 128.0, 127.5, 127.3, 127.0, 126.7, 125.8, 121.9, 120.0, 80.7, 50.0, 29.6, 22.3, 21.4; IR (film, cm^{-1}) 3058, 2927, 1237; MS(ESI): 315.1747 (315.1743 calcd for $C_{23}H_{22}O$, M + H^+).



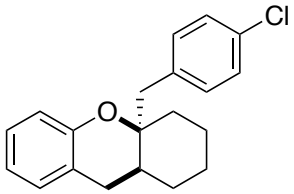
V-38

(±)-2-[4-(*tert*-Butyl)benzyl]-2-phenylchroman (**V-38**). The coupling of 2-(3-phenylbut-3-en-1-yl)phenol (25 mg, 0.11 mmol) with 4-bromo-tert-butylbenzene (35 µL, 0.22 mmol) was conducted following General Procedure 4. This procedure afforded 24.3 mg (61%) of the title compound as an amber oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.17 (m, 7 H), 7.15–7.09 (m, 1 H), 7.07–7.01 (m, 3 H), 6.89–6.85 (m, 1 H), 6.76 (dt, *J* = 1.2, 7.4 Hz, 1 H), 3.22 (d, *J* = 13.7 Hz, 1 H), 3.06 (d, *J* = 13.7 Hz, 1 H), 2.60–2.51 (m, 1 H), 2.46–2.35 (m, 2 H), 2.04–1.95 (m, 1 H), 1.29 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 149.0, 144.0, 133.4, 130.5, 129.3, 128.1, 127.2, 126.7, 125.7, 124.6, 121.8, 119.8, 117.0, 80.8, 49.6, 34.3, 31.4, 29.3, 22.3; IR (film, cm^{-1}) 2962, 1490, 1237; MS(ESI): 209.0963 (209.0966 calcd for $C_{26}H_{28}O$, $[M - C_{11}H_{15}]^+$).



V-39

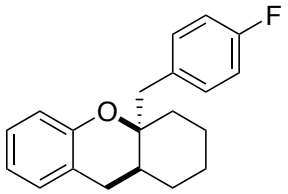
(±)-(3aS*,9aR*)-3a-(Naphthalen-2-ylmethyl)-1,2,3,3a,9,9a-hexahydrocyclopenta[b]chromene (**V-39**). The coupling of 2-[(2-methylenecyclopentyl)methyl]phenol (25 mg, 0.13 mmol) with 2-bromonaphthalene (55 mg, 0.26 mmol) was conducted following General Procedure 4. This procedure afforded 25.6 mg (61%) of the title compound as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.71 (m, 3 H), 7.61 (s, 1 H), 7.46–7.39 (m, 2 H), 7.36–7.32 (m, 1 H), 7.15 (t, *J* = 7.6 Hz, 1 H), 7.10 (d, *J* = 7.0 Hz, 1 H), 6.90–6.83 (m, 2 H), 3.18 (d, *J* = 13.7 Hz, 1 H), 3.04 (dd, *J* = 6.5, 17.0 Hz, 1 H), 2.83 (d, *J* = 13.7 Hz, 1 H), 2.68 (d, *J* = 16.4 Hz, 1 H), 2.21–2.12 (m, 1 H), 1.88–1.64 (m, 4 H), 1.62–1.42 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 135.6, 133.3, 132.2, 130.0, 128.9, 128.6, 127.6, 127.4, 127.3, 125.8, 125.3, 120.2, 120.0, 117.5, 86.1, 69.0, 42.1, 39.9, 36.8, 29.0, 25.4, 20.4; IR (film, cm^{-1}) 2916, 1456, 1231; MS(EI): 314.1666 (314.1671 calcd for $C_{23}H_{22}O$,M^+).



V-40

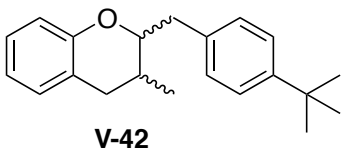
(±)-(4aS*,9aR*)-4a-(4-Chlorobenzyl)-2,3,4,4a,9,9a-hexahydro-1H-xanthene (**V-40**). The coupling of 2-[(2-methylenecyclohexyl)methyl]phenol (20 mg, 0.10 mmol) with 4-bromochlorobenzene (37.8 mg, 0.20 mmol) was conducted following General Procedure 4. This procedure afforded 23 mg (76%) of the title compound as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.19 (m, 2 H), 7.14 (t, *J* = 7.4 Hz, 1 H), 7.07 (d, *J* = 7.6 Hz, 1 H), 7.04–6.99 (m, 2 H), 6.89–6.82 (m, 2 H), 3.23 (dd, *J* = 6.3, 16.8 Hz, 1 H), 3.08 (d, *J* = 13.8 Hz, 1 H), 2.47 (d, *J* =

13.7 Hz, 1 H), 2.41 (d, *J* = 17.0 Hz, 1 H), 1.81–1.72 (m, 1 H), 1.68–1.59 (m, 3 H), 1.51–1.41 (m, 2 H), 1.39–1.16 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 132.1, 131.9, 131.8, 130.1, 127.9, 127.4, 120.0, 117.3, 76.4, 42.6, 42.1, 36.0, 34.6, 29.2, 28.6, 25.2, 21.2; IR (film, cm^{-1}) 2920, 1456, 1247; MS(EI): 312.1281 (312.1278 calcd for $C_{20}H_{21}ClO$, M^+).



V-41

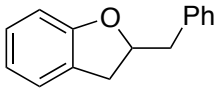
(±)-(4aS*,9aR*)-4a-(4-Fluorobenzyl)-2,3,4,4a,9,9a-hexahydro-1H-xanthene (**V-41**). The coupling of 2-[(2-methylenecyclohexyl)methyl]phenol (20 mg, 0.10 mmol) with 4-bromofluorobenzene (22 µL, 0.20 mmol) was conducted following General Procedure 4. This procedure afforded 21 mg (72%) of the title compound as an amber oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (t, *J* = 7.6 Hz, 1 H), 7.10–7.01 (m, 3 H), 6.96–6.90 (m, 2 H), 6.89–6.83 (m, 2 H), 3.24 (dd, *J* = 6.4, 16.8 Hz, 1 H), 3.08 (d, *J* = 13.9 Hz, 1 H), 2.48 (d, J = 13.9 Hz, 1 H), 2.41 (d, *J* = 16.8 Hz, 1 H), 1.81–1.73 (m,1 H), 1.68–1.60 (m, 2 H), 1.51–1.42 (m, 3 H), 1.39–1.30 (m, 1 H), 1.30–1.19 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 152.8, 132.7, 131.9, 131.8 (q, J = 254.8 Hz), 129.7, 120.1, 119.9,117.3, 114.7 (q, *J* = 21.0 Hz), 76.5, 42.4, 36.0, 34.6, 28.7, 25.8, 25.2, 21.2; IR (film, cm^{-1}) 2952, 1736, 1249; MS(EI): 296.1579 (296.1576 calcd for $C_{20}H_{21}FO$, M^+).



V-42

(±)-2-[4-(tert-Butyl)benzyl]-3-methylchroman (**V-42**). The coupling of 2-(2-methylbut-3-en-1-yl)phenol (30 mg, 0.19 mmol) with 4-bromo-*tert*-butyl benzene (60 µL, 0.37 mmol) was conducted following General Procedure 4. This procedure afforded 0.036 mg (65%) of the title compound as an amber oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.31 (m, 6.60 H), 7.29–7.24 (m, 3.78 H), 7.23–

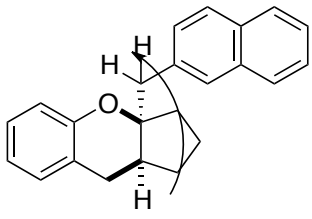
7.19 (m, 1.43 H), 7.13–7.07 (m, 1.90 H), 7.06–7.01 (m, 2.33 H), 6.88–6.76 (m, 4.10 H), 4.71 (d, *J* = 10.9 Hz, 0.10 H), 4.47 (t, *J* = 6.4 Hz, 0.55 H), 4.25 (dt, *J* = 2.2, 8.2 Hz, 0.49 H), 4.18–4.14 (m, 0.63 H), 4.01 (dt, *J* = 4.3, 7.4 Hz, 1 H), 3.07–2.98 (m, 1.75 H), 2.96–2.76 (m, 3.56 H), 2.53–2.41 (m, 2.43 H), 2.16–2.08 (m, 0.57 H), 1.98–1.86 (m, 1.73 H), 1.36–1.27 (m, 27.84 H), 1.12–1.08 (m, 4.72 H), 1.06 (d, *J* = 6.8 Hz, 1.52 H), 1.01–0.98 (m, 0.36 H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 153.5, 149.1, 148.9, 139.3, 137.9, 135.2, 135.1, 130.1, 129.6, 129.4, 129.3, 129.1, 128.9, 127.1, 127.0, 125.3, 125.2, 125.1, 121.5, 121.4, 121.1, 120.2, 120.0, 119.9, 116.9, 116.6, 82.7, 81.2, 79.4, 51.7, 38.4, 37.1, 34.4, 34.3, 32.9, 31.9, 31.4, 31.3, 31.1, 29.6, 28.2, 27.7, 18.3, 18.1, 13.1; IR (film, cm^{-1}) 2962, 1249; MS(EI): 294.1991 (294.1984 calcd for $C_{21}H_{26}O$, M^+).



V-43

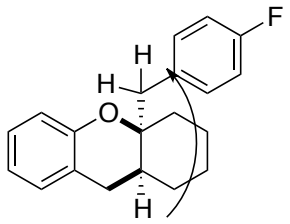
(±)-2-Benzyl-2,3-dihydrobenzofuran (**V-43**). The coupling of 2-allylphenol (20 mg, 0.15 mmol) with bromobenzene (0.31 μL, 0.30 mmol) was conducted following General Procedure 4. This procedure afforded 13.5 mg (43%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.20 (m, 5 H), 7.14–7.07 (m, 2 H), 6.84–6.75 (m, 2 H), 5.04–4.96 (m, 1 H), 3.24–3.14 (m, 2 H), 2.98–2.89 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4, 129.4, 128.5, 128.0, 126.5, 125.0, 120.2, 109.4, 83.5, 41.9, 34.9, 2 signals missing due to incidental equivalence; IR (film, cm^{-1}) 2920, 1653, 1456; MS(EI): 210.1049 (210.1045 calcd for $C_{15}H_{14}O$, M^+).

Assignment of Stereochemistry



V-39

The relative stereochemistry of **V-39** was assigned on the basis of signals observed in 1H NMR nOe experiments. Relevant nOe data is shown below.



V-41

The relative stereochemistry of **V-41** was assigned on the basis of signals observed in 1H NMR nOe experiments. Relevant nOe data is shown below. The stereochemistry of compound **V-40** was assigned based on analogy to **V-41**.

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[10] Only a single example of a Pd-catalyzed alkene difunctionalization reaction that generates a tetrahydropyran product has been reported. See reference 6c.

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[13] Ligand definitions: S-Phos = 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl; Ru-Phos = 2-dicyclohexylphosphino-2',6'-di-i-propoxy-1,1'-biphenyl; Me-Phos = 2-dicyclohexylphosphino-2'-methylbiphenyl; Dave-Phos = 2-dicyclohexylphosphino-2′-(N,N-dimethylamino)-biphenyl; Brett-Phos = 2-(dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-tri-i-propyl-1,1'-biphenyl ; Dpe-Phos = bis(diphenylphosphinophenyl)ether; (R)- Siphos-PE = (+)-(11aR)-10,11,12,13-Tetrahydroindeno[7,1-de:1',7'fg][1,3,2]dioxaphosphocin-5-bis[(R)-1-phenylethyl]amine.

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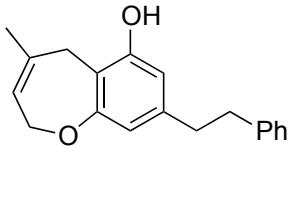
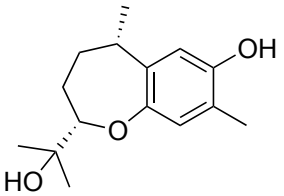
Chapter 6: Synthesis of Benzoxepines via Palladium-Catalyzed Carboetherification Reactions

6.1 Introduction

Benzoxepines are benzo-fused 7-membered ring heterocycles found in a variety of biologically active natural products such as randulanin A (**VI-1**) and heliannuol D (**VI-2**), which are illustrated in Figure 6-1.[1,2] Thus, the synthesis of benzoxepines is an important objective for organic and medicinal chemists,[3] and many methods have been applied for their synthesis, including Bayliss-Hilman reactions[4], Pd-catalyzed reactions,[5] and Grubb's catalysis.[6] Nevertheless, a concise method that can be used to rapidly synthesize a variety of different analogs would be a useful tool. For this purpose, we desired to apply our Pd-catalyzed carboetherification methodology, which has been used for the synthesis of various oxygenated heterocycles such as tetrahydrofurans and benzopyrans, for the production of benzoxepines.[7] However, palladium-catalyzed carboetherification reactions have never been employed to produce 7-membered rings.



Radulanin A
VI-1



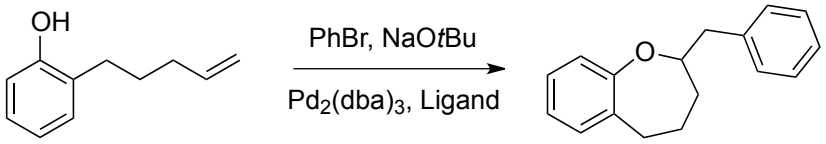
Heliannuol D
VI-2

Figure 6.1. Biologically Active Benzoxepines

6.2 Reaction Optimization

To identify optimal conditions for the synthesis of benzoxepines via palladium-catalyzed carboetherification reactions, substrate **VI-3** was prepared in 4 steps

according to a literature procedure[8] and was coupled to bromobenzene in the presence of a variety of different catalyst systems, including those based on bidentate and monodentate phosphine ligands, as shown in Table **VI-1**. A catalyst system composed of $Pd_2(dba)_3$/Ru-Phos gave the best results, and the desired product was obtained in 65% isolated yield (84% H-NMR yield).



VI-3 **VI-4**

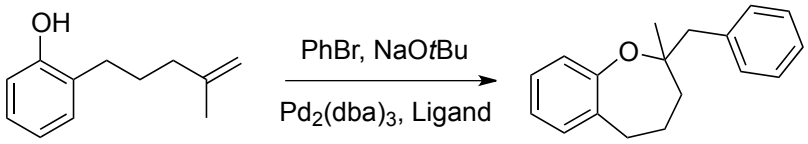
Ligand	H-NMR Yield
Xantphos	0%
Dpe-Phos	0%
dppb	0%
BrettPhos	0%
S-Phos	65%
RuPhos	84%

a Conditions: 1.0 equiv of **VI-3** 2.0 equiv of PhBr, 2.0 equiv of NaO_tBu, 2 mol % of $Pd_2(dba)_3$, 4 mol % of ligand, toluene, 110 °C.

Table 6.1. Catalyst System Optimization

6.3 Substrates Bearing 1,1-Disubstituted and Internal Alkenes

With the optimized conditions in hand, we elected to examine the substrate scope of the reaction. To this end, compound **VI-5**, which possesses a 1,1-disubstituted alkene, was synthesized according to a previously described procedure[9] and subjected to the optimized reaction conditions. Unfortunately, in the presence of several different catalyst systems, including the optimized catalyst, the desired product was not obtained (Table 6-2), and only various amounts of starting material or complex mixtures were observed.



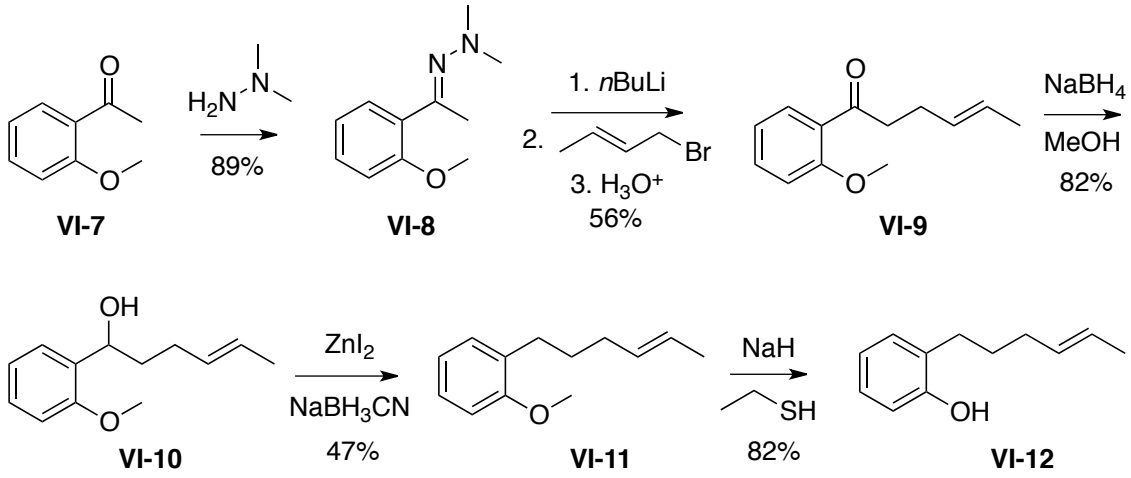
VI-5 **VI-6**

Ligand	Result
Xantphos	complex mixture
Dpe-Phos	complex mixture
dppb	complex mixture
BrettPhos	50% SM
S-Phos	66% SM
RuPhos	68% SM
PMe_3HBF_4	84% SM
NiXantphos	decomposition
dppf	decomposition

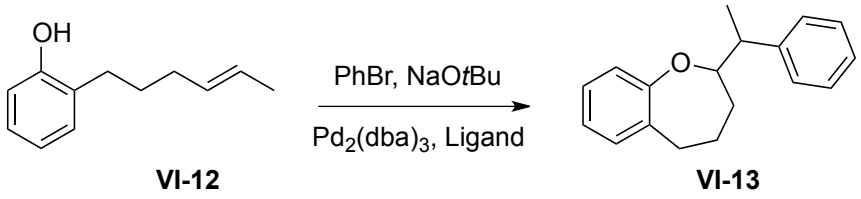
[a] Conditions: 1.0 equiv of **VI-6,** 2.0 equiv of PhBr, 2.0 equiv of NaOtBu, 2 mol % of $Pd_2(dba)_3$, 4 mol % of ligand, xylene, 140 °C.

Table 6.2. Efforts Toward the Pd-Catalyzed Carboetherification of 1,1-Disubstituted Alkene Substrates

In addition, compound **VI-12**, which possesses an internal alkene, was synthesized according to the method outlined in Scheme 6-1. Namely, the hydrazone of 2-methoxyacetophenone was produced, monoalkylated with (E)-1-bromobut-2-ene and transformed to the corresponding ketone in 50% overall yield. Subsequently, the ketone was reduced to the alcohol, which was further reduced using ZnI_2 and $NaBH_3CN$. Lastly, the methoxy aryl ether was deprotected to the corresponding phenol to obtain **VI-12** in 82% yield. Similar to the results obtained with **VI-6**, which contains a 1,1-disubstituted alkene, only starting material and decomposition were observed, as shown in Table 6-3.



Scheme 6-1. Synthesis of Substrate **VI-12**



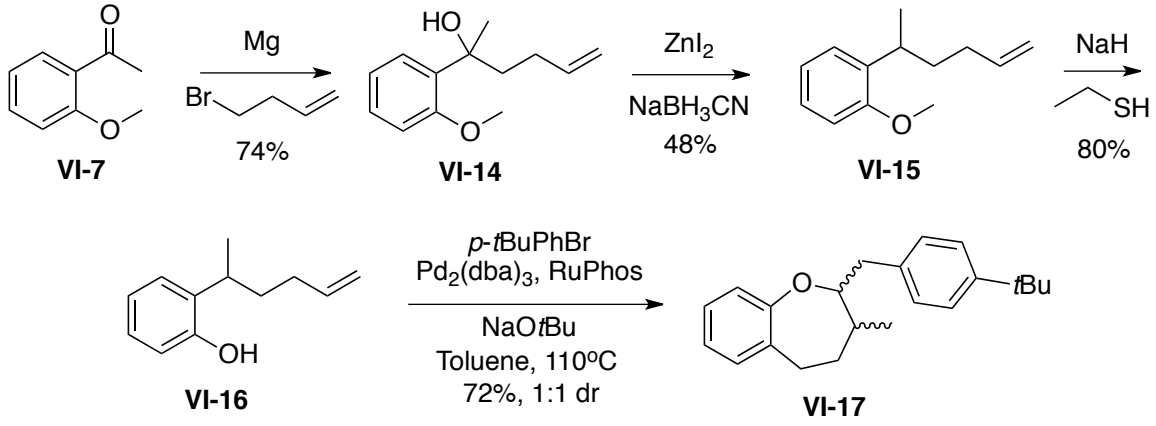
Ligand	Result
Xantphos	88% SM
Dpe-Phos	64% SM
dppb	80% SM
BrettPhos	90% SM
S-Phos	82% SM
RuPhos	84% SM
PMe_3HBF_4	40% SM
NiXantphos	decomposition
dppf	decomposition

[a] Conditions: 1.0 equiv of **VI-12** 2.0 equiv of PhBr, 2.0 equiv of NaO_tBu, 2 mol % of $Pd_2(dba)_3$, 4 mol % of ligand, xylene, 140 °C.

Table 6.3. Efforts Toward the Pd-Catalyzed Carboetherification of Substrates Bearing an Internal Alkene

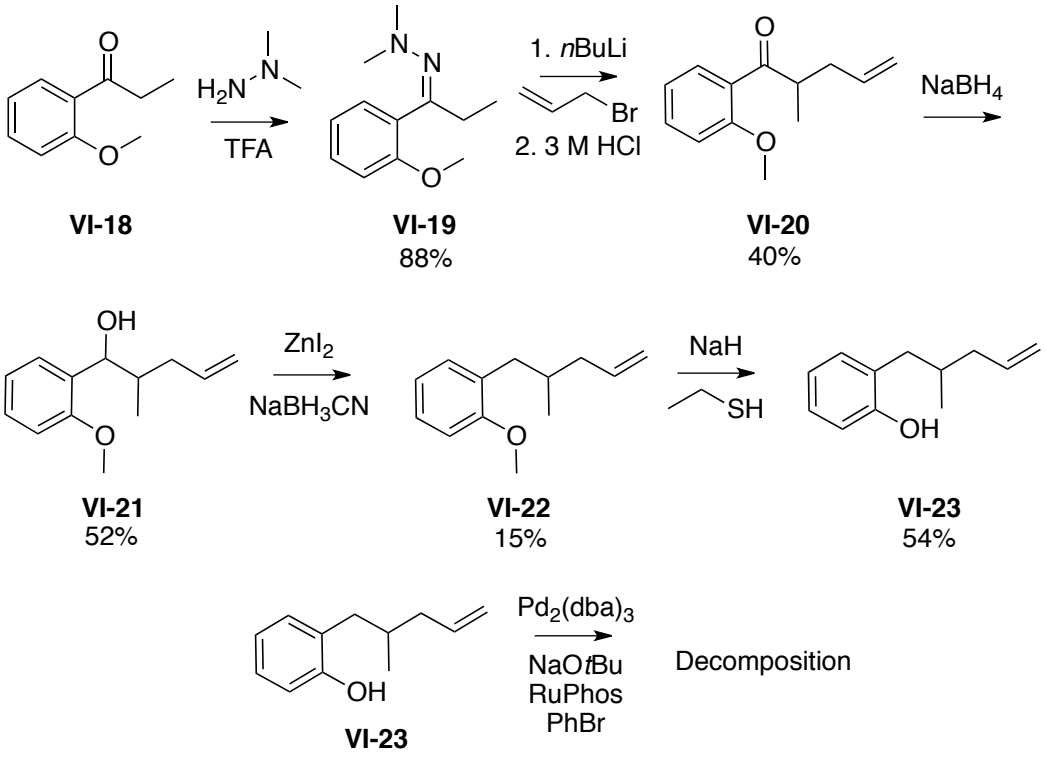
6.4 Synthesis of 2,3-, 2,4- and 2,5-Disubstituted Benzoxepines

To determine the diastereoselectivity of the reaction for the formation of 2,3-, 2,4-, and 2,5-disubstituted benzoxepines, substrates bearing different substituents along the backbone were evaluated. For instance, to evaluate the synthesis of 2,3-disubstituted benzoxepines, **VI-16** was prepared according to the route shown in Scheme 6-2, which is similar to that shown in Scheme 6-1. Upon subjection to the optimized reaction conditions, **VI-17** was obtained as 1:1 mixture of diastereomers in 72% yield.



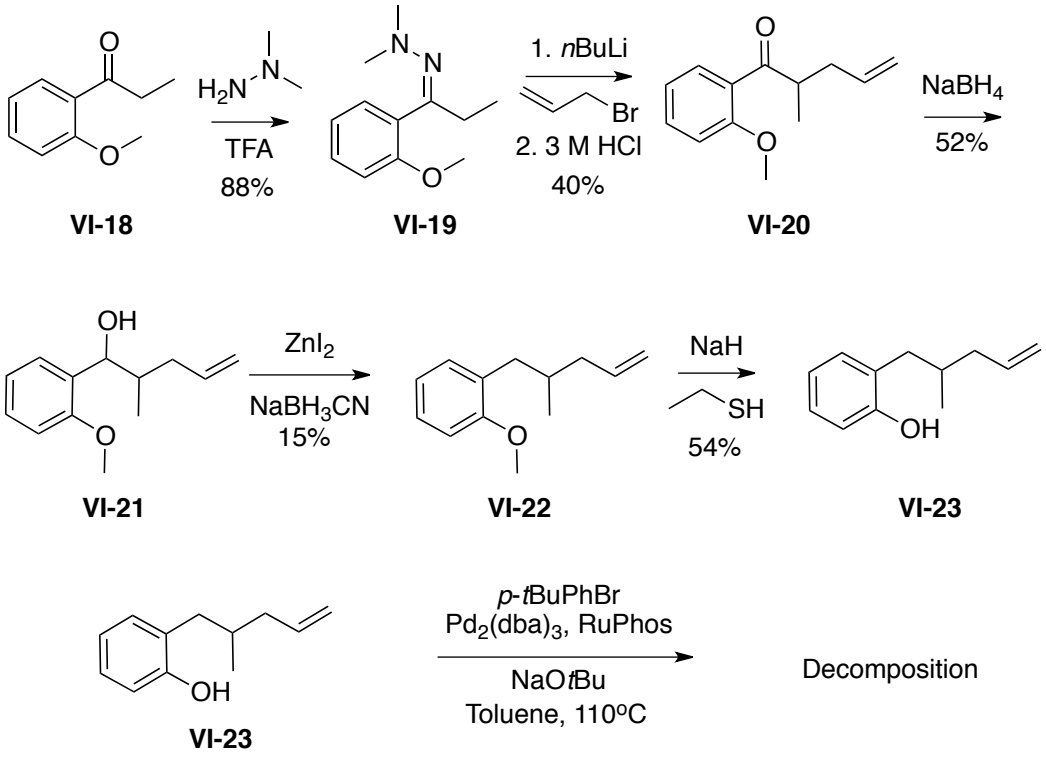
Scheme 6-2. Synthesis and Pd-Catalyzed Carboetherification Reaction of Substrate **VI-16**

The formation of 2,4-disubstituted benzoxepines via Pd-catalyzed carboetherification was also evaluated. To this end, **VI-23** was synthesized according to the route shown in Scheme 6-3. However, upon subjection to the optimized Pd-catalyzed carboetherification reaction conditions, decomposition occurred.



Scheme 6-3. Synthesis and Attempted Pd-Catalyzed Carboetherification Reaction of Substrate **VI-23**

Lastly, the formation of 2,5-disubstituted benzoxepines was assessed. **VI-24** was synthesized using a literature procedure,[10] and was transformed into **VI-25** by applying the method shown in Scheme 6-4. Upon subjection to the optimized reaction conditions, decomposition was observed, and the desired product was not obtained.



Scheme 6-4. Synthesis and Attempted Pd-Catalyzed Carboetherification Reaction of Substrate **VI-25**

6.5 Conclusions

Although the synthesis of benzoxepines was achieved via palladium-catalyzed carboetherification reactions, the scope of the reaction was limited. For the synthesis of 2,3-disubstituted benzoxepines, the yield of the reaction was high but stereocontrol was poor. Moreover, benzoxepines with other substitution patterns were not produced under the optimized reaction conditions; thus, novel catalyst systems must be developed in order to improve the diastereoselectivity of the reaction and to expand the substrate scope. Based on our previous results with benzopyrans[11] and pyrrolidines[12], phosphite and phosphoramidite ligands should be explored for the synthesis of benzoxepines via palladium-catalyzed carboetherification reactions.

6.6 Experimental

All reactions were carried out under a nitrogen atmosphere in oven or flame dried glassware. Tris(dibenzylideneacetone)dipalladium (0) and all phosphine ligands were purchased from Strem Chemical Co. and used without further purification. All aryl bromides were obtained from commercial sources (Aldrich Chemical Co. or Acros Chemical Co.) and were used as obtained. Toluene and THF were purified using a GlassContour solvent purification system. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by 1H NMR.

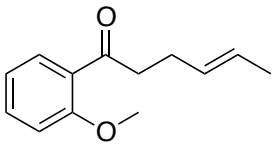
General Procedure 1: Alkylation of hydrazones.[13] An oven-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with the appropriate hydrazone (1 equiv) and THF (1 M). The resulting solution was cooled to 0 °C and a solution of n-BuLi (1 equiv, 1.6 M in hexanes) was added dropwise. The reaction mixture was stirred at 0 °C for 1 hr, then the alkyl halide (1 equiv) was added dropwise as a 1 M solution in THF, and the reaction mixture was warmed to rt. The mixture was stirred at rt until GC analysis indicated that the starting materials were fully consumed, then 1 M HCl was added (10 mL), and the reaction was stirred for 4 hr at rt. Brine (5 mL) and EtOAc (5 mL) were added, and the mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over anhydrous MgSO4, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel.

General Procedure 2: Reduction of Ketones[14] A round bottom flask equipped with a magnetic stirbar and a rubber septum was cooled under a stream of nitrogen and charged with the ketone substrate (1 equiv) and methanol (1 M). The reaction mixture was cooled to 0 ^{o}C and a 1 M solution of $NaBH_4$ in 1 M NaOH (1.0 equiv) was added dropwise. The resulting mixture was stirred at rt until the starting material had been completely consumed as judged by tlc analysis. A sat'd solution of NaCl (5 mL) and EtOAc (5 mL) were added. The

mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 20 mL), and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel.

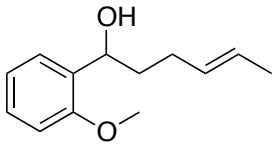
General Procedure 3: Removal of Alcohol Group[15] A round bottom flask equipped with a magnetic stirbar and a rubber septum was cooled under a stream of nitrogen and charged with the alcohol substrate (1 equiv) and dichloroethane (0.25 M). Next, ZnI_2 was added (1.5 equiv), followed by $NaBH_3CN$ (7.0 equiv). The resulting mixture was stirred at rt until the starting material had been completely consumed as judged by tlc analysis. The reaction mixture was filtered through celite, and a sat'd solution of NH_4Cl (5 mL) and EtOAc (5 mL) were added to the filtrate. The mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 20 mL), and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel.

General Procedure 4: Removal of Aryl(methyl)ether Protecting Group A flame-dried round-bottomed flask equipped with a magnetic stirbar, reflux condenser and a rubber septum was cooled under a stream of nitrogen and charged with NaH (4 equiv) and DMF (2 M). The reaction mixture was cooled to 0 ^oC and a 2 M solution of ethanethiol (2.6 equiv) in DMF was added dropwise. The resulting mixture was stirred at rt for 30 min, then the methyl ether substrate (1 equiv) was added and the reaction mixture was heated to 160 ^oC until the starting material had been completely consumed as judged by tlc analysis. The reaction mixture was then cooled to rt and 1 M HCl (5 mL) and EtOAc (5 mL) were added. The mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 20 mL), and the combined organic layers were dried over anhydrous MgSO4, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel.



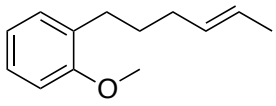
VI-9

(E)-1-(2-methoxyphenyl)hex-4-en-1-one (**VI-9**). General Procedure 1 was used for the conversion of (E)-2-(1-(2-methoxyphenyl)ethylidene)-1,1-dimethylhydrazine[16] (5.0 g, 26.0 mmol) to the title compound. This procedure afforded 3.0 g (56%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 1.7, 7.6 Hz, 1 H), 7.46–7.41 (m, 1 H), 7.01–6.93 (m, 2 H), 5.49–5.46 (m, 2 H), 3.89 (s, 3 H), 3.02 (t, *J* = 7.3 Hz, 2 H), 2.39–2.34 (m, 2 H), 1.66–1.63 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.3, 158.4, 133.3, 133.2, 130.2, 130.1, 125.4, 120.6, 111.5, 55.4, 43.6, 27.4, 17.9; IR (film, cm^{-1}) 2961, 1684; MS(ESI): 227.1045 (227.1043 calcd for $C_{13}H_{16}O_2$, M+Na^+).



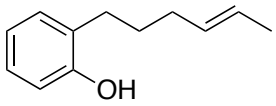
VI-10

(E)-1-(2-methoxyphenyl)hex-4-en-1-ol (**VI-10**). General Procedure 2 was used for the conversion of (E)-1-(2-methoxyphenyl)hex-4-en-1-one (2.68 g, 13.1 mmol) to the title compound. This procedure afforded 2.21 g (81%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.30 (m, 1 H), 7.28–7.23 (m, 1 H), 6.97 (dt, *J* = 1.0, 7.6 Hz, 1 H), 6.91–6.87 (m, 1 H), 5.50–5.47 (m, 2 H), 4.88 (t, *J* = 6.3 Hz, 1 H), 3.86 (s, 3 H), 2.74 (s, 1 H), 2.21–2.13 (m, 1 H), 2.11–2.03 (m, 1 H), 1.92–1.78 (m, 2 H), 1.69–1.66 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 132.5, 131.0, 128.2, 127.0, 125.1, 120.7, 110.5, 70.5, 55.2, 37.1, 29.1, 18.0; IR 3403, 2917, 1456 (film, cm^{-1}); MS(ESI): 229.1209 (229.1199 calcd for $C_{13}H_{18}O_2$, M+Na^+).



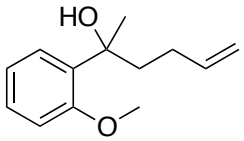
VI-11

(E)-1-(hex-4-en-1-yl)-2-methoxybenzene (**VI-11**). General Procedure 3 was used for the conversion of (E)-1-(2-methoxyphenyl)hex-4-en-1-ol (2.09 g, 10.1 mmol) to the title compound. This procedure afforded 0.91 g (47%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.20 (m, 2 H), 6.97 (t, *J* = 9.3 Hz, 1 H), 6.92 (d, *J* = 10.0 Hz, 1 H), 5.58–5.53 (m, 2 H), 3.89 (s, 3 H), 2.72 (t, *J* = 9.5 Hz, 2 H), 2.20–2.10 (m, 2 H), 1.79–1.73 (m, 4 H), 1.45–1.36 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 131.5, 131.1, 129.9, 126.9, 124.8, 120.4, 110.2, 55.2, 32.6, 29.8, 29.7, 18.0; IR 2920, 1652, 1456 (film, cm^{-1}); MS(EI): 191.1357 (191.1358 calcd for $C_{13}H_{18}O_2$, M^+).



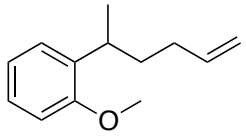
VI-12

(E)-2-(hex-4-en-1-yl)phenol (**VI-12**). General Procedure 3 was used for the conversion of (E)-1-(hex-4-en-1-yl)-2-methoxybenzene (0.91 g, 4.7 mmol) to the title compound. This procedure afforded 0.69 g (82%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12–7.03 (m, 2 H), 6.85 (dt, *J* = 1.0, 7.4 Hz, 1 H), 6.74 (d, *J* = 7.8 Hz, 1 H), 5.47–5.43 (m, 2 H), 4.63 (s, 1 H), 2.58 (t, *J* = 7.4 Hz, 3 H), 2.07–2.00 (m, 2 H), 1.70–1.62 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 131.5, 129.9, 126.9, 124.9, 120.4, 110.2, 55.2, 32.6, 29.9, 29.8, 18.0; IR (film, cm^{-1}) 3405, 1652, 1456; MS(EI): 176.1202 (176.1201 calcd for $C_{12}H_{16}O$, M^+).



VI-14

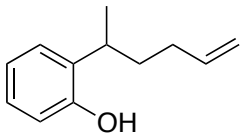
2-(2-methoxyphenyl)hex-5-en-2-ol (**VI-14**). To a suspension of Mg (1.48 g) in ether (50 mL) at 0 ^{o}C, 4-bromobut-1-ene (5.0 mL) was added. The reaction mixture was raised to RT and stirred for 30 min. Upon completion, the solution was transferred to a round bottom flask charged with a stir bar and a septum and was cooled to 0 ^{o}C. A solution of 1-(2-methoxyphenyl)ethanone (6.19 g) in ether (50 mL) was added dropwise and the reaction mixture was raised to RT and stirred until the starting material was consumed, as judged by TLC analysis. A 1 M solution of HCl (10 mL) and EtOAc (10 mL) were added. The mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 20 mL), and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel. This procedure afforded 5.82 g (74%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 2.1, 9.5 Hz, 1 H), 7.25–7.19 (m, 1 H), 7.00–6.88 (m, 2 H), 5.84–5.73 (m, 1 H), 4.98–4.82 (m, 2 H), 3.88 (s, 3 H), 2.59 (s, 3 H), 2.10–1.88 (m, 4 H), 1.57 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 139.1, 133.6, 128.1, 126.7, 120.9, 114.0, 111.3, 75.0, 55.4, 55.3, 41.2, 31.8, 28.9, 27.4; IR (film, cm^{-1}); 3519, 2841, 1672. MS(EI): 206.1305 (206.1307 calcd for $C_{13}H_{18}O_2$, M^+).



VI-15

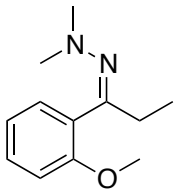
1-(hex-5-en-2-yl)-2-methoxybenzene (**VI-15**). General Procedure 3 was used for the conversion of 2-(2-methoxyphenyl)hex-5-en-2-ol (2.0 g, 30.2 mmol) to the title compound. This procedure afforded 0.88 g (48%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.29-7.22 (m, 2 H), 7.04-6.97 (m, 1 H), 6.95-6.91 (m, 1 H), 5.96-5.86 (m, 1 H), 5.10-4.99 (m, 2 H), 3.89 (s, 3 H), 3.37-3.29 (m, 1 H), 2.18-2.02 (m, 2 H), 1.87-1.78 (m, 1 H), 1.76-1.66 (m, 1 H), 1.31 (d, J = 7.0 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) 157.1, 139.2, 128.9, 126.8, 120.6,

120.5, 114.1, 110.5, 55.3, 36.4, 32.0, 31.6, 22.0, 20.9.IR (film, cm^{-1}) 2959, 1492; MS(EI): 190.2864 (190.1353 calcd for $C_{13}H_{18}O$, M^+).



VI-16

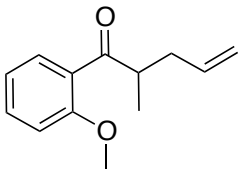
2-(hex-5-en-2-yl)phenol (**VI-16**). General Procedure 4 was used for the conversion of 1-(hex-5-en-2-yl)-2-methoxybenzene (0.77 g, 4.1 mmol) to the title compound. This procedure afforded 0.62 g (87%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (dd, *J* = 6.1, 7.8 Hz, 1 H), 7.15–7.10 (m, 1 H), 6.98 (dt, *J* = 1.0, 7.3 Hz, 1 H), 6.80 (dd, *J* = 1.2, 8.0 Hz, 1 H), 5.94–5.84 (m, 1 H), 5.13 (s, 1 H), 5.10–4.99 (m, 2 H), 3.17 (sextet, *J* = 7.1 Hz, 1 H), 2.13–2.03 (m, 2 H), 1.87–1.79 (m, 1 H), 1.77–1.69 (m, 1 H), 1.32 (d, *J* = 6.8 Hz, 3 H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 139.1, 133.2, 127.2, 126.7, 121.0, 115.5, 114.5, 36.3, 31.8, 31.7, 20.9. IR (film, cm^{-1}) 3423, 2919, 1456; MS(EI): 176.1195 (176.1201 calcd for $C_{12}H_{16}O$, M^+).



VI-19

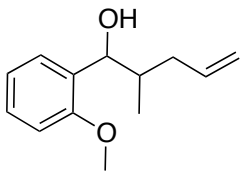
2-(1-(2-methoxyphenyl)propylidene)-1,1-dimethylhydrazine (**VI-19**). To a round bottom flask equipped with a magnetic stirbar, Dean-Stark trap, reflux condenser and a rubber septum, 1-(2-methoxyphenyl)propan-1-one (2.86 g, 17.4 mmol, 1 equiv),[17] trifluoroacetic acid (0.1 mL, 0.87 mmol, 0.05 equiv), 1,1-dimethylhydrazine (1.25 mL, 20.8 mmol, 1.2 equiv) and benzene (24.8 mL) was added. The reaction was heated to reflux until the starting material had been completely consumed as judged by tlc analysis. Upon completion, the reaction mixture was concentrated in vacuo and used without further purification. This

procedure afforded 3.59 g (88%) of the title compound as a 1:1 mixture of E:Z isomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.27 (m, 2 H), 7.23 (dd, *J* = 1.8, 7.4 Hz, 1 H), 7.05 (dd, *J* = 1.7, 7.4 Hz, 1 H), 7.00–6.91 (m, 3 H), 6.87 (d, *J* =8.2 Hz, 1 H), 3.82 (s, 3 H), 3.80 (s, 3 H), 2.90–2.81 (m, 2 H), 2.60 (s, 6 H), 2.51 (q, *J* = 7.6 Hz, 2 H), 2.43 (s, 6 H), 1.01 (t, *J* = 7.4 Hz, 3 H), 0.90 (t, *J* = 7.4 Hz, 3 H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 154.4, 152.6, 127.5, 127.4, 127.1, 126.7, 125.4, 125.3, 118.1, 117.9, 117.8, 108.2, 108.1, 52.8, 52.7, 45.0, 44.4, 29.0, 21.5, 8.6, 8.5. IR (film, cm^{-1}) 2954, 1678, 1496; MS(EI): 207.1492 (207.1492 calcd for $C_{12}H_{18}N_2O$, M^+).



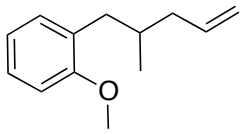
VI-20

1-(2-methoxyphenyl)-2-methylpent-4-en-1-one (**VI-20**). General Procedure 1 was used for the conversion of 2-(1-(2-methoxyphenyl)propylidene)-1,1-dimethylhydrazine (2.0 g, 12.2 mmol) to the title compound. This procedure afforded 0.79 g (40%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 5.9, 7.6 Hz, 1 H), 7.46–7.41 (m, 1 H), 7.02–6.89 (m, 2 H), 5.82–5.71 (m, 1 H), 5.06–4.96 (m, 2 H), 3.88 (s, 3 H), 2.56–2.48 (m, 1 H), 2.16–2.07 (m, 1 H), 2.05–1.94 (m, 1 H), 1.11 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.9, 157.8, 136.4, 132.8, 130.2, 120.7, 116.3, 111.3, 55.5, 55.4, 45.0, 37.5, 16.0. IR (film, cm^{-1}) 2916, 1676, 1459; MS(EI): 204.1149 (204.1150 calcd for $C_{13}H_{16}O_2$, M^+).



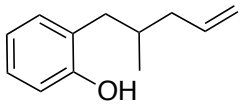
VI-21

1-(2-methoxyphenyl)-2-methylpent-4-en-1-ol (**VI-21**). General Procedure 2 was used for the conversion of 1-(2-methoxyphenyl)-2-methylpent-4-en-1-one (0.7 g, 3.5 mmol) to the title compound. This procedure afforded 0.37 g (52%) of the title compound as a 1:1 mixture of diastereomers (data are for both compounds). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 1.5, 7.4 Hz, 1 H), 7.27–7.23 (m, 2 H), 7.23–7.21 (m, 1 H), 6.98–6.92 (m, 2 H), 6.90–6.85 (m, 2 H), 5.90–5.73 (m, 2 H), 5.10–4.97 (m, 4 H), 4.75 (t, *J* = 6.0 Hz, 1 H), 4.56 (t, *J* = 7.4 Hz, 1 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 2.65 (d, *J* = 7.2 Hz, 1 H), 2.57–2.50 (m, 1 H), 2.43 (d, *J* = 6.4 Hz, 1 H), 2.17–2.09 (m, 1 H), 2.04–1.96 (m, 3 H), 1.95–1.86 (m, 1 H), 0.94 (d, *J* = 6.6 Hz, 3 H), 0.73 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 156.4, 137.6, 137.5, 131.5, 131.2, 128.4, 128.2, 128.1, 120.6, 120.5, 115.9, 115.8, 110.6, 110.4, 75.9, 55.2, 38.9, 38.5, 38.3, 37.9, 31.6, 22.7, 16.1, 14.4, 14.1. IR (film, cm^{-1}) 3437, 1490; MS(EI): 206.1308 (206.1307 calcd for $C_{13}H_{18}O_2$, M^+).



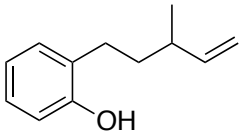
VI-22

1-methoxy-2-(2-methylpent-4-en-1-yl)benzene (**VI-22**). General Procedure 3 was used for the conversion of 1-(2-methoxyphenyl)-2-methylpent-4-en-1-ol (0.35 g, 1.7 mmol) to the title compound. This procedure afforded 0.05 g (15%) of the title compound as an amber oil. ^{1}H NMR (400 MHz, CDCl3) δ 7.18 (t, *J* = 7.4 Hz, 1 H), 7.09 (d, *J* = 7.0 Hz, 1 H), 6.91–6.82 (m, 2 H), 5.90–5.76 (m, 1 H), 5.06–4.96 (m, 2 H), 3.80 (s, 3 H), 2.66 (dd, *J* = 5.9, 13.2 Hz, 1 H), 2.40 (dd, *J* = 7.8, 13.2 Hz, 1 H), 2.17–2.08 (m, 1 H), 1.98–1.83 (m, 2 H), 0.85 (d, *J* = 6.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 137.7, 130.9, 129.8, 126.9, 120.1, 115.5, 110.2, 55.2, 41.2, 37.3, 33.3, 19.3. IR (film, cm^{-1}) 2965, 1490; MS(EI): 190.1360 (190.1358 calcd for $C_{13}H_{18}O$, M^+).



VI-23

2-(2-methylpent-4-en-1-yl)phenol (**VI-23**). General Procedure 4 was used for the conversion of 1-methoxy-2-(2-methylpent-4-en-1-yl)benzene (0.04 g, 0.2 mmol) to the title compound. This procedure afforded 0.02 g (54%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11–7.04 (m, 2 H), 6.87–6.82 (m, 1 H), 6.76–6.71 (m, 1 H), 5.88–5.76 (m, 1 H), 5.07–4.99 (m, 2 H), 4.58 (s, 1 H), 2.64 (dd, *J* = 5.9, 13.7 Hz, 1 H), 2.40–2.33 (m, 1 H), 2.17–2.07 (m, 1 H), 1.99–1.81 (m, 2 H), 0.88 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 137.4, 131.3, 127.2, 120.6, 116.1, 115.3, 41.1, 36.9, 33.5, 19.4, one peak missing due to incidental equivalence. IR (film, cm^{-1}) 3400, 2917, 1616; MS(EI): 176.1200 (176.1201 calcd for $C_{12}H_{16}O$, M^+).

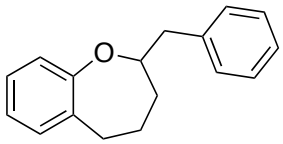


VI-26

2-(3-methylpent-4-en-1-yl)phenol (**VI-26**). General Procedure 3 and 4 was used for the conversion of 1-methoxy-2-(3-methylpent-4-en-1-yl)benzene (1.98 g, 9.5 mmol) to the title compound. This procedure afforded 0.24 g (28%) of the title compound as a orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11–7.04 (m, 2 H), 6.87–6.82 (m, 1 H), 6.76–6.71 (m, 1 H), 5.88–5.76 (m, 1 H), 5.07–4.99 (m, 2 H), 4.58 (s, 1 H), 2.64 (dd, *J* = 5.9, 13.7 Hz, 1 H), 2.40–2.33 (m, 1 H), 2.17–2.07 (m, 1 H), 1.99–1.81 (m, 2 H), 0.88 (d, *J* = 6.4 Hz, 3 H; ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 137.4, 131.3, 127.2, 120.6, 116.1, 115.3, 41.1, 36.9, 33.5, 19.4, one peak missing due to incidental equivalence. IR (film, cm^{-1}) 3423, 2919, 1456; MS(EI): 176.1200 (176.1201 calcd for $C_{12}H_{16}O$, M^+).

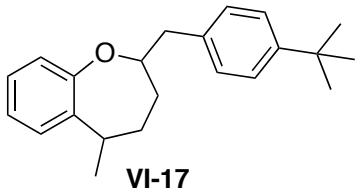
Synthesis of Benzoxepines via Pd-Catalyzed Alkene Carboetherification

General Procedure 5: Palladium-Catalyzed Carboetherification Reactions. An oven or flame-dried Schlenk tube was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (2 mol% complex, 4 mol % Pd), Ru-Phos (4 mol %), NaO*t*Bu (2.0 equiv), and the aryl bromide (2.0 equiv). The tube was purged with nitrogen and the alcohol substrate (1.0 equiv), and toluene (0.25 M substrate concentration) were added. The mixture was heated to 110 °C with stirring until the starting material had been consumed as judged by GC or 1H NMR analysis. The mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl (2 mL), and diluted with ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.



VI-4

2-benzyl-2,3,4,5-tetrahydrobenzo[b]oxepine (**VI-4**). The coupling of 2-(pent-4-en-1-yl)phenol (20 mg, 0.12 mmol) with bromobenzene (30 µL, 0.24 mmol) was conducted following General Procedure 5. This procedure afforded 20 mg (70%) of the title compound as an amber oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.29 (m, 4 H), 7.28–7.23 (m, 1 H), 7.11–7.08 (m, 1 H), 7.03 (dt, *J* =1.9, 7.6 Hz, 1 H), 6.94 (dt, *J* = 5.9, 6.1 Hz, 1 H), 6.61 (dd, *J* = 1.2, 7.8 Hz, 1 H), 3.82–3.76 (m, 1 H), 3.08 (dd, *J* = 8.3, 13.7 Hz, 1 H), 2.93 (t, *J* = 13.1 Hz, 1 H), 2.86 (dd, *J* = 5.1, 13.9 Hz, 1 H), 2.74–2.68 (m, 1 H), 2.05–1.98 (m, 2 H), 1.92–1.81 (m, 1 H), 1.54–1.45 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 139.1, 136.0, 130.0, 129.5, 128.2, 127.2, 126.2, 123.4, 121.3, 84.3, 43.6, 37.1, 33.7, 26.0.; MS(EI): 238.1361 (238.1358 calcd for $C_{17}H_{18}O$, M^+).



VI-17

2-(4-(tert-butyl)benzyl)-5-methyl-2,3,4,5-tetrahydrobenzo[b]oxepine (**VI-17**). The coupling of 2-(hex-5-en-2-yl)phenol (20 mg, 0.12 mmol) with 4-bromo-*tert*-butylbenzene (34 µL, 0.24 mmol) was conducted following General Procedure 5. This procedure afforded 25 mg (72%) of the title compound as a 1:1 mixture of diastereomers (data are for both isomers). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.31 (m, 2 H), 7.22-7.18 (m, 2 H), 7.17-7.12 (m, 1 H), 7.04-6.98 (m, 2 H), 6.67-6.61 (m, 1 H), 3.83-3.69 (m, 1 H), 3.16-2.99 (m, 2 H), 2.83-2.76 (m, 1 H), 1.96-1.72 (m, 2 H), 1.33-1.32 (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 135.8, 129.1, 127.2, 126.9, 126.8, 126.0, 125.0, 123.6, 122.2, 121.5, 84.5, 83.7, 78.3, 77.3, 76.7, 76.6, 43.1, 42.8, 38.7, 35.9, 34.7, 34.4, 33.9, 31.9, 31.6, 31.4, 31.2, 20.3, 18.7, 2 peaks missing due to incidental equivalence; IR (film, cm^{-1}) 2961, 1485; MS(EI): 308.2103 (308.2140 calcd for $C_{22}H_{18}O$, M^+).

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