# NEW DEVELOPMENTS IN PLATINUM-CATALYZED CYCLIZATION AND FLUORINATION OF POLYENES

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## ABSTRACT

NIKKI A COCHRANE: New Developments in Platinum-Catalyzed Cyclization and Fluorination of Polyenes
(Under the direction of Dr. Michel R. Gagné)

This dissertation encompasses two major components, both focused around the platinum(II) catalyzed cyclization of polyenes into polycyclic compounds. Previous studies have determined that in the Wacker-type platinum(II) catalyzed net dehydrogenative cyclization reactions, [Pt]-H is stable towards elimination, making typical 2-electron oxidants ineffective in these systems. As a result, $Ph_3C^+$ was used to abstract hydride from the [Pt]-H resulting in triphenylmethane and turning over the catalytic cycle. There are many inherent problems using $Ph_3C^+$, in particular, the steric bulk and cumbersome workup. For this reason, this dissertation focuses on exploring alternative turnover mechanisms for these platinum(II) cascade cyclization reactions of polyenes.

The first project focuses on the development of a system with a hydride abstractor that is more atom economical than $Ph_3C^+$ and can provide facile workup procedures. We found that dimethoxymethane, although slower, performed as well as $Ph_3COMe$. In addition, dimethoxymethane suppressed the formation of byproducts and was easily removed during product isolation.

Also described in this thesis is the development of a platinum(II) catalyzed enantioselective cyclization/fluorination reaction for formation of C-F bonds in polycyclic compounds. After extensive optimization, it was discovered that a bidentate phosphine

ligand, (*S*)-(xylyl-phanephos), can generate the desired bicyclic product in approximately 70% yield with enantioselectivities as high as 87%.

We propose that the platinum(II) catalyzed cyclization/fluorination proceeds through electrophilic fluorine addition to a $[Pt]^{II}$-alkyl complex resulting in a putative $[Pt]^{IV}$-F species. As this platinum (IV) species has never been observed in our catalytic system, we sought to develop a model $[Pt]^{IV}$-F complex to investigate its viability as a catalytic intermediate. Initial studies have indicated the formation of a [Pt]-F species, but its identity has not yet been determined.

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# LIST OF ABBREVIATIONS AND SYMBOLS

| | |
|---|---|
| ° | degrees |
| Å | angstroms |
| **a** | Pd(alkene)-$OH_2$ complex |
| atm | atmospheres |
| **b** | $P_2$Pt-alkene complex |
| β | beta |
| BINAP | 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl |
| BIPHEP | 2,2'-bis(diphenylphosphino)-1,1'-biphenyl |
| BLA | Brønsted Lewis Acid |
| Bn | benzyl |
| BQ | benzoquinone |
| br | broad |
| BrettPhos | 2’,4’,6’- triisopropyl-3,6-dimethoxy-1,1’-biphenyl |
| **c** | $P_2$Pt(alkyl)(nitrile) complex |
| °C | degrees Celsius |
| $CD_2Cl_2$ | deuterated methylene chloride |
| $CDCl_3$ | deuterated chloroform |
| $CD_3CN$ | deuterated acetonitrile |
| $CD_3NO_2$ | deuterated nitromethane |
| COD | 1,5-cyclooctadiene |
| d | doublet |
| **d** | [M]-benzyl methyl ether complex |
| δ | chemical shift |

| | |
|---|---|
| dcpe | 1,2-bis(dicyclohexylphosphino)ethane |
| dmpe | 1,2-Bis(dimethylphosphino)ethane |
| DMSO | dimethylsulfoxide |
| dppe | 1,2-bis(diphenylphosphino)ethane |
| **e** | $P_2Pt$-π-allyl complex |
| ee | enantiomeric excess |
| Et | ethyl |
| EtOAc | ethyl acetate |
| Eq. | equation |
| equiv | equivalents |
| **f** | $P_2Pt$-H complex |
| **g** | $P_2Pt^{IV}$-F alkyl nitrile complex |
| GC | gas chromatography |
| GC-MS | gas chromatography mass spectrometry |
| h | hours |
| HOTf | triflic acid |
| HRMS | high resolution mass spectrometry |
| Hz | hertz |
| (I) | monovalent |
| (II) | divalent |
| *J* | three bond H-H coupling |
| $J_{F\text{-}H}$ | two bond F-H coupling |
| $J_{Pt\text{-}P}$ | one bond Pt-P coupling |
| $J_{Pt\text{-}H}$ | one bond Pt-H coupling |
| $J_{P\text{-}P}$ | two bond P-P coupling |

| | |
|---|---|
| K | Kelvin |
| kcal | kilocalorie |
| m | multiplet |
| M | Molarity |
| [M] | metal complex |
| M(0) | zerovalent metal complex |
| M(I) | monovalent metal complex |
| M(II) | divalent metal complex |
| Me | methyl |
| MeO-BIPHEP | 2,2’-bis(diphenylphosphino)-6,6’-dimethoxy-1,1’-biphenyl |
| mg | milligram |
| MHz | megahertz |
| mL | milliliter |
| min | minutes |
| µL | microliter |
| mmol | millimole |
| µmol | micromole |
| mol | mole |
| mol % | molar percentage |
| MS | mass spectrometry |
| *m/z* | mass-to-charge ratio |
| NFSI | N-fluorobenzenesulfonimide |
| NHTf | triflamide |
| NIS | *N*-iodosuccinimide |

| | |
|---|---|
| NMR | nuclear magnetic resonance |
| OMe | methoxy |
| OEt | ethoxy |
| OR | alkoxy |
| OTf | triflate |
| $P_2$ | bidentate phosphine ligand |
| Pa | Pascal |
| Ph | phenyl |
| $Ph_2NH$ | diphenylamine |
| $[Ph_2NH_2][BF_4]$ | diphenylammonium tetrafluoroborate |
| Phanephos | 4,12-bis(diphenylphosphino)-[2.2]-paracyclophane |
| ppm | parts per million |
| PPP | bis(2-diphenylphosphinoethyl)phenylphosphine |
| psi | pounds per square inch |
| Pt | platinum |
| PTFE | polytetrafluoroethylene |
| R | alkyl |
| *rac* | racemic |
| RT | room temperature |
| s | singlet |
| SEGPHOS | 5,5’-bis(diphenylphosphino)-4,4’-1,3-benzodioxole |
| t | triplet |
| THF | tetrahydrofuran |
| triphos | bis(2-diphenylphosphinoethyl)phenylphosphine |

| | |
|---|---|
| *t*-Bu | tertiary butyl |
| TMS | trimethylsilyl |
| Ts | (4-methylphenyl)sulfonamide |
| vs | versus |
| xylyl | 3,5-dimethylphenyl |

# Chapter 1

# Cascade Cyclizations: Natural and Synthetic

## 1.1. Introduction to cascade cyclization

### 1.1.1 Enzymatic cascades

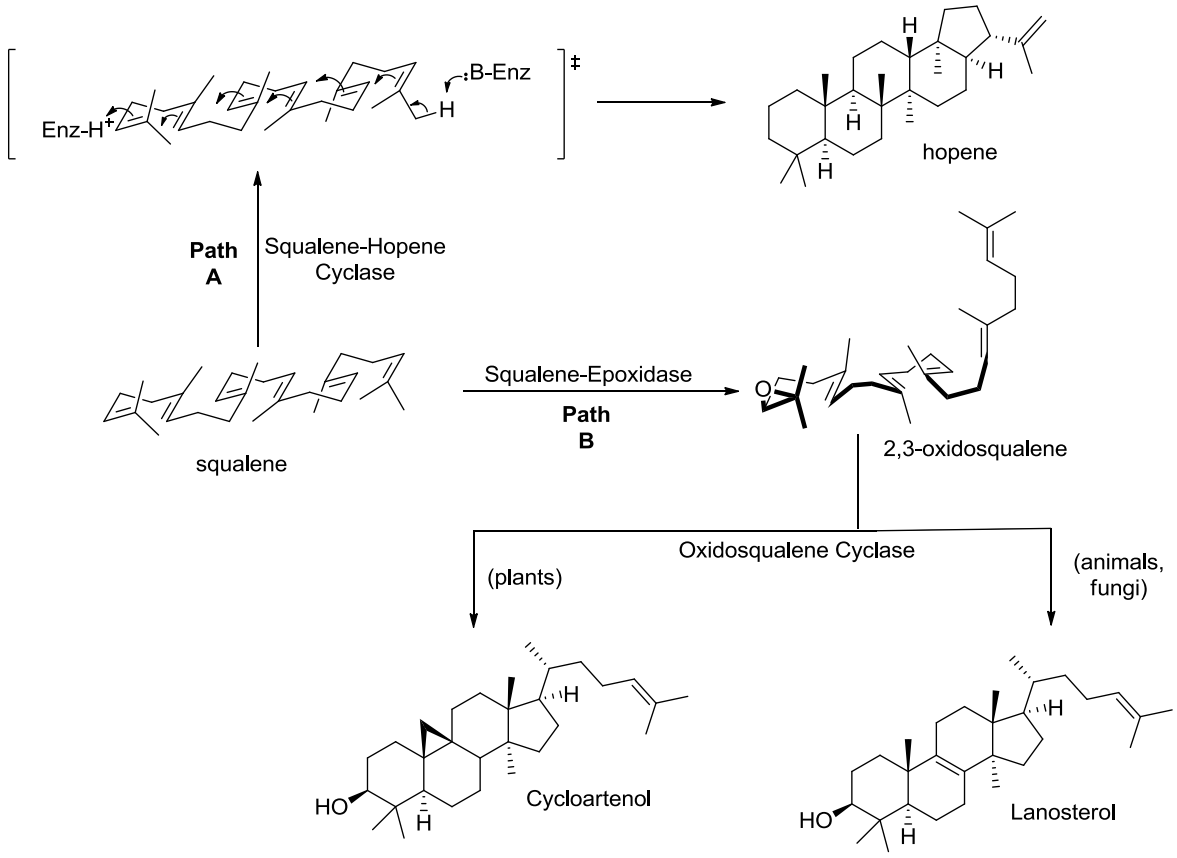
Nature has perfected one of the most impressive biochemical phenomena, the enzyme-controlled selective cyclization of poly-alkenes into terpenes, which are themselves common starting materials for multiple natural products.[1] Terpenes have isoprenoid skeletons, and although they are not derived from isoprene itself, generally cyclize to form polycyclic compounds which are the basis of many natural products.[1] These enzyme-catalyzed polyene cyclization reactions form carbon-carbon bonds, and in the sterol biosynthesis manifold, produce tetra- and penta-cyclic products with multiple stereocenters from achiral polyolefin substrates. The selectivity, specificity and efficiency with which these terpenes are cyclized by enzymes has enthused scientists for decades.

The cyclase enzyme class, in particular, has been shown to selectively generate stereospecific polycyclic compounds in bacteria, plants and animals through the use of enzymes that are tuned for specific transformations from a common polyene.[1] As an example, the bacterial enzyme squalene-hopene cyclase efficiently cyclizes the polyene

[1](a) Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730. (b) Wendt, K. U. *Angew. Chem. Int. Ed.* **2005**, *44*, 3966. (c) Wendt, K. U.; Schulz, G. E.; Corey, E. J.; Liu, D. R. *Angew. Chem. Int. Ed.* **2000**, *39*, 2812. (d) Abe, I.; Rohmer, M.; Prestwich, G. D. *Chem. Rev.* **1993**, *93*, 2189.

squalene into the plant steroid hopene, a pentacyclic compound containing nine stereocenters (Scheme 1-1).[1] The mechanisms for this and all other terpene cyclase enzymatic transformations are thought to be based on the cation-olefin reaction, wherein a transiently formed carbocation reacts with an olefin to form a ring and regenerate the cation.

**Scheme 1-1.** Selective Enzyme Catalyzed Cyclization.




In **Path A** in Scheme 1-1, squalene-hopene cyclase forms a pocket around squalene, and in so doing, pre-organizes it for cyclization. The cyclase then initiates cyclization through proton transfer to the 2,3-alkene followed by stabilization of the putative carbocations generated during cyclization (shown as the transition state in Scheme 1-1). It is important to note that these cyclizations are thought to go through a concerted mechanism

because discrete carbocationic intermediates are never observed. Termination then results from deprotonation forming the unsaturated hopene product.[2]

If instead, catalytic squalene epoxidase is present, squalene is enantioselectively epoxidized using molecular oxygen to afford 2,3-oxidosqualene (**Path B**, Scheme 1-1).[1] A large family of oxidosqualene cyclases convert 2,3-oxidosqualene into multiple unique natural products. As shown in Scheme 1-1, two possible natural products, cycloartenol or lanosterol (a cholesterol precursor), can be generated using two specific oxidosqualene cyclases either in plants or animals and fungi.

It has often been stated that the high stereochemical control of the cyclized products is due to the preorganization of the polyolefin substrate that is achieved by the pocket within the enzyme active site. In the formation of hopene, squalene is organized in a chair-chair-chair conformation by the squalene-hopene cyclase, resulting in cyclohexane C-ring formation. In contrast, oxidosqualene epoxidase, which is the dominant enzyme in animals and fungi, arranges 2,3-oxidosqualene into a chair-boat-chair conformation, which is then in the proper conformation for multiple 1,2-methyl and hydride shifts to form natural products with the specific stereochemistry and carbon skeleton observed in lanosterol.[1a,2] These conformations are shown in Scheme 1-1. Since cyclase enzymes are specific for a single class of polyene substrates and they typically form a single product, alternative methods to reproduce the outstanding stereo-and regioselectivity have been sought for decades.

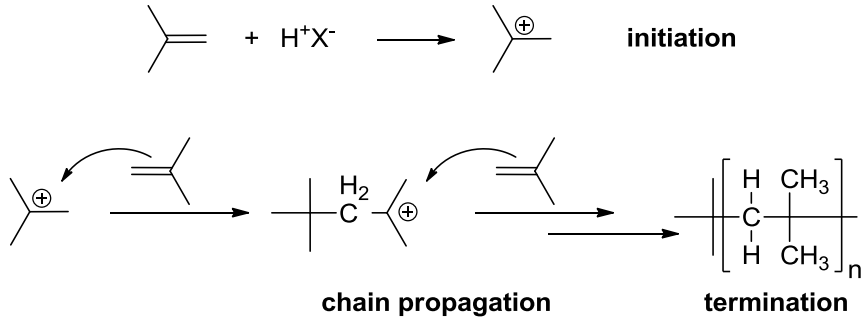
### 1.1.2. Cation-olefin cascade cyclization

To this end, cation-olefin reactions have been developed and biomimetic reactions utilized to access a broad class of natural products and natural product-like compounds. A

[2]Hoshino, T. Sato, T. *Chem. Commun.* **2002**, 291.

simple cation-olefin intermolecular reaction is the cationic polymerization of isobutylene (Scheme 1-2).[3] Initiation of the isobutylene monomer by a Brønsted acid/base pair ($H^+X^-$) generates a carbocation, which upon reaction with another monomer results in chain propagation and growth. This cation-olefin polymerization is terminated by deprotonation/elimination.

**Scheme 1-2**. The cationic polymerization of isobutylene to polyisobutylene.



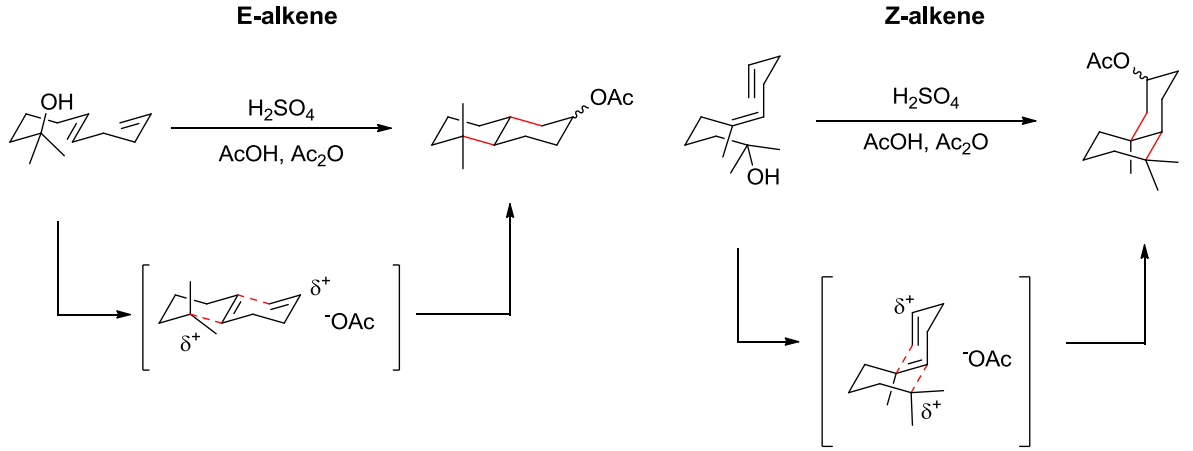

The reaction involved in C-C bond formation in isobutylene polymerization (the cation-olefin reaction) is also responsible for the C-C bond formation in terpene cyclase reactions, where the process occurs intramolecularly to build rings. That is, 1,5-dienes undergo intramolecular cation-olefin cyclization to generate bicyclic decalin products.[1a] The formation of these cyclized products are favored because of the exothermicity associated with the conversion of C=C to C-C during ring formation ($\Delta E$ = -20 kcal/mol, thermodynamics) and also the low activation barrier (< 3 kcal/mol) for the formation of a six membered ring (kinetics). For the latter feature intramolecular carbocation addition to a

[3]Lisovskii, A.; Nelkenbaum, E.; Volkis, V.; Semiat, R.; Eisen, M. S. *Inorganica Chimica Acta* **2002**, *334*, 243.

carbon-carbon double bond, is entropically favorable and is the dominant C-C bond forming process in terpene biosynthesis.[1b,4]

Stork and Eschenmoser studied similar systems to determine the basis for the diastereoselectivity in cyclic systems that are not under enzyme control.[5] To this end they developed the Stork-Eschenmoser postulate, which states that the stereochemistry at the ring junction is dictated by the geometry of the alkenes in the starting polyolefins (Figure 1-1). They found that polyolefins containing *E*-olefins form trans ring junctions, while those with *Z*-olefins form cis ring junctions. In addition, Eschenmoser and Schinz provided evidence for anti-addition of a carbenium ion to an olefin, that is, the two additions to the original alkene occur on opposite faces.[5c] Studies of this system also demonstrated that these bi-cyclizations were concerted with putative carbocation formation.

**Figure 1-1.** Stork-Eschenmoser Postulate.

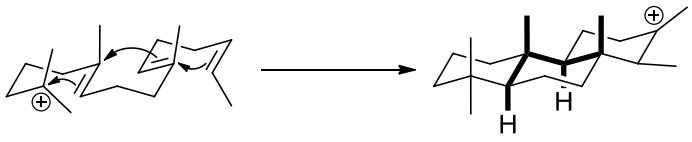



[4]Jensen, C.; Jorgenson, W. L. *J. Am. Chem. Soc.* **1997**, *119*, 10846.

[5](a) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068. (b) Eschenmoser, A.; Arigoni, D. *Helv. Chim. Acta* **2005**, *88*, 3011. (c) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890.

Similarly, terpenes adhere to the Stork-Eschenmoser postulate and generate a trans-anti-trans relative stereochemistry as evidence of the formation of six membered rings from a chair-like transition state (Figure 1-2).[5] An analysis of natural terpenes indicate that most polyenes adopt orientations that lead to trans-anti-trans product structures, suggesting their formation is concerted and that stereochemical information encoded into the polyene is expressed in the products. If the cyclizations were step-wise with discrete carbocations, then multiple ring stereochemistries might be expected.

**Figure 1-2.** Polyene cyclization**.**

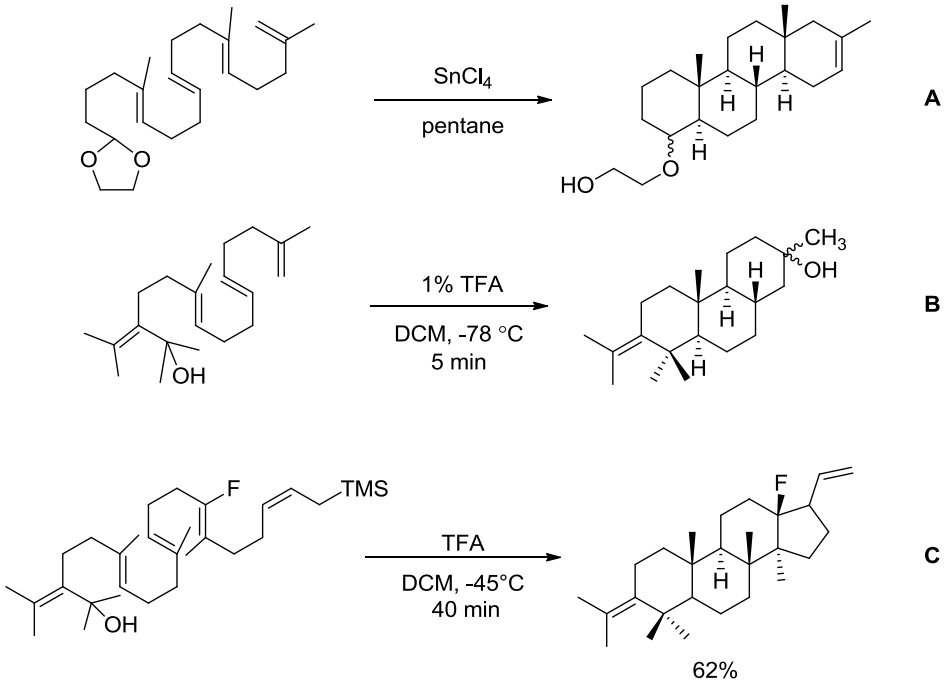



**chair-chair-chair transition state** **trans-anti-trans ring junctions**

### 1.1.2. Previous work in cation-olefin cascade cyclization

Due to its challenging nature and biological importance, enzyme chemistry has motivated chemists to develop biomimetic variants displaying similar selectivity and efficiency. Some of the first major attempts to mimic enzyme reactivity in cyclization reactions encompassed Johnson's work in developing initiators (acetals), terminators (alkynes and allyl silanes), and cation stabilizing groups (fluorine) to facilitate such non-enzymatic cyclization reactions.

**Scheme 1-3**. Biomimetic reactions by W.S. Johnson.



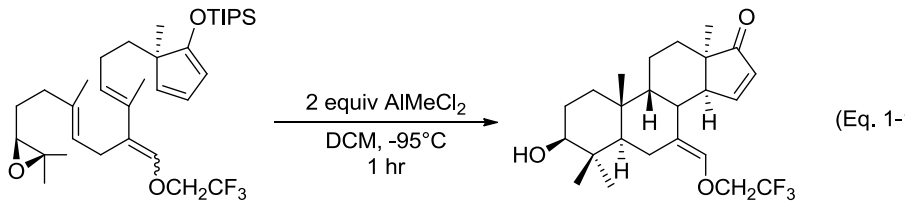

Upon investigating initiators, Johnson reported that acetals activated with tin tetrachloride, introduced functionality on the A ring, which extended the synthetic utility of these cyclization reactions (A, **Scheme 1-3**).[6] Johnson additionally found that allyl alcohols were effective initiators for the biomimetic tricyclization under mild reaction conditions (trifluoroacetic acid in methylene chloride, B, **Scheme 1-3**).[7] Johnson also reported the first non-enzymatic biomimetic cyclization of a pentacyclic compound using fluorine on the polyolefin backbone as a carbocation stabilizing moiety (C, **Scheme 1-3**). This fluorine was

[6](a) Fish, P. V.; Johnson, W. S. *J. Org. Chem.* **1994**, *59*, 2324. (b) Bartlett, W. R.; Johnson, W. S.; Plummer, M. S.; Small, V. R. *J. Org. Chem.* **1990**, *55*, 2215. (c) Guay, D.; Johnson, W. S.; Schubert, U. *J. Org. Chem.* **1989**, *54*, 4731. (d) Schmid, R.; Huesmann, P. L.; Johnson, W. S. *J. Am. Chem. Soc.* **1980**, *102*, 5122. (e) Johnson, W. S.; Wiedhaup, K.; Brady, S. F.; Olson, G. L. *J. Am. Chem. Soc.* **1974**, *96*, 3979. (f) Bartlett, P. A.; Johnson, W. S. *J. Am. Chem. Soc.* **1973**, *95*, 7501. (g) Johnson, W. S.; Li, T.-T.; Harbert, C. A.; Bartlett, W. R.; Herrin, T. R.; Staskun, B.; Rich, D. H. *J. Am. Chem. Soc.* **1970**, *92*, 4461. (h) Johnson, W. S.; Semmelhack, M. F.; Sultanbawa, M. U. S.; Dolak, L. A. *J. Am. Chem. Soc.* **1968**, *90*, 2994. (i) Johnson, W. S.; Jensen, N. P.; Hooz, J.; Leopold, E. J. *J. Am. Chem. Soc.* **1968**, *90*, 5872. (j) Johnson, W. S.; Wiedhaup, K.; Brady, S. F.; Olson, G. L. *J. Am. Chem. Soc.* **1968**, *90*, 5277. (k) Johnson, W. S.; van der Gen, A.; Swoboda, J. J. *J. Am. Chem. Soc.* **1967**, *89*, 170.

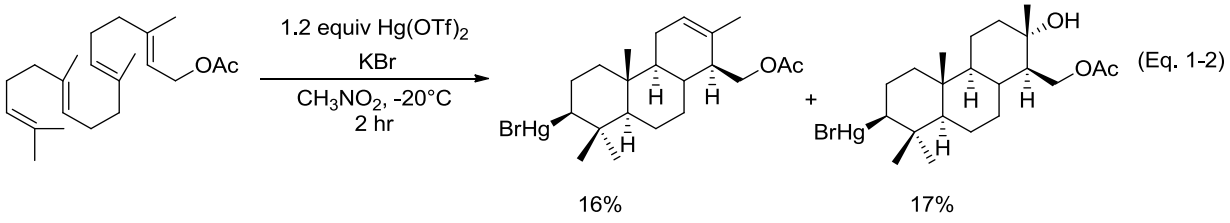
[7]Johnson, W. S.; Bartlett, W. R.; Czeskis, B. A.; Gautier, A.; Lee, C. H.; Lemoine, R. M.; Leopold, E. J.; Luedtke, G. R.; Bancroft, K. J. *J. Org. Chem.* **1999**, *64*, 9587.

found to help control the regioselectivity of C-ring formation to afford a cyclohexyl ring rather than a cyclopentyl ring, expected from carbocation stability considerations.

In extending this work, in 1996, Corey used Lewis acidic aluminum-based complexes to open the epoxide ring through oxygen activation and initiate the diastereoselective tricyclization (Eq. 1-1).[8] As an alternative to Lewis acids, Nishizawa found that mercuric salts were also effective for the initiation of cascade cyclization reactions. He showed that a stoichiometric amount of mercury(II) triflate aided in the cyclization of farnesyl acetate resulting in an organometallic mercury complex. He noted, however that the selectivity between the products was poor (Eq. 1-2).[9]




(Eq. 1-1)



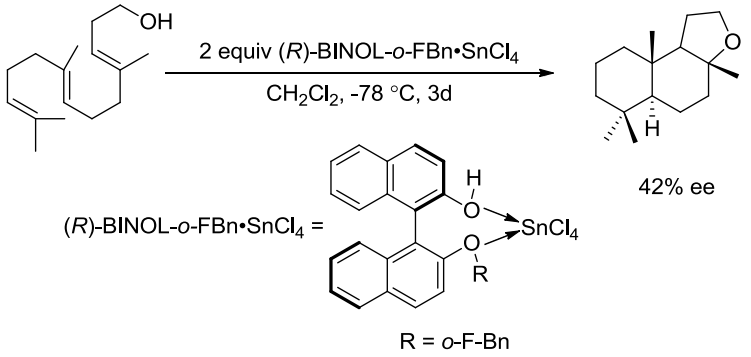

(Eq. 1-2)

[8]Corey, E. J.; Wood, H. B. *J. Am. Chem. Soc.* **1996**, *118*, 11982. (b) Gnanadesikan, V.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 8089. (c) Mi, Y.; Schreiber, J. R. V.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 11290. (d) Corey, E. J.; Lin, S. *J. Am. Chem. Soc.* **1996**, *118*, 8765. (e) Corey, E. J.; Lee, J. *J. Am. Chem. Soc.* **1993**, *115*, 8873.

[9]Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Org. Chem.* **1986**, *51*, 806. (b) Namba, K.; Yamamoto, H.; Sasaki, I.; Mori, K.; Imagawa, H.; Nishizawa, M. Org. Lett. **2008**, *10*, 1767.

Although cyclization worked using these stoichiometric metal complexes, enantioselective variants are relatively rare. In 2002, the Yamamoto group reported the first enantioselective biomimetic cyclization of polyenes utilizing Lewis-acid assisted chiral Brønsted acids (BLA) generated from tin tetrachloride and an optically active binaphthol derivative for the tricyclization of a triene alcohol (Scheme 1-4).[10] The catalytic activity of these BLA compounds are slightly inhibited due to the nucleophilic hydroxyl group on the ligand that acts as a terminator in the cyclization of some polyolefinic alcohols.

**Scheme 1-4.** Yamamoto Enantioselective BLA assisted biomimetic cyclization.

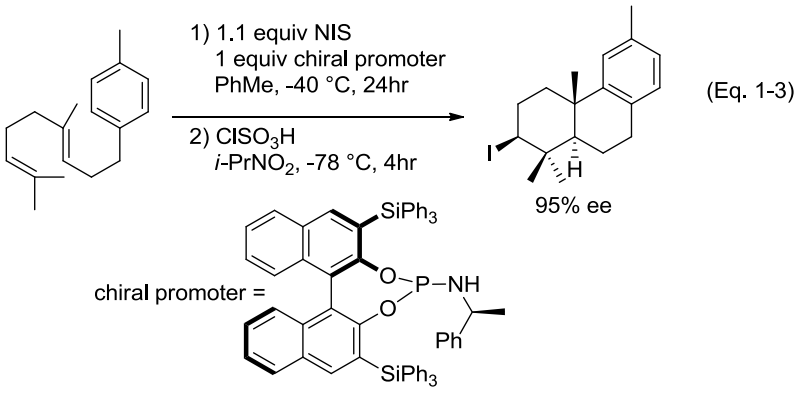



With these BLA complexes, moderate enantioselectivities in the cyclized products were observed. Ishihara improved upon the scope of enantioselective cascade cyclization of polyolefins in 2007 by reporting the first enantioselective halocyclizations of polyprenoids using a chiral BINOL-derived phosphoramidite with *N*-iodosuccinimide (Eq. 1-3).[11] Exploring other possible initiators for biomimetic cyclization reactions, the Loh group recently investigated chiral *N*-acetals (as promoters) in conjunction with $TiCl_4$ to generate

[10](a) Ishibashi, H.; Ishihara, K.; Yamamoto, H. *The Chemical Record* **2002**, *2*, 177. (b) Uyanik, M.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2006**, *8*, 5649. (c) Uyanik, M.; Ishibashi, H.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 1601. (d) Ishibashi, H.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 11122. (e) Kumazawa, K.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2004**, *6*, 2551. (f) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2002**, *124*, 3647.

[11]Sakakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900.

either an oxocarbenium or iminium, which reacts with the 2,3-alkene of the polyolefin starting material to initiate cyclization (Eq. 1-4).[12] The product observed after initial cyclization is a side-chain cleaved chloride species, which upon stirring in wet silica gel, forms the final alcohol product in reasonable yields and enantioselectivities. The mechanism of these *N*-acetal promoted reactions is still under investigation. Despite the progress in biomimetic cyclization of polyenes since Johnson's work in the 1960s, many scientists focus on the development of new systems to increase yields and enantioselectivities of polycyclic products.



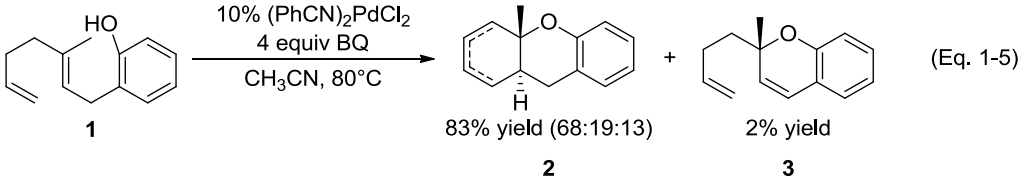

### 1.1.3. Pd(II) and Pt(II) complexes in cascade cyclization (Gagné group)

Similar to the Lewis acid catalysts previously discussed, transition metals, in particular group 10 metals, are known to be electrophilic. In contrast to other soft Lewis acids, transition metals such as Pd(II) and Pt(II) have been shown to favor coordination and

[12]Zhao, Y.-J.; Loh, T.-P. *J. Am. Chem. Soc.* **2008**, *130*, 10024.

activation of the least substituted alkene of polyenes; in addition they exhibit a preference for $d^8$ square planar geometry.[13,14] The preference for coordination to the terminal alkene serves to activate the substrate to cyclize via the cation-olefin process to the desired bicyclic product.

As an example, the use of $(PhCN)_2PdCl_2$ as the catalyst for the cyclization of **1** under Wacker-type (discussed in detail in Section 1.2) conditions using benzoquinone as an oxidant, facilitated the conversion of **1** to the net-dehydrogenated product, **2**, as a mixture of regioisomers (Eq. 1-5).[15] In addition, a "Wacker" product was observed in low yields, **3**. Inspired by work by the Vitagliano group,[16] the Gagné group used pincer tridentate triphos Pt(II) complexes to trap the cationic [Pt]-alkyl intermediate, **4** (Eq. 1-6).[16b]

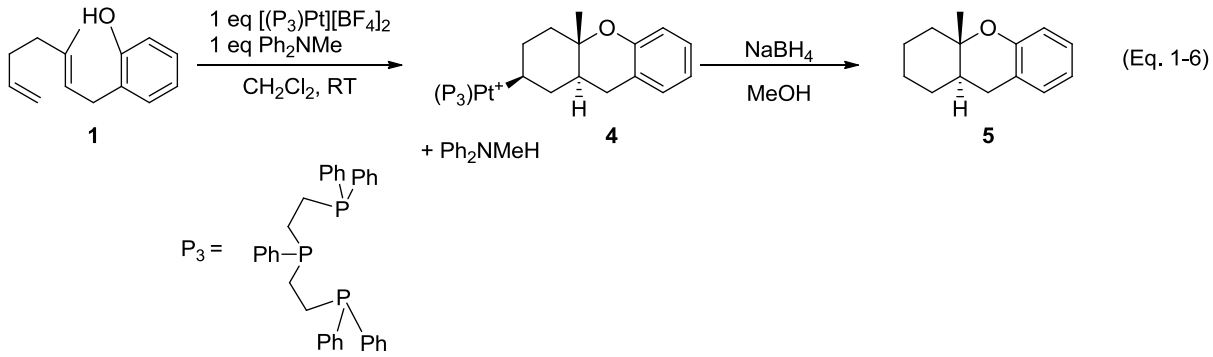



[13](a) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*; University Science Books: Mill Valley, CA, 1994; pp 199-236. (b) Hegedus, L. S. *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds. Pergamon Press: Oxford, 1990; Vol. 4, pp 571-583.

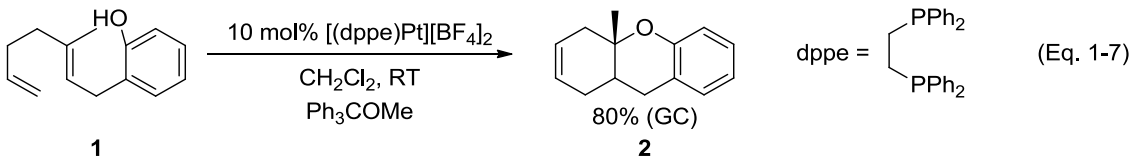
[14](a) Chianese, A. R.; Lee, S. J.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 4042. (b) Pizzo, E.; Sgarbossa, P.; Scarso, A.; Michelin, R. A.; Strukul, G. *Organometallics* **2006**, *25*, 3056. (c) Cucciolito, M. E.; D'Amora, A.; Vitagliano, A. *Organometallics* **2005**, *126*, 3359. (d) Liu, C.; Han, X.; Wang, X.; Widenhoefer, R. A.; *J. Am. Chem. Soc.* **2004**, *126*, 3700.

[15]Koh, J. H.; Mascarenhas, C.; Gagné, M. R. *Tetrahedron* **2004**, *60*, 7405.

[16]Hahn, C.; Cucciolito, M. E.; Vitagliano, A. *J. Am. Chem. Soc.* **2002**, *124*, 9038. (b) Koh, J. H.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 3459.



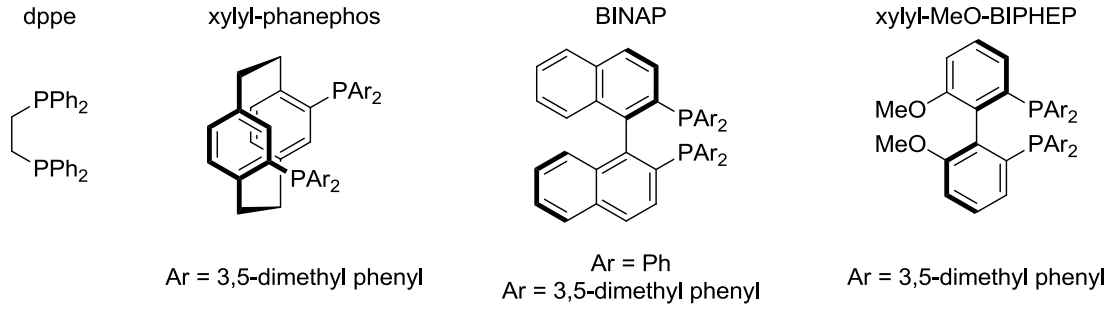

Using a stoichiometric amount of the activated $(PPP)Pt^{2+}$ (activated by halide extraction with silver salts), a cationic [Pt]-alkyl complex was isolable. It was observed that the [Pt]-C bond of **4** could be cleaved using $NaBH_4$ providing **5**, which was isolated and crystallized. X-ray diffraction of the major stereoisomer of **5** confirmed the A-B *trans* ring and structure displayed in Eq. 1-6.[16b] The [Pt]-alkyl, **4**, is however, unable to turn over catalytically because there is no open *cis* coordination site available on the metal center to accommodate β-H elimination. As a result, bidentate phosphines were studied as possible ligands for catalytic reactions with **1** (Figure 1-3)**.**[17] Initial studies using achiral ligands such as diphenylphosphinoethane, (dppe), formed the desired product, **2**, in good yields as one regioisomer (Eq. 1-7). This reaction required the use of $Ph_3COMe$ as the stoichiometric oxidant, functioning to turn over the catalytic cycle by abstracting the hydride of a putative intermediate [Pt]-H, and also absorbing $H^+$ to form MeOH (discussed in detail in 1.2.2 and Chapter 2).




[17]Mullen, C. A.; Gagné, M. R. *J. Am. Chem. Soc.* **2007**, *129*, 11880.

As expected, the ring junction between rings A and B is *trans*, as determined by comparison to the hydrogenated product, **5**. The reaction conditions were optimized for base and solvent to give a 73% isolated yield. This chemistry was extended to include chiral bidentate phosphines, which enhanced the enantioselectivity of the product. Binaphthyl and other biaryl bidentate phosphine ligands were screened, with the most enantioselective being (*S)*-xylyl-phanephos (Figure 1-3).[18]

**Figure 1-3.** Various $P_2$ ligands tested in cyclization.

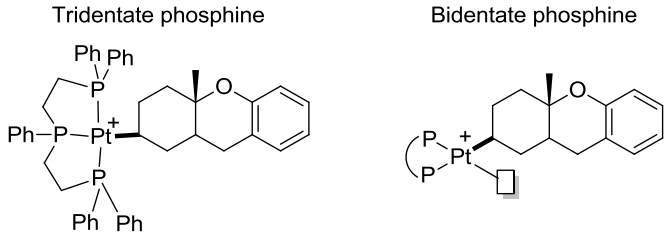



Using these bidentate ligands, an open *cis* coordination site on the platinum metal center was available for β-H elimination (Figure 1-4), however, unlike most Pd(II) based catalytic systems, routine oxidants like benzoquinone, peroxides, or $O_2$ and $CuCl_2$ were not effective in this system. This is rationalized by considering that the Pt(II)-H is less acidic than its Pd(II)-H analogs and is therefore, resistant to deprotonation or reductive elimination to generate Pt(0). Under catalytic conditions, 2-electron oxidants that are effective in Wacker chemistry are ineffective in this system. The Gagné group has found that direct hydride abstraction from the putative Pt(II)-hydride using $Ph_3CBF_4$ resulted in the most

[18]Mullen, C. A.; Campbell, A. N.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 6011.

success with catalytic turnover, the mechanism of which is described in Section 1.2.3 and in Chapter 4.[19]

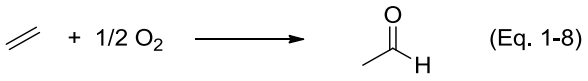
**Figure 1-4.** Square planar structure of cationic $P_2Pt$-alkyl complex with an open coordination site suitable for β-H elimination.




## 1.2. Wacker chemistry

### 1.2.1. Traditional Wacker chemistry

The Wacker process was first developed by Smidt in the late 1960s and was defined as the metal catalyzed conversion of ethylene into acetaldehyde, which has also been extended to other alkenes, always containing a terminal olefin (Eq. 1-8).[13a]




(Eq. 1-8)

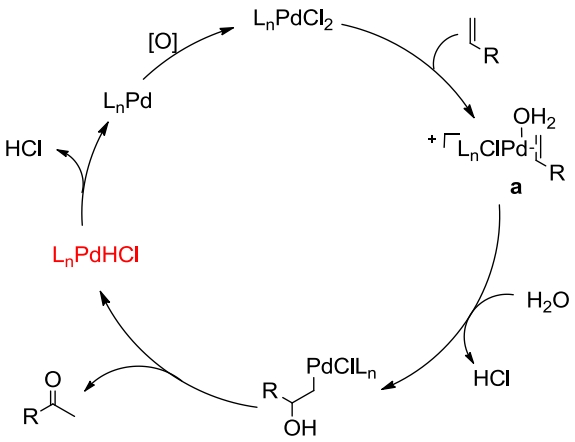
Generally a palladium(II) complex is used as the catalyst for these transformations, which have a preference for binding to the terminal olefin of the substrate. Multiple studies have contributed to the proposed mechanism including, kinetic studies, isotope effect studies, stereochemical studies and computational studies.[20] The proposed mechanism begins with

[19]Campbell, A. N. Platinum (II) Catalyzed Diene Cyclizations, Ph.D. Thesis, University of North Carolina at Chapel Hill, Chapel Hill NC, December 2008.

[20](a) Keith, J. A.; Henry, P. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 9038. (b) Takacs, J. M.; Jiang, X. *Curr. Org. Chem.* **2003**, *7*, 369. (c) Tsuji, J. *Pure Appl. Chem.* **1999**, *71*, 1539. (d) Henry, P. M. *Annals New York Academy of Sciences* **1970**. Presented at Section of Catalysis Meeting.

coordination of the alkene to the palladium(II) salt (Scheme 1-5), generating a Pd($\eta^2$-alkene). A chloride ligand is then replaced with water to make a Pd(alkene)-$OH_2$ adduct (**a**). The rate-determining step is the nucleophilic *anti*-addition of water or *syn*-addition of a hydroxide group to the alkene resulting in a (β-hydroxyalkyl) palladium complex. β-hydride elimination affords an enol which tautomerizes to the desired ketone and generates a putative Cl-Pd-H complex, which rapidly reductively eliminates ($H^+$ loss) giving a Pd(0) complex. This Pd(0) complex is then re-oxidized to Pd(II) via its reaction with an oxidant such as $CuCl_2/O_2$, $O_2$, or benzoquinone. The in situ reduction of Cu(II) to Cu(I) by the Pd(0) generates Pd(II). Cu(I) is then re-oxidized to Cu(II) by the reaction with molecular oxygen, benzoquinone or a peroxide, thus making this oxidant catalytic (Eq. 1-9).

**Scheme 1-5.** Proposed Wacker process for the conversion of ethylene into acetaldehyde.



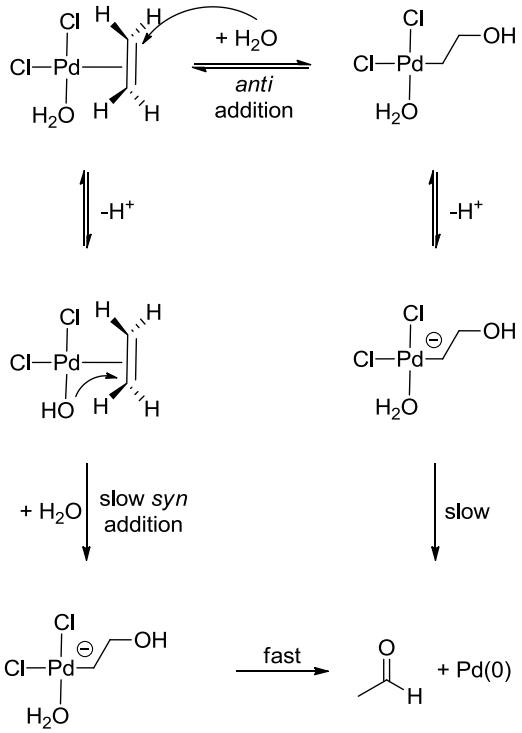

Reoxidation of Cu(I) to Cu(II)

$$2\ CuCl + (1/2)O_2 + 2\ HCl \longrightarrow 2\ CuCl_2 + H_2O \qquad \text{(Eq. 1-9)}$$

The chemical conditions including the concentration of reagents used during catalysis influence the stereochemistry of the nucleophilic addition, proceeding either via the *syn* or the *anti*-pathway.[20a] As an example, a high concentration of chloride or the presence of pyridine or hydroxide facilitates the *anti*-pathway; in contrast, low chloride concentrations,

the inclusion of a bidentate diamine ligand or the use of $H_2O_2$ as oxidant, shifts the bias towards the *syn*-addition (Scheme 1-6).

**Scheme 1-6.** *Syn* versus *Anti*-addition of nucleophile across olefin




The Wacker reaction was the first method for the industrial production of acetaldehyde from ethylene. In fact, the reaction was also the first of many organopalladium, and more broadly, organometallic reactions to proceed on an industrial scale. Due to the high commercial availability of ethylene and high production yields of acetaldehyde, the reaction is economically and chemically practical, and thus is still in use today. On an industrial scale, the conversion of ethylene into acetaldehyde is carried out under aqueous hydrochloric acid under oxygen pressure in the presence of $PdCl_2/CuCl_2$ as catalyst. Although these are most commonly utilized conditions, the acidic reaction environment is highly corrosive and the presence of a high chloride concentration can lend itself to the formation of chlorinated by-products. For this reason, chemists have developed alternative

methodologies to enhance functional group tolerance under milder conditions including solvent variability and choice of palladium catalyst and re-oxidant.

### 1.2.2. Extension of Wacker chemistry to aza-Wacker systems

*N*-heterocyclic compounds are a class of important organic products with widespread applications in the pharmaceutical and fine chemical industry; therefore, it is important to efficiently and selectively form C-N bonds that directly generate cyclic structures.[21] Numerous methods for C-N bond formation exist, with an emphasis on late-transition metal chemistry, in particular $Pd^{0/II}$ systems.[21,22,23] In addition, procedures for the direct amination of olefins, in particular oxidative aminations, are synthetically attractive due to the resultant net increase in substrate functionality.[24] As a result, aza-Wacker conditions have been developed for the formation of indoles.

Hegedus reported the first example a palladium-assisted intramolecular formation of indoles.[25] This reaction occurred under mild conditions with a wide substrate scope including secondary and primary aniline analogs. He determined that the cyclization was not limited to neutral or weakly basic conditions, but more basic benzylamines could also

[21](a) Krüger, K.; Tillack, A.; Beller, M. *ChemSusChem*. **2009**, *2*, 715. (b) Tamaru, Y.; Kimura, M. *Synlett*. **1997**, 749. (c) Hartwig, J.F.; *Angew. Chem., Int. Ed*. **1998**, *37*, 2046.

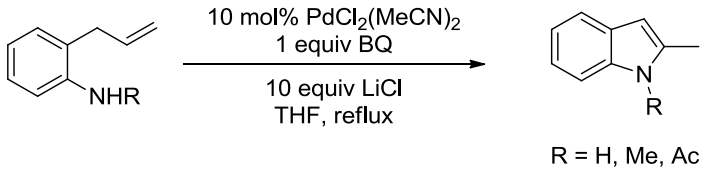
[22]For Buchwald-Hartwig Pd catalyzed aminations see: (a) Hartwig, J.F. *Organotransition Metal Chemistry*, 1st ed..; University Science Books: California, **2010**. (b) Kienle, M.; Dubbaka, S. R.; Brade, K.; Knochel, P. Eur. *J. Org. Chem.* **2007**, 4166. (c) Shi, C.; Ojima, I. *Tetrahedron* **2007**, *63*, 8563. (d) Nettekoven, U.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 1166. (e) Hartwig, J. F. *Acc. Chem. Res*. **1998**, *31*, 852. (f) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res*. **1998**, *31*, 805. (g) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc*. **1997**, *119*, 8451.

[23]For Ullmann condensation with [Cu] catalyst complexes: (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *43*, 5400. (b) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428.

[24](a) Timokhin, V. I.; Stahl, S. S. *J. Am. Chem. Soc*. **2005**, *127*, 17888. (b) Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2003**, *125*, 12996.

[25]Hegedus, L. S.; Allen, G. F.; Waterman, E. L. *J. Am. Chem. Soc.* **1976**, *98*, 2674.

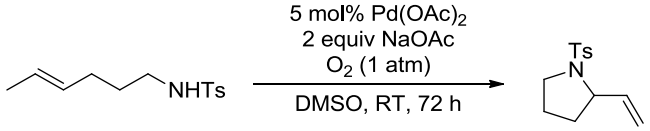
undergo cyclization. Even though this reaction was successful, it was stoichiometric in palladium; prompting him to develop a catalytic variant (Eq. 1-10).[26]




(Eq. 1-10)

These catalytic protocols utilized nucleophilic amines for cyclization; however, *N*-protonation due to acidic reaction conditions and facile binding of the amine moiety to the metal, were found to inhibit catalytic turnover. As a result, amine protecting groups, such as 4-toluenesulfonyl (Ts), were employed to eliminate both the protonation and non-productive binding of the amine to the catalyst.[22g]

Approximately a decade later, seminal studies by Larock reported the first intramolecular cyclization of *N*-tosylated aliphatic amines using $O_2$ as the stoichiometric oxidant in DMSO (Eq. 1-11).[27] Such aerobic methods eliminated the need for co-catalysts ($CuCl_2$) or stoichiometric oxidants like benzoquinone, which required cumbersome removal procedures upon reaction completion.




(Eq. 1-11)

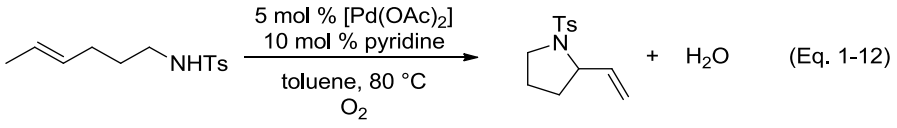
A disadvantage to Larock's system included the use of DMSO as solvent, which likely coordinated to the palladium metal center inhibiting the complexation with substrate or

[26](a) Hegedus, L. S.; McKearin, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 2445. (b) Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc*. **1978**, *100*, 5800.

[27]Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org Chem.* **1996**, *61*, 3584.

asymmetric ligands.[28] As a result, the development of an alternative system with mild reaction conditions and similar turnover was needed. For this reason, the Stahl group investigated catalytic turnover in non-coordinating non-polar solvents such as toluene and *p*-xylene. In addition, Stahl found that the catalytic reaction proceeded with faster turnover rates (70 $h^{-1}$ during the first two hours) and high turnover numbers (250-300) with a lower catalyst loading ([$Pd(OAc)_2$] (0.2 mol %)/pyridine (0.4 mol %) in *p*-xylene), as compared to previous oxidative amination reactions.[29]

Examination of the [$Pd(OAc)_2$]/$O_2$/DMSO system by the Stahl group revealed that the re-oxidation of Pd(0) to Pd(II) was the turnover limiting step. Furthermore, they determined that pyridine or other imine donor ligands promoted the oxidation of palladium, increasing the catalytic efficiency of these amination reactions. The use of pyridine coupled with toluene or *p*-xylenes was found to operate effectively and generate yields in excess of 80 % (Eq. 1-12)[29,30]



(Eq. 1-12)

Despite the extensive development of oxidative amination reactions, the mechanism of these reactions is still under investigation, however, the general mechanism is similar to the Wacker process (Scheme 1-7) in that the alkene and nucleophile must both coordinate to the palladium metal center, either *syn* or *anti*. This alkyl aminopalladate complex undergoes

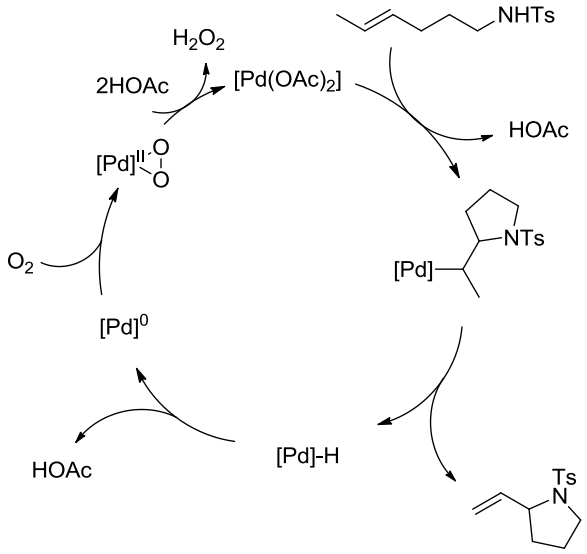
[28]Trend, R.; Ramtohul, Y.; Stoltz, B. *J. Am. Chem. Soc.*, **2005**, *127*, 17778.

[29]Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem. Int. Ed.*, **2002**, *41*,164.

[30]Ye, X.; Liu, G.; Popp, B.V.; Stahl, S. S. *J. Org. Chem.*, **2011**, *76*, 1031.

β-H elimination generating the desired heterocyclic product and a putative palladium hydride. This [Pd]-H quickly reductively eliminates giving a Pd(0) complex, which must be re-oxidized to the active Pd(II) catalyst by molecular oxygen.

**Scheme 1-7.** Catalytic aza-Wacker reaction mechanism.




The alkene aminopalladation elementary step of the cycle was the subject of some controversy. Early studies indicated that the amine nucleophiles reacted via an outer sphere mechanism with external attack on the coordinated olefin giving the product of *trans*-aminopalladation.[31,32] However, recent studies have found that it is in fact the *cis*-alkene insertion into the amino-palladium, an inner sphere mechanism, that is generally preferred.[33] The propensity for aminopalladation to proceed via a *syn* or *anti* pathway can be altered by the presence of additives, such as Brønsted acids, or by changing the identity of the nitrogen

[31]Bäckvall, J. E. *J. Am. Chem. Soc*., **1992**, *114*, 6374.

[32]Åkermark, B.; Bäckvall, J. E.;Siirala-Hansén, K.; Sjöberg, K.; Zetterberg, K. *Tetrahedron Lett.*, **1974**, *15*, 1363.

[33](a) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179. (b) Muñiz, K.; Hövelmann, C. H.; Streuff, J. *J. Am. Chem. Soc*, **2007**, *130*, 763. (c) Ney, J. E.; Wolf, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 8644.

nucleophile. The configuration of the aminopalladation intermediate is dependent on a combination of the substrate identity, the catalyst and reaction conditions.[34]

Undoubtedly, the highest levels of enantioselectivity would be observed when only a single aminopalladation pathway is operating.[34] Due to the competing pathways, the scope of asymmetric oxidative amination reactions is limited to a handful of examples, despite the extensive efforts to refine the reaction conditions and develop asymmetric methods.[28,35]

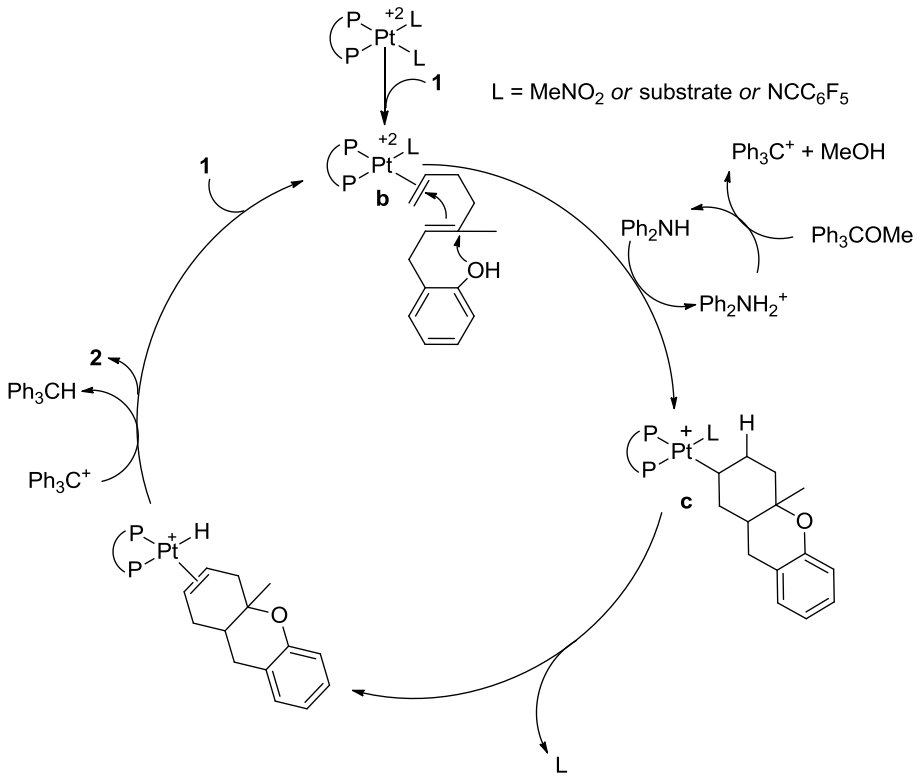
### 1.2.2. Extension of Wacker chemistry to platinum-catalyzed polyolefin cyclization

The Gagné group has studied the platinum catalyzed cation-olefin cyclization of polyenes, in particular a dienephenol (**1**) substrate as described in Section 1.1.3. The proposed mechanism for this transformation shown in Scheme 1-8 includes initial coordination of substrate **1** to the dicationic [Pt] species to form $\eta^2$ alkene platinum, similar to the Wacker process.[19] Complex **b** quickly cyclizes to **c** with the aid of a base (diphenylamine), forming a [Pt]-alkyl cationic species and a diphenylammonium salt. Complex **c** undergoes β-H elimination to form the desired product **2** and a putative [Pt]-H. $Ph_3C^+$, liberated from the reaction of the diphenylammonium salt with $Ph_3COMe$, rapidly abstracts the hydride from the putative [Pt]-H, regenerating the catalytically active [Pt] dicationic complex. In the absence of $Ph_3C^+$, no catalytic turnover is observed. This Wacker-type platinum-catalyzed cyclization was further optimized by varying the hydride abstractor to enhance the atom economy and efficiency of this reaction (For details, see Chapter 2).

[34]Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 6328.

[35]Yip, K. T.;Yang, M.; Law, K. L.; Zhu, N. Y.; Yang, D. *J. Am. Chem. Soc.* **2006**, *128*, 3130.

**Scheme 1-8**. Proposed Catalytic Cycle for Platinum-Catalyzed Cation-Olefin Cyclization of Olefins




## 1.3. Fluorination chemistry

Organofluorine compounds are important in many pharmaceuticals, materials, fine chemicals and agrochemicals, with approximately 35% of agrochemicals and 20% of pharmaceuticals containing one or more C-F bonds.[36] Due to their prominence in industry, methods for the synthesis of organofluorine compounds are in demand. The following introduction provides an overview of the fluorine atom, C-F bonds, details regarding electrophilic fluorine sources such as $XeF_2$ and recent advances in transition-metal mediated fluorination chemistry.

[36](a) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (b) Cahard, D.; Xu, X.; Couve-Bonnaire, S.; Pannecoucke, X. *Chem. Soc. Rev.* **2010**, *39*, 558. (c) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305. (d) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. (e) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (f) Ametamey, S. M.; Honer, M.; Schubiger, P. A. *Chem. Rev.* **2008**, *108*, 1501. (g) Muller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (h) Jeschke, P. *ChemBioChem* **2004**, *5*, 570.

### 1.3.1. Properties of fluorine

Fluorine is the most electronegative atom on the periodic table due to its low energy valence shell and few core electrons to provide shielding from the positively charged nucleus, which affords very highly polarized C-F bonds. This polarization is responsible for geometry changes as hydrocarbons are converted to fluorocarbons and electron density migrates from predominately carbon-based to fluorine-based.[37] Another feature that dominates the chemistry is its C-F bond strength, which is the strongest in organic chemistry (105 kcal/mol), in part due to the heightened electrostatic component of the carbon-fluorine bond.

In addition, fluorine has a small atomic radius (approximately 1.47 Å), which is between that of hydrogen (1.20 Å) and oxygen (1.52 Å).[38] In medicinal chemistry, fluorine is used as the best steric replacement for hydrogen; however electronically this fluorinated product is drastically different than the protonated variant. Based on size and electronegativity alone, fluorine would be an approximately neutral (little change in sterics and electronics) substitute for oxygen. However, substitution of a C=O bond with a C-F or C-$F_2$ requires a hybridization change at carbon. Similarly, the replacement of C-OH with C-F results in net loss of an acidic proton, and a change in hydrogen bonding character of the fragment. In general, organofluorine compounds with $sp^3$ C-F bonds are favored over $sp^2$ hybridized C-F bonds.[37]

### 1.3.2. Nucleophilic vs electrophilic fluorinations

Conventional methods for the formation of aryl fluorides, such as the Balz-Schiemann reaction, generally require high temperatures or harsh reagents, thus limiting the substrate scope of

[37]O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308.

[38](a) Bondi, A. *J. Phys. Chem.*, **1964**, *68*, 441. (b) Mantina, M.; Chamberlin, A. C.; Valero, R.; Cramer, C. J.; Truhlar, D. J. *J. Phys. Chem.* **2009**,*113*, 5806.

the reaction.[36a] In addition, the strength of C-F bonds means that most C-F bonds are thermodynamically favorable, however, their formation is kinetically challenging. To this end, interest in transition metal catalysis for bringing fluorination processes under kinetic control has increased drastically. Early transition metals are known to form stronger metal-fluorine bonds than late transition metals due to the π-donation of the fluoride ligand into the empty d-orbital on the metal center. The larger difference in electronegativity of the metal and fluoride causes early transition metal fluoride complexes to also have more polarized, hence stronger metal-fluorine bonds, making them kinetically inert For this reason, late transition metals are used most often for fluorinations.

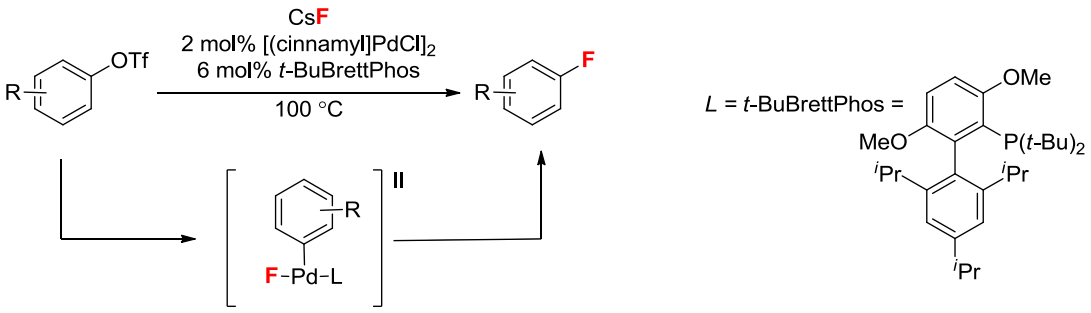
Methods for C-F bond formations in organic compounds have evolved along two pathways, those utilizing nucleophilic and those taking advantage of electrophilic fluorination sources.[36,39,40] The nucleophilic fluorination of organic compounds is challenging and therefore underdeveloped because of inherent limitations in reactivity of $F^-$. The nucleophilic nature of $F^-$ affords tight ion pairs in aprotic solvents that require significant amounts of energy to overcome these barriers. In addition, $F^-$ is readily solvated in protic solvents, causing an overall reduction in the nucleophilicity/reactivity of fluoride. Recently, the Buchwald group reported the first example of a palladium (0) catalyzed aryl-fluoride cross-coupling reaction that effectively converted aryl triflates to aryl-fluoride compounds using a $[(\text{cinnamyl})\text{PdCl}]_2$ catalyst coupled with CsF as a nucleophilic fluorine source (Scheme 1-9).[39a] The use of a bulky monophosphine t-BuBrettPhos (2-(Di-tert-

[39]For nucleophilic fluorination examples see: Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661. (b) Braun, M.-G.; Katcher, M. H.; Doyle, A. G. *Chem. Sci.* **2013**, *4*, 1216. (c) Kalow, J. A.; Doyle, A. G. *J. Am. Chem. Soc.* **2011**, *133*, 16001.

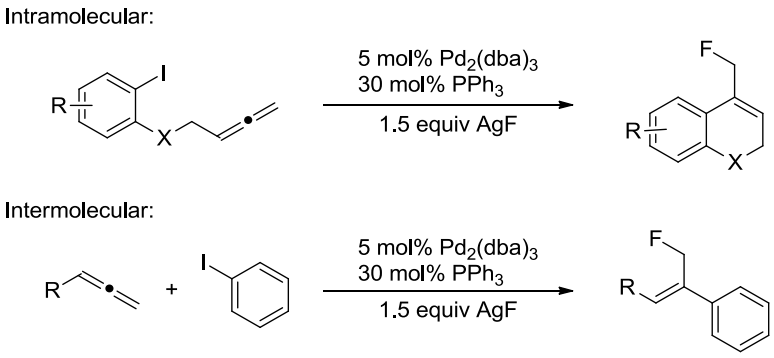
[40]For electrophilic fluorination examples see: (a) Vigalok, A. *Organometallics* **2011**, *30*, 4802. (b) Vigalok, A.; Kaspi, A. W. *Top. Organomet. Chem.* **2010**, *31*, 19. (c) Lectard, S.; Hamashima, Y.; Sodeoka, M. *Adv. Synth. Catal.* **2010**, *352*, 2708. (d) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1. (e) Dinoiu, V. *Revue Roumaine de Chemie* **2007**, *52*, 219. (f) Audouard, C.; Ma, J. –A.; Cahard, D. *Adv. Org. Synth.* **2006**, *2*, 431.

butylphosphino)-2′,4′,6′-triisopropyl-3,6-dimethoxy-1,1′-biphenyl) was the key to the generation of a three coordinate arylpalladium(II) fluoride complex necessary for reductive elimination. This nucleophilic fluorination of aryl triflates was extended to the formation of a wide scope of aryl fluorides.

**Scheme 1-9.** Buchwald system for Pd(0)-catalyzed aryl-fluoride cross-coupling reaction using nucleophilic fluorine source, CsF.




**Scheme 1-10** . Intra- and intermolecular carbofluorinations using a Pd(0) catalyst and nucleophilic fluorine source, AgF.




Additionally, the Doyle group has developed the first examples of intra- and intermolecular carbofluorinations of olefins using a Pd(0) catalysts and a stoichiometric amount of AgF as the nucleophilic fluorine source (Scheme 1-10).[39b]

We describe herein methods for the electrophilic fluorination of organic compounds because this method is the most direct without the complications that arise when solvent reacts with $F^-$ in solution (further discussion of electrophilic fluorination in Sections 1.3.4 and 1.3.5). Although numerous methods exist for electrophilic fluorination, the overall

transformation still remains challenging. Transition metal complexes, in particular, provide viable routes for accessing fluorinated compounds with both regio- and stereocontrol. In particular, high valent group 10 M-F complexes allow for increased stereocontrol in the development of fluorinated products.[40]

### 1.3.3. Properties of $XeF_2$ and other electrophilic fluorine sources

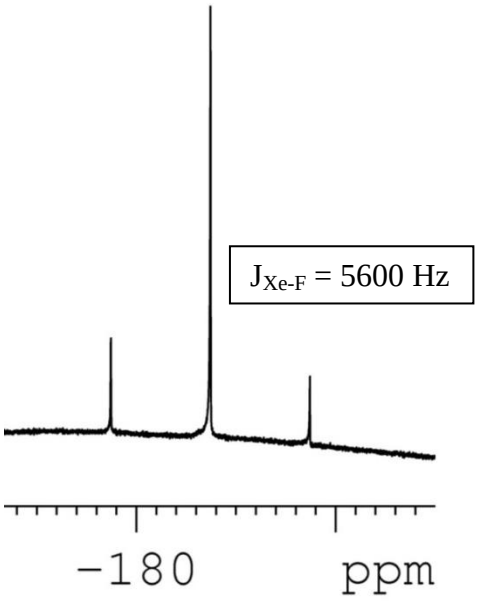
$XeF_2$ is a stable white solid at room temperature that sublimes at room temperature under vacuum (vapor pressure $6.0 \times 10^2$ Pa).[41] In solid form, each Xe atom has two fluorine atoms in a linear centro-symmetric structure, as deduced from vibrational spectra. $XeF_2$ is stabilized by other $XeF_2$ molecules through strong intermolecular electrostatic interactions. In addition, $XeF_2$ is soluble in multiple organic solvents without oxidation or reduction, for example, it reacts with acetonitrile at a negligible reaction rate with solvent. In halogenated solvents such as methylene chloride and chloroform, it was observed that chlorine-fluorine exchange occurred on a short time scale.

Because $^{129}Xe$ is spin active (spin ½, 26.4% abundance), $^{19}F$ NMR is a powerful tool to determine the presence of $XeF_2$. Figure 1-5 shows the $^{19}F$ NMR spectrum of $XeF_2$ in nitromethane with a characteristic resonance at -184 ppm and with a $J_{Xe\text{-}F}$ coupling constant of ~5600 Hz. Nitromethane was used for this spectrum since it is the solvent used in the studies outlined in this thesis.

Due to its low bond energy (32 kcal/mol), $XeF_2$ has the potential to be a very reactive oxidant in electrophilic fluorination. In addition, after fluorination, the byproduct of Xe is inert towards other reactivity and is a gas, which makes this an ideal candidate for electrophilic fluorination.

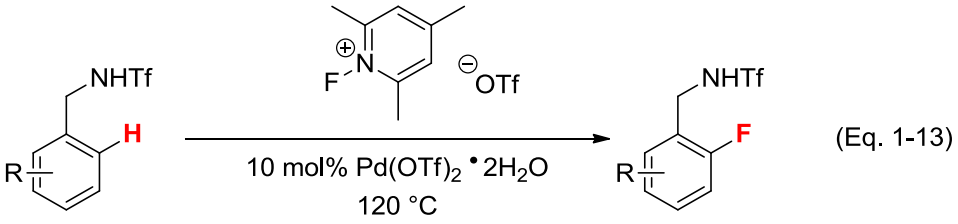
[41] Tramšek,M.; Žemva, B. *Acta Chim. Slov.* **2006**, *53*, 105.

**Figure 1-5**. $^{19}F$ NMR spectrum of $XeF_2$ in nitromethane.



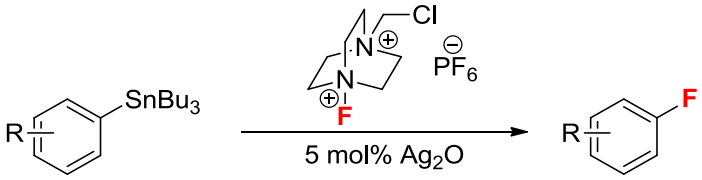

### 1.3.4. Aryl electrophilic fluorination using late transition metals

The most direct way to regioselectively form C-F bonds is through the use of directing groups for the functionalization of a particular (e.g. C-H) bond. Covalently attached directing groups, which can pre-coordinate to a transition metal catalyst, and through proximity, lower the activation energy for preferentially cleaving a specific C-H bond and thus achieving an efficient direct fluorination at the kinetically activated position. Usually, directing groups provide a mechanism for C-H bond functionalization *ortho* to the directing group on the aryl ring. In 2009, the Yu group developed a Pd(II) catalyzed directed electrophilic fluorination of triflamide functionalized aromatics (Eq. 1-13). The obvious limitation of the directed electrophilic fluorination strategy is that fluorine can only be incorporated into the *ortho* position to the directing group.



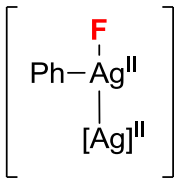

(Eq. 1-13)

**Scheme 1-11**. Silver-catalyzed C-F bond formation from aryl stannanes using an electrophilic fluorine source.




In addition to group 10 metals, the Ritter group reported the first silver-catalyzed transmetallation to form carbon-heteroatoms via an electrophilic fluorination of aryl stannanes (Scheme 1-11).[42] This electrophilic fluorination occurs under mild conditions, leading to high functional group tolerance and applicability to late stage fluorinations of small complex molecules. The key to the late stage fluorination of small molecules may be metal-metal redox interactions that result from silver aggregates. These interactions are proposed to reduce the barrier to C-F reductive elimination. (Figure 1-6). The major drawback of this system, however, is the use of toxic aryl stannanes, which must be synthesized from phenols or arenes through aryl triflates or aryl halides.[43]

**Figure 1-6.** Possible Ag(II)-Ag(II) complex suitable for C-F reductive elimination.




[42]Tang, P.; Furuya, T.; Ritter, T. *J. Am. Chem. Soc*. **2010**, *132*, 12150.

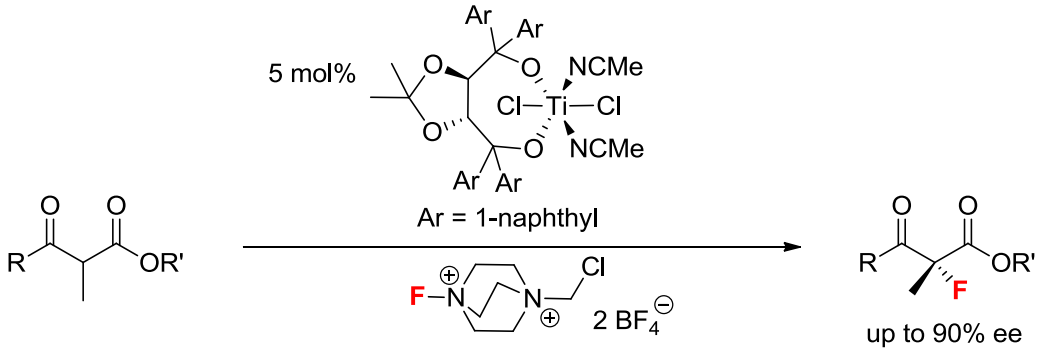
[43]Azizian, H.; Eaborn, C.; Pidcock, A. *J. Organomet. Chem.*, **1981**, *215*, 49.

### 1.3.5. Aliphatic asymmetric fluorinations

Aliphatic C-F bonds are prominent in many pharmaceuticals, materials and agrochemicals.[36] The electrophilic fluorination of racemic α-fluoro carbonyl compounds have been known for years, however, until recently, asymmetric fluorination relied on the relay of existing stereochemistry. For this reason, scientists have embarked on new reaction development for asymmetric fluorination of aliphatic hydrocarbons.[36a]

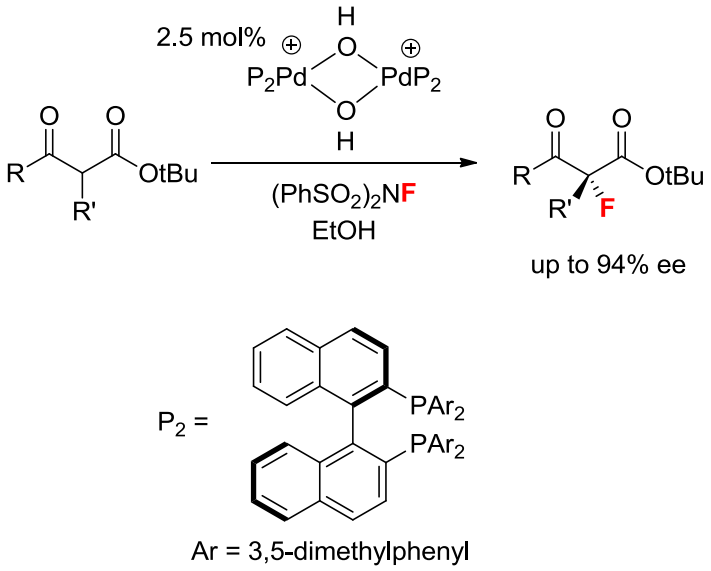
In 2000 Togni developed the first enantioselective transition-metal mediated electrophilic fluorination.[44] Using an analog of Ti(TADDOL)$Cl_2$, the regio- and stereoselective fluorination of β-ketoesters was achieved (Scheme 1-12). In these reactions the bulky Lewis acidic catalyst triggers the enolization of the β-ketoester making the enolized substrate susceptible to external electrophilic fluorination on the *re* side by Selectfluor [1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)].

**Scheme 1-12.** Asymmetric fluorinations of Togni using [$TiCl_2$(*R, R*)-(TADDOLato)] and Selectfluor as electrophilic fluorinating reagent.




[44](a) Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4359. (b) Togni, A.; Mezzetti, A.; Barthazy, P.; Becker, C.; Devillers, I.; Frantz, R.; Hintermann, L.; Perseghini, M.; Sanna, M. *CHIMIA Int. J. Chem.* **2001**, *55*, 801.

**Scheme 1-13.** Enantioselective Fluorination of b-ketoesters using (BINAP)Pd complexes.




A few years later, the Sodeoka group developed an enantioselective electrophilic fluorination of various β-ketoesters using NFSI (*N*-Fluorobenzenesulfonimide) as the fluorinating reagent and a (BINAP)Pd(II) dimeric complex as the catalyst (Scheme 1-13).[45] This was an early example of transition metal-catalyzed electrophilic fluorination that resulted in good yields and enantioselectivities under conditions that were not free of water or air. In addition, the catalyst could be recycled multiple times with no loss in catalytic reactivity. Although, the yields and enantioselectivies are excellent for these reactions, the fluorination is opportunistic, meaning that the fluorine addition only occurs at an "activated" site (in these cases, an enolate).

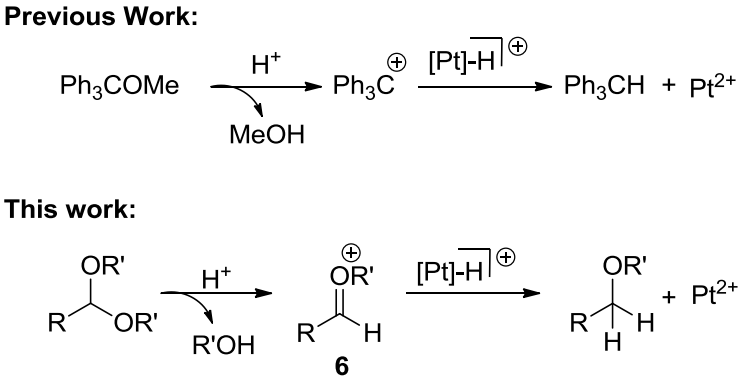
## 1.4. Research objectives

The research goals of this thesis are two-fold. First, we want to study the hydride abstraction in Pt(II)-catalyzed cascade cyclization of **1**. Previous work had shown that catalytic turnover was achieved by a hydride abstraction from a putative [Pt]-H by

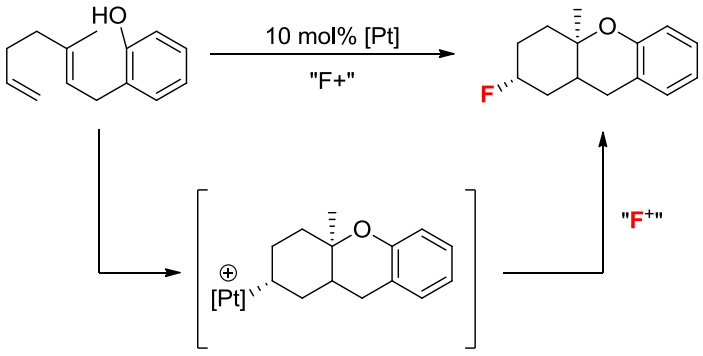
[45]Hamashima, Y.; Yagi, K.; Takano, H.; Tamás, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 14530.

$Ph_3C^+$.[17,18,19] My goal was to find an alternative hydride abstractor to $Ph_3C^+$ that possessed the same reactivity but with increased atom economy and provided improved product isolation conditions. As will be discussed, this was achieved by utilizing acetals and ketals in an activated oxocarbenium form as an alternative triphenylcarbenium source (Scheme 1-14). From studies initiated on model compounds, the most promising candidates were transitioned to catalytic systems to determine which acetals could be used as alternatives to $Ph_3C^+$.

**Scheme 1-14**. Previous hydride abstraction using $Ph_3C^+$ compared to work described in this thesis.




**Scheme 1-15.** Proposed fluorination described in this thesis.




Since there are limited non-enolate based asymmetric fluorination reactions,[40] the second major thrust of my dissertation research was to fluorinate the [Pt]-C bond of the in situ generated [Pt]-alkyl intermediate in catalysis to generate a C3-fluorinated product.

Utilizing electrophilic fluorination methods, we describe a cyclization/fluorination reaction for **1** (Scheme 1-15).

# Chapter 2

## Hydride Abstraction in Pt-Catalyzed Cascade Cyclizations

### 2.1. Introduction

Reactions that proceed via a Wacker-type oxidative cyclization have provided net-dehydrogenative routes to a broad variety of heterocycles (as discussed in Chapter 1).[1] The formation of these heterocyclic compounds typically involve the same sequence of steps including activation of an alkene by an electrophilic metal center, attack of a nucleophile (e.g. $H_2O$), and β-H elimination of the resulting metal-alkyl complex to yield a metal hydride and product alkene. The challenge in rendering these processes catalytic has been the turnover mechanism to return the catalyst to its electrophilic "activated" state. In the case of Pd(II) catalysts, the resulting [Pd]-H typically undergoes reductive elimination (deprotonation) to generate Pd(0), which is re-oxidized to Pd(II) using oxidants such as $CuCl_2$, benzoquinone (BQ), or $O_2$.[1,2]

---

[1](a) Hartwig, J. F. *Organometallic Metal Chemistry*; University Science Books: Sausalito, CA, 2010; p 717-744. (b) Wang, F.; Yang, G.; Zhang, Y. J.; Zhang, W. *Tetrahedron* **2008**, *64*, 9413. (c) Minatti, A.; Muniz, K. *Chem. Soc. Rev.* **2007**, *36*, 1142. (d) Muñiz, K. *Adv. Synth. Catal.* **2004**, *346*, 1425. (e) Takacs, J. M.; Jiang, X. *Curr. Org. Chem.* **2003**, *7*, 369. (f) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules;* University Science Books: Mill Valley, CA, 1994; p 199-236.

[2](a) Stahl has recently demonstrated that the significant process challenges of using $O_2$ can be mitigated under flow conditions, see McDonald, R. I.; Stahl, S. S. *Angew. Chem. Int. Ed.* **2010**, *49*, 5529. (b) Korotchenko, V. N.; Gagné, M. R. *J. Org. Chem.* **2007**, *72*, 4877. (c) Cornell, C. N.; Sigman, M. S. *Inorg. Chem.* **2007**, *46*, 1903. (d) Muzart, J. *Tetrahedron* **2007**, *63*, 7505. (e) Popp, B. V.; Thorman, J. L.; Stahl, S. S. *J. Mol. Catal. A.* **2006**, *251*, 2. (f) Koh, J. H.; Mascarenhas C.; Gagné, M. R. *Tetrahedron* **2004**, *60*, 7405.

While Pt complexes display many of the same reactivity profiles as Pd complexes, they have, until recently, typically not been used for Wacker-type transformations.[3] The use of platinum in these transformations has been hindered due to the lower acidity of a platinum hydride, deterring its elimination and the higher binding strength of Pt(II) to counterions like $Cl^-$, which poison its electrophilic character, hence its catalytic activity. Previous efforts in the Gagné group on electrophilic dicationic Pt(II) complexes demonstrated that Wacker-like activity could be achieved with polyene substrates that proceed via cation-olefin pathways.[4] Similar to Wacker systems, β-H elimination resulted in the regioselective organic polycyclic product, **2**, and a putative [Pt]-H. Conventional 2-electron oxidants such as benzoquinone, $O_2$, and $CuCl_2$ were unsuccessful at achieving catalytic turnover. Fortunately, triphenylcarbenium (trityl) cation, $[Ph_3C^+][BF_4^-]$, was found to efficiently abstract the hydride to form $Ph_3CH$ and regenerate $Pt^{2+}$ free of coordinating anions (Scheme 2-1).[5,6]

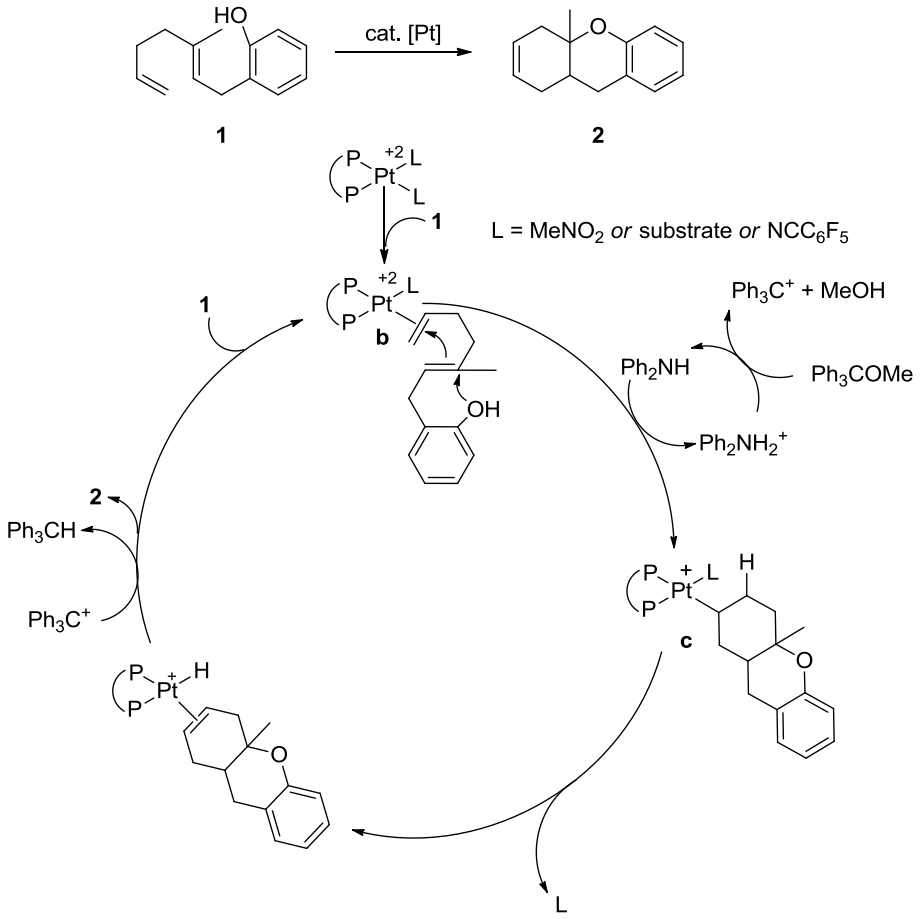
[3](a) Chianese, A. R.; Lee, S. L.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2007**, *46*, 4042. (b) Helger, D. S.; Atwood, J. D. *Organometallics* **2004**, *23*, 2412. (c) Matsumoto, K.; Magai, Y.; Matsunami, J.; Mizuno, K.; Abe, T.; Somuzawa, R.; Kinoshita, J.; Shimura, H. *J. Am. Chem. Soc.* **1998**, *120*, 2900. (d) Matsumoto, K.; Mizuno, K.; Abe, T.; Kinoshita, J.; Shimura, H. *Chem. Lett.* **1994**, 1325.

[4]For additional non-catalytic variants of alkene cascades by Pd(II) and Pt(II) see: (a) Feducia, J. A.; Campbell, A. N.; Doherty, M. Q.; Gagné, M. R. *J. Am. Chem. Soc.* **2006**, *128*, 13290. (b) Koh, J. H.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2004**, *43*, 3459.

[5](a) Mullen, C. A.; Campbell, A. N.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2008**, *47*, 6011. (c) Mullen, C. A.; Gagné, M. R. *J. Am. Chem. Soc.* **2007**, *129*, 11880.

[6]In addition, Bullock has used $Ph_3C^+$ as a hydride abstractor for various [M]-H complexes. See references: (a) Cheng, T.-Y.; Bullock, R. M. *Inorg. Chem.* **2006**, *45*, 4712. (b) Cheng, T.-Y.; Bullock, R. M. *Organometallics* **2002**, *21*, 2325. (c) Cheng, T.-Y.; Bullock, R. M. *J. Am. Chem. Soc.* **1999**, *121*, 3150.

**Scheme 2-1**. Platinum-catalyzed polyene cascade cyclization reaction and mechanism displaying the [Pt]-H and $Ph_3C^{+\cdot}$

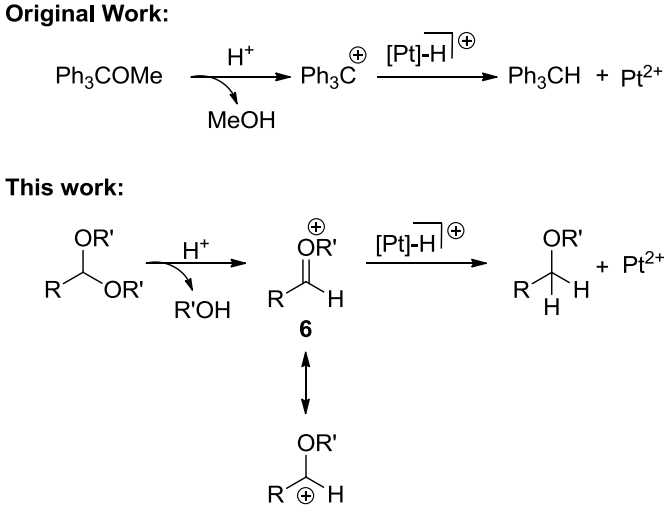



Use of $Ph_3C^+$ provides an approach to Pt(II) Wacker-type catalysts and access to regioselective reactions not available to Pd variants.[3a,5,7] In this first-generation platinum-catalyzed Wacker-type cyclization, the use of $Ph_3COMe$ which, upon reacting with $[Ph_2NH_2][BF_4]$, as "$H^+$" (the by-product of the electrophilic activation), liberated MeOH and the active $Ph_3C^+$ was convenient and served to keep the concentration of the reactive species ($Ph_3C^+$) at relatively low levels. This ultimately enabled the development of catalytic, enantio- and regioselective oxidative cascade cyclizations.

[7]For recent reviews on electrophilic Pt catalysts see reference 3a and Fürstner, A.; Davies, P. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3410.

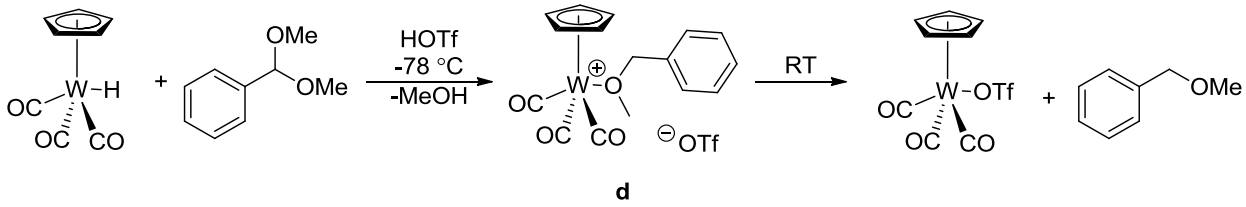
A major disadvantage of utilizing $Ph_3C^+$, however, was the consequent generation of a full equivalent of $Ph_3CH$, which, combined with unreacted $Ph_3COMe$, makes workup and product isolation cumbersome. To combat this, a trityl-bound polystyrene resin was utilized. Due to its heterogeneous nature, the trityl-bound resin is easily removed from the reaction mixture during workup; however, batch to batch variability was observed with some reduction in activity. To circumvent these limitations, we sought an alternative "oxidant" or hydride abstractor that would react similarly to $Ph_3C^+$ but also encompass the following qualities (1) would not react unless liberated by an in situ generated acid keeping the relative concentration low; (2) small in size, so that the reaction would be atom economical and (3) conveniently removed during reaction workup (i.e. vacuum). To this end, we considered the possibility that acetals, ketals, and ortho-esters might be capable of hydride abstraction under acidic conditions (Scheme 2-2).

**Scheme 2-2**. Comparison of previous work using $Ph_3C^+$ and our proposal to use an acetal to abstract a hydride from a [Pt]-H.



Supporting the idea that acetals could be used as potential hydride abstractors were ionic hydrogenations of acetals reported by Bullock.[8] In contrast to the mechanism for traditional hydrogenation of ketones (which includes insertion of the ketone into a [M]-H bond), ionic hydrogenations deliver $H_2$ to a ketone in the form of protonation by a strong acid followed by direct hydride transfer from a [M]-H. In 1996, Bullock reported the ionic hydrogenation of acetals using a $Cp(CO)_3WH$ complex (Scheme 2-3).[8a] After protonation by triflic acid and loss of methanol in benzaldehyde dimethyl acetal, the Bullock group was able to observe and isolate a [M]-benzyl methyl ether complex, **d**, at low temperatures. They found that overtime at room temperature benzyl methyl ether displaced from **d**, suggesting that **d** is kinetically stable and thermodynamically unstable. These results suggested that acetals had the potential to first react with a proton source, generated from the deprotonation during cyclization, then react with a [M]-H to abstract the hydride, generating an ether and turning over the catalytic cycle.

**Scheme 2-3.** Ionic hydrogenation of acetals and ketals generating a [M]-ether complex as kinetic intermediate.




**d**

## 2.2. Results and discussion

### 2.2.1. Synthesis and characterization [Pt]-H

In our systems, the $P_2Pt^{2+}$-catalyzed polyene cyclization reactions are buffered with $Ph_2NH$; therefore, we first tested whether its conjugate acid, $Ph_2NH_2^+$, could generate a

[8](a) Song, J.-S.; Szalda, D. J.; Bullock, R. M. *J. Am. Chem. Soc.* **1996**, *118*, 11134. (b) Bullock, R. M. *Chem. Eur. J.* **2004**, *10*, 2366. (c) Song, J.-S.; Szalda, D. J.; Bullock, R. M. *Organometallics* **2001**, *20*, 3337. (d) Song, J.-S.; Szalda, D. J.; Bullock, R. M.; Lawrie, C. J. C.; Rodkin, M. A.; Norton, J. R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1233.

putative oxocarbenium ion, which would later be the active hydride abstractor.[9] As a starting point, benzaldehyde dimethyl acetal was combined with isolated $[Ph_2NH_2][BF_4]$ and 10 equivalents of $CD_3OD$ in an NMR tube. In < 5 min at room temperature, complete exchange gave $PhCH(OCD_3)_2$, which was observed by $^1H$ NMR spectroscopy (Eq. 2-1). This suggested that the putative oxocarbenium ion, **7**, was readily accessible under known compatible reaction conditions for the substrates in $P_2Pt^{2+}$-catalyzed cyclizations (Figure 2-1).

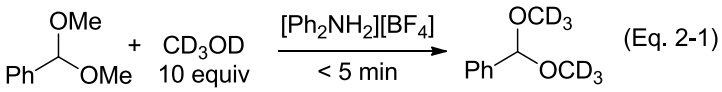
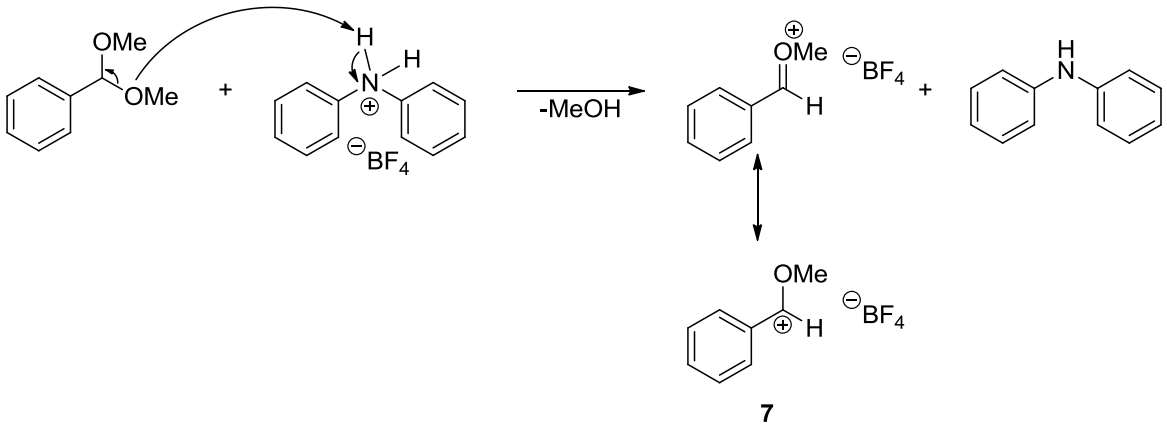


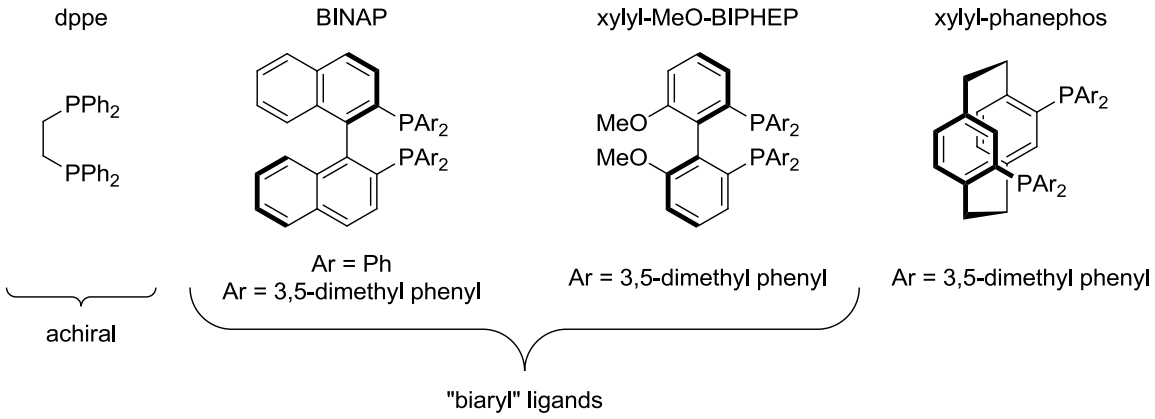

**Figure 2-1.** Generation of a putative oxocarbenium compound.



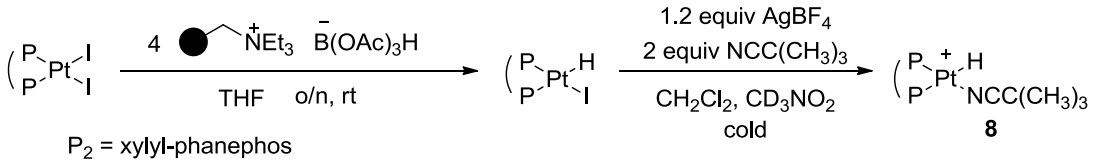

The ability of these reactive oxocarbenium compounds, such as **7**, to abstract hydride from a catalytic $[P_2Pt\text{-}H]^+$ intermediate was examined using [(xylyl-phanephos)Pt(H)(NCC$(CH_3)_3$)][$BF_4$], **8,** a mimic of the putative $[P_2Pt\text{-}H]^+$ intermediate in our reaction mechanism. Interesting to note that using achiral or biaryl ligands (Figure 2-2) to synthesize the $P_2Pt$-H complexes resulted in decomposition of the [Pt] species and complex reaction mixtures.

[9]Portions of this chapter were adapted with permission from Cochrane, N. A.; Brookhart, M. S.; Gagné, M. R. *Organometallics* **2011**, *30*, 2457.

**Figure 2-2.** Commercially available $P_2$ ligands for coordination to [Pt] for catalytic cascade cyclization.




**Scheme 2-4**. Synthesis of [(*S*)-(xylyl-phanephos)Pt(H)(NCC(CH$_3$)$_3$)][BF$_4$], **8**, from (*S*)-(xylyl-phanephos)PtI$_2$



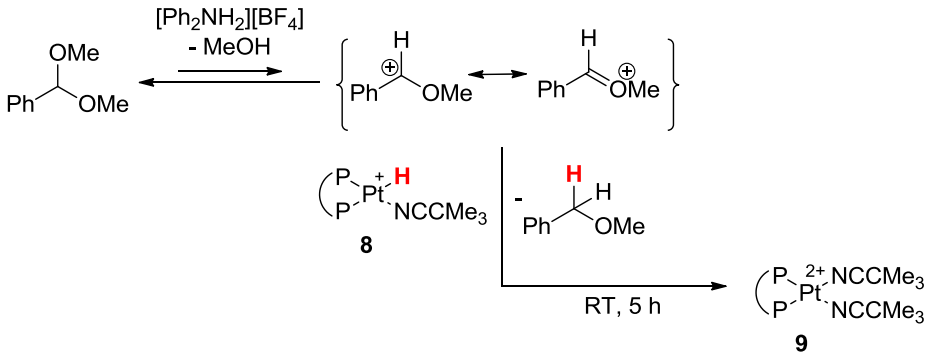

Complex **8** could be generated in situ from the corresponding $P_2$Pt(H)I, dissolved in $CD_2Cl_2$, by halide abstraction with $AgBF_4$ in the presence of excess $NCC(CH_3)_3$ at low temperatures (Scheme 2-4). The resulting complex was not stable in $CD_2Cl_2$ and would decompose to $P_2PtCl_2$, for this reason, $CD_3NO_2$ was added in a 3:2 mixture with $CD_2Cl_2$ to minimize byproduct formation. For these reactions it was important that at least two equivalents of a coordinating nitrile, $NCC(CH_3)_3$ were used to stabilize the cationic complex. Interestingly, when attempting to synthesize this [Pt]-H complex using $NCC_6F_5$, the nitrile used during catalytic reactions due to its lability, more than 10 equivalents of nitrile had to be used to generate a moderately stable [Pt]-H complex. In addition, $BF_4$ was the ideal counter-ion for our systems due to convenience and innocuous nature towards the metal complexes.

All attempts to isolate this complex resulted in decomposition to multiple unknown species. $P_2Pt(H)I$ was isolated as a yellow solid from the reaction of $P_2PtI_2$ with polystyrene-bound triacetoxyborohydride at room temperature overnight (see Section 2.4.2 for further details).

### 2.2.2. Stoichiometric results

To observe possible hydride abstraction activity, a stoichiometric amount of **8** was added to a premixed solution of a 1:1 ratio of benzaldehyde dimethyl acetal and $[Ph_2NH_2][BF_4]$ in an NMR tube with $CD_3NO_2$, the solvent of choice for catalysis (Scheme 2-5). The reaction was monitored by $^{31}P$ NMR spectroscopy. Over the course of 5 h, **8** cleanly converted to $[(xylyl\text{-}phanephos)Pt(NCC(CH_3)_3)_2][(BF_4)_2]$, **9**, with no observed intermediates. By $^{1}H$ NMR, the byproducts of benzyl methyl ether and methanol were observed. In addition, benzyl methyl ether was observed by GC-MS (m/z = 122). These results are consistent with Scheme 2-5. Under identical conditions, a mixture of $Ph_3COMe$ with a stoichiometric amount of $[Ph_2NH_2][BF_4]$ was allowed to react, then added to **8** resulting in > 95% conversion to **9**. As expected, $Ph_3CH$ was observed as the only byproduct by $^{1}H$ NMR and GC-MS (m/z = 244).

**Scheme 2-5.** Predicted pathway for activation and hydride abstraction using benzaldehyde dimethyl acetal.



With a reliable protocol in hand for testing the viability of acetal-based hydride abstraction, including the use of $[Ph_2NH_2][BF_4]$ as the $H^+$ source, other convenient commercially available aromatic, cyclic and aliphatic acetals and ketals were tested. As shown in Table 2-1, the most successful aromatic hydride abstractor candidates included benzaldehyde dimethyl acetal and 4-methoxy benzaldehyde dimethyl acetal, each giving 95% conversion to **9** within 24 h. Noteworthy is the observation that parent benzaldehyde was equally effective and presumably paralleled the ionic hydrogenation of carbonyl compounds reported by Bullock, Tilset, Norton and others.[8a,b, d, 10,11,12] In particular, the Casey group reported the ionic hydrogenation of benzaldehyde using a [Ru]-H complex, in which isotope effects suggest that the protonation and hydride transfer happen simultaneously,[13] while that is not operative in our system, the hydride transfer from a [M]-H to benzaldehyde is possible.

Tilset has previously demonstrated that hydride abstraction by triflic acid in acetone is proportional to the steady state concentration of $(CH_3)_2C{=}OH^+$.[11] This observation reasonably suggests that the rate of the reactions described in Table 2-1 depend on a combination of factors including the steady state concentration of the oxocarbenium ion along with its electrophilicity. Stabilized ions will be present in higher steady state concentrations (entry 4, Table 2-1) but they are less electrophilic, making their reactions with the [Pt]-H less favored than the more electrophilic oxocarbenium compounds. Similarly, more electrophilic ions (entry 3, Table 2-1) will be present at lower concentrations than

[10]Voges, M. H.; Bullock, R. M. *J. Chem. Soc., Dalton Trans.* **2002**, 759.

[11]Smith, K.-T.; Norton, J. R.; Tilset, M. *Organometallics* **1996**, *15*, 4515.

[12]Guan, H.; Iimura, M.; Magee, M. P.; Norton, J. R.; Zhu, G. *J. Am . Chem. Soc.* **2005**, *127*, 7805.

[13](a) Casey, C. P.; Johnson, J. B. *J. Am. Chem. Soc.* **2005**, *127*, 1883. (b) Casey, C. P.; Singer, S. W.; Powell, D. R.; Hayashi, R. K.; Kavana, M. *J. Am. Chem. Soc.* **2001**, *123*, 1090.

stabilized ions, but would compensate with higher reactivities. The results suggest that the balance of forces tend to favor the more stabilized oxocarbenium ions (entries 2-4 and 9-10).

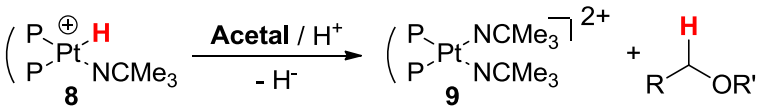
Within one hour of reacting anisaldehyde dimethyl acetal with $[Ph_2NH_2][BF_4]$, 60% methanol and 40% starting material (acetal) were observed by $^1H$ NMR. In a similar experiment with 4-chlorobenzaldehyde dimethyl acetal, no MeOH was observed after 24h by $^1H$ NMR suggesting that the oxocarbenium is highly unfavored, supporting our original hypothesis that the stabilized oxocarbenium ions are favored.

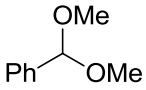
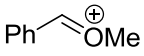
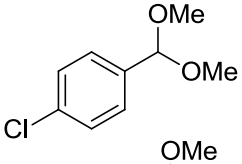
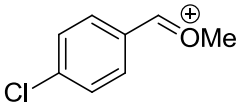
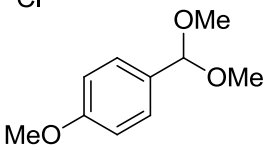
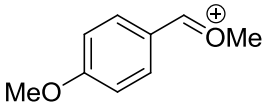
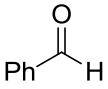
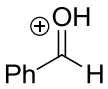
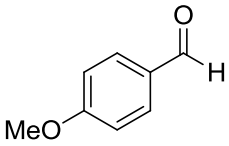
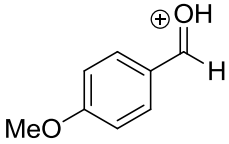
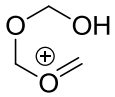
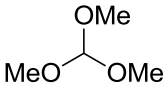
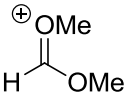
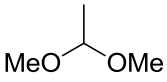
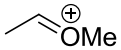
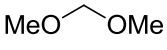
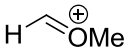
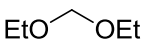
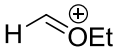
Considering two possible competing forces involved in these stoichiometric reactions, it is possible that the benzaldehyde dimethyl acetal and benzaldehyde are successful at hydride abstraction due to oxocarbenium stability from conjugation with the phenyl rings. Compared with $Ph_3COMe$ or $Ph_3C^+$, there is far less conjugation because there is only one aromatic ring as opposed to three ($Ph_3C^+$), however, there is conjugation which would help to stabilize the formation of a carbenium ion, so these species would in turn abstract the [Pt]-H because there would be a putative oxocarbenium ion present to react.

Despite the lack of observable intermediates, it is hypothesized that these reactions follow those reported by both Bullock and Tilset where hydride abstraction from [M]-H complexes by protonated ketones proceed through a pathway wherein oxygen coordination to the metal, generating the kinetically stabilized ether complex, immediately follows [M]-H breakage and yields alcohols as the organic products (Scheme 2-3).[8,10,11,14]

[14](a) Fagan, P. J.; Voges, M. H.; Bullock, R. M. *Organometallics* **2010**, *29*, 1045. (b) Kimmich, B. F. M.; Fagan, P. J.; Hauptman, E.; Marshall. W. J.; Bullock R. M. *Organometallics* **2005**, *24*, 6220.

**Table 2-1**. Stoichiometric hydride abstraction from [Pt]-H using acetals and ketals.




| Entry | Acetal | Hydride Abstractor | % **9**[a] |
|---|---|---|---|
| 1 | $Ph_3COMe$ | $Ph_3C^+$ | >95% |
| 2 |  |  | >95% |
| 3 |  |  | 39% |
| 4 |  |  | >95% |
| 5 |  |  | >95% |
| 6 |  |  | 61% |
| 7 |  |  | 52% |
| 8 |  |  | 18% |
| 9 |  |  | 71% |
| 10 |  |  | >95% |
| 11 |  |  | 83% |

[a] Acetal added to $[Ph_2NH_2][BF_4]$ in 0.1 mL $CD_3NO_2$ for 5 min at RT, subsequently [Pt] in 0.2 mL $CD_2Cl_2$ / 0.3 mL $CD_3NO_2$ was added. [b] % conversion to **9** after 24 h as determined by $^{31}P$ NMR spectroscopy.

In addition to aromatic acetals, aliphatic acetals were also examined and found to be viable sources of oxocarbenium ions for hydride abstraction (entries 7-11, Table 2-1). These

aliphatic acetals seem to follow a trend consistent with the observations of the Bullock group where secondary carbenium ions are more reactive than tertiary ions (entries 8-11, Table 2-1).[8,15,16] There also seems to be a slight steric effect, as seen with entries 10 and 11 in Table 2-1. In addition, the fast ring closure of the trioxane oxocarbenium perhaps contributed to the low steady state concentration, resulting in an ineffective hydride abstractor. In contrast, trimethoxymethane generates a oxocarbenium stabilized by two methoxy groups, suggesting that the oxocarbenium is in a high steady state concentration, but is not very electrophilic, therefore, it likely suffers from a slow hydride abstraction rate resulting in the low conversion of **8** to **9** over 24h (entry 8, Table 2-1). The results obtained from the acetals derived from formaldehyde and acetaldehyde, especially dimethoxymethane, were encouraging, generating **9** in high yields. Since both the reaction products and dimethoxymethane are volatile, workup using this re-oxidant is particularly attractive.

### 2.2.3. Catalytic results

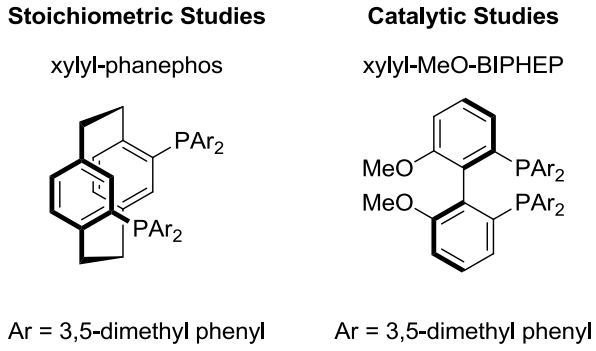
Based on the stoichiometric hydride abstraction reactions, the most efficient hydride abstractor candidates were submitted to catalytic reaction conditions using the well-studied and well-behaved biaryl xylyl-MeO-BIPHEP catalyst based on previous Pt(II) cascade cyclization in the Gagné group.[5] Interesting to note that catalysts derived from xylyl-phanephos provided complex reaction mixtures, while the hydride could not be reliably generated for the biaryl ligand complexes. This study, therefore, relied on a combination of both ligands (xylyl-phanephos for stoichiometric studies, xylyl-MeO-BIPHEP for catalytic studies, see Figure 2-3). For these catalytic reactions, $Ph_2NH$ was used as the base to buffer

[15]Song, J.-S.; Bullock, R. M. *J. Am. Chem. Soc.* **1994**, *116*, 8602.

[16](a) Mayr, H.; Lang, G.; Ofial, A. R. *J. Am. Chem. Soc.* **2002**, *124*, 4076. (b) Mayr, H.; Patz, M. *Angew. Chem,. Int. Ed. Engl.* **1994**, *33*, 938.

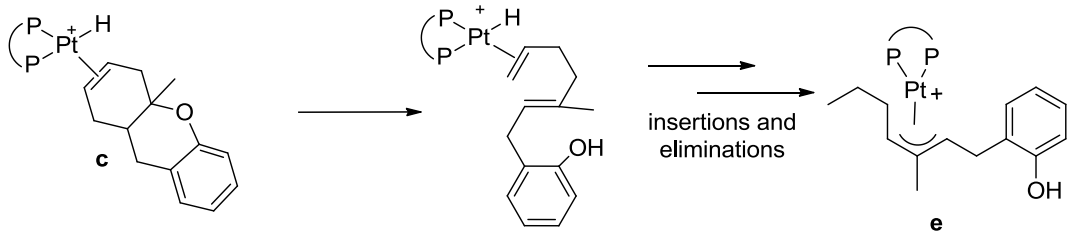
the reactions and $CH_3NO_2$ was used as solvent because of its success in previous catalytic cyclization reactions.

**Figure 2-3.** (*S*)-(xylyl-phanephos) and (*R*)-(xylyl-MeO-BIPHEP) ligands used in these studies.




Under catalytic conditions, if hydride abstraction is slow, the [Pt]-H reacts with additional equivalents of substrate causing the catalyst to become inactive as the π-allyl complex, **e** (Scheme 2-6).[17] With an inactive catalyst, the substrate is then subjected to catalysis with the in situ generated $[Ph_2NH_2][BF_4]$ resulting in mono-cyclized compound **10** (Scheme 2-7).

**Scheme 2-6.** Deactivation of the [Pt] catalyst through formation of the π-allyl complex.




[17]Campbell, A. N. Platinum (II) Catalyzed Diene Cyclizations, Ph.D. Thesis, University of North Carolina at Chapel Hill, Chapel Hill NC, December 2008.

**Scheme 2-7**. Acid-catalyzed byproduct formation of substrate **1**.

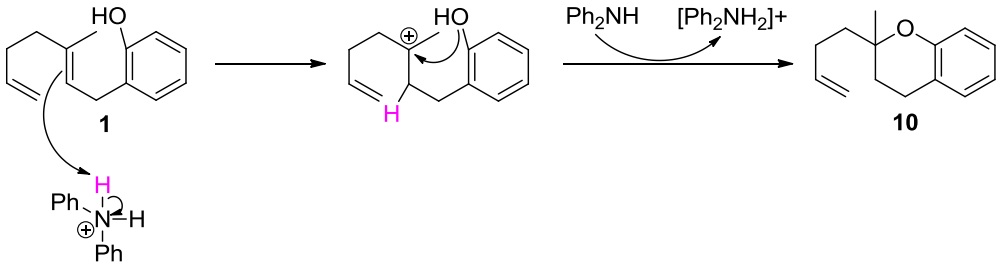
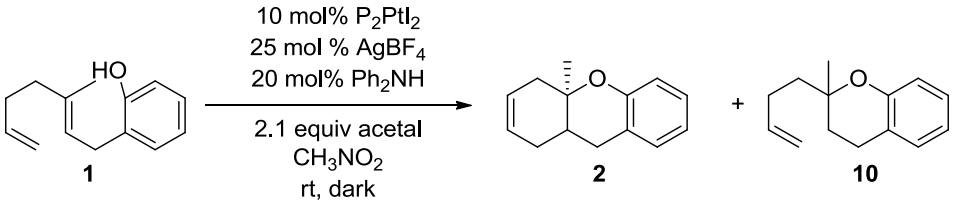
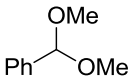
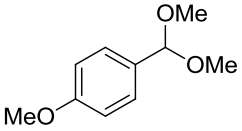
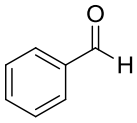
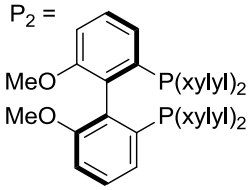



**Table 2-2**. Hydride abstraction using acetals under catalytic conditions.




| Entry | Acetal | **%2** (ee)[b] | **%10**[b] |
|---|---|---|---|
| 1 | $Ph_3COMe$ | 67 (36) | 33 |
| 2 |  | 35 (35) | 3 |
| 3 |  | 7 (38) | 0.4 |
| 4 |  | 48 (38) | 20 |
| 5[c] |  | 50 (37) | 4 |

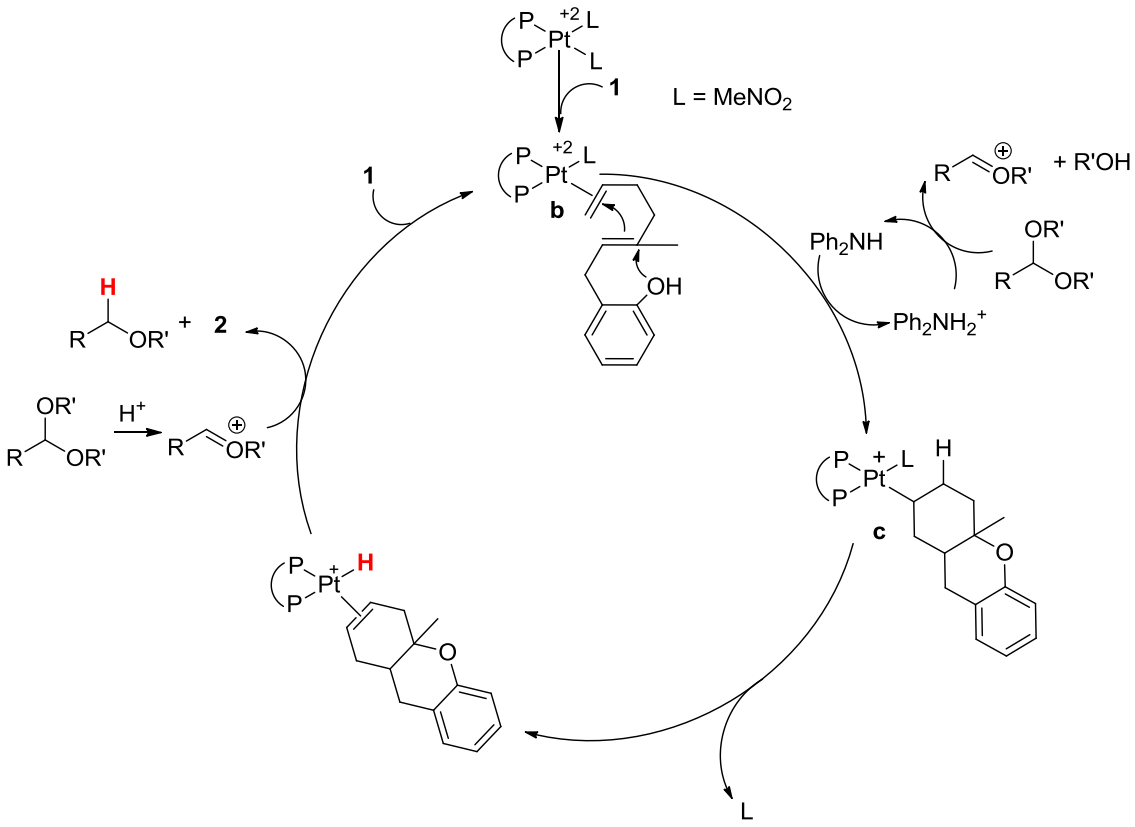



[a] All reactions performed under standard catalytic conditions with 13 mM solution of 10 mol% [(R)-(xylyl-MeO-BIPHEP)]$PtI_2$, 25 mol% $AgBF_4$, 20 mol% $Ph_2NH$, 2.1 equiv acetal in $CH_3NO_2$. [b] Yields and % ee determined by chiral GC after 24 h. The mass balance was unreacted **1**. [c] Results after 48 h.

The results in Table **2-2** show that benzaldehyde dimethyl acetal favors the formation of the desired β-H eliminated product, **2**, indicating that the hydride abstraction step is rapid. This reaction, however, has a low yield as compared with $Ph_3COMe$. Dimethoxymethane as hydride abstractor candidate in catalytic reactions forms comparable yields to those reactions using the standard $Ph_3COMe$; however, unlike $Ph_3COMe$, these reactions are competitive with Brønsted acid catalysis, suggesting that the hydride abstraction is efficient with dimethoxymethane.

Our working mechanism for this new protocol is shown in Scheme 2-8. Similar to previous studies, the $P_2Pt$ dication coordinates to the least substituted alkene and initiates the cyclization of **1** to give cationic $P_2Pt$-alkyl that regioselectively β-H eliminates to generate **2**. The transiently generated oxocarbenium ion abstracts the hydride from the putative $P_2Pt$-H to turn the catalytic cycle over by regenerating the electrophilic $P_2Pt^{2+}$ initiator. It is interesting to note that unlike traditional Wacker reactions, platinum remains as Pt(II) throughout this catalytic cycle. Even with $Ph_2NH$ as a buffer, acid buildup can initiate a Brønsted cyclization to generate **10** (Scheme 2-7). As shown in Table **2-2**, the acetals, while generally more sluggish than $Ph_3COMe$, were also less likely to generate Brønsted products. Dimethoxymethane was especially selective, giving a high preponderance of the desired **2** over **10**. Enantioselectivities were unchanged compared to experiments using $Ph_3COMe$.[5] Product isolation of **2** for entry 5 (Table **2-2**) simply involved running the reaction mixture through a plug of silica gel to remove the catalyst, followed by removal of the methanol and dimethylether byproducts via vacuum concentration.

**Scheme 2-8**. Proposed catalytic cycle using an oxocarbenium ion as hydride abstractor.



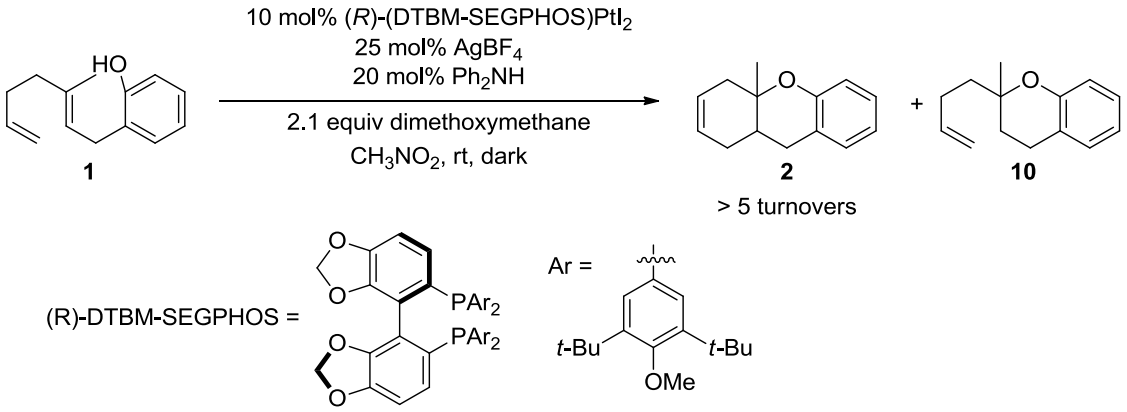

## 2.3. Conclusion

Overall, these data suggest that the previously described model stoichiometric reactions using activated acetals outlined in Table 2-1 correlate to their utility as catalytic hydride abstractors in our oxidative cascade cyclizations. Due to poor atom economy as well as demanding isolation conditions of $Ph_3C^+$, the chemistry herein has presented alternative hydride abstractors. From both stoichiometric and catalytic reactions, dimethoxymethane seems to be the most useful in that it is the smallest and the easiest to remove as the product of hydride abstraction is dimethyl ether.

With access to these smaller and easily removed hydride abstractors, catalytic systems in which hydride abstraction was previously inaccessible, is now achievable as seen

with the bulky (*R*)-(DTBM-SEGPHOS) system (Scheme 2-9). These results indicate that using dimethoxymethane allows for approximately 5 catalytic turnovers, however, the enantioselectivity is poor. Attempts to extend this chemistry to other Wacker-type systems are described in Appendix C.

**Scheme 2-9**. Catalytic reaction using (DTBM-SEGPHOS)$Pt^{2+}$ as the active catalyst showed catalytic turnover using dimethoxymethane as hydride abstractor.




To our knowledge, these results demonstrate that acetals can, for the first time, serve as stoichiometric oxidants in Wacker-type catalysis with concomitant improvements in atom efficiency and ease of use over alternative oxidants (e.g. benzoquinone and $Ph_3COMe$).

## 2.4. Experimental details

### 2.4.1 Materials and methods

Metal-catalyzed reactions were carried out under an atmosphere of nitrogen in a nitrogen-filled glovebox. Stoichiometric reactions were carried out in oven-dried NMR tubes, whereas catalytic reactions were carried out in 3.5 mL vials purchased from Fisher Scientific. $CD_3NO_2$ was purchased from Cambridge Isotope Laboratories and freeze-pump-

thaw degassed before use. $CH_3NO_2$ was purified as previously described,[18] dried with $MgSO_4$, distilled from $CaSO_4$, and freeze-pump-thaw degassed before use. (S)-xylyl-PHANEPHOS, (R)-xylyl-MeO-BIPHEP and (*R*)-DTBM-SEGPHOS were purchased from Strem Chemicals Inc. and used as received. 2,3,4,5,6-pentafluorobenzonitrile, $AgBF_4$ and acetals were purchased from Aldrich and used without further purification. Triethylammonium methylpolystyrene triacetoxyborohydride was purchased from Biotage and used without further purification. **1**,[2f] $(COD)PtI_2$[19] and $(P_2)PtI_2$[20] were prepared according to literature procedures. $^1H$, $^{31}P$ NMR data were collected on a Bruker 400 and 600 MHz Avance spectrometer. Chemical shifts are reported in ppm and referenced to residual solvent peaks for $^1H$ NMR spectroscopy or to 85% $H_3PO4$, an external standard, for $^{31}P$ NMR spectroscopy. GC-MS data was performed with an Agilent G4350A GC/MSD system containing a 7820A GC with an HP-5MS column (length 30m; I. D. 0.250 mm) connected to an Agilent 5975 MSD. The GC method consisted of the following parameters: inlet temperature 250 ˚C; inlet and column pressure of 11.9 psi He; column flow rate 1 mL/min; oven temperature held at 125 ˚C for 3 min then ramped 20 ˚C/min to 250 ˚C. The temperature was then held at 250 ˚C for 5 minutes. The detector temperature was set to 280 ˚C. Achiral GC was performed on an Agilent 6890 using an Agilent HP-5 column with the following parameters: inlet temperature 250 ˚C; 19.99 psi of helium; oven temperature held at 100 ˚C for 3 min then ramped to 250 ˚C at 10 ˚C/min. The 30 m chiral column with 320 µm diameter was run using 19.99 psi at 9.2 mL/min; the FID detector was held at 250 ˚C with a flow rate of 40 mL/min $H_2$, 450 mL/min air and makeup flow of 45 mL/min helium.

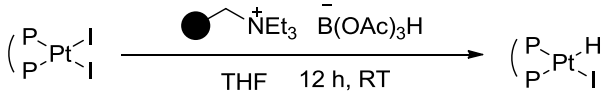
[18]Commercial nitromethane contains nitrile impurities that poison $Pt^{2+}$ species, for purification see: Parrett, F. W.; Sun, M. S. *J. Chem. Ed*. **1977**, *54*, 448.

[19]Clark, H.; Manzer, L. E. *J. Organomet.Chem*. **1973**, *59*, 411.

[20]Colacot, T. J.; Qian, H.; Cea-Olivares, R.; Hernandez-Ortega, S. *J. Organomet.Chem*. **2001**, *691*, 637.

Chiral GC was performed on an Agilent 6890 using an Agilent β-Cyclosil column with the following parameters: inlet temperature 250 ˚C, 19.99 psi of helium; oven temperature held at 80 ˚C for 5 min then ramped to 170 ˚C at 2 ˚C/min. The 30 m chiral column with 250 μm diameter was run using 19.99 psi at 1.7 mL/min; the FID detector was held at 250 ˚C with a flow rate of 40 mL/min $H_2$, 450 mL/min air and makeup flow of 45 mL/min helium.

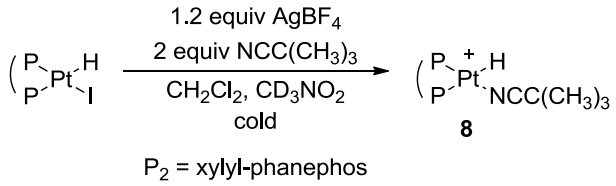
### 2.4.2. Synthesis of Pt complexes




$P_2$ = xylyl-phanephos

**Synthesis of (S)-(xylyl-phanephos)Pt(H)(I):**

To a solution of (*S*)-(xylyl-phanephos)$PtI_2$ (155 mg, 0.15 mmol) in dry THF (4 mL) was added 4 equivalents of triethylammonium methylpolystyrene triacetoxyborohydride resin (254 mg, 0.6 mmol). The reaction mixture was stirred overnight at room temperature. Upon completion of the reaction, the mixture was filtered over a silica plug using $CH_2Cl_2$ and washed with pentane. The yellow filtrate was concentrated to provide a yellow solid (80% yield). $^1$H NMR: (400 MHz, $CD_2Cl_2$) δ 7.66 (m, 3H), 7.61 (m, 3H), 7.24 (d, 4H, $J$ = 11.0 Hz), 7.13 (d, 2H, $J$ = 10.9 Hz), 7.02 (s, 1H), 6.97 (s, 1H), 6.54 (m, 2H), 6.45 (m, 2H), 2.67-2.30 (m, 8H), 2.28-2.23 (m, 24H), -8.75 (dd, 1H, $J_{P\text{-}H}$ = 9.9, 191 Hz, $J_{Pt\text{-}H}$ = 693 Hz). $^{31}$P NMR: (161.85 MHz, $CD_2Cl_2$) δ 32.8 (s, 1P, $J_{Pt\text{-}P}$ = 2025 Hz), 27.8 (s, 1P, $J_{Pt\text{-}P}$ = 4331 Hz). HRMS (ESI) [M]/z calc. 1011.2158, found 1011.2079.



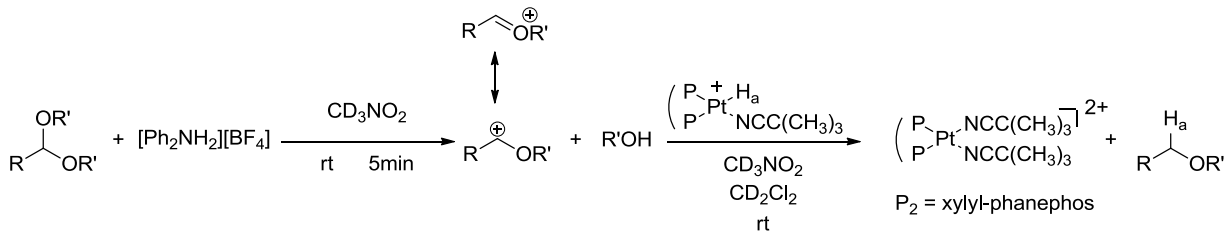

**In-situ Generation of [(S)-(xylyl-phanephos)Pt(H)(NCC(CH$_3$)$_3$)][BF$_4$] (8):**

(S)-(xylyl-phanephos)Pt(H)(I) (15 mg, 0.015 mmol) was preweighed as a solid into a 3.5 mL vial in a glovebox. In an NMR tube was added $CD_3NO_2$ (0.3 mL) and 1.2 equivalents of $AgBF_4$ (3.5 mg, 0.018 mmol) relative to [Pt]. The solution was frozen in a coldwell containing copper beads, cooled with liquid nitrogen. To the frozen $CD_3NO_2$ solution was added $NCC(CH_3)_3$ (3 µL, 0.03 mmol) via microsyringe. A premixed yellow solution of 0.2 mL $CD_2Cl_2$with [Pt](H)(I) was added via syringe to the frozen reaction. The NMR tube was capped with a septum and shaken, resulting in an orange solution with a white precipitate. All attempts to isolate **8** resulted in decomposition to an unknown species. $^1$H NMR: (400 MHz, $CD_3NO_2$) δ 8.02 (d, 1H, J = 19.4 Hz), 7.8 (br, 4H), 7.50 (s, 1H), 7.47 (m, 5H), 7.13 (s, 1H), 6.96 (m, 3H), 6.72 (d, 1H, J = 8.1 Hz), 6.59 (m, 3H), 2.83 (m, 2H), 2.67 (m, 4H), 2.38 (s, 2H), 2.37 (s, 6H), 2.36 (s, 6H), 2.25 (s, 6H), 2.24 (s, 6H), 1.38 (s, 9H), -7.95 (dd, 1H, $J_{P\text{-}H}$ = 19.0, 182.6 Hz, $J_{Pt\text{-}P}$ = 1121 Hz). $^{31}$P NMR: (161.85 MHz, $CD_3NO_2$) δ 31.5 (s, 1P, $J_{Pt\text{-}P}$ = 2064 Hz), 21.5 (s, 1P, $J_{Pt\text{-}P}$ = 4356 Hz).

**Synthesis of [(S)-(xylyl-phanephos)Pt(NCC(CH3)3)2][(BF4)2] (9).**

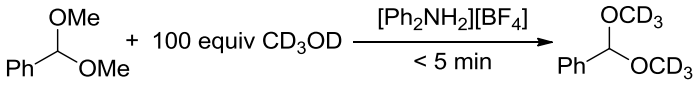
(S)-(xylyl-phanephos)$PtI_2$ (10 mg, 0.008 mmol) was weighed as a solid into a 3.5 mL vial in a glovebox. To this was added $AgBF_4$ (4.3 mg, 0.022 mmol) and $NCC(CH_3)_3$ (2 µL, 0.018 mmol). Upon addition of 0.2 mL $CD_3NO_2$ an immediate color change from orange to yellow was observed. The reaction was then stirred for 1.5 h at RT in the dark. $AgBF_4$ was removed from the reaction mixture via a PTFE 0.2 µm filter resulting in a colorless solution.

All isolation attempts resulted in decomposition to multiple unknown species. $^{1}$H NMR: (600 MHz, CD3NO2) δ 8.02 (s, 4H), 7.60 (s, 1H), 7.57 (s, 1H), 7.52 (s, 2H), 7.44 (s, 2H), 7.42 (s, 2H), 7.36(s, 2H), 6.79 (d, 2H, J = 8.4 Hz), 6.64 (d, 2H, J = 6.0 Hz), 2.84 (t, 2H, J = 20.4 Hz), 2.75 (t, 2H, J = 22.8 Hz), 2.58 (t, 2H, J = 25.2 Hz), 2.46 (m, 2H), 2.41 (s, 12H), 2.35 (s, 12H), 1.42 (s, 18H). $^{31}$P NMR: (242.92 MHz, CD3NO2) δ 15.1 (s, 2P, JPt-P = 3889 Hz).




**General Procedure for stoichiometric reactions on NMR scale:**

To an NMR tube was added a stoichiometric amount of acetal and $[Ph_2NH_2][BF_4]$ (3.9mg, 0.015 mmol). $CD_2Cl_2$ (0.1 mL) was added to the NMR tube and allowed to stand at room temperature for 5 min. To this solution was added 2 via syringe. The reaction was shaken and monitored for the formation of $[(S)\text{-}(xylyl\text{-}phanephos)Pt(NCC(CH_3)_3)_2][(BF_4)_2]$ (**9**) by $^{1}$H NMR and $^{31}$P NMR spectroscopy.




**Exchange reaction with benzaldehyde dimethyl acetal:**

An NMR tube was charged with $[Ph_2NH_2][BF_4]$ (4.6 mg, 0.02 mmol). To this was added benzaldehyde dimethyl acetal (3 µL, 0.02 mmol) via microsyringe; an immediate color

change to yellow was observed on mixing. $CD_3OD$ (10 µL, 0.2 mmol) was added via microsyringe and monitored by GC-MS. The GC-MS indicated that in < 5 min, the peak for benzaldehyde dimethyl acetal (m/z = 152) had disappeared and a peak for benzaldehyde dimethyl acetal-$d_6$ formed (m/z = 158).

**Hydride Abstraction with benzaldehyde dimethyl acetal:**

To an NMR tube was added benzaldehyde dimethyl acetal (2.1 µL, 0.015 mmol) and $[Ph_2NH_2][BF_4]$ (3.9 mg, 0.015 mmol), followed by $CD_2Cl_2$ (0.1 mL). The reaction was shaken and after 5 min at room temperature a solution of **8** (0.015 mmol) was added via syringe. The reaction was shaken, resulting in a color change from orange to green/brown within 5 min. The reaction was monitored by $^1H$ NMR and $^{31}P$ NMR spectroscopy for the formation of $[(S)\text{-}(xylyl\text{-}phanephos)Pt(NCC(CH_3)_3)_2][(BF_4)_2]$ (**9**).

**General procedure for catalytic reactions:**

$AgBF_4$ (2.5 equiv) was added to a 13 mM solution of $[(P_2)Pt]I_2$ in $CH_3NO_2$. The reaction was stirred for 1 hour in the dark. To this was added acetal (21 equiv) followed by $Ph_2NH$ (2 equiv) and 10 equivalents of dienephenol substrate **1**. The reaction mixture was stirred at room temperature in the dark until the reaction was complete by GC analysis. The yield and enantiomeric excess were determined by chiral stationary gas chromatography.

# Chapter 3

## Catalytic Cyclization/Fluorination of Polyenes

### 3.1. Introduction

Due to the prominence of fluorinated compounds in materials, agrochemicals and pharmaceuticals, many studies have focused on the formation of C-F bonds.[1] Specifically, the fluorination of pharmaceutical drug candidates provides increased bioavailability and lipophilicity in addition to masking metabolic hot spots to enhance metabolic stability.[2] Electrophilic fluorination has been used extensively in the last decade to achieve selective fluorination.[3] Despite recent progress with electrophilic fluorinating reagents, the synthesis of fluorinated pharmaceutical drug candidates is still challenging and many deficiencies remain. Enantioselective fluorination is of particular importance for medicinal compounds since each enantiomer generally possesses unique biological properties.[4] Asymmetric fluorination, especially of non-enolate-based carbon nucleophiles

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[1]Hiyama, T. *Organofluorine Compounds*; Springer: Berlin, **2000.**

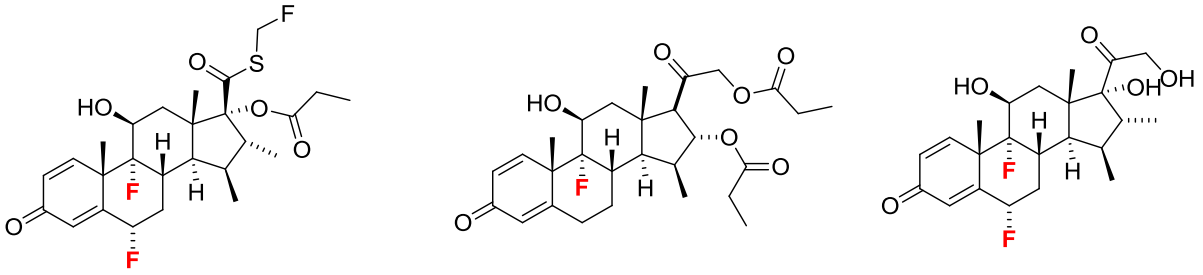
[2](a) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. (b) Furuya, T.; Kuttruff, C. A.; Ritter, T. *Curr. Opin. Drug Discovery* **2008**, *11*, 803., and references therein. (c) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305. (d) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (e) Morgenthaler, M.; Schweizer, E.; Hoffmann-Röder, A.; Benini, F.; Martin, R. E.; Jaeschke, G.; Wagner, B.; Fischer, H.; Bendels, S.; Zimmerli, D.; Schneider, J.; Diederich, F.; Kansy, M.; Müller, K. *ChemMedChem* **2007**, *2*, 1100. (f) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881.

[3]For enantioselective fluorination reviews: (a) Cahard, D.; Xu, X.; Couve-Bonnaire, S.; Pannecoucke, X. *Chem. Soc. Rev.* **2010**, *39*, 558. (b) Lectard, S.; Hamashima, Y.; Sodeoka, M. *Adv. Synth. Catal.* **2010**, *352*, 2708. (c) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1. (d) Pihko, P. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 544. (e) Audouard, C.; Ma, J. A.; Cahard, D. *Adv. Org. Synth.* **2006**, *2*, 431.

[4]Soloshonok, V. A.; Mikami, K.; Yamazaki, T.; Welch, J. T.; Honek, J. F. *Current Fluororganic Chemistry: New Synthetic Directions, Technologies, Materials and Biological Applications*; American Chemical Society, Oxford University Press: USA, **2007.**

has until recently remained elusive and is still challenging for chemists.[5] Fluorinated steroids (Scheme 3-1), in particular, are important bioactive compounds with a paucity of methods for their synthesis.[6] It is important to note that the fluorination in these molecules is regioselective due to the activated enolate carbons, basically these steroids are fluorinated on carbons where fluorination is favorable.

**Scheme 3-1.**Common fluorinated steroids**.**




De novo syntheses of carbocycles with the flexibility for F-incorporation are rare, though such methods would considerably expand the accessibility of such structures.[1,2]

[5]For non-enolate organic enantioselective electrophilic fluorinations: (a) Rauniyar, V.; Lackner, A. D.; Hamilton, G. L.; Toste, F. D. *Science* **2011**, *334*, 1681. (b) Dinoiu, V. *Rev. Roum. Chim.* **2007**, *52*, 219. (c) Kim, S. M.; Kang, Y. K.; Cho, M. J.; Mang, J. Y.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2007**, *28*, 2435. (d) Togni, A. Mezzetti, A. Barthazy, P. Becker, C.; Devillers, I.; Frantz, R.; Hintermann, L.; Perseghini, M.; Sanna, M. *Chimia* **2001**, *55*, 801. (e) Qiu, S.; Xu, T.; Zhou, J.; Guo, Y.; Liu, G. *J. Am. Chem. Soc.* **2010**, *132*, 2856.

[6]For aromatic electrophilic fluorinations, see for example: (a) Grushin, V. V. *Acc. Chem. Res.* **2010**, *43*, 160. (b) Gouverneur, V. *Nat Chem* **2012**, *4*, 152. (c) Borodkin, G. I.; Shubin, V. G. *Russ. Chem. Rev.* **2010**, *79*, 259. (d) Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 10795. (e) Chan, K. S. L.; Wasa, M.; Wang, X.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2011**, *50*, 9081. (f) Tang, P.; Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 12150. (g) Wang, X.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520. (h) Furuya, T.; Kaiser, H. M.; Ritter, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 5993. (i) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134.

Transition metal catalyzed cyclizations, if suitably coupled to M-C fluorination reactions,[7] could provide a route to complex fluorinated carbo- and hetero-cycles with control of absolute and relative stereochemistry.

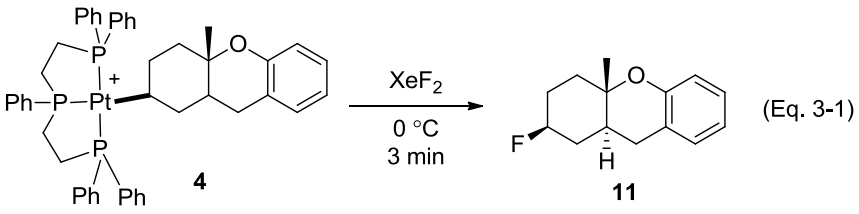
In an effort to explore group 10 metal complexes for the fluorination of organic substrates, the Gagné group, hoped to provide a route that encompassed cyclization of a polyene followed by selective fluorination to generate an organofluorine compound. Previously, the Gagné group has shown that electrophilic Pt(II) complexes are effective initiators of C-C bond forming cation-olefin cascades.[8,9] Using triphos as the ligand, the isolable [(triphos)Pt-R][$BF_4$] species rapidly and stereospecifically reacts with $XeF_2$ to yield C-F products (Eq. 3-1), which suggests that the desired interception might be feasible.[10]

[7]For electrophilic fluorinations that proceed through M-C bonds, see for example: (a) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature*, **2011**, *473*, 470. (b) Vigalok, A. *Organometallics* **2011**, *30*, 4802. (c) Engle, K. M.; Mei, T.-S.; Wang, X.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2011**, *50*, 1478. (d) Vigalok, A.; Kaspi, A. W. *Top. Organomet. Chem.* **2010**, *31*, 19. (e) Mankad, N. P.; Toste, F. D. *Chem. Sci.* **2012**, *3*, 72. (f) Racowski, J. M.; Gary, J. B.; Sanford, M. S. *Angew. Chem. Int. Ed.* **2012**, *51*, 3414. (g) Dubinsky-Davidchik, I. S.; Potash, S.; Goldberg, I.; Vigalok, A.; Vedernikov, A. N. *J. Am. Chem. Soc.* **2012**, *134*, 14027. (h) Bloom, S.; Pitts, C. R.; Miller, D. C.; Haselton, N.; Holl, M. G.; Urheim, E.; Lectka, T. *Angew. Chem. Int. Ed.* **2012**, *51*, 10580. (i) Furuya, T.; Benitez, D.; Tkatchouk, E.; Strom, A. E.; Tang, P.; Goddard, W. A.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 3793. (j) Furuya, T.; Klein, J. E. M. N.; Ritter, T. *Synthesis* **2010**, *11*, 1804. (k) Ball, N. D.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 3796. (l) Kaspi, A. W.; Yahav-Levi, A.; Goldberg, I.; Vigalok, A. *Inorg. Chem.* **2008**, *47*, 5. (m) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134. (n) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790.

[8](a)Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208. (b) Fürstner, A.; Davies, P. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3410. (c) Chianese, A. R.; Lee, S. J.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2007**, *46*, 4042.

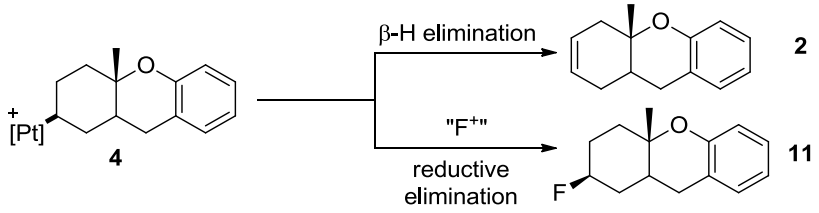
[9](a) Mullen, C. A.; Campbell, A. N.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2008**, *47*, 6011. (b) Mullen, C. A.; Gagné, M. R. *J. Am. Chem. Soc.* **2007**, *129*, 11880. (c) Kerber, W. D.; Gagné, M. R. *Org. Lett.* **2005**, *7*, 3379. (d) Koh, J. H.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2004**, *43*, 3459. (e) Kerber, W. D.; Koh, J. H.; Gagné, M. R. *Org. Lett.* **2004**, *6*, 3013. (f) Koh, J. H.; Larsen, A. O.; Gagné, M. R. *Org. Lett.* **2001**, *3*, 1233.

[10]Zhao, S.-B.; Becker, J. J.; Gagne, M. R. *Organometallics* **2011**, *30*, 3926.




The fate of the organometallic intermediate (**4**) of the polyene cascades can be controlled through the choice of ligand. Using bisphosphine as the supporting ligand, **4** is susceptible to β-H elimination and leads to net dehydrogenated products (**2**). If the Pt-C bond in complex **4** were instead intercepted by an electrophilic fluorine, a cyclization/fluorination protocol could be optimized to result in access to C3-fluorinated compounds (Scheme 3-2).

**Scheme 3-2.** Possible reactions of cationic organometallic Pt-intermediate, **4.**




## 3.2. Results and discussion

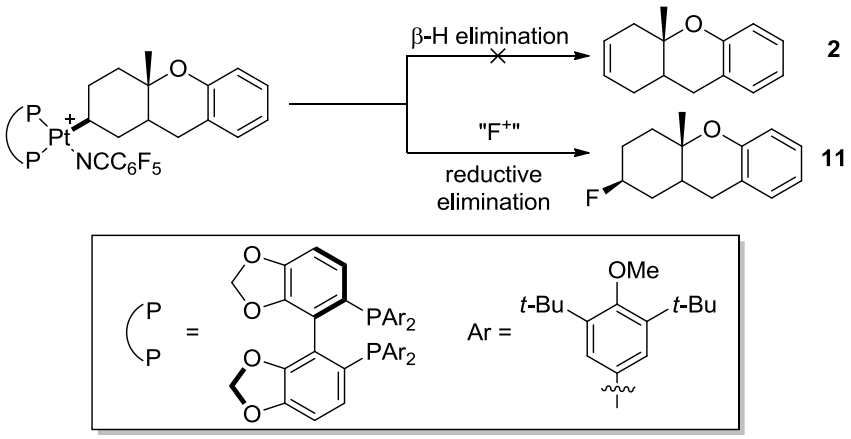
### 3.2.1. Stoichiometric reaction

Since the tridentate triphos ligand does not display catalytic activity,[9,10] the focus of these studies were to utilize a bisphosphine ligand set to develop a catalytic route for fluorination.[11] As mentioned above, one caveat of using bisphosphine ligands are competing pathways to fluorination including β-H elimination and Brønsted acid catalysis (Scheme 3-2

[11]Portions of this chapter were adapted with permission from Cochrane, N. A.; Nguyen, H.; Gagné, M. R. *J. Am. Chem. Soc.* **2013**, *135*, 628.

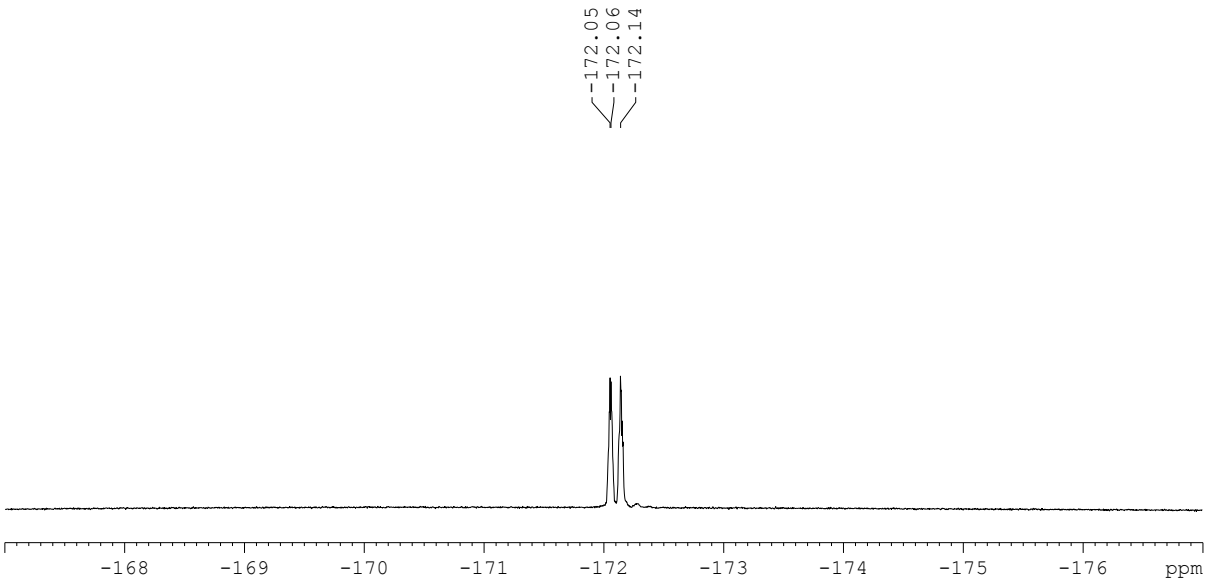
and Chapter 2). For this reason, initial stoichiometric studies used a $P_2$ ligand containing *t*-butyl moieties to increase the steric bulk, thus stabilizing the [Pt]-alkyl intermediate (**c**) and inhibiting β-H elimination in an effort to determine the viability of using a $P_2$ ligand for this chemistry.

**Scheme 3-3**. (DTBM-SEGPHOS)Pt(alkyl)nitrile complex prefers fluorination over β-H elimination.




Interestingly, using stoichiometric chiral (R)-DTBM-SEGPHOS ((*R*)-(−)-5,5′-Bis[di(3,5-di-tert-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole, [(4R)-(4,4′-bi-1,3-benzodioxole)-5,5′-diyl]bis[bis(3,5-di-tert-butyl-4-methoxyphenyl)phosphine]) resulted in 75% yield (determined by GC) of the stereoretentive desired product **11**, which was observed by $^{19}F$ NMR (Figure 3-1), in less than 5 min at 0 °C with $XeF_2$ (Scheme 3-3). The fluorinated product displays a distinct doublet by $^{19}F$ NMR (Figure 3-1) due to the coupling with the geminal proton of approximtely 50Hz. Unfortunately, the product was racemic by chiral GC.

**Figure 3-1.** $^{19}$F NMR spectrum of fluorinated product, **11**, showing coupling to geminal proton.

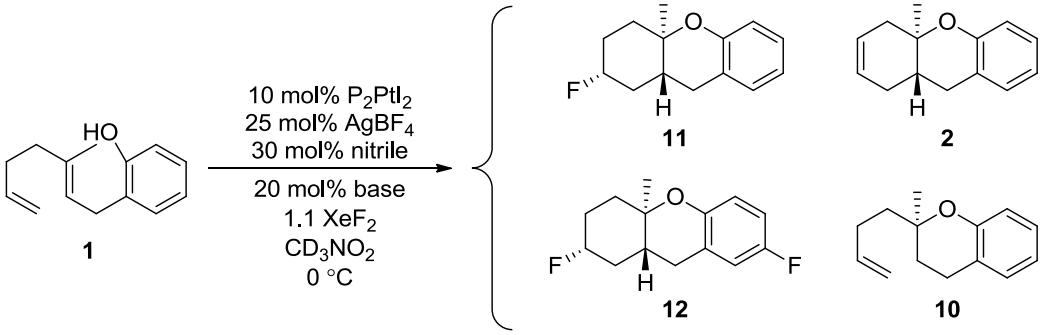



### 3.2.2. Optimization

Since this stoichiometric reaction was successful in showing that a diphosphine was a viable ligand for fluorination, therefore a catalytic variant was developed. In the diphosphine catalyst series that have been examined, (*S*)-xylyl-phanephos ((*S*)-(–)-4,12-bis[di(3,5-xylyl)phosphine]-[2,2]-paracyclophane) has consistently provided the highest enantioselectivity for various cyclization chemistries.[9a] As a starting point for the catalytic cyclization/fluorination, conditions previously optimized for cyclization/β-H elimination reactions were adapted. The modified conditions included use of $AgBF_4$ and nitrile to generate the "active" $[(P_2)Pt(nitrile)_2][(BF_4)_2]$ catalyst. Subsequent addition of a base (to facilitate cyclization), substrate and an electrophilic fluorine source generated the desired product (**11**) as a single (stereoretentive) diastereomer, along with variable quantities of β-H eliminated product (**2**) and the Brønsted product (**10**). When proton sequestering is

inefficient then a slow Brønsted background reaction takes place leading to monocyclized products.

**Table 3-1.** Selected conditions for optimization of the ligand, nitrile and base.



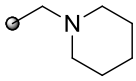
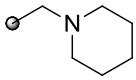
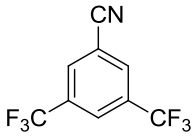
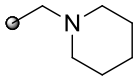
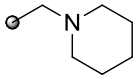
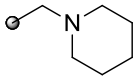
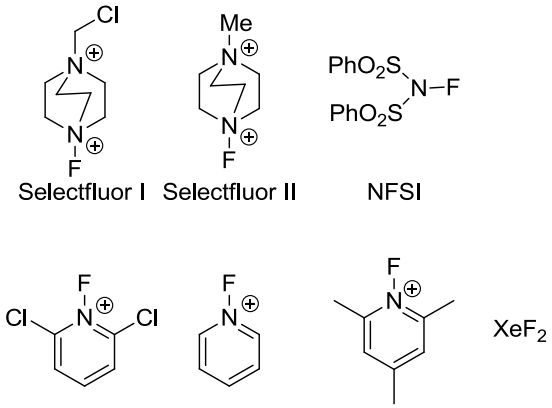

| Entry | $P_2$ | Nitrile | Base | % 11[a] (%ee)[b] | %2[a] | %12[a] | % 10[a] |
|---|---|---|---|---|---|---|---|
| 1 | (*R*)-DTBM-SEGPHOS | $NCC_6F_5$ | None | 20 | 14 | 0 | 57 |
| 2 | (*R*)-DTBM-SEGPHOS | $NCC_6F_5$ | $Ph_2NH$ | 34 | 28 | trace | 14 |
| 3 | (*R*)-DTBM-SEGPHOS | $NCC_6F_5$ | KF | 35 | 0 | 32 | 0 |
| 4 | (*R*)-DTBM-SEGPHOS | $NCC_6F_5$ |  | 63 (13) | 8 | 11 | 0 |
| 5 | (*R*)-DTBM-SEGPHOS | $NCC(CH_3)_3$ |  | 20 | 0 | 0 | 0 |
| 6 | (*R*)-DTBM-SEGPHOS |  |  | 51 | 16 | 5 | 0 |
| 7 | (*R*)-xylyl-MeO-BIPHEP | $NCC_6F_5$ |  | 85 (5) | 10 | 3 | 0 |
| 8 | (*S*)-xylyl-phanephos | $NCC_6F_5$ |  | 72 (75) | 7 | 3 | trace |

Table 3-1 shows the optimization of nitrile and bases added to the reaction; several additional phosphines are included for comparison of enantioselectivities and yield. In Table 3-1, it is obvious that the nitrile present influences the sterics and electronics of the metal. In

these studies, the formation of the $[P_2Pt(NCR')_2][(BF_4)_2]$ and the $[P_2Pt(alkyl)(NCR')][BF_4]$ indicate that differences in the nitrile would either stabilize (more coordinating, electron-donating nitrile such as $NCC(CH_3)_3$) or destabilize (labile ligand such as $NCC_6F_5$) the metal complex, thus effecting reactivity. Similar to previous dehydrogenative cascade cyclization,[9] (*S*)-xylyl-phanephos was uniquely enantioselective (~75%) for controlling the % ee of the cation-olefin cascades while providing a reasonable yield of C-F product (**11**). This $P_2Pt^{2+}$ in conjunction with a labile nitrile ($NCC_6F_5$), resin-bound piperidine base, substrate and $XeF_2$ produced the desired product in both high yields and enantioselectivies.

In screening a variety of electrophilic fluorine sources, it was discovered that only $XeF_2$ effectively competed with β-H elimination. Other less reactive $F^+$ sources showed predominantly elimination products including β-H elimination to **2.**

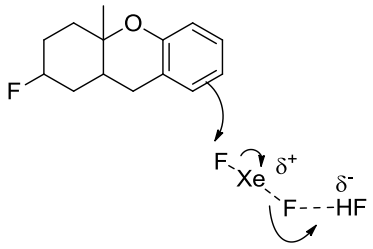
**Figure 3-2.** Electrophilic fluorinating reagents tested under catalytic conditions.



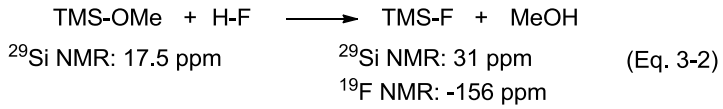

In addition to the desired **11**, over fluorination to **12** was also observed. Since controls showed that **11** does not react with $XeF_2$ and acid is known to enhance the $F^+$ potential of $XeF_2$, we surmised that the HF byproduct of cyclization was activating the $XeF_2$

as shown in Scheme 3-4.[12] This problem was easily solved by the addition of TMS-OMe as an HF sponge, which additionally obviates the need for a base.

**Scheme 3-4.** Proposed reaction to generate the double fluorination product (**12**).



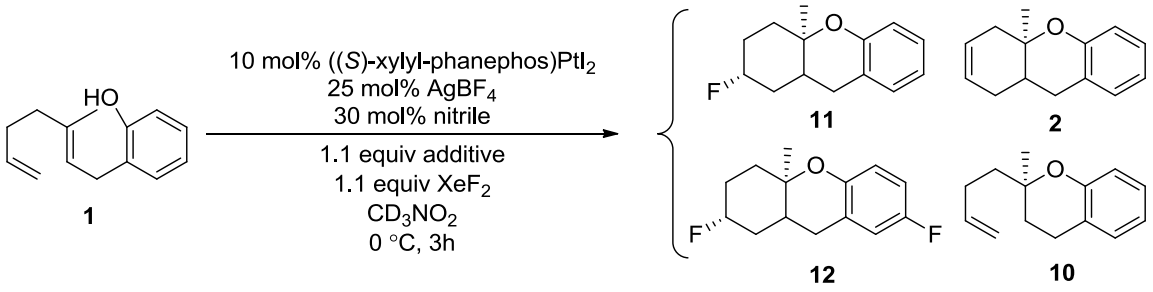

$^{19}F$ and $^{29}Si$ NMR spectra were acquired and it was observed that TMS-OMe was gone and that TMS-F was present, indicating that TMS-OMe indeed is acting as an HF sponge (Equation 3.2).




Optimization studies included testing multiple bisphosphines, solvents, and other TMS-X derivatives (Table 3-1, Table 3-2) . Of the tested HF scavengers, TMS-OMe was the most effective inhibitor of double fluorination. A catalyst formulation comprised of 10 mol% (*S*)-(xylyl-phanephos)$PtI_2$, 25 mol% $AgBF_4$, 30 mol% $NCC_6F_5$ and stoichiometric quantities of $XeF_2$ and TMS-OMe at 0 °C in nitromethane provided **11** in 67% yield and with 75% enantiomeric excess.

[12](a) Tramšek,M.; Žemva, B. *Acta Chim. Slov.* **2006**, *53*, 105. (b) Tius, M. A. *Tetrahedron* **1995**, *51*, 6605.

**Table 3-2.** Optimization of silanes and silyl ethers.



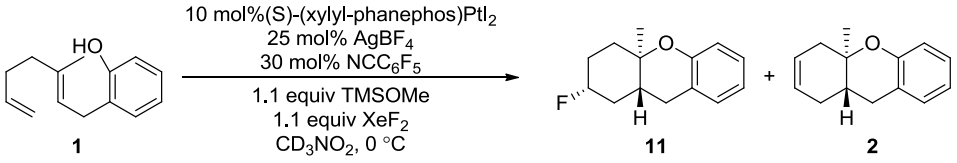

| Entry | Additive | % 11[a] | %2[a] | % 12[a] | % 10[a] |
|---|---|---|---|---|---|
| 1 | $Me_3Si-O-SiMe_3$ | 56 | 3 | 2 | 0 |
| 2 | TMS-OMe | 74 | 5 | trace | 0 |
| 3 | $(Me_2)(MeO)_2Si$ | 66 | 3 | 0 | 0 |
| 4[b] | $Me(EtO)_3Si$ | 57 | 8 | 0 | 0 |
| 5 | $Me_6Si_2$ | 71 | 4 | 11 | 0 |
| 6 | $Et_3SiH$ | 24 | trace | 0 | 0 |
| 7 | $(EtO)_3SiH$ | 11 | 0 | 0 | 0 |

(a) Uncorrected GC percentages. Mass balance is unreacted starting material. (b) Unknown by-products formed in ~5%.

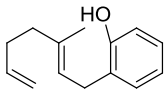
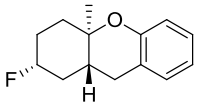
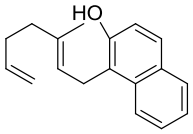
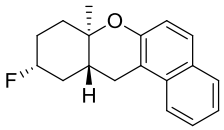
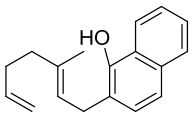
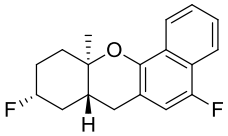
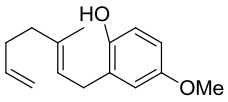
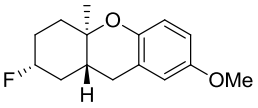
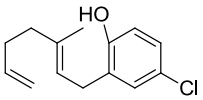
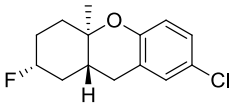
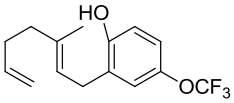
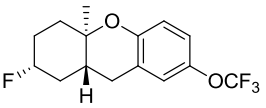
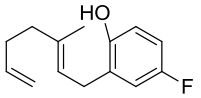
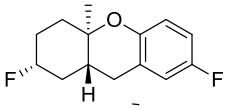
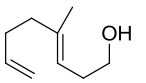
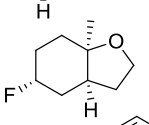
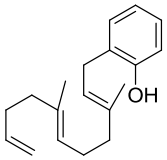
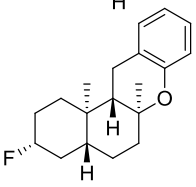
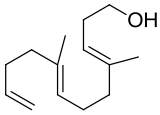
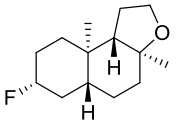
### 3.2.3. Substrate scope

The optimized conditions, described above, were subsequently applied to a variety of alcohol and phenol terminated dienes and trienes (Table 3-3). In most cases, high conversion of substrate occurred within three hours; however, the reactions were allowed to proceed for 24 h at 0 ˚C to ensure complete consumption of the $XeF_2$. For the substrates in Table 3-3, no Brønsted acid derived products like **10** were observed, and a single diastereomer consistent with stereoretentive fluorination of the intermediate $P_2Pt$-alkyl cation, **c**, was observed.

**Table 3-3.** Substrate Scope for catalytic electrophilic fluorination.[a]




**1** **11** **2**

| Entry | Polyene | Product | Yield **11** (%ee)[b] | Yield **2**[c] |
|---|---|---|---|---|
| 1 |  |  | 67% (75) | 14% |
| 2 |  |  | 67% (73) | 15% |
| 3[d] |  |  | 49% (86) | 15%[e] |
| 4 |  |  | 56% (81) | 16% |
| 5 |  |  | 60% (87) | 13% |
| 6 |  |  | 68% (83) | 24% |
| 7 |  |  | 80% (81) | trace |
| 8[f] |  |  | 63%[g] | 22% |
| 9[f] |  |  | 69% (10) | 10%[e] |
| 10[h] |  |  | 56% (78) | 0% |

[a] Conditions: 10 mol% (*S*)-(xylyl-phanephos)$PtI_2$, 25 mol% $AgBF_4$, 30 mol% $NCC_6F_5$, 1.1 equiv TMS-OMe, 1.1 equiv $XeF_2$, 0.4 mL $CD_3NO_2$, 0 °C, 24 h. Starting material is mass balance of reaction. [b] Isolated yield, % ee determined by chiral GC. [c] GC yield. [d] Reaction run using 1.6 equiv $XeF_2$. [e] Percentage is fluorinated elimination species only [f] Reaction with 20 mol% polystyrene-bound piperidine base run, no TMS-OMe, see SI for details. [g] Due to the volatility of this compound, a GC yield is reported. [h] Contains 23% unidenfied species, mass balance is unreacted starting material. Cannot separate the unidenitified species from the product, therefore GC yield reported.

As shown in Table 3-3, variation on the phenol termini were well tolerated, including substituents para to the alcohol moiety. Unexpectedly, both electron-withdrawing and electron-donating substituents in the phenol ring improved the enantioselectivity (entries 4-7, Table 3-3). The α-naphthol substrate (entry 3, Table 3-3) was less tolerated under the optimized conditions whereby competitive fluorination of the aryl ether product occurs even in the presence of TMS-OMe. In situ monitoring by $^{19}$F NMR indicated that aryl fluorination occurred post cyclization/Pt-C fluorination. Since aryl fluorination of this substrate consumes $XeF_2$, extra was used to compensate for the difluorination stoichiometry.

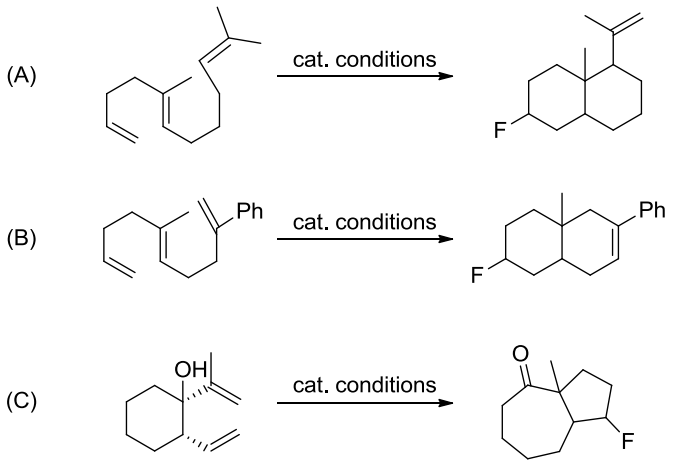
Dienyl- and trienyl alcohols and phenols were also viable substrates though in some cases, the behavior was unexpected. In the case of entries 8 and 9, the yields were poor under standard conditions, but could be recovered by exchanging TMS-OMe for a polystyrene-bound piperidine base (see Table 3-1). In contrast, the triene alcohol in entry 10 performed better under the standard conditions. The effect and exact role of the base are not yet understood for this system.

In addition to phenol and alcohol terminating groups, substrates with alkene termini have been investigated and found to cyclize and β-H eliminate;[13] however, under catalytic electrophilic fluorination conditions, very little conversion was observed and no fluorinated product was generated (Scheme 3-5 A and B). These alkene-terminated substrates have been shown to cyclize slower than dienephenol, **1**, which provides time for the $XeF_2$ to react with solvent or [Pt] to decomposition products before reacting with the cyclized species.

[13]Sokol, J. G.; Korapala, C. S.; White, P. S.; Becker, J. J.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2011**, *50*, 5658.

Similarly using 1,ω-dienols (Scheme 3-5c), which have previously cyclized and rearranged with [Pd] complexes generating a ketone product afforded no desired fluorinated products.[14]

**Scheme 3-5.** Various substrates that produced no fluorinated product under catalytic conditions.




### 3.3. Conclusion

In summary, a $P_2Pt$-dicationic catalyst can mediate the enantioselective cation-olefin cyclization/fluorination reactions of polyenes to yield C3-fluorinated carbocycles. Although multiple dienyl substrates containing phenol and alcohol termini were tolerated, the reactivity is not well understood. In general, most substrates gave good yields and enantioselectivies, however, certain substrates behaved differently producing lower yields or enantioselectivies, no clear trend in the reactivity has been observed. Interestingly, substrates containing other terminating groups generated no desired fluorinated cyclized product due to competing cyclization/elimination pathways. Mechanistic studies could provide insight to these competing pathways.

[14]Korotchenko, V. N.; Gagne, M. R. *J. Org. Chem.* **2007**, *72*, 4877.

## 3.4. Experimental details

### 3.4.1 Materials and methods

Metal-catalyzed reactions were carried out under an atmosphere of nitrogen in a nitrogen-filled glovebox in oven-dried 3.5 mL vials purchased from Fisher Scientific. $CD_3NO_2$ was purchased from Cambridge Isotope Laboratories and freeze-pump-thaw degassed before use. $CH_3NO_2$ was purified as previously described,[15] dried with $MgSO_4$, distilled from $CaSO_4$, and freeze-pump-thaw degassed before use. (S)-xylyl-PHANEPHOS, (R)-xylyl-MeO-BIPHEP and (*R*)-DTBM-SEGPHOS were purchased from Strem Chemicals Inc. and used as received. $XeF_2$, 2,3,4,5,6-pentafluorobenzonitrile, $AgBF_4$ and TMS ethers were purchased from Aldrich and used without further purification. Polystyrene bound piperidine resin base (4.1mmol/g) was purchased from NovaBioChem and used without further purification. $(COD)PtI_2$[16] and $(P_2)PtI_2$[17] were prepared according to literature procedures. $^1H$, $^{13}C$ and $^{19}F$ NMR data were collected on a Bruker 600 MHz Avance spectrometer. Chemical shifts are reported in ppm and referenced to residual solvent peaks for $^1H$ and $^{13}C$ NMR. GC-MS data was performed with an Agilent G4350A GC/MSD system containing a 7820A GC with an HP-5MS column (length 30m; I. D. 0.250 mm) connected to an Agilent 5975 MSD. The GC method consisted of the following parameters: inlet temperature 250 ˚C; inlet and column pressure of 11.9 psi He; column flow rate 1 mL/min; oven temperature held at 125 ˚C for 3 min then ramped 20 ˚C/min to 250 ˚C. The temperature was then held at 250 ˚C for 5 minutes. The detector temperature was set to 280 ˚C. Achiral GC was performed on an Agilent 6890 using an Agilent HP-5 column with the

[15]Commercial nitromethane contains nitrile impurities that poison $Pt^{2+}$ species, for purification see: Parrett, F. W.; Sun, M. S. *J. Chem. Ed*. **1977**, *54*, 448.

[16]Clark, H.; Manzer, L. E. *J. Organomet.Chem*. **1973**, *59*, 411.

[17]Colacot, T. J.; Qian, H.; Cea-Olivares, R.; Hernandez-Ortega, S. *J. Organomet.Chem*. **2001**, *691*, 637.

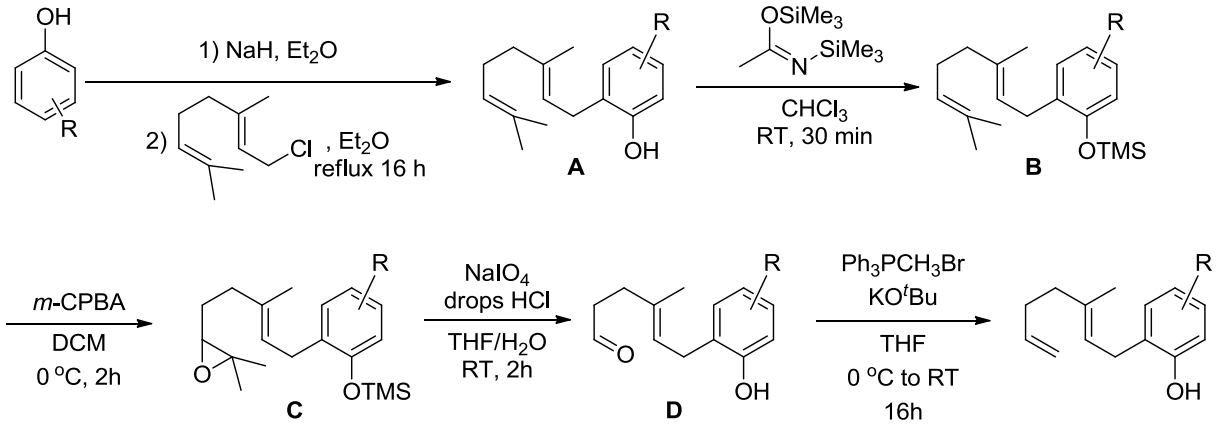
following parameters: inlet temperature 250 ˚C; 19.99 psi of helium; oven temperature held at 100 ˚C for 3 min then ramped to 250 ˚C at 10 ˚C/min. The 30 m chiral column with 320 μm diameter was run using 19.99 psi at 9.2 mL/min; the FID detector was held at 250 ˚C with a flow rate of 40 mL/min $H_2$, 450 mL/min air and makeup flow of 45 mL/min helium. Chiral GC was performed on an Agilent 6890 using an Agilent β-Cyclosil column with the following parameters: inlet temperature 250 ˚C, 19.99 psi of helium; oven temperature held at 80 ˚C for 5 min then ramped to 170 ˚C at 2 ˚C/min. The 30 m chiral column with 250 μm diameter was run using 19.99 psi at 1.7 mL/min; the FID detector was held at 250 ˚C with a flow rate of 40 mL/min $H_2$, 450 mL/min air and makeup flow of 45 mL/min helium.

### 3.4.2. Synthesis of substrates

NaH, *N*,*O*-Bis(trimethylsilyl)acetamide, 3-Chloroperbenzoic acid, sodium *meta*-periodate and all phenol derivatives were purchased from Sigma Aldrich and used without further purification. Methyltriphenylphosphoniumbromide was purchased from Sigma Aldrich and stored in a 3-neck round bottom flask with septa under nitrogen. The bromide compound was placed under vacuum for multiple days then stored under $N_2$. Solvents were dried on an $Al_2O_3$ column and stored under a constant flow of argon. Anhydrous $CHCl_3$was purchased from Sigma Aldrich in a Sure-seal bottle and stored under $N_2$; similarly anhydrous THF was purchased from Fisher Scientific in an Acros-Seal bottle and stored under $N_2$.

Substrates were synthesized via two different methods as outlined below:

**Method A**:




In a flame-dried three neck round bottom flask, evacuated with nitrogen, NaH (60% dispersion in mineral oil) was massed (1.4 equiv) as a solid. Dry $Et_2O$ was added making a 0.6M suspension. A 2.0 M solution of phenol in dry $Et_2O$ (1.2 equiv) was added to the suspension and stirred at room temperature for 1 hour. Geranyl chloride[18] (1 equiv) was added, the vessel was fitted with a condenser and refluxed at 40 °C overnight. The reaction was quenched using saturated $NH_4Cl$, and the product extracted three times with diethyl ether. The organics were washed with brine, dried over $MgSO_4$, filtered and concentrated to give the crude coupled product, **A**, as a brown oil. The crude product was then purified by flash chromatography (hexanes/ethyl acetate = 9:1) to give a yellow oil.

1 equivalent of *N,O*-Bis(trimethylsilyl)acetamide was added to a 0.1 M solution of coupled product **A** in anhydrous $CHCl_3$ under a stream of nitrogen. The reaction was stirred at room temperature for 30 minutes. The reaction mixture was then concentrated *in vacuo*. The residue, containing **B**, was dissolved in dichloromethane and cooled to 0 °C.

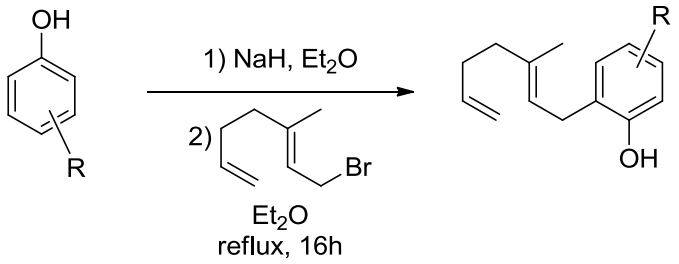
[18]Corey, E.J.; Kim, C.U.; Takeda, M. *Tetrahedron Lett.* **1972**, *13*, 4339.

3-Chloroperbenzoic acid (1.1 equiv) was added and the reaction was stirred at 0 °C for 2 hours. The reaction was quenched with a saturated solution of $Na_2S_2O_3$, and the product extracted three times with dichloromethane. The organics were washed with saturated solutions of $Na_2CO_3$ and brine, dried over $MgSO_4$, filtered and concentrated to give a yellow oil. The oil was taken to the next step without further purification.

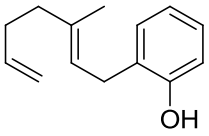
To a 0.1 M solution of epoxide (**C**) in THF/$H_2O$ (10:1) was added sodium *meta*-periodate (1.1 equiv). Concentrated hydrochloric acid was added (~10 drops) and the reaction was stirred for 2 hours at room temperature. A saturated solution of $Na_2S_2O_3$ was added and the precipitate was filtered off. The aqueous layer was extracted three times with diethyl ether. The organics were washed with saturated solutions of $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated to give a brown oil. The crude product was then purified by flash chromatography (hexanes/ethyl acetate = 4:1) to give **D** as a yellow oil.

In a flame-dried Schlenk flask cooled under nitrogen, a 0.1 M solution of methyltriphenylphosphoniumbromide in THF (1.2 equiv) was made. A 1.0 M solution of potassium tert-butoxide in THF (2.2 equiv) was added at 0 °C to the $Ph_3P$-$CH_3Br$ solution. The reaction was stirred for 2 hours at 0 °C. 1 equivalent of aldehyde **D** dissolved in dry THF was then added to the phosphoniumylide at 0 °C. The reaction mixture was allowed to warm to room temperature overnight. The reaction was quenched using a saturated solution of $NH_4Cl$. The aqueous layer was extracted three times with diethyl ether. Combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated to give a brown oil. The crude product was then purified by flash chromatography, parameters specified for each compound.

**Method B:**

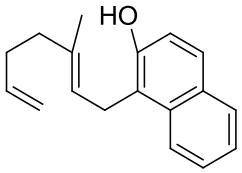



In a flame-dried three neck round bottom flask, evacuated with nitrogen, NaH (60% dispersion in mineral oil) was massed (1.4 equiv) as a solid. Dry $Et_2O$ was added making a 0.6 M suspension. A 2.0 M solution of phenol in dry $Et_2O$ (1.2 equiv) was added to the suspension and stirred at room temperature for 1 hour. The solution was stirred at room temperature for 1 hour. (*E*)-7-bromo-5-methylhepta-1,5-diene[13] was then added, and the solution was refluxed at 40 °C overnight. The reaction was quenched using saturated $NH_4Cl$, and the product was extracted three times with diethyl ether. The organics were washed with brine, dried over $MgSO_4$, filtered and concentrated to give the crude coupled product as a brown oil, which was purified by flash column chromatography as described below.

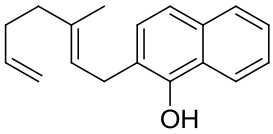



**(*E*)-2-(3-methylhepta-2,6-dien-1-yl)phenol (1)**[19] was obtained via method A. The product was purified by flash chromatography (hexanes/ethyl acetate = 4:1, $R_f$ = 0.55) to give a colorless oil (1.6 g, 12 % overall yield).

[19]Koh, J. H.; Mascarenhas, C.; Gagné M. R. *Tetrahedron* **2004**, *60*, 7405.

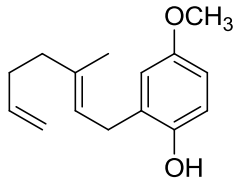



**(*E*)-1-(3-methylhepta-2,6-dien-1-yl)naphthalen-2-ol** was obtained via method B. The product was purified by flash chromatography (hexanes/ethyl acetate = 4:1, $R_f$ = 0.5) to give a red oil (0.5 g, 75 %).$^1$H NMR: (600 MHz, $CDCl_3$) δ 7.94 (d, 1H, $J_{H-H}$ = 8.4 Hz), 7.80 (d, 1H, $J_{H-H}$ = 7.8 Hz), 7.67 (d, 1H, $J_{H-H}$ = 9 Hz), 7.50 (t, 1H, $J_{H-H}$ = 7.8 Hz), 7.36 (t, 1H, $J_{H-H}$ = 7.8 Hz), 7.10 (d, 1H, $J_{H-H}$ = 9 Hz), 5.82-5.76 (m, 1H), 5.41 (d, 1H, $J_{H-H}$ = 10.2 Hz), 5.31 (t, 1H, $J_{H-H}$ = 6.6 Hz), 5.03 ( d, 1H, $J_{H-H}$ = 17.1 Hz), 4.96 (d, 1H, $J_{H-H}$ = 10.2 Hz), 3.80 (d, 2H, $J_{H-H}$ = 6.6 Hz), 2.22-2.13 (m, 4H), 1.93 (s, 3H). $^{13}$C NMR: (150.92 MHz, $CDCl_3$) δ 151.3, 138.3, 137.1, 133.1, 129.4, 128.6, 127.9, 126.3, 123.0, 123.0, 122.4, 118.6, 118.1, 114.6, 38.9, 32.1, 24.3, 16.4. HRMS (EI): $[M]^+$ Calculated for $C_{18}H_{20}O$: 252.15142, observed: 252.15094

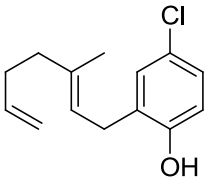



**(*E*)-2-(3-methylhepta-2,6-dien-1-yl)naphthalen-1-ol** was obtained via method A. The product was purified by flash chromatography (hexanes/ethyl acetate = 10:1, $R_f$ = 0.5) to give a yellow oil (0.3 g, 9% overall yield).$^1$H NMR: (600 MHz, $CDCl_3$) δ 8.22 (d, 1H, $J_{H-H}$ = 7.8 Hz), 7.81 (d, 1H, $J_{H-H}$ = 7.8 Hz), 7.51-7.45 (m, 2H), 7.42 (d, 1H, $J_{H-H}$ = 8.4 Hz), 7.27 (d, 1H, $J_{H-H}$ = 8.4 Hz), 5.89-5.79 (m, 1H), 5.80 (s, 1H, -OH), 5.46 (t, 1H, $J_{H-H}$ = 7.2 Hz), 5.09 (d, 1H, $J_{H-H}$ = 17.7 Hz), 5.04 (d, 1H, $J_{H-H}$ = 10.2 Hz), 3.57 (d, 2H, $J_{H-H}$ = 7.2 Hz), 2.28-2.23 (m, 4H), 1.89 (s, 3H). $^{13}$C NMR: (150.92 MHz, $CDCl_3$) δ 149.7, 138.9, 133.6, 128.3, 127.5,

125.6, 125.2, 194.9, 122.1, 121.4, 120.1, 119.6, 115.1, 39.0, 32.1, 30.5, 16.4. HRMS (EI): $[M]^+$ Calculated for $C_{18}H_{20}O$: 252.15142, observed: 252.15221.

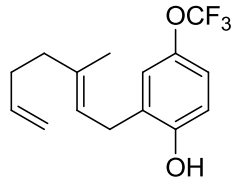



**(*E*)-4-methoxy-2-(3-methylhepta-2,6-dien-1-yl)phenol** was obtained via method B. The product was purified by flash chromatography (hexanes/ethyl acetate = 4:1, $R_f$ = 0.55) to give a yellow oil (0.8 g, 55 %).$^1$H NMR: (600 MHz, $CDCl_3$) δ 6.75 (d, 1H, $J_{H-H}$ = 8.7 Hz ), 6.72 (d, 1H, $J_{H-H}$ = 3 Hz), 6.67 (dd, 1H, $J_{H-H}$ = 3.0, 8.4 Hz), 5.85-5.78 (m, 1H), 5.35 (t, 1H, $J_{H-H}$ = 7.5 Hz), 5.05 (d, 1H, $J_{H-H}$ = 17.1 Hz), 4.99 (d, 1H, $J_{H-H}$ = 9.6 Hz), 3.77 (s, 3H, -OMe), 3.35 (d, 2H, $J_{H-H}$ = 7.2Hz), 2.23-2.17 (m, 4H), 1.77 (s, 3H). $^{13}$C NMR: (150.92 MHz, $CDCl_3$) δ 153.5, 148.1, 138.2, 137.7, 128.2, 121.8, 116.2, 115.6, 114.7, 111.9, 55.6, 38.9, 32.1, 29.5, 16.1. HRMS (EI): $[M]^+$ Calculated for $C_{15}H_{20}O_2$ : 232.14633, observed: 232.14563.

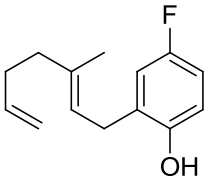



**(*E*)-4-chloro-2-(3-methylhepta-2,6-dien-1-yl)phenol** was obtained via method A. The product was purified by flash chromatography (hexanes/ethyl acetate = 4:1, $R_f$ = 0.55) to give a yellow oil (0.6 g, 12 % overall yield).$^1$H NMR: (600 MHz, $CDCl_3$) δ 7.09 (d, 1H, $J_{H-H}$ = 2.4 Hz), 7.04 (dd, 1H, $J_{H-H}$ = 2.4, 8.4 Hz), 6.73 (d, 1H, $J_{H-H}$ = 8.4 Hz), 5.84-5.77 (m, 1H), 5.32 (s, 1H, -OH), 5.29 (t, 1H, $J_{H-H}$ = 7.2 Hz), 5.03 (d, 1H, $J_{H-H}$ = 17.1 Hz), 4.96 (d, 1H, $J_{H-H}$ = 10.2 Hz), 3.32 (d, 2H, $J_{H-H}$ = 7.2Hz), 2.22-2.14 (m, 4H), 1.74 (s, 3H). $^{13}$C NMR: (150.92

MHz, $CDCl_3$) δ 152.9, 138.4, 138.4, 129.5, 129.0, 126.9, 125.1 121.0, 116.7, 114.5, 38.9, 32.1, 28.9, 15.9. HRMS (EI): $[M]^+$ Calculated for $C_{14}H_{17}OCl$: 236.09763, observed: 236.09680.




**(*E*)-2-(3-methylhepta-2,6-dien-1-yl)-4-(trifluoromethoxy)phenol** was obtained via method A. The product was purified by flash chromatography (hexanes/ethyl acetate = 4:1, $R_f$ = 0.5) to give a yellow oil (0.4 g, 11 % overall yield).$^1$H NMR: (600 MHz, $CDCl_3$) δ 6.98 (br, 1H), 6.96 (br, 1H), 6.78 (d, 1H, $J_{H-H}$ = 9 Hz), 5.83-5.75 (m, 1H), 5.32 (t, 1H, $J_{H-H}$ = 7.5 Hz), 5.19 (s, 1H, -OH), 5.03 (d, 1H, $J_{H-H}$ = 15.6 Hz), 4.98 (d, 1H, $J_{H-H}$ = 10.2 Hz), 3.35 (d, 2H, $J_{H-H}$ = 7.2Hz), 2.25-2.15 (m, 4H), 1.75 (s, 3H). $^{13}$C NMR: (150.92 MHz, $CDCl_3$) δ 152.8, 142.6, 139.0, 138.1, 128.2, 122.7, 120.9, 120.6 (q, $J_{C-F}$ = 255 Hz, -O<u>C</u>$F_3$), 120.2, 116.3, 114.9, 38.9, 32.0, 29.5, 16.2. $^{19}$F NMR: (564.63 MHz, $CDCl_3$) δ -58.3 (s). HRMS (EI): $[M]^+$ Calculated for $C_{15}H_{17}O_2F_3$: 286.11807, observed: 286.11843.



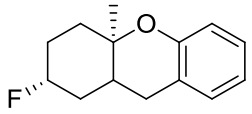

**(*E*)-4-fluoro-2-(3-methylhepta-2,6-dien-1-yl)phenol** was obtained via method B. The product was purified by flash chromatography (hexanes/ethyl acetate = 4:1, $R_f$ = 0.55) to give a brown oil (0.3 g, 30 %).$^1$H NMR: (600 MHz, $CDCl_3$) δ 6.83 (dd, 1H, $J_{H-H}$ = 2.8, 9.2 Hz), 6.78 (dd, 1H, $J_{H-H}$ = 3.2, 8.2 Hz), 6.73 (dd, 1H, $J_{H-H}$ = 4.8, 8.8 Hz), 5.84-5.76 (m, 1H), 5.3 (t, 1H, $J_{H-H}$ = 7.8 Hz), 5.03 (d, 1H, $J_{H-H}$ = 17.1 Hz), 4.98 (d, 1H, $J_{H-H}$ = 10.2Hz), 3.3 (d,

2H, $J_{H\text{-}H}$ = 7.2Hz), 2.28-2.10 (m, 4H), 1.75 (s, 3H). $^{13}C$ NMR: (150.92 MHz, $CDCl_3$) δ 157.05 (d, $J_{C\text{-}F}$ = 237 Hz), 150.08 (d, $J_{C\text{-}F}$ = 2 Hz), 138.5, 138.2, 128.5 (d, $J_{C\text{-}F}$ = 7 Hz), 121.1, 116.2 (d, $J_{C\text{-}F}$ = 9 Hz), 116.1 (d, $J_{C\text{-}F}$ = 23 Hz), 114.8, 113. 5 (d, $J_{C\text{-}F}$ = 23 Hz), 38.9, 32.1, 29.3, 16.1. $^{19}F$ NMR: (564.63 MHz, $CDCl_3$) δ -124.1 (m, 1F). HRMS (EI): $[M]^+$ Calculated for $C_{14}H_{17}O$ F: 220.12635, observed: 220.12690.

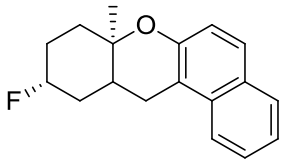
### 3.4.3. Typical catalytic reaction

(*S*)-(xylyl-phanephos)$PtI_2$ (5 mg, 0.004 mmol) and $AgBF_4$ (2.1 mg, 0.01 mmol) were massed into a 3.5 mL vial followed by $NCC_6F_5$ (1.7 µL, 0.013 mmol) which was added via microsyringe. The vial was covered in foil and 0.1 mL $CD_3NO_2$ added. The reaction was stirred for 1 hour in the dark at room temperature. The [Pt] mixture was pushed through a 0.2 µm PTFE syringe filter into a 3.5 mL vial containing a frozen solution of dienephenol (8.9 mg, 0.04 mmol) 0.1mL $CD_3NO_2$, cooled with liquid $N_2$ in a glovebox cold well. The syringe filter was rinsed with an additional 0.1 mL $CD_2NO_2$. To the resulting frozen reaction solution was added $XeF_2$ (8.2 mg, 0.05 mmol) in 0.1 mL $CD_3NO_2$. The reaction was capped with a septum cap. Outside of the glovebox, TMS-OMe (6.7 µL, 0.05 mmol) was added via microsyringe to the capped reaction. The reaction mixture was stirred in cryocool (by NesLab) at 0 °C for 18 h. Crude reaction mixture was pushed through a silica gel pipette plug using $Et_2O$ to remove all metals. GC and GC-MS were used to determine the crude yield. Products were isolated by preparative TLC. Solvent systems, yields and enantiomeric excess values are reported for all products.

### 3.4.4. Product characterization



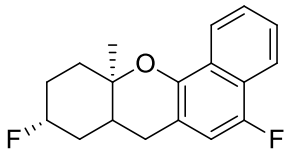
**(2*R*,4a*R*)-2-fluoro-4a-methyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene (1)**[20] was purified by preparative TLC (hexanes/EtOAc/DCM = 95:5:5, $R_f$ = 0.43). After extracting from the silica gel with diethyl ether, evaporation of the solvent resulted in a white solid (6.5 mg, 67%, 75 %ee). Enantiomeric excess values determined by chiral GC analysis (Agilent β-Cyclosil 30m long 250 μm diameter, 19.99 psi helium, 1.7 mL/min, oven temperature held for 5 min 80 ˚C, ramped to 170 ˚C at 2 ˚C/min, $t_r$-major 46.4 min, $t_r$-minor 45.9 min).



**(7a*R*,10*R*)-10-fluoro-7a-methyl-8,9,10,11,11a,12-hexahydro-7aH-benzo[a]xanthene** was purified by preparative TLC (hexanes/EtOAc/DCM = 95:5:5, $R_f$ = 0.6). After extracting from the silica gel with diethyl ether, evaporation of the solvent resulted in a white solid (7.2mg, 67%, 73% ee). Enantiomeric excess values determined by chiral GC analysis (Agilent β-Cyclosil 30m long 250 μm diameter, 19.99 psi helium, 1.7 mL/min, oven temperature held for 5 min 80 ˚C, ramped to 170 ˚C at 2 ˚C/min, $t_r$-major 46.3 min, $t_r$-minor 45.8 min). $^1$H NMR: (600 MHz, $CDCl_3$) δ 7.81 (d, 1H, $J_{H\text{-}H}$ = 8.4 Hz), 7.78 (d, 1H, $J_{H\text{-}H}$ = 7.8 Hz), 7.65 (d, 1H, $J_{H\text{-}H}$ = 9 Hz), 7.50 (t, 1H, $J_{H\text{-}H}$ = 7.5 Hz), 7.36 (t, 1H, $J_{H\text{-}H}$ = 7.2 Hz), 7.04 (d, 1H, $J_{H\text{-}H}$ = 9 Hz), 4.76-4.67 (m, 1H, $^2J_{H\text{-}F}$ = 51Hz, FC<u>H</u>), 3.04 (dd, 1H, $J_{H\text{-}H}$ = 5.4,

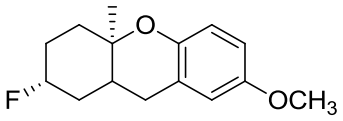
[20]Zhao, S.-B.; Becker, J. J.; Gagne, M. R. *Organometallics* **2011**, *30*, 3926.

16.8 Hz), 2.66 (dd, 1H, $J_{H\text{-}H}$ = 12.6, 16.8 Hz), 2.35-2.33 (m, 1H), 2.25 (br, 1H), 2.10-2.07 (m, 1H), 2.01-1.96 (m, 1H), 1.78-1.73 (m, 2H), 1.60-1.52 (m, 1H), 1.25 (s, 3H). $^{13}$C NMR: (150.92 MHz, $CDCl_3$) δ 150.8, 132.8, 128.8, 128.4, 128.1, 126.4, 123.2, 121.9, 119.6, 112.8, 90.0 (d, $^1J_{C\text{-}F}$ = 173.5 Hz), 75.8, 36.8 (d, $^3J_{C\text{-}F}$ = 12.0 Hz), 36.3 (d, $^3J_{C\text{-}F}$ = 12.0 Hz), 35.7 (d, $^2J_{C\text{-}F}$ = 19.5 Hz), 29.7 (d, $^2J_{C\text{-}F}$ = 19.5 Hz), 16.1. $^{19}$F NMR: (564.63 MHz, $CDCl_3$) δ -172.1 (d, $J_{H\text{-}F}$ = 51 Hz). HRMS (EI): $[M]^+$ Calculated for $C_{18}H_{19}OF$: 270.14200, observed: 270.14177.

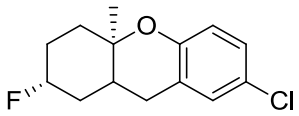



**(9*R*,11a*R*)-5,9-difluoro-11a-methyl-7a,8,9,10,11,11a-hexahydro-7H-benzo[c]xanthene** was purified by preparative TLC (hexanes/EtOAc = 98.5:2.5, $R_f$ = 0.56). After extracting from the silica gel with diethyl ether, evaporation of the solvent resulted in a colorless oil (7.3mg, 49%, 86% ee, used 0.05 mmol of starting material). Enantiomeric excess values determined by chiral GC analysis (Agilent β-Cyclosil 30m long 250 μm diameter, 19.99 psi helium, 1.7 mL/min, oven temperature held for 5 min 80 ˚C, ramped to 170 ˚C at 2 ˚C/min, $t_r$-major 70.3 min, $t_r$-minor 67.5 min). $^1$H NMR: (600 MHz, $CDCl_3$) δ 8.16-8.15 (m, 1H), 7.99-7.97 (m, 1H), 7.51-7.48 (m, 2H), 6.82 (d, 1H, $J_{H\text{-}H}$ = 11.0 Hz), 4.74-4.63 (m, 1H, $J_{H\text{-}F}$ = 51 Hz), 2.68 (dd, 1H, $J_{H\text{-}H}$ = 16.8, 5.4 Hz), 2.63 (dd, 1H, $J_{H\text{-}H}$ = 16.8, 12.6 Hz), 2.25-2.23 (m, 2H), 2.17-2.15 (m, 1H), 1.98-1.94 (m, 1H), 1.85-1.76 (m, 2H), 1.46-1.51 (m, 1H), 1.24 (s, 3H). $^{13}$C NMR: (150.92 MHz, $CDCl_3$) δ 152.3 (d, $^1J_{C\text{-}F}$ = 245.0 Hz), 144.1, 126.3 (d, $^3J_{C\text{-}F}$ = 4.5 Hz), 126.0, 125.9, 123.3 (d, $^2J_{C\text{-}F}$ = 18.0 Hz), 121.7, 120.2 (d, $^3J_{C\text{-}F}$ = 3.0 Hz), 113.8 (d, $^3J_{C\text{-}F}$ = 9.0 Hz), 110.0 (d, $^2J_{C\text{-}F}$ = 21.0 Hz), 91.0 (d, $^1J_{C\text{-}F}$ = 173.5 Hz), 76.1, 36.8 (d, $^3J_{C\text{-}F}$ = 10.5 Hz), 36.3 (d, $^3J_{C\text{-}F}$ = 13.5 Hz), 35.4 (d, $^2J_{C\text{-}F}$ = 19.5 Hz), 29.6 (d, $^2J_{C\text{-}F}$ = 19.5 Hz), 29.4,

16.3. $^{19}$F NMR: (564.63 MHz, $CDCl_3$) δ -172.16 (d, $J_{H\text{-}F}$ = 51 Hz), -134.2 (d, $J_{H\text{-}F}$ = 11 Hz). HRMS (EI): $[M]^+$ Calculated for $C_{18}H_{18}OF_2$: 288.13258, observed: 288.13330.

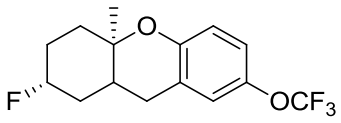



**(2*R*,4a*R*)-2-fluoro-4a,7-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene** was purified by preparative TLC (hexanes/EtOAc = 98.5:2.5, $R_f$ = 0.18). After extracting from the silica gel with diethyl ether, evaporation of the solvent resulted in a white solid (6.3 mg, 56%, 81% ee). Enantiomeric excess values determined by chiral GC analysis (Agilent β-Cyclosil 30m long 250 μm diameter, 19.99 psi helium, 1.7 mL/min, oven temperature held for 5 min 80 ˚C, ramped to 170 ˚C at 2 ˚C/min, $t_r$-major 65.0 min, $t_r$-minor 64.0 min). $^1$H NMR: (600 MHz, $CDCl_3$) δ 6.72 (d, 1H, $^2J_{H\text{-}H}$ = 9.0 Hz), 6.69 (dd, 1H, $^2J_{H\text{-}H}$ = 9.0 Hz, $^3J_{H\text{-}H}$ = 2.4 Hz), 6.58 (d, 1H, $^3J_{H\text{-}H}$ = 2.4), 4.70-4.57 (m, 1H, FC<u>H</u>, $^2J_{H\text{-}F}$ = 49.0 Hz), 2.59 (dd, 1H, $J_{H\text{-}H}$ = 16.8 Hz, $J_{H\text{-}H}$ = 5.4 Hz), 2.52 (dd, 1H, $J_{H\text{-}H}$ = 16.8 Hz, $J_{H\text{-}H}$ = 12.6 Hz), 2.19-2.15 (m, 2H), 2.00-1.98 (m, 1H), 1.87-1.82 (m, 1H), 1.71-1.67 (m, 2H), 1.46-1.38 (m, 1H), 1.18 (s, 3H). $^{13}$C NMR: (150.92 MHz, $CDCl_3$) δ 53.1, 147.3, 121.7, 117.8, 113.9, 113.6, 91.0 (d, $^1J_{C\text{-}F}$ = 173.5 Hz), 75.5, 55.7, 36.8 (d, $^3J_{C\text{-}F}$ = 10.5 Hz), 36.3 (d, $^3J_{C\text{-}F}$ = 12.0 Hz), 35.5 (d, $^2J_{C\text{-}F}$ = 19.5 Hz), 29.6 (d, $^2J_{C\text{-}F}$ = 21 Hz), 29.4, 16.2. $^{19}$F NMR: (564.63 MHz, $CDCl_3$) δ -172.1 (d, 1F, $J_{H\text{-}F}$ = 49 Hz). HRMS (EI): $[M]^+$ Calculated for $C_{15}H_{19}O_2F$: 250.13691, observed: 250.13729.



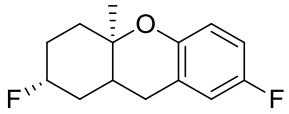

**(2*R*,4a*R*)-7-chloro-2-fluoro-4a-methyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene** was purified by preparative TLC (hexanes/EtOAc/DCM = 95:5:5, $R_f$ = 0.81). After extracting

from the silica gel with diethyl ether, evaporation of the solvent resulted in a white solid (6.1 mg, 60%, 87% ee). Enantiomeric excess values determined by chiral GC analysis (Agilent β-Cyclosil 30m long 250 μm diameter, 19.99 psi helium, 1.7 mL/min, oven temperature held for 5 min 80 ˚C, ramped to 170 ˚C at 2 ˚C/min, $t_r$-major 63.6 min, $t_r$-minor 63.1 min). $^1$H NMR:(600 MHz, $CDCl_3$) δ 7.05 (dd, 1H, $J_{H-H}$ = 2.4, 9.0 Hz), 7.02 (d, 1H, $J_{H-H}$ = 2.4 Hz), 6.72 (d, 1H, $J_{H-H}$ = 9.0 Hz), 4.71-4.58 (m, 1H, $J_{H-F}$ = 51 Hz, FC<u>H</u>), 2.59 (dd, 1H, $J_{H-H}$ = 16.8, 5.4 Hz), 2.52 (dd, 1H, $J_{H-H}$ = 16.8, 12.6 Hz), 2.20-2.17 (m, 2H), 2.02-2.00 (m, 1H), 1.86-1.81 (m, 1H), 1.70-1.68 (m, 2H), 1.47-1.41 (m, 1H), 1.19 (s, 3H). $^{13}$C NMR: (150.92 MHz, $CDCl_3$) δ 152.1, 128.9, 127.6, 124.7, 122.7, 118.7, 90.8 (d, $J_{C-F}$ = 173 Hz), 76.0, 36.5 (d, $J_{C-F}$ = 12.1 Hz), 36.2 (d, $J_{C-F}$ = 12.1 Hz), 35.3 (d, $J_{C-F}$ = 19.6 Hz), 29.5 (d, $J_{C-F}$ = 19.6 Hz), 28.9, 16.4. $^{19}$F NMR: (564.63 MHz, $CDCl_3$) δ -172.3 (d, $J_{H-F}$ = 51 Hz). HRMS (EI): $[M]^+$ Calculated for $C_{14}H_{16}OFCl$: 254.08737, observed: 254.08795.

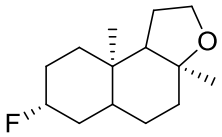



**(2*R*,4a*R*)-2-fluoro-4a-methyl-7-(trifluoromethoxy)-2,3,4,4a,9,9a-hexahydro-1H-xanthene** was purified by preparative TLC (hexanes/EtOAc/DCM = 95:5:5, $R_f$ = 0.69). After extracting from the silica gel with diethyl ether, evaporation of the solvent resulted colorless oil (8.3 mg, 68%, 83% ee). Enantiomeric excess values determined by chiral GC analysis (Agilent β-Cyclosil 30m long 250 μm diameter, 19.99 psi helium, 1.7 mL/min, oven temperature held for 5 min 80 ˚C, ramped to 170 ˚C at 2 ˚C/min, $t_r$-major 48.5 min, $t_r$-minor 47.9 min). $^1$H NMR:(600 MHz, $CDCl_3$) δ 6.96 (d, 1H, $J_{H-H}$ = 9.0 Hz), 6.9 (s, 1H), 6.77 (d, 1H, $J_{H-H}$ = 9.0 Hz), 4.70-4.58 (m, 1H, $J_{H-F}$ = 49 Hz, FC<u>H</u>), 2.62 (dd, 1H, $J_{H-H}$ = 16.8 Hz, 5.4 Hz), 2.54 (dd, 1H, $J_{H-H}$ = 16.8 Hz, 12.6 Hz), 2.20-2.19 (m, 2H), 2.03-2.01 (m, 1H), 1.88-1.80

(m, 1H), 1.70-1.68 (m, 2H), 1.45-1.42 (m, 1H), 1.21 (s, 3H). $^{13}$C NMR: (150.92 MHz, $CDCl_3$) δ 52.0, 142.1, 122.1, 122.0, 120.7, 118.2, 90.8 (d, $J_{C\text{-}F}$ = 175.0 Hz), 36.5 (d, $J_{C\text{-}F}$ = 11.5 Hz), 36.2 (d, $J_{C\text{-}F}$ = 12.0 Hz), 35.3 (d, $J_{C\text{-}F}$ = 20.0 Hz), 29.5 (d, $J_{C\text{-}F}$ = 20.0 Hz), 29.0, 16.5. $^{19}$F NMR: (564.63 MHz, $CDCl_3$) δ -172.4 (d, 1F, $J_{H\text{-}F}$ = 49 Hz), -58.3 (s, 3F, -$OCF_3$). HRMS (EI): $[M]^+$ Calculated for $C_{15}H_{16}O_2F_4$: 304.10864, observed: 304.10897.



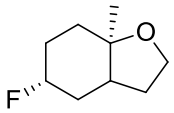

**(2*R*,4a*R*)-2,7-difluoro-4a-methyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene** was purified by preparative TLC (hexanes/EtOAc/DCM = 95:5:5, $R_f$ = 0.46). After extracting from the silica gel with diethyl ether, evaporation of the solvent resulted colorless oil (9.5 mg, 80%, 81% ee). Enantiomeric excess values determined by chiral GC analysis (Agilent β-Cyclosil 30m long 250 μm diameter, 19.99 psi helium, 1.7 mL/min, oven temperature held for 5 min 80 ˚C, ramped to 170 ˚C at 2 ˚C/min, $t_r$-major 48.4 min, $t_r$-minor 48.1 min). $^1$H NMR: (600 MHz, $CDCl_3$) δ 6.80 (ddd, 1H, $^3J_{H\text{-}F}$ = 8.5 Hz, $^3J_{H\text{-}H}$ = 9.0 Hz, $^4J_{H\text{-}F}$ = 3.0 Hz), 6.75 (dd, 1H, $^3J_{H\text{-}F}$ = 9.0 Hz, $^4J_{H\text{-}H}$ = 3.0 Hz), 6.72 (d, 1H, $^3J_{H\text{-}F}$ = 9.0 Hz, $^4J_{H\text{-}F}$ = 5.0 Hz, $^3J_{H\text{-}H}$ = 9.0 Hz), 4.70-4.58 (m, 1H, $J_{H\text{-}F}$ = 49.0 Hz, FC<u>H</u>), 2.60 (dd, 1H, $J_{H\text{-}H}$ = 16.8 Hz, 5.4 Hz), 2.52 (dd, 1H, $J_{H\text{-}H}$ = 16.8 Hz, 12.6 Hz), 2.20-2.17 (m, 2H), 2.02-2.00 (m, 1H), 1.87-1.82 (m, 1H), 1.70-1.67 (m, 2H), 1.46-1.39 (m, 1H), 1.29 (s, 3H). $^{13}$C NMR: (150.92 MHz, $CDCl_3$) δ 156.6 (d, $^1J_{C\text{-}F}$ = 237.0 Hz), 149.4, 122.2 (d, $^3J_{C\text{-}F}$ = 7.5 Hz), 118.1 (d, $^3J_{C\text{-}F}$ = 9.0 Hz), 115.2 (d, $^2J_{C\text{-}F}$ = 23.0 Hz), 114.3 (d, $^2J_{C\text{-}F}$ = 23.0 Hz), 90.9 (d, $^1J_{C\text{-}F}$ = 173.0 Hz), 75.9, 36.6 (d, $^3J_{C\text{-}F}$ = 12 Hz), 36.3 (d, $^3J_{C\text{-}F}$ = 12 Hz), 35.6 (d, $^2J_{C\text{-}F}$ = 19.5 Hz), 29.6 (d, $^2J_{C\text{-}F}$ = 19.5 Hz), 29.2, 16.3. $^{19}$F NMR: (564.63 MHz, $CDCl_3$) δ -124.7 (m, 1F), -172.3 (d, 1F, $J_{H\text{-}F}$ = 47 Hz). HRMS (EI): $[M]^+$ Calculated for $C_{14}H_{16}O\,F_2$: 238.11693, observed: 238.11664.



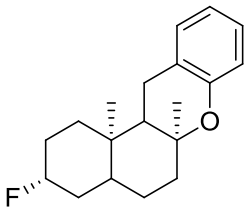

**(3a*S*,7*R*,9a*R*)-7-fluoro-3a,9a-dimethyldodecahydronaphtho[2,1-b]furan** was unable to be isolated from the starting material and other unknown species. Yield in table is uncorrected yield calculated from GC. Enantiomeric excess values determined by chiral GC analysis (Agilent β-Cyclosil 30m long 250 μm diameter, 19.99 psi helium, 1.7 mL/min, oven temperature held for 5 min 80 ˚C, ramped to 170 ˚C at 2 ˚C/min, $t_r$-major 45.9 min, $t_r$-minor 45.7 min). Diagnostic peak in $^1$H NMR (600MHz, $CDCl_3$) δ 4.61-4.44 (m, 1H) for the geminal proton to the C-F. $^1$H NMR spectrum also contains some starting material and other unknown species. $^{19}$F NMR: (564.63 MHz, $CDCl_3$) δ -167.2 (d, $J_{H-F}$ = 45 Hz). HRMS (EI): [M-CH3]+ Calculated for C13H20O F: 211.14982, observed: 211.14922.

The following products were made by using the following catalytic conditions:

(*S*)-(xylyl-phanephos)$PtI_2$ (5mg, 0.004mmol) and $AgBF_4$ (2.1mg, 0.01mmol) were massed into a 3.5 mL vial. $NCC_6F_5$ (1.7μL, 0.013mmol) was added via microsyringe. The vial was covered in foil and 0.1 mL $CD_3NO_2$ added. The reaction was stirred for 1 hour in the dark at room temperature. The [Pt] mixture was pushed through a 0.2 μm PTFE syringe filter into a 3.5 mL vial containing a frozen solution of dienephenol (8.9 mg, 0.04 mmol) and piperidine resin base (2.1mg, 0.009mmol) in 0.1mL $CD_3NO_2$, cooled with liquid $N_2$ in a glovebox cold well. The syringe filter was rinsed with an additional 0.1 mL $CD_2NO_2$. To the resulting frozen reaction solution was added $XeF_2$ (8.2 mg, 0.05 mmol) in 0.1 mL $CD_3NO_2$. The capped reaction mixture was subsequently stirred in cryocool (by NesLab) at 0 ˚C for 18h. The crude reaction mixture was pushed through a silica gel pipette plug using $Et_2O$ to remove all metals. Crude yields were determined by GC and GC-MS.



**(5*R*,7a*R*)-5-fluoro-7a-methyloctahydrobenzofuran**[20] is very volatile. For this reason, the GC yield is reported as 63%. Since the product cannot be isolated, and there are multiple species present in the reaction, the enantiomeric ratio cannot be determined with certainty.



**(3*R*,6a*S*,12b*R*)-3-fluoro-6a,12b-dimethyl-2,3,4,4a,5,6,6a,12,12a,12b-decahydro-1H-benzo[a]xanthenes** was purified by preparative TLC (hexanes/EtOAc/DCM = 95:5:5, $R_f$ = 0.55). After extracting from the silica gel with diethyl ether, evaporation of the solvent resulted in a colorless oil (11.5 mg, 69%, 10% ee). Enantiomeric excess values determined by chiral GC analysis (Agilent β-Cyclosil 30m long 250 μm diameter, 19.99 psi helium, 1.7 mL/min, oven temperature held for 5 min 80 ˚C, ramped to 170 ˚C at 2 ˚C/min, $t_r$-major 55.3 min, $t_r$-minor 53.9 min). $^1$H NMR: (600 MHz, $CDCl_3$) δ 7.09-7.05 (m, 2H), 6.83 (td, 1H, $J_{H-H}$ = 7.5 Hz, 1.0 Hz), 6.76 (d, 1H, $J_{H-H}$ = 8.4 Hz), 4.60-4.46 (m, 1H, $J_{H-F}$ = 51 Hz, FC<u>H</u>), 2.69-2,67 (m, 2H), 2.03 (dt, 1H, $J_{H-H}$ = 12.6 Hz, 3.0 Hz), 2.0-1.98 (m, 1H), 1.85-1.80 (m, 2H), 1.74-1.67 (m, 2H), 1.63 (dd, 1H, $J_{H-H}$ = 10.2 Hz, 7.8 Hz), 1.55-1.51 (m, 1H), 1.49-1.45 (m, 2H), 1.26 (br, 1H), 1.24 (s, 3H), 1.08 (td, 1H, $J_{H-H}$ = 13.2 Hz, 3.6 Hz), 0.88 (s, 3H). $^{13}$C NMR: (150.92 MHz, $CDCl_3$) δ 153.1, 129.7, 127.2, 122.0, 119.8, 117.1, 92.3 (d, $^1J_{C-F}$ = 172.0 Hz), 50.0 (d, $J$ = 1.5 Hz), 44.5 (d, $J$ = 9.0 Hz), 40.21, 36.5 (d, $J$ = 12.0 Hz), 35.5, 34.2 (d, $J$ = 18.0 Hz), 27.8 (d, $J$ = 18.0 Hz), 26.3, 22.8, 21.0, 12.1. $^{19}$F NMR: (564.63 MHz,

$CDCl_3$) δ -168.4 (d, 1F, $J_{H\text{-}F}$ = 51 Hz). HRMS (EI): $[M]^+$ Calculated for $C_{19}H_{25}O$ F: 288.18895, observed: 288.18868.

# Chapter 4

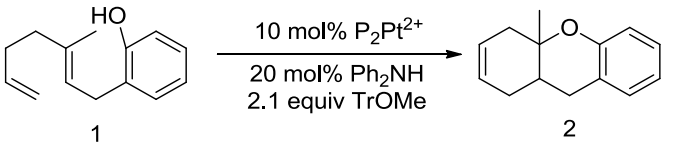
## Preliminary Mechanistic Investigation into Cyclization/Fluorination

### 4.1. Introduction

For chemistry within the Gagné group, diphosphine ligands can be grouped into three categories: achiral, biaryl and xylyl-phanephos ligands(Figure 4-1). Although the catalytic cyclization/fluorination studies were done using (*S*)-(xylyl-phanephos)$PtI_2$ there are inherent challenges using this catalyst for mechanistic studies, as described in section 4.1.1. For this reason, we decided to begin our investigation of the mechanism using either biaryl (BINAP) or achiral (dppe) catalyst complexes because they are well-behaved and well-studied in our net-dehydrogenative cascade cyclization mechanism.

#### 4.1.1. Previous mechanistic studies on the Pt(II)-catalyzed cascade cyclization

In the past decade, the Gagné group has studied the Pt(II)-catalyzed cation-olefin cascade cyclization of polyolefins, such as compound **1**.(Eq. 4-1).[1]

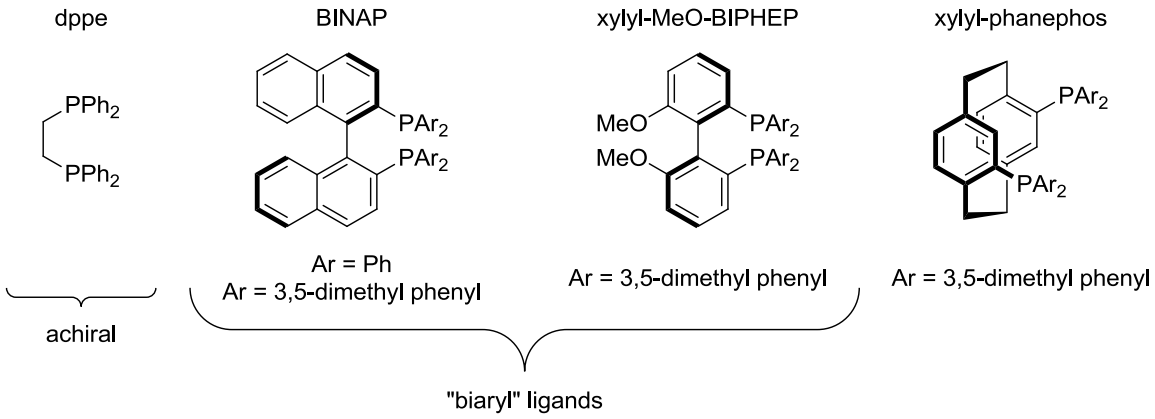



(Eq. 4-1)

[1](a) Mullen, C. A.; Campbell, A. N.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 6011. (b) Feducia, J. A.; Gagné, M. R. *J. Am. Chem. Soc.* **2007**, *130*, 592. (c) Mullen, C. A.; Gagné, M. R. *J. Am. Chem. Soc.* **2007**, *129*, 11880. (d) Chianese, A. R.; Lee, S. J.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 4042.

The proposed mechanism for this cation-olefin cyclization is initiated by halide abstraction from $P_2PtI_2$ by excess $AgBF_4$ making the active catalytic species, $P_2Pt^{2+}$, where $P_2$ is a bidentate phosphine ligand such as dppe, a biaryl (BINAP), or xylyl-phanephos (Figure 4-1, Scheme 4-1 ).[2]

**Figure 4-1**. Various $P_2$ commercially available ligands for coordination to [Pt] for catalytic cascade cyclization.

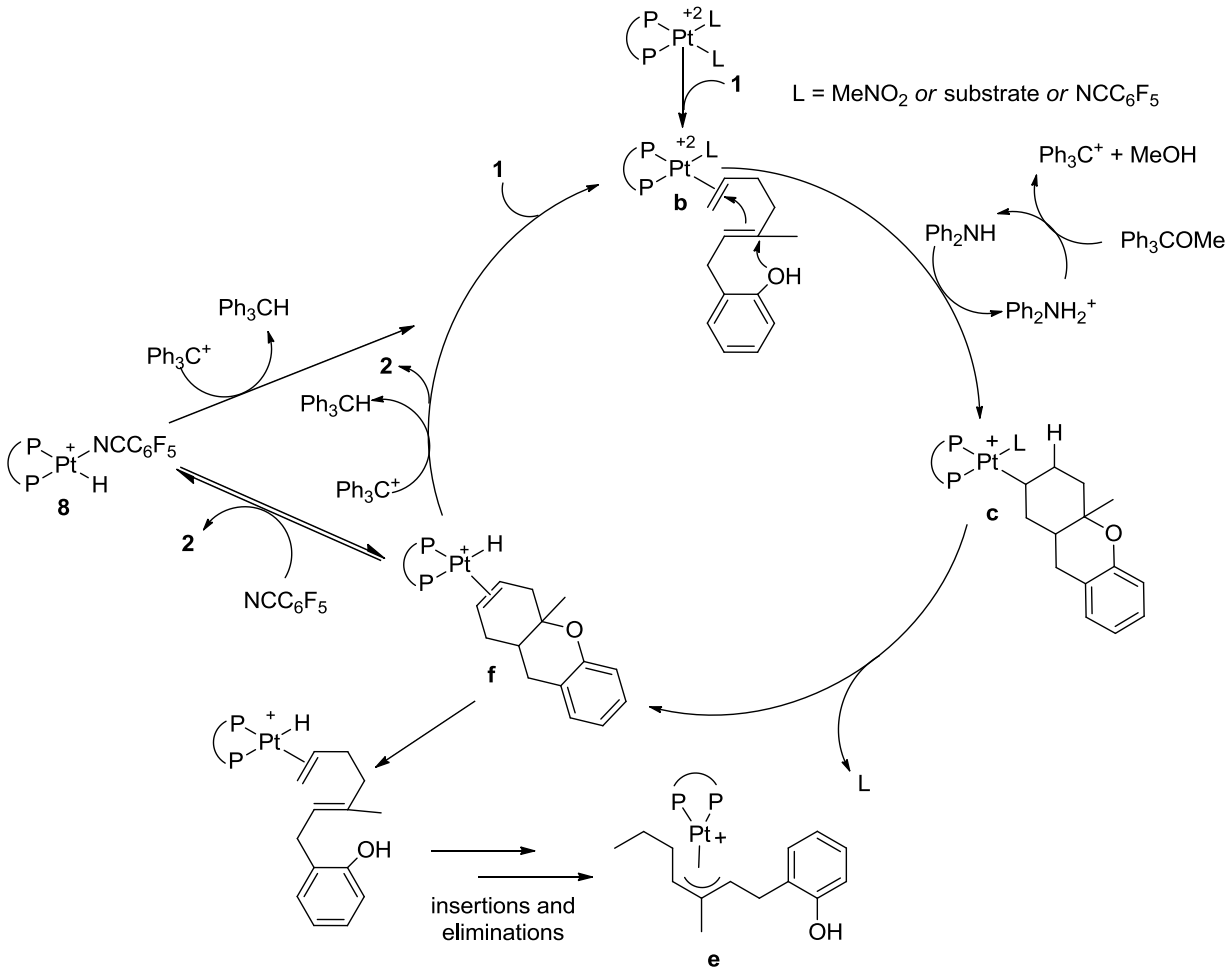



Coordination of the $P_2Pt^{2+}$ complex in a square planar geometry to the terminal alkene of the polyolefin substrate initiates the cascade cyclization, which is terminated by phenol deprotonation with a base, usually diphenylamine ($Ph_2NH$) producing its conjugate acid $(Ph_2NH_2)^+$ and a $P_2Pt$-alkyl nitrile cation (**c**). Mechanistic studies indicate that for achiral and biaryl $P_2$ ligands, **c** is the resting state of the catalyst, determined by different *trans* coupling constants for Pt-P observed in $^{31}P$ NMR, whereas xylyl-phanephos rests at an unknown symmetric species with a $J_{Pt\text{-}P}$ = 4050 Hz.[2] β-H elimination of **c**, liberates the desired product, **2**, and a putative $P_2Pt$-H cation, **f**. The hydride from **f** is abstracted by $Ph_3C^+$, transiently generated from the reaction of $Ph_3COMe$ with $(Ph_2NH_2)^+$. This hydride abstraction regenerates the active $P_2Pt^{2+}$ species, thus turning over the catalytic cycle.

[2]Campbell, A. N. Platinum (II) Catalyzed Diene Cyclizations, Ph.D. Thesis, University of North Carolina at Chapel Hill, Chapel Hill NC, December 2008.

As an aside, catalyst decomposition, which is an off cycle process, is proposed to occur by displacement of the alkene-coordinated product, **2**, from [Pt]-H complex, **f**, with another equivalent of substrate; subsequent insertions and eliminations lead to the $P_2$Pt-allyl complex, **e**. This pathway will not be discussed further in this thesis as catalyst decomposition was not observed in our studies.

**Scheme 4-1.** Proposed catalytic cycle for Pt(II)-catalyzed cation-olefin cyclization.




Despite the fact that different catalyst resting states were observed for achiral and biaryl versus the xylyl-phanephos systems, the same general mechanism was proposed for all three ligand types. For this reason, a readily available achiral ligand, dppe, which removes

the complications of diastereomers in the intermediate structures and also produces a well-behaved resting state, was used for the studies presented in this chapter.

### 4.1.2. High valent $[Pt]^{IV}$-F complexes

Reductive elimination from high valent late transition metal fluoro complexes has become a route for the formation of fluorinated organic compounds.[3,4] Reductive elimination from Pd(IV) complexes has been extensively studied,[4] and more recently, interest in Pt(IV) has increased.[5] The Vigalok group, in particular, has developed various Pt(II) and Pt(IV) fluoro complexes using both mono and bidentate phosphine ligands.[6,7] Oxidative addition of $XeF_2$ to platinum (II) bisaryl complexes containing monodentate phosphine ligands generated a Pt(IV)-bisfluoro complex, which is stabilized by the two fluoro ligands and only undergoes reductive elimination of Ar-Ar after dissociation of a phosphine ligand. (Scheme 4-2). In contrast, subjecting a *cis*-chelating bidentate phosphine platinum (II) complex to $XeF_2$ gives rapid reductive elimination of the aryl groups forming a C-C bond and a Pt(II) $P_2PtF_2$ complex. The Vigalok group did, however, find that a stable $[Pt]^{IV}$-F species (**13**) with a *cis*-

[3](a) Furuya, T.; Benitez, D.; Tkatchouk, E.; Strom, A. E.; Tang, P.; Goddard, W. A.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 3793.

[4](a) Racowski, J. M.; Gary, J. B.; Sanford, M. S. *Angew. Chem. Int. Ed.* **2012**, *51*, 3414. (b) Vigalok, A.; Kaspi, A. W. *Top. Organomet. Chem.* **2010**, *31*, 19. . (c) Furuya, T.; Benitez, D.; Tkatchouk, E.; Strom, A. E.; Tang, P.; Goddard, W. A.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 3793. (d) Ball, N. D.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 3796 (e) Furuya, T.; Ritter, T. *J.Am. Chem. Soc.* **2008**, *130*, 10060. (f) Kaspi, A. W.; Yahav-Levi, A.; Goldberg, I.; Vigalok, A. *Inorg. Chem.* **2007**, *47*, 5. (g) Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 15142. (h) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134. (i) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790.

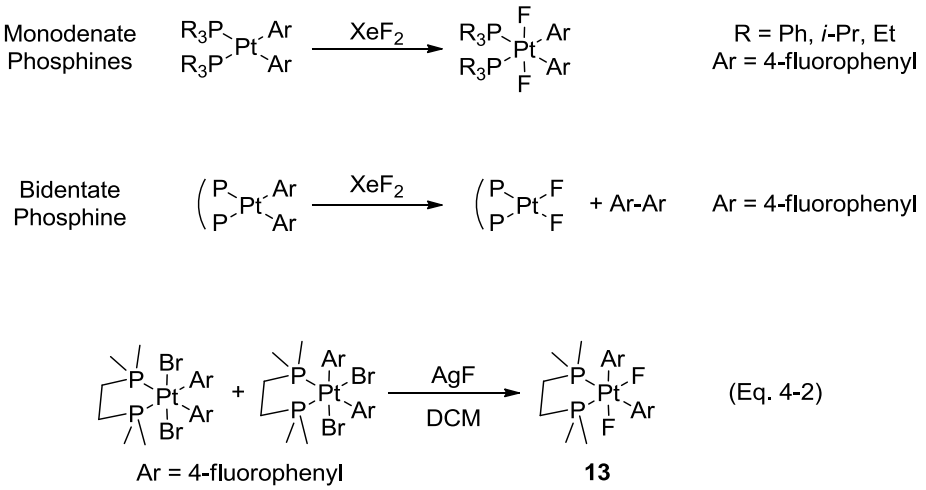
[5](a) Zhao, S.-B.; Wang, R.-Y.; Nguyen, H.; Becker, J. J.; Gagné, M. R. *Chem. Commun.* **2012**, *48*, 443. (b) Grice, K.; Scheuermann, M.; Goldberg, K.; Canty, A. J. In *Top. Organomet. Chem.*; Springer Berlin / Heidelberg, **2011**; Vol. 503; pp 1. (c) Wang, T.; Love, J. A. *Organometallics* **2008**, *27*, 3290.

[6]For Vigalok papers containing Pt(II)-F complexes: (a) Vigalok, A. *Organometallics* **2011**, *30*, 4802. (b) Yahav, A.; Goldberg, I.; Vigalok, A. *J. Am. Chem. Soc.* **2003**, *125*, 13634.

[7]For Vigalok papers containing Pt(IV)-F complexes: (a) Yahav-Levi, A.; Goldberg, I.; Vigalok, A. *J. Fluorine Chem.* **2010**, *131*, 1100. (b) Kaspi, A. W.; Goldberg, I.; Vigalok, A. *J. Am. Chem. Soc.* **2010**, *132*, 10626. (c) Yahav, A.; Goldberg, I.; Vigalok, A. *Inorg. Chem.* **2005**, *44*, 1547.

chelating bidentate phosphine ligand could be synthesized through the reaction of a six coordinate $P_2Pt(aryl)_2Br_2$ complex with a nucleophilic fluorine source, AgF (Eq. 4-2).[7a] Structural analysis of this $[Pt]^{IV}$-$F_2$ complex determined that the platinum arranged in an octahedral geometry with *cis* aryl groups and *cis* fluoride ligands.[7a] These results indicate that the formation of a $[Pt]^{IV}$-F complex using a *cis*-chelating bidentate phosphine ligand requires specific reaction conditions and is not trivial.

**Scheme 4-2**. Reactivity of platinum (II) complexes containing monodentate or bidentate phosphine ligands with $XeF_2$.

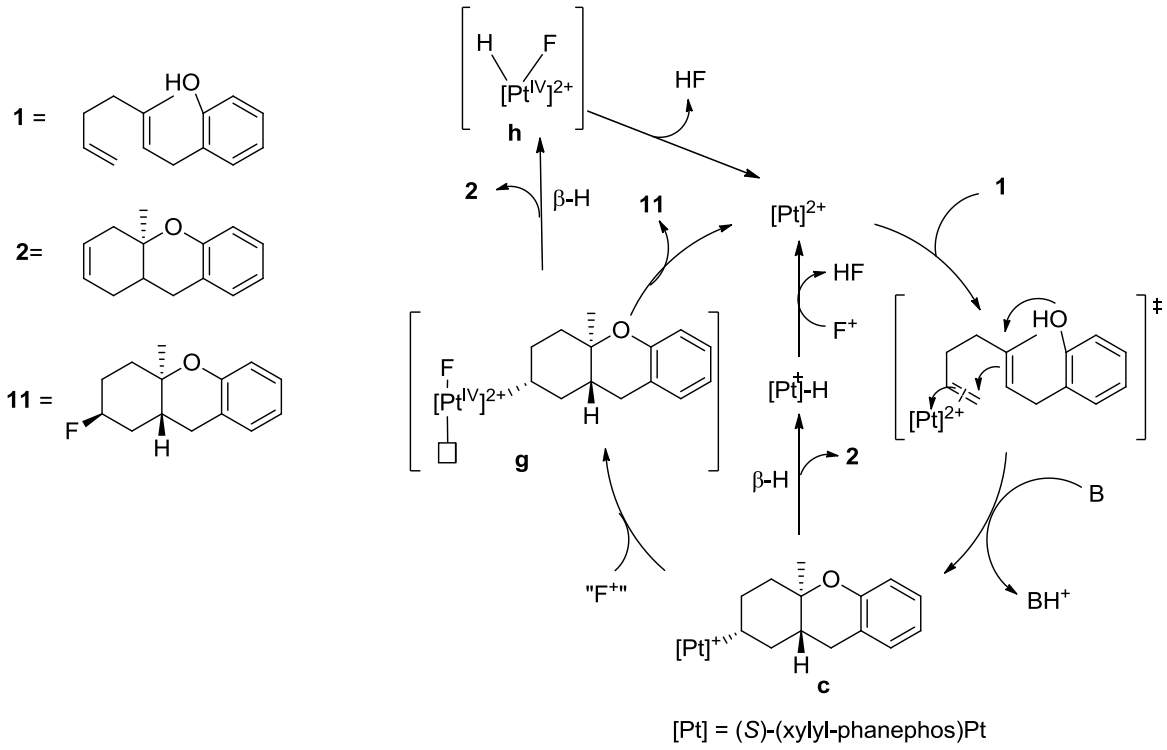



## 4.2. Initial mechanistic studies for the cyclization/fluorination reaction: results and discussion

The mechanism studied previously for the net-dehydrogenative cascade cyclization in Eq. 4-1 formed the basis for the cyclization/fluorination process shown in the catalytic cycle in Scheme 4-3. In contrast to a β-H elimination as the carbocycle deplatination step in the dehydrogenative cyclization mechanism (Scheme 4-1), the cyclization/fluorination process has the $P_2Pt$-alkyl cationic intermediate, **c**, intercepted with an electrophilic fluorine source (Scheme 4-3). The addition of an electrophilic fluorine source is proposed to generate a $[Pt]^{IV}$-F complex, which is depicted as a six coordinate complex with solvent or nitrile

present in the sixth coordination site (complex similar to **g**), however, this complex has never been directly observed. Reductive elimination from the putative $[Pt]^{IV}$-F complex yields the desired C-F coupled organic product (**11**) and regenerates the active $P_2Pt^{2+}$ catalyst complex, thus turning over the catalytic cycle.

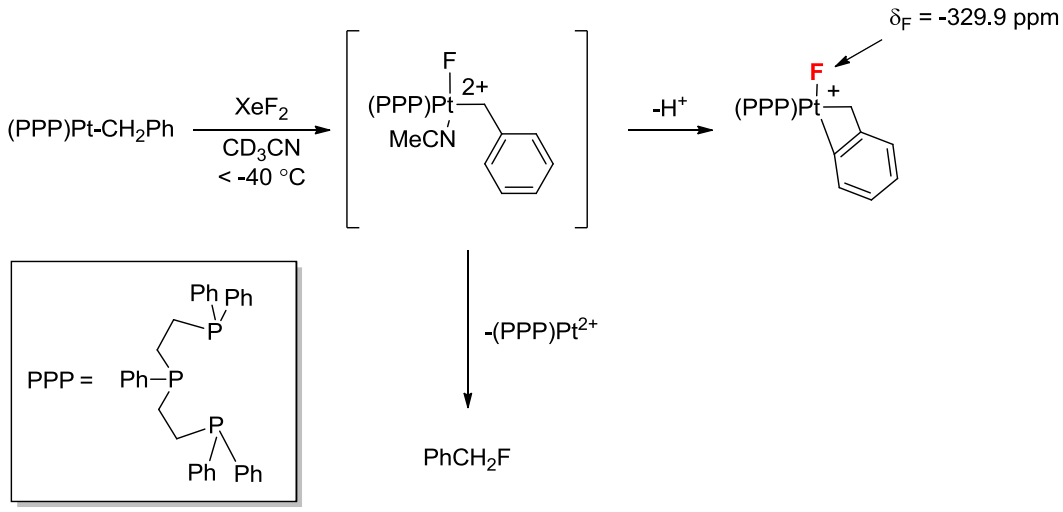
**Scheme 4-3.** Proposed mechanism for the Pt(II)-catalyzed cascade cyclization/fluorination of dienephenol.




As seen in Chapter 3, β-H eliminated product was a minor product observed from the catalytic fluorination reaction. We propose a competing pathway that generates **2** and a putative $P_2Pt$-H cation. Since the [Pt]-H is not observed, we propose that the hydride is removed by the electrophilic fluorine source to produce HF and regenerate the dicationic $P_2Pt$ system. This latter conversion of the $P_2Pt$-H cation to the active $P_2Pt^{2+}$ has not been definitively proven. It is also possible that β-H elimination is competitive with C-F reductive elimination (forming **h**). Similar conversions have been previously noted during the

electrophilic fluorination of otherwise stable cationic $P_3$Pt-alkyl complexes, where $P_3$ = tridentate phosphine ligand (triphos), which do not β-H eliminate at the square planar $d^8$ state.[8] Previous studies on this tridentate system indicated that the steric bulk of the alkyl dictates which pathway is favored. When the steric bulk of the alkyl group is large, concerted C-F reductive elimination pathway is dominant, whereas less bulky substituents favor β-H elimination from the $[Pt]^{IV}$-F.

**Scheme 4-4**. Cyclometallation of (PPP)Pt-benzyl fluoride complex to generate a (PPP)$[Pt]^{IV}$-F intermediate.




To probe this (PPP)Pt-alkyl fluorination mechanism, the reaction of a $P_3$Pt-benzyl complex with $XeF_2$ at low temperatures in melting acetonitrile was performed, where a putative dicationic $[Pt]^{IV}$-F benzyl complex is generated.[8] As expected, the $[Pt]^{IV}$-F complex quickly undergoes reductive elimination to $PhCH_2F$ and $(PPP)Pt^{2+}$, but interestingly evidence was observed for a cyclometallated benzyl $[Pt]^{IV}$-F complex by $^1H$, $^{19}F$ and $^{31}P$ NMR (Scheme 4-4), indicating that $[Pt]^{IV}$-F complexes are indeed involved in the fluorination mechanism for $P_3$Pt systems.[8]

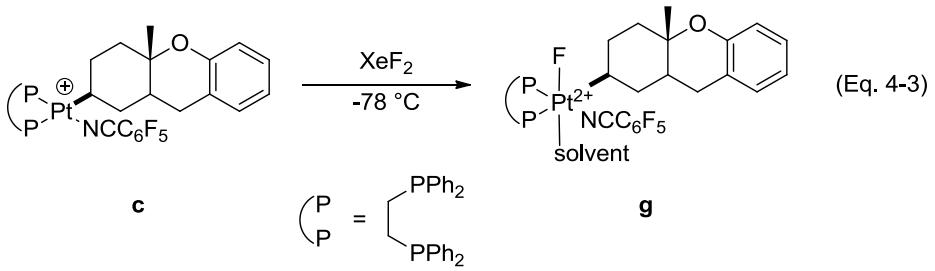
[8]Zhao, S.-B.; Becker, J. J.; Gagné, M. R. *Organometallics* **2011**, *30*, 3926.

In situ monitoring of a catalytic cyclization/fluorination of **1** using (xylyl-phanephos)$Pt^{2+}$ as the active catalyst showed, by $^{31}P$ NMR, that the resting state is the "active" form of the catalyst, dicationic $P_2Pt^{2+}$, which through the course of the reaction generates the same unknown symmetrical species ($J_{Pt-P}$ = 4050 Hz) observed in the dehydrogenative cascade cyclization chemistry (Scheme 4-1).[2] In contrast, using the (*rac*-BINAP)$Pt^{2+}$ system, the catalyst rested as **c**. This data suggests that like in the dehydrogenative cascade cyclization chemistry, mechanistic details for the xylyl-phanephos complexes differ from those in the *rac*-BINAP system.

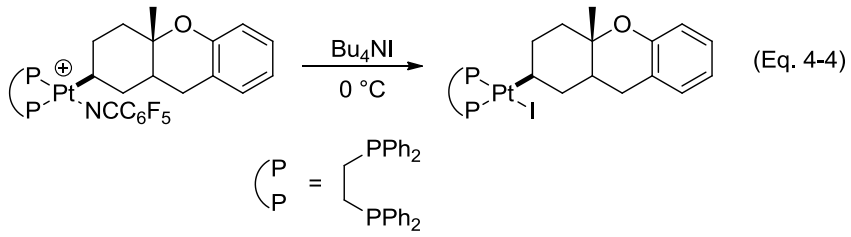
Based on our proposed mechanism for these fluorination reactions (Scheme 4-3), these results suggest for the xylyl-phanephos system, coordination of the [Pt] to the substrate is turnover limiting. In contrast, with *rac*-BINAP, the catalyst rests at **c** suggesting that the cyclization is fast and indicating that either the fluorination or C-F reductive elimination is turnover limiting for the *rac*-BINAP system. The fact that a $[Pt]^{IV}$-F complex is never observed during the catalytic reaction indicates that C-F reductive elimination is rapid. These data and observations therefore suggest that electrophilic fluorination to a putative $[Pt]^{IV}$-F is turnover limiting in the *rac*-BINAP system. These data support our current view of the mechanism (Scheme 4-3), that has **c** competitively undergoing β-H elimination or $F^+$ attack to generate a $[Pt]^{IV}R(F)$ dication, which undergoes a stereoretentive reductive elimination to **11**. At this point, we cannot definitively rule out a mechanism in which β-H elimination from a $[Pt]^{IV}$-F occurs to generate a putative [Pt]-H(F) complex, **h**. Neither the $[Pt]^{IV}$ nor the [Pt]-H species are observable by NMR, although literature precedence suggests that both routes are viable.[5,7]

### 4.2.1. Synthesis of Pt-F complexes

To begin probing this mechanism, studies were carried out to gain evidence for the viability of a $[Pt]^{IV}$-F dicationic intermediate. First attempts to access $[Pt]^{IV}$-F complexes involved the combination of complex **c**, using dppe as the $P_2$ ligand (for reasons described above), with electrophilic fluorine sources at low temperatures (Eq. 4-3). All reactions were monitored by low temperature $^{19}F$ and $^{31}P$ NMR spectroscopy. Unfortunately, complex **g** quickly underwent C-F reductive elimination even at reduced temperatures (200 K) generating **11** as confirmed by $^{19}F$ NMR and GC-MS. The resulting metal-containing complexes as observed by $^{31}P$ NMR are a mixture of **c** and multiple other unidentified species.

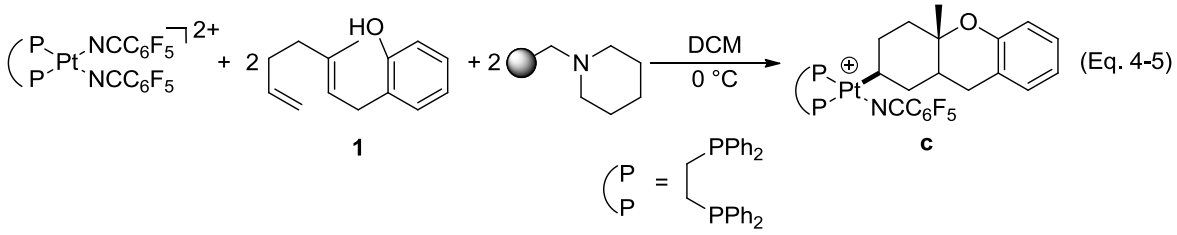



In an effort to slow reductive elimination, we hoped to stabilize the putative $[Pt]^{IV}$-F through ligand exchange with the labile nitrile ligand and a halide on **c**, which would afford a stabilized $P_2$Pt-alkyl intermediate. The cationic $P_2$Pt-alkyl nitrile complex, **c**, was reacted with tetra-butyl ammonium iodide providing a "stabilized" $P_2$Pt(alkyl) iodide species (Eq. 4-4). Previous studies suggest that this complex is isolable under cold conditions, however, for the initial mechanistic studies, this complex was generated and used as an in situ solution.




(Eq. 4-4)

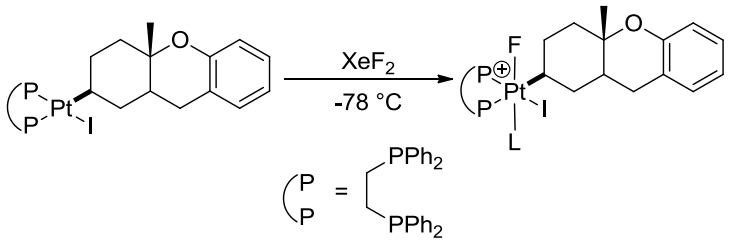
It is important to note that **c** was generated at 0 °C, conditions wherein the complex was stable to β-H elimination (Eq. 4-5).[2] In this system, excess substrate is necessary to ensure complete consumption of the dicationic $P_2Pt^{2+}$. In addition, a polystyrene-bound piperidine base was used for deprotonation because of ease of removal upon reaction completion. Upon warming **c** to room temperature, β-H elimination, to give **2**, was observed; for this reason, all reactions were performed at sub 0 °C temperatures.



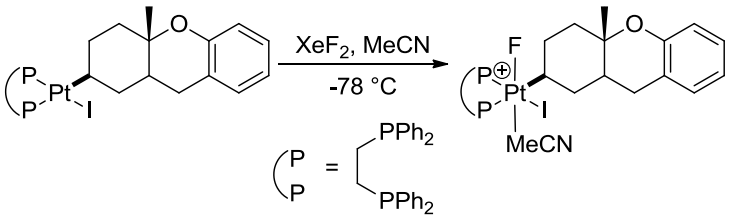

(Eq. 4-5)

Upon treating the $P_2Pt$-alkyl iodide species with $XeF_2$ at 200K (Eq. 4-6), where solvent occupies the sixth coordination site, C-F reductive elimination was observed generating the C-F coupled organic product, **11**, observed by $^{19}F$ NMR and GC-MS. The resulting metal-containing complexes are a mixture of **c** and other unidentified peaks as observed in $^{31}P$ NMR. Hoping to slow the reductive elimination and provide a more stabilized [Pt]-F complex, $XeF_2$ was dissolved in $CH_3CN$, which was added to **c** as a solution at -78 °C (Eq. 4-7). Acetonitrile is known to coordinate strongly with [Pt], and irreversibly with $P_2Pt^{2+}$ complexes, which suggests that it may be a suitable trapping ligand for a six-coordinate $[Pt]^{IV}$-F complex. Interestingly, all attempts with other $F^+$ sources resulted in no

[Pt]-F species observed by $^{19}F$ NMR. In addition, no **11** was observed by $^{19}F$ NMR or by GC-MS.



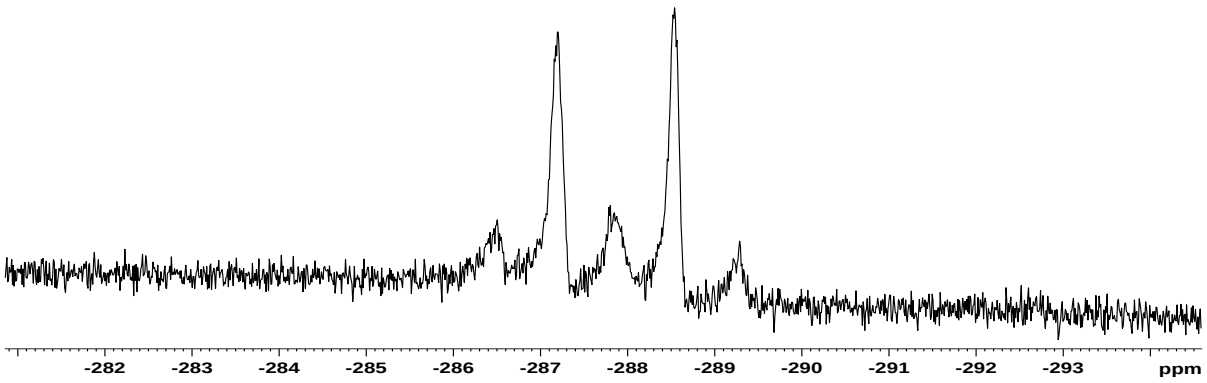

(Eq. 4-6)




(Eq. 4-7)

$^{19}F$ NMR spectra taken at 200K (Figure 4-2) provided evidence for a potential $[Pt]^{IV}$-F complex with two diastereomeric peaks at -287 ppm and -288.5 ppm ($J_{Pt-F}$ = ~800 Hz), which is in a range consistent with similar $[Pt]^{IV}$-F complexes previously observed.[7] The possible diastereomers and enantiomers are shown in Scheme 4-5, where each diastereomer (**I** and **II**) is a racemate with corresponding enantiomers (**III** and **IV**, respectively). We propose that the peaks observed by $^{19}F$ NMR can be attributed to two different diastereomers of a chiral metal complex, suggesting that the [Pt]-F complex is a 6-coordinate octahedral $[Pt]^{IV}$-F complex. Interestingly, this complex was stable at 200K for at least 1h, a time frame wherein the kinetic complexes could undergo ligand scrambling, introducing additional stereoisomers; however, for this thesis, only the kinetic products will be considered.

**Figure 4-2.** $^{19}F$ NMR spectrum of [M]-F region (-280 to -300ppm) at 200K of potential $[Pt]^{IV}$-F complex using dppe as $P_2$ ligand.

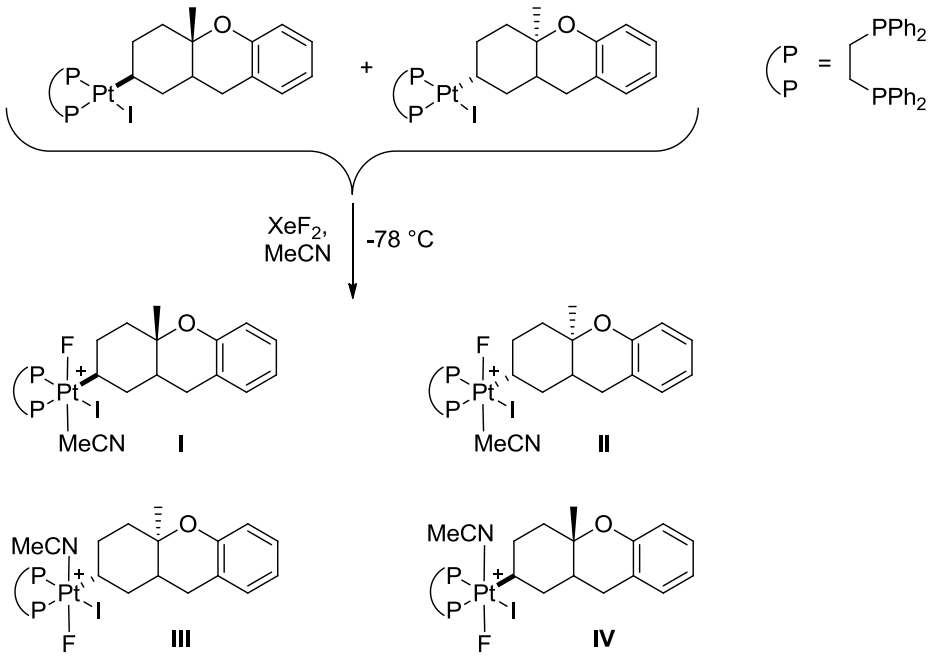



Upon warming this reaction and monitoring by $^{19}F$ NMR, the [Pt]-F species represented in Figure 4-2 (likely a $[Pt]^{IV}$-F), slowly disappears above 235K. At 250K, this species has completely disappeared by $^{19}F$ NMR and a new broad peak consistent with a [M]-F bond is present at -255 ppm. The species with a peak at -255 ppm is stable at RT and is consistent with previous reports of a Pt(II)-F complex.[6] We propose that reductive elimination of the C-F coupled product, **11**, occurs followed $F^-$ attack on the metal center generating a $[Pt]^{II}$-F in addition to multiple other [Pt] containing compounds, which is obvious by the complex $^{31}P$ NMR spectrum. At RT, $^{19}F$ NMR indicates the presence of C-F coupled product, **11** (doublet at approx.-170 ppm, Figure 3-1), which was confirmed by GC-MS. Interestingly, the GC-MS of the reaction mixture indicated the presence of the C-I coupled product (analogous to **11**) and β-H elimination product (**2**) in addition to **11** in an approximate ratio of 1:7:6 for C-I, β-H, C-F products, respectively.

Although $^{19}F$ NMR spectroscopy is a useful tool for indicating if a [M]-F bond has been made, the signals for $[Pt]^{IV}$-F complexes, which extend over a large range from approximately -250 ppm to -410 ppm also overlap with peaks consistent with $[Pt]^{II}$-F

complexes. In addition, some phosphine containing $[Pt]^{IV}$-F complexes have unresolved P-F coupling constants because this coupling is usually small. Likewise, the Pt-satellites are rarely detectable above the baseline noise. For this reason, $^{19}F$ NMR alone is not enough to provide definitive assignment of a $[Pt]^{IV}$-F versus a $[Pt]^{II}$-F, which can only be made using solid state structural analysis or a combination of multiple characterization techniques. More evidence is required to confidently suggest that a $[Pt]^{IV}$-F complex was indeed generated and converted to a $[Pt]^{II}$-F species.

**Scheme 4-5.** Possible enantiomers and diastereomers for the reaction of $P_2Pt(alkyl)(I)$ with $XeF_2$.



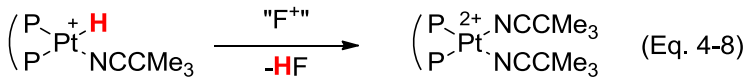

### 4.3. Conclusion and future directions

Preliminary studies of the mechanism involved in the cyclization/fluorination of dienephenol suggest that analogous to the net-dehydrogenative cyclization catalytic cycle, the bisphosphine ligand used determines the resting state of the catalyst during the reaction. In the xylyl-phanephos system, the dicationic $P_2Pt^{2+}$ is the major species observed,

suggesting that the metal coordination/ substrate cyclization is the turnover limiting step. In contrast, using biaryl catalyst complexes, the resting state is the cationic $P_2Pt$-alkyl nitrile species, **c**, indicating that the fluorination to the $[Pt]^{IV}$-F is likely the turnover limiting step.

Initial studies to test the viability of a $[Pt]^{IV}$-F intermediate suggested the formation of a Pt-F complex using dppe as the $P_2$ ligand and acetonitrile as the trapping ligand. The exact identity of this complex is not yet known. Future studies should be done on this system to determine the oxidation state of the metal and the exact ligands surrounding it, by isolating the iodide analog of **c** to remove any excess substrate or $Bu_4NI$ remaining in the in situ reaction mixtures. This could provide an overall cleaner and reproducible product. Additional trapping reagents should be tested, which could include ligands that would irreversibly bind to the metal center, and are stable toward $XeF_2$.

In addition, the β-H elimination route should be probed using an electrophilic fluorine source. Initial studies could include stoichiometric protocols similar to those in Chapter 2, using an in situ generated $[P_2Pt(H)(NCC(CH_3)_3)][BF_4]$ complex in combination with an electrophilic fluorine source (Eq. 4-5) would indicate whether "$F^+$" was a viable route to remove a hydride and regenerate $P_2Pt^{2+}$.

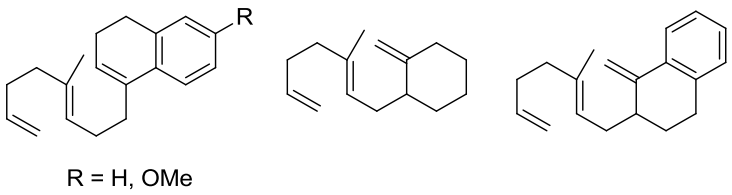



(Eq. 4-8)

**8** $P_2$ = xylyl-phanephos **9**

These studies could then be extended to cyclization reactions with substrates that require longer cyclization times and in some cases react with $Ph_3C^+$ forming byproducts. The use of a "milder" hydride abstractor such as "$F^+$" could minimize byproduct formation for these substrates, while still providing catalytic turnover.

**Figure 4-3.** Substrates that are known to react with $Ph_3C^+$ prior to cyclization due to slow cyclization rates.[9]




## 4.4. Experimental details

### 4.4.1 Materials and methods

Stoichiometric reactions were carried out under an atmosphere of nitrogen in a nitrogen-filled glovebox in oven-dried NMR tubes purchased from Fisher Scientific. $CD_2Cl_2$ was purchased from Cambridge Isotope Laboratories and freeze-pump-thaw degassed before use. (S)-xylyl-PHANEPHOS was purchased from Strem Chemicals Inc. and used as received. $XeF_2$, 2,3,4,5,6-pentafluorobenzonitrile, $AgBF_4$ and *rac*-BINAP were purchased from Aldrich and used without further purification. Polystyrene bound piperidine resin base (4.1mmol/g) was purchased from NovaBioChem and used without further purification. Acetonitrile was purchased from Fisher Scientific, dried over $CaH_2$ and distilled before use. **1**[10],(COD)$PtI_2$[11], ($P_2$)$PtI_2$[12], **c**[2] were prepared according to literature procedures. $^1H$, $^{13}C$ and $^{19}F$ NMR data were collected on a Bruker 600 MHz Avance spectrometer. Chemical shifts are reported in ppm and referenced $^-BF_4$ in $^{19}F$ NMR. GC-MS data was performed with an Agilent G4350A GC/MSD system containing a 7820A GC with an HP-5MS column (length 30m; I. D. 0.250 mm) connected to an Agilent 5975 MSD. The GC method consisted of the following parameters: inlet temperature 250 ˚C; inlet and column pressure of 11.9 psi He;

[9]Unpublished work, Joseph G. Sokol.

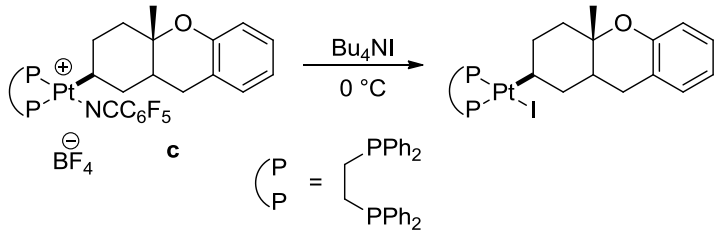
[10]Koh, J. H.; Mascarenhas, C.; Gagné M. R. *Tetrahedron* **2004**, *60*, 7405.

[11]Clark, H.; Manzer, L. E. *J. Organomet.Chem*. **1973**, *59*, 411.

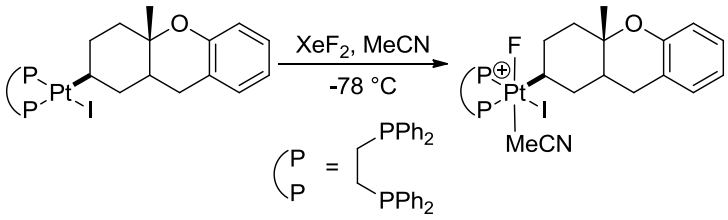
[12]Colacot, T. J.; Qian, H.; Cea-Olivares, R.; Hernandez-Ortega, S. *J. Organomet.Chem*. **2001**, *691*, 637.

column flow rate 1 mL/min; oven temperature held at 125 ˚C for 3 min then ramped 20 ˚C/min to 250 ˚C. The temperature was then held at 250 ˚C for 5 minutes. The detector temperature was set to 280 ˚C.

### 4.4.2. Synthesis and characterization of complexes



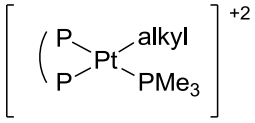

To an in situ generated solution of (dppe)Pt(alkyl)nitrile **c** (10 mg, 9µmol) at 0 ˚C in 0.5 mL $CD_2Cl_2$ in a 3.5 mL vial was added 1.2 equivalents of tetrabutylamonium iodide as a solid. The reaction was kept at 0 ˚C and stirred for 2h. The reaction mixture was filtered through a PTFE syringe filter into a pre-cooled NMR tube. This complex was observed by $^{31}P$ NMR to ensure its formation. Preliminary attempts to isolate this complex have resulted in decomposition of the [Pt] species leading to complex $^{31}P$ NMR spectra.




The solution of (dppe)Pt(alkyl)(I), described previously, was syringed into an NMR tube cooled to -78 ˚C in a dry-ice acetone bath with a septum. The reaction was then monitored by $^{19}F$ and $^{31}P$ NMR a various temperatures.

# Appendix A

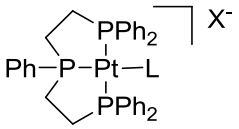
**Table A-1.** $^{31}$P NMR chemical shifts for ($P_2$P)Pt-alkyl methyl complexes.[1]




| | $P_2$ = (*R*)-DTBM SEGPHOS | | $P_2$ = (*R*)-xylyl-PHANEPHOS | | $P_2$ = (*R*)-BINAP | |
|---|---|---|---|---|---|---|
| | δ (ppm) | $J_{Pt-P}$ (Hz) | δ (ppm) | $J_{Pt-P}$ (Hz) | δ (ppm) | $J_{Pt-P}$ (Hz) |
| $P_{cis}$ | 17.76 | 1270 | 13.8 | 1450 | 13.9 | 1610 |
| $P_{trans}$ | 2.47 | 1750 | -0.5 | 1680 | 4.2 | 1860 |
| $P_{PMe3}$ | -2.88 | 1260 | -15.3 | 2268 | -15.8 | 2570 |

[1] Joseph G. Sokol, unpublished work.

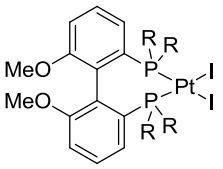
**Table A-2**. $^{31}P$ NMR chemical shifts for (PPP)Pt complexes.[2]

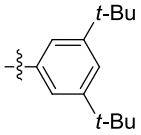
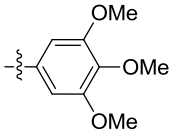
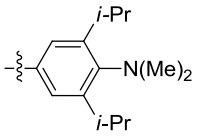
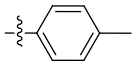
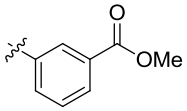
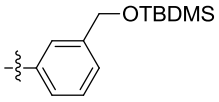
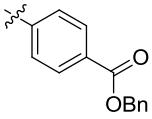
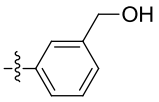
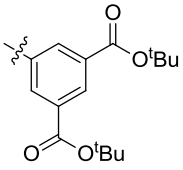
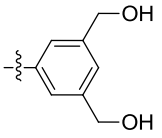
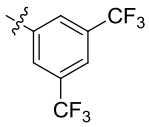



| L | $X^-$ | δ $^{31}P$ *trans* (ppm) | *Trans* coupling constant (Hz) | δ $^{31}P$ *cis* (ppm) | *Cis* coupling constant (Hz) | Solvent |
|---|---|---|---|---|---|---|
| **$NCC_6F_5$** | $(BF_4)_2$ | 86.1 | 3329 | 49.3 | 2352 | $CD_3NO_2$ |
| **$NCC_6F_5$** | $(BF_4)_2$ | 86 | 3329 | 49 | 2359 | $EtNO_2$ |
| **$NCC_6F_5$** | $(BF_4)_2$ | 84.7 | 3344 | 48.5 | 2352 | $CH_2Cl_2$ |
| **MeOH** | $(BF_4)_2$ | 86 | 2923 | 46.3 | 2419 | $CD_3NO_2$ |
| **MeOH** | $(BF_4)_2$ | 86 | 2921 | 46 | 2421 | $EtNO_2$ |
| **MeOH** | $(BF_4)_2$ | 85.2 | 2924 | 45.3 | 2417 | $CH_2Cl_2$ |
| **1-Butanol** | $(BF_4)_2$ | 85.1 | 2911 | 44.5 | 2422 | $CH_2Cl_2$ |
| **$^-OMe$** | $(BF_4)_2$ | 73.8 | 2665 | 40.9 | 2686 | $CH_2Cl_2$ |
| **$^-CH_2NO_2$** | $(BF_4)_2$ | 93.6 | 1940 | 45.7 | 2557 | $CD_3NO_2$ |
| **Acetone** | $(BF_4)_2$ | 80.4 | 3469 | 51.3 | 2446 | Acetone-D6 |
| **Acetone** | $(BF_4)_2$ | 79.1 | 3510 | 50.4 | 2436 | $CD_3NO_2$ |
| **I** | I | 92.2 | 2886 | 42.4 | 2421 | $CDCl_3$ |
| **Cl** | Cl | 86.3 | 3028 | 42.3 | 2484 | $CH_2Cl_2$ |
| **1-Hexene** | $(BF_4)_2$ | 106.4 | 2959 | 50.2 | 2265 | $CH_2Cl_2$ |

[2] Ryan J. Felix, unpublished work.

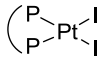
**Table A-3**. $^{31}P$ NMR shifts of $P_2PtI_2$ complexes containing various $P_2$ ligands with a MeO-BIPHEP backbone.

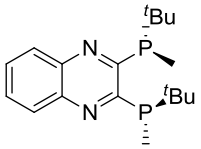
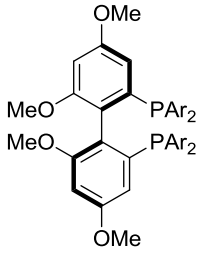
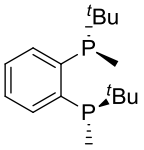
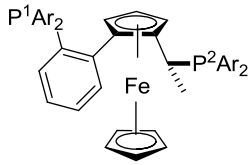
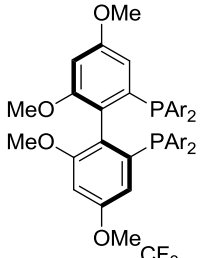
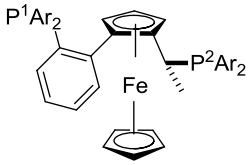
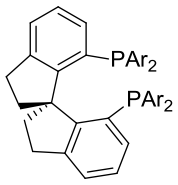
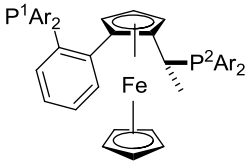



| R | δ $^{31}P$ (ppm) | Coupling Constant (Hz) | Solvent | R | δ $^{31}P$ (ppm) | Coupling Constant (Hz) | Solvent |
|---|---|---|---|---|---|---|---|
|  | 21.24 | 3476 | $CD_2Cl_2$ |  | -31.5[a] | 3648[a] | $CD_2Cl_2$ |
|  | 6.94 | 3498 | $CD_2Cl_2$ |  | 6.52[a] | 3523[a] | $CD_2Cl_2$ |
|  | 2.96 | 3497 | $CD_2Cl_2$ |  | 2.0[a] | 3480[a] | $CD_2Cl_2$ |
|  | 2.98 | 3440 | $CD_2Cl_2$ |  | Not soluble in NMR solvents | | |
|  | 2.19 | 3430 | $CD_2Cl_2$ |  | Not soluble in NMR solvents | | |
|  | 2.06 | 3446 | $CD_2Cl_2$ |  | Not soluble in any NMR solvents | | |
|  | 5.64 | 3364 | $CD_2Cl_2$ | | | | |

a) Perez-Powell, I. *Platinum Catalysed Wacker-Type Reactions* **2011**, Honours degree of MSci Chemistry Thesis.

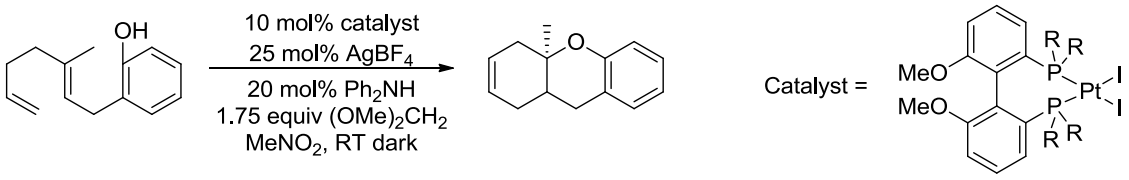
**Table A-4.** $^{31}P$ NMR shifts of $P_2PtI_2$ complexes containing various $P_2$ ligands.

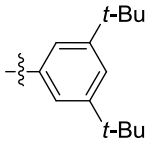
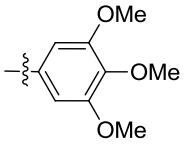
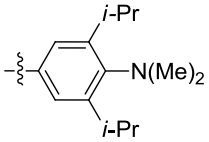
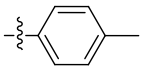
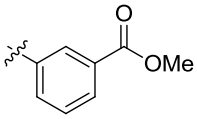
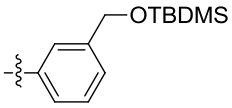
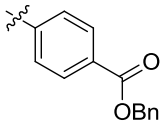
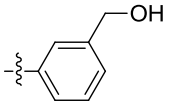
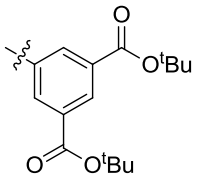
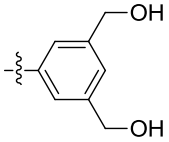
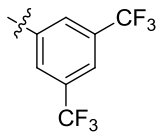


|  | δ $^{31}P$ (ppm) | Coupling Constant (Hz) | Solvent |  | δ $^{31}P$ (ppm) | Coupling Constant (Hz) | Solvent |
|---|---|---|---|---|---|---|---|
|  | 32.0 | 3248 | $CD_2Cl_2$ |  | 3.0 | 3486 | $CD_2Cl_2$ |
|  | 50.0 | 3366 | $CD_2Cl_2$ | | | | |
|  | 22.4<br>2.97 | 3413<br>3515 | $CD_2Cl_2$ |  | 5.0 | 3366 | $CD_2Cl_2$ |
|  | 22<br>2.92 | 3423<br>3498 | $CD_2Cl_2$ |  | 12.8 | 3424 | $CD_2Cl_2$ |
|  | 20.3<br>1.71 | 3444<br>3364 | $CD_2Cl_2$ | | | | |

## Appendix B

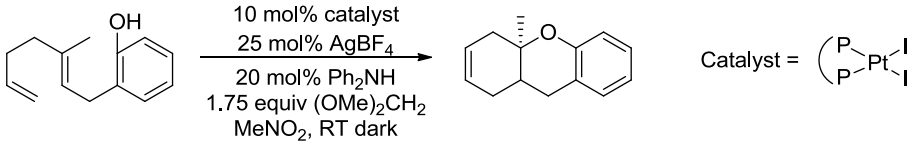
**Table B-1.** Enantioselectivities of dehydrogenative cascade cyclization determined from using $P_2PtI_2$ complexes containing various $P_2$ ligands with a MeO-BIPHEP backbone.

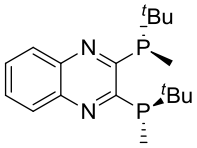
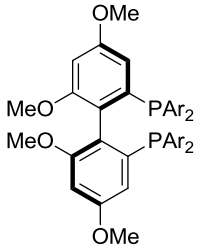
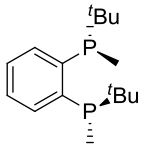
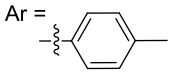
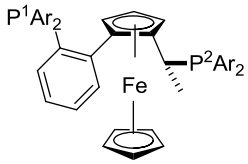
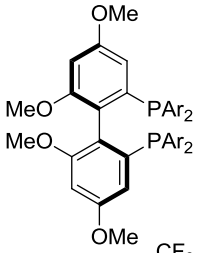
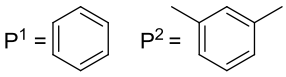
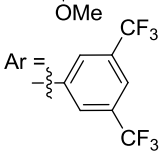
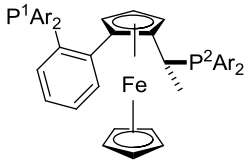
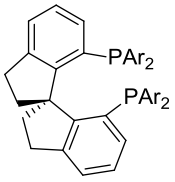
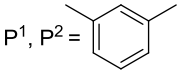
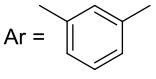
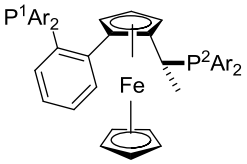
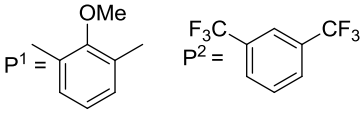



| R | % yield (GC-MS) | % ee (Chiral GC) | R | % yield (GC-MS) | % ee (Chiral GC) |
|---|---|---|---|---|---|
|  | 60 | 9 |  | 23 | 18 |
|  | 70 | 9 |  | 29 | 40 |
|  | NR | NR |  | 15 | 3 |
|  | 20 | 27 |  | 15[a] | 15[a] |
|  | 26 | 20 |  | 64 | 20 |
|  | 18 | 24 |  | 14 | 60 |
|  | 29 | 19 | | | |

a) Run using TrOMe instead of dimethoxymethane

**Table B-2.** Enantioselectivies of dehydrogenative cascade cyclization determined from using $P_2PtI_2$ complexes containing various $P_2$ ligands.



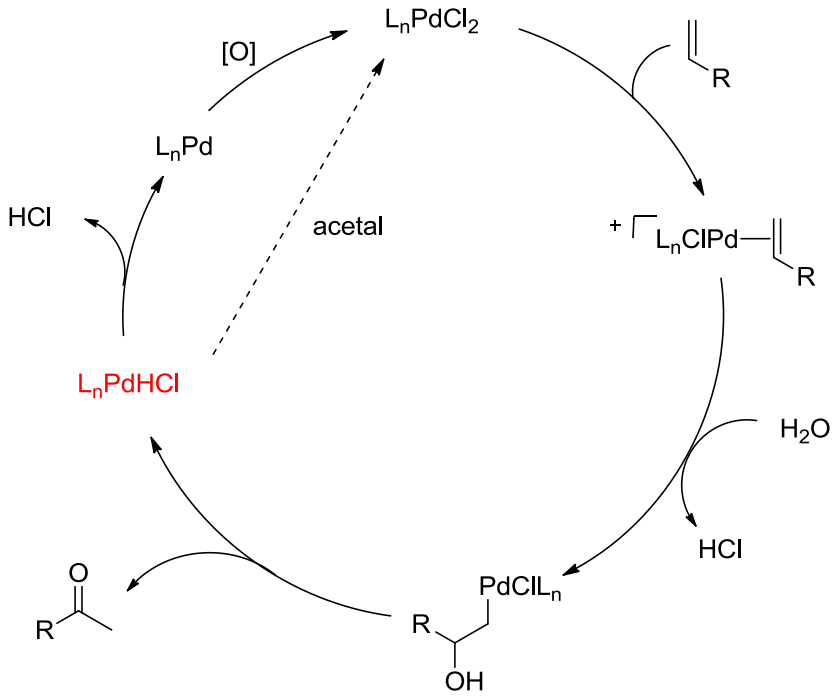

| P,P | % yield (GC-MS) | % ee (Chiral GC) | P,P | % yield (GC-MS) | % ee (Chiral GC) |
|---|---|---|---|---|---|
|  | trace | n.d. |  | 46 | 21 |
|  | 61 | 32 |  | | |
|  | 25 | 18 |  | 29 | 22 |
|  | | |  | | |
|  | 23 | 13 |  | 12 | 37 |
|  | | |  | | |
|  | 18 | 24 | | | |
|  | | | | | |

n.d. = not determined

## Appendix C

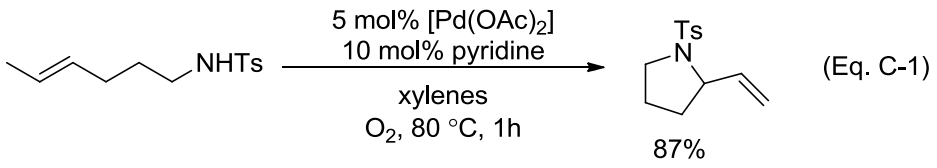
In many Wacker systems, the putative Pd-H complex quickly undergoes reductive elimination generating a Pd(0) complex, which is then re-oxidized using a 2-electron oxidant (Scheme C-1). We hypothesized that we could bypass the redox chemistry, Pd(II) to Pd(0) then back to Pd(II), using an acetal to directly abstract the hydride from the Pd-H and maintain a Pd(II) species throughout the catalytic reaction, similar to the processes described in Chapter 2.

**Scheme C-1.** Traditional Wacker catalytic cycle with hypothesized hydride abstraction using an acetal.

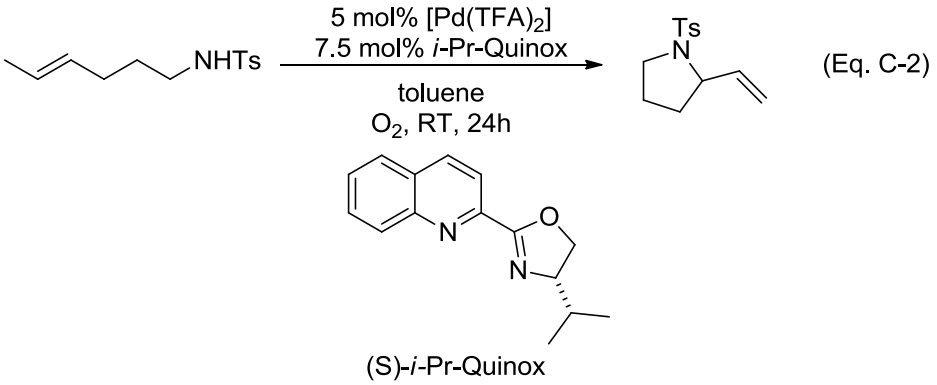



For this chemistry we sought a system that was well studied and well-behaved. For this reason, we tested the monocyclization of tosyl amide substrates, which have been

extensively studied in the Stahl group.[1] Initial studies repeated the Stahl conditions for a direct comparison to the chemistry using the acetals instead of oxygen (Eq. C-1 and Eq. C-2). The catalytic cycle for the Stahl chemistry includes the formation of a Pd-alkyl complex followed by β-H elimination liberating the desired product and a Pd-H complex. This Pd-H quickly undergoes reductive elimination giving a Pd(0) complex, which in the presence of molecular oxygen is re-oxidized to the "active" Pd(II) complex through a Pd-peroxy complex (Scheme C-2).



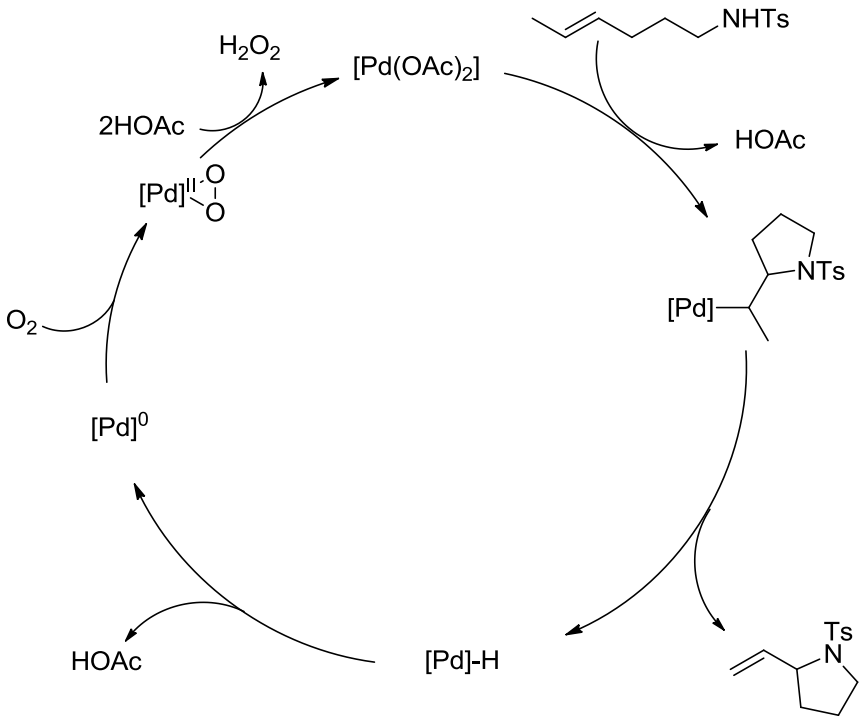

(Eq. C-1)




(Eq. C-2)

[1](a) McDonald, R. I.; White, P. B.; Weinstein, A. B.; Tam, C. P.; Stahl, S. S. *Org. Lett.* **2011**, *13*, 2830. (b)Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem. Int. Ed.*, **2002**, 41, 164

**Scheme C-2.** Proposed Catalytic Cycle for the monocyclization of tosyl amide substrates in the Stahl group.




Concomitant catalytic cyclization of these tosyl amide substrates using platinum(II) complexes resulted in no desired monocyclized product, rather alkene isomerization of the starting material.[2] Attempts to use tridentate triphos platinum complexes in stoichiometric cyclization of the tosyl amide substrates forming cationic Pt-alkyl complexes resulted in no coordination of the metal center to the internal alkene of the substrate. For this reason, an analogous substrate containing a monosubstituted terminal alkene was synthesized and utilized in cyclization with Pd catalytic conditions (Eq.C-3). The catalytic conditions were adapted from the Stahl chemistry to include the use of an acetal as opposed to molecular oxygen as the oxidant. Table C-1 includes the investigation of various acetals and acetals in Stahl-like reaction conditions for the aza-Wacker cyclization of tosyl amide substrates.

[2]Perez-Powell, I. *Platinum Catalysed Wacker-Type Reactions* **2011**, Honours degree of MSci Chemistry Thesis.

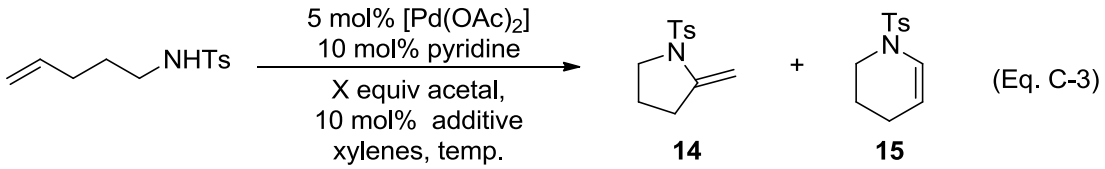



**Table C-1.** Conditions varying the acetal and additive in Stahl-like conditions for the monocyclization of terminal tosyl amide substrates.

| Acetal | Equiv | Additive | Temp. (˚C) | Result |
|---|---|---|---|---|
| $PhCH(OMe)_2$ | 17.5 | | 75 | 5% **14**, 10% **15** |
| $MeOCH_2OMe$ Oxygen free | 17.5 | | RT | 25% **14,** 10% **15** 4% **14**, 5% **15** |
| $MeOCH_2OMe$ Oxygen free | 1.75 | $[Ph_2NH_2][BF_4]$ | RT | trace reaction 9% **15** |
| $MeOCH_2OMe$ | 1.75 | | RT | 4% **14**, 7% **15** |
| $TrBF_4$ | 1.75 | | RT | No products |
| -- | -- | $[Ph_2NH_2][BF_4]$ | RT | 13% **15** |

For all entries in Table C-1, the amount of desired product, **14**, was approximately equal to the catalyst loading suggesting that the acetals used are not suitable for catalytic turnover in these aza-Wacker systems using $Pd(OAc)_2$ as the catalyst. Similarly, using $Pd(TFA)_2$ as catalyst in the presence of dimethoxymethane and a chiral ligand provided poor conversion to desired products (Eq. C-4, Table C-2). These results suggest that acetals are not suitable alternatives to traditional 2-electron oxidants in the monocyclization of tosyl amide substrates.

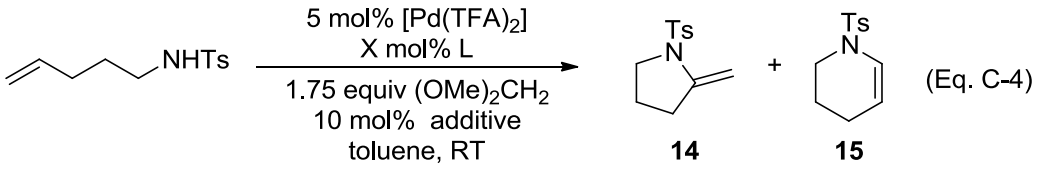
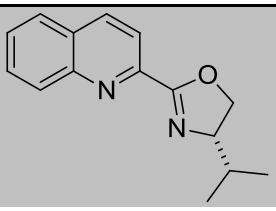
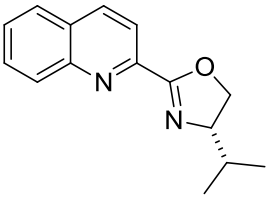
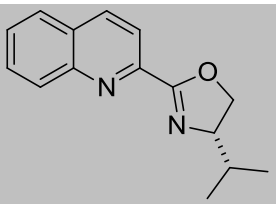


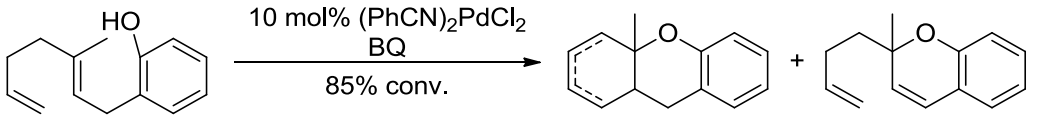

**Table C-2.** Conditions using dimethoxymethane as turnover mechanism in Stahl-like conditions for the monocyclization of terminal tosyl amide substrates.

| L | Mol % | Additive | Result |
|---|---|---|---|
|  | 7.5 | 1 ATM $O_2$ instead of acetal | 12% **14**, 45% **15** |
|  | 7.5 | | 25% **15**, other minor product isomers |
|  | 7.5 | $[Ph_2NH_2][BF_4]$ | 43% **15**, starting material isomers present |
| pyridine | 10 | | 6% **15** |

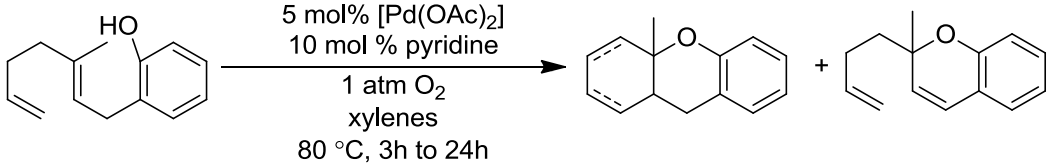
Since the conversion to desired monocyclized tosyl amide product was poor, we sought to utilize Stahl conditions for the bicyclization of dienephenol substrate, **1**. Previous work in the Gagné group has shown that cyclization and β-H elimination of **1** occur using $(PhCN)_2PdCl_2$ and benzoquinone in good conversions with poor regioselectivity of the product alkene (Eq. C-5).[3] We hypothesized that the cyclization would occur with similar conversion and selectivity to the $(PhCN)_2PdCl_2$ system. Upon reaction of **1** under Stahl reaction conditions with either $Pd(OAc)_2$ complete consumption of starting material was

[3]Koh, J. H.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 3459.

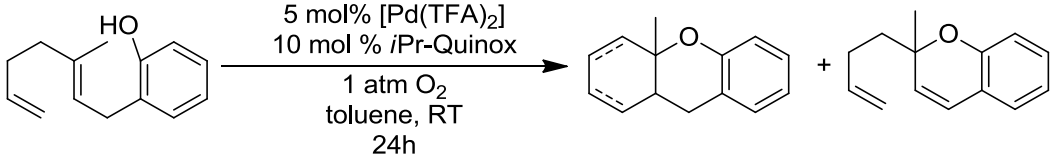
observed and cyclized product observed with multiple alkene isomers present, however, no previously observed net-dehydrogenative product, **2**, was observed by GC-MS (Eq. C-6). In contrast, reacting **1** with $Pd(TFA)_2$ resulted in no conversion of the starting material, **1** (Eq. C-7). These results suggest that the cyclization of **1** is tolerant of specific reaction conditions and that oxygen is not a suitable turnover mechanism for these reactions.




(Eq. C-5)




(Eq. C-6)




(Eq. C-7)

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