Development of Novel Enantioselective Cyclative Functionalization of Alkenes and Alkynes: Pd(II/IV) and Pd(0/II) Catalysis Using SPRIX Ligand

A Thesis Submitted in Conformity With the Requirements for
The Degree of Doctor of Philosophy to the Department of Chemistry
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By

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Chapter 3

Carbonylation of Propargyl Carbamates with Palladium-SPRIX/Bisoxazoline Catalysis: Towards Efficient Synthesis of 5-Methoxy-3(2*H*)-furanones

{A Collaborative Work with Prof. K. Kato, Toho University, Chiba, Japan}

List of Abbreviations

$[\alpha]_D$	specific rotation at wavelength of sodium D line
°C	degrees Celsius
Å	angstrom
Ac	acetyl
acac	acetylacetonate
APCI	Atmospheric-pressure chemical ionization
aq.	aqueous
atm	atmosphere
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
BOXAX	(S,S)-2,2'-bis(4-isopropyloxazolyl)-1,1'-binaphthyl
bpy	bipyridine
BQ	benzoquinone
Br	broad
BSA	benzene sulfonic acid
Bu	butyl
c	concentration for specific rotation measurements
calcd	calculated
cat.	catalytic
cm	centimeter
CO	carbon monoxide
cod	1,5-cyclooctadien
CPME	cyclopentyl methyl ether
d	doublet
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	double doublet
DIH	1,3-diiodo-5,5-dimethylhydantoin

DME	1,2-dimethoxyethane
DMSO	dimethylsulfoxide
dt	double triplet
ee	enantiomeric excess
EI	electron spray
eq	equation
equiv.	equivalents
ESI	electron spray ionization
Et	ethyl
FT	Fourier transform
g	gram(s)
h	hour(s)
hfacac	hexafluoroacetylacetonate
HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectroscopy
Hz	hertz
IPA	isopropyl alcohol
i-Pr	isopropyl
IR	infrared
J	coupling constant
m	multiplet
Me	methyl
mg	milligram
MHz	megahertz
min	minute(s)
mL	milliliter(s)
mol	moles
Ms	methanesulfonyl
MTBE	methyl *tert*-butyl ether
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide

ND	not detected
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NR	no reaction
p	para
PG	protecting group
Ph	phenyl
Phth	phthalimide
PIDA	phenyl iodo diacetate
Piv	pivaloyl
ppm	part(s) per million
q	quartet
rac	racemic
ref.	reference
rt	room temperature
s	singlet
sat.	saturated
sep	septet
SPRIX	spiro bis(isoxazoline) ligands
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
ter/t	tertiary
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA/tfa	trifluoro acetic acid (acetate)
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
Ts	4-toluenesulfonyl
UV	ultraviolet

δ	chemical shift
μL	microliter
μmol	micromolar

Chapter 1

1.1 Introduction

1.1.1 Asymmetric Catalysis

Biological systems, in most cases, recognize a pair of enantiomers as different substances, and the two enantiomers will elicit different responses. Thus, one enantiomer may act as a very effective therapeutic drug whereas the other enantiomer is highly toxic. It is the responsibility of synthetic chemists to provide highly efficient and reliable methods for the synthesis of desired compounds in an enantiomerically pure state.

Organic chemistry is the study of carbon-based compounds, the chemistry of life. If organic chemists wish to synthesize the molecules that nature has produced then, they must be able to prepare the same enantiomer as occurs naturally. Synthetic chemists not only want to copy nature but to synthesize totally novel chiral structures.

Organic synthesis come up to challenges arise from the demand of society and industry, usually to be more selective, to be more efficient and to be greener. The transition metals are being extensively used in catalysis such as Pd, Ni, Pt, Rh, Fe, Co, Cu and so on. The full synthetic potential of transition metals in C-C bond forming reaction was not well recognized until 1950. What is the special about the transition metals to use them on chemistry? What metals such as palladium, iron and nickel different from metals such as sodium, magnesium and lithium? The answer lies in the availability of d-orbitals, filled or empty, that have energy suitable for interaction with a wide variety of functional groups of organic molecules. The other is their ability to undergo simultaneously and reversibly both oxidation and reduction under one set of reaction condition. By definition, catalysis increases the reaction rate by lowering the activation energy of the reaction, therefore allowing the chemical transformation to take place under much milder conditions over the uncatalyzed process.

In an important example, transition metals can interact with alkenes very efficiently to make them active, which are being ignored by almost all bases and nucleophiles. The C-H bond activation tremendously influenced by transition metals. Thus, the use of transition metals enables the organic chemist to do the reactions that are more difficult or, more often, impossible otherwise, opening up new synthetic pathway and selectivity.

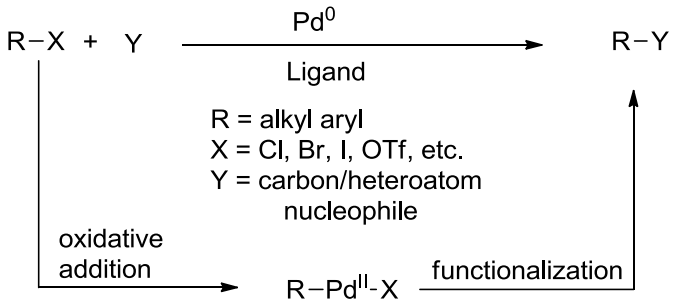
Molecular catalysts consisting of a metal and a chiral organic ligand are widely used for asymmetric synthesis, in which the ligand play a vital role in varying reactivity on the metal center by way of coordination through various donor atoms installed on chiral ligands. That is

why, design and synthesis of appropriate ligand for the induction of high reactivity and selectivity is very essential.

The significance of the asymmetric catalysis and its proven impact on the advancement of science was recognized by Nobel Prize in chemistry. {Contributed by Knowles, Noyori and Sharpless; 2001}

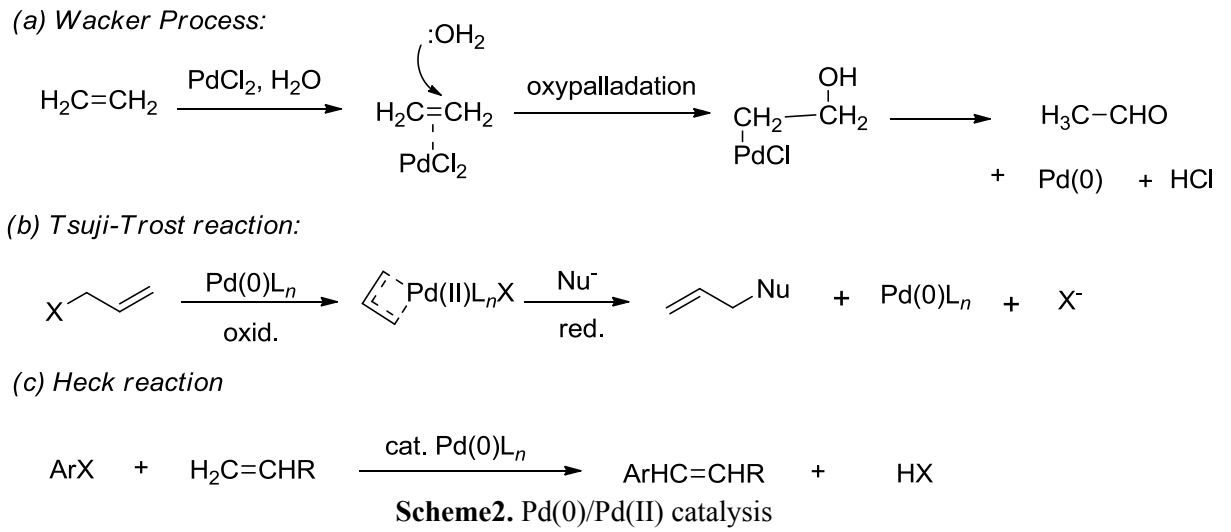
1.1.2 Pd Catalysis in Asymmetric Synthesis: Pd(0)/Pd(II) Catalysis

Among the transition metals, palladium catalysis has gained enormous relevance in various reactions such as Heck coupling, cross coupling (Kumada, Stille, Negishi, Suzuki, Miyaura, and Hiyama), Tsuji-Trost allylation, and Buchwald-Hartwig reactions. Many products could be synthesized by this methodology. Palladium is perhaps the most active and versatile transition metal employed in organic synthesis, catalyzing both oxidative and nonoxidative transformations. A common and critical feature of these catalytic processes is the formation of aryl or alkyl palladium(II) intermediates which can be subsequently functionalized to form carbon-carbon and carbon-heteroatom bonds (Scheme 1).



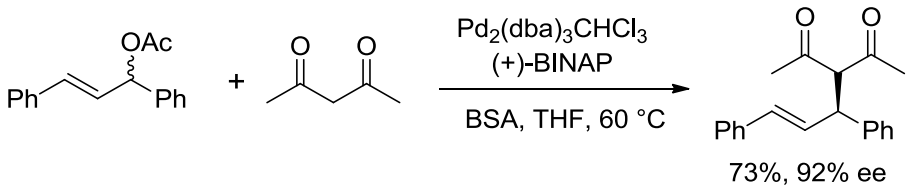
Scheme 1. Pd(0)/Pd(II) catalysis

Prominent examples include the Wacker process (oxidative, Scheme 2a) and numerous cross-coupling reactions (nonoxidative, Scheme2b-2c). This established process realized that palladium and its compounds can serve as catalyst for redox reactions.[1] Mechanistic consideration of Wacker oxidation led to the discovery of palladium catalyzed carbon-carbon bond forming reactions developed by Tsuji et al. in 1965 (Scheme 2b). Another important C-C bond forming reaction developed by Heck in 1986 (Scheme 2c).



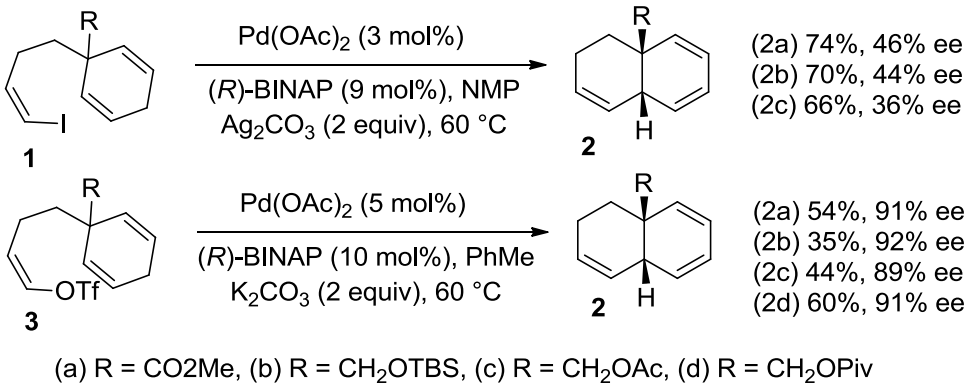
Scheme2. Pd(0)/Pd(II) catalysis

Asymmetric Pd(0)/Pd(II) catalysis undoubtedly found widespread application across the chemical field including in the synthesis of pharmaceuticals, natural products and agrochemicals.[2] Moreover, a breakthrough in Pd-catalyzed transformations has been achieved with the development of enantioselective C-C, C-N and C-O bond formation. Among the asymmetric palladium(0) catalysis for C-C bond formation, Trost asymmetric allylic alkylation is highly popular and extensively applied. Palladium catalyzed asymmetric allylic alkylation using various carbon nucleophiles were studied by many groups, and detailed study on site selectivity and stereoselectivty were reported.[3] The following examples shows the allylic alkylation using enolisable active methylene nucleophile (eq. 1).[4] In which, malonate ester derivatives can be successfully employed in palladium-catalyzed asymmetric allylic alkylation. The method examined here has the advantage of utilizing simple and readily available diphosphine chiral ligands.



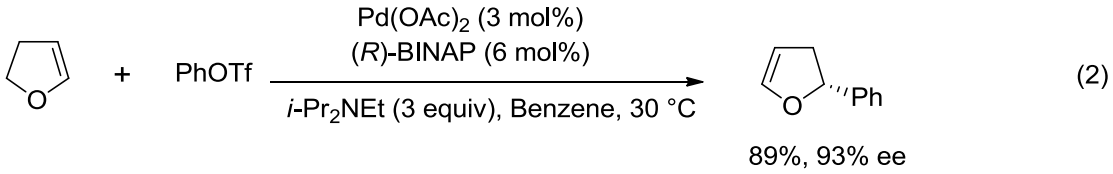
(1)

Another example in enantioselective C-C bond formation is Heck reaction. The first investigation in the field of enantioselective intramolecular Heck reactions by Shibasaki et al.,[5] which involved the conversion of the prochiral alkenyl iodides or alkenyl triflate (**1 or 3**) into the chiral decalin systems **2** (Scheme 3). They have explained the role of silver salt and prefunctionalized substrate **3** in detailed.

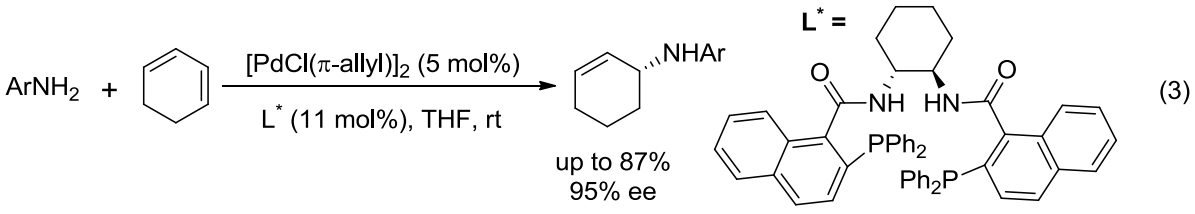


Scheme 3. First asymmetric intramolecular Heck reaction

The first example of an intermolecular asymmetric Heck reaction was reported by Hayashi and co-workers and involved the asymmetric arylation of 2,3-dihydrofurans using aryl triflate (eq. 2).[6]



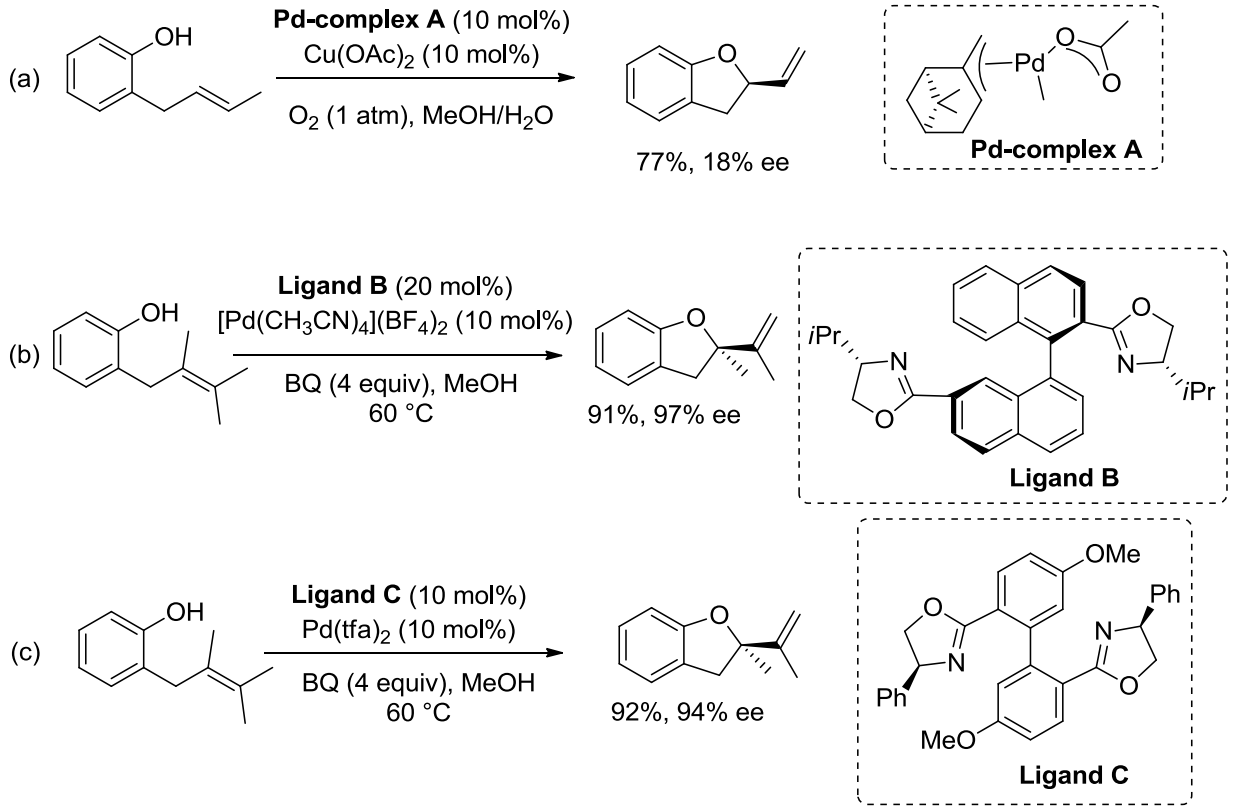
A highly enantioselective palladium-catalyzed hydroamination of cyclic 1,3-dienes has been reported by Hartwig and co-workers.[7] In their work, hydroamination of cyclic dienes using various aryl amines were achieved with high enantioselectivity (eq. 3).



After discovery of Wacker processes, a number of research groups demonstrated that Pd(II) could facilitate the addition of different nucleophiles to alkenes, and a variety of oxidative and non-oxidative C-O, C-N and C-C bond forming transformations have been developed. The

Pd(II)-alkyl intermediate formed in the nucleopalladation step can participate in number of subsequent transformation, which is called as Wacker type reactions. The Wacker type reactions often generates the new stereogenic center, and the synthetic utility of the catalytic reactions is enhanced significantly if the stereochemical course of C-Nu bond formation can be controlled.

The pioneering work of Hosokawa, Murahashi and et al. (1978) in asymmetric oxy-palladation of *ortho*-allyl phenol catalyzed by π-allyl Pd-acetate dimer, by using excess *p*-benzoquinone as an oxidant, gives the dihydrobenzofuran in 77% yield and only 18% ee (Scheme 4a).[8a] Following this initial work, in 1997, Uozumi and Hayashi showed that a novel BOXAX was a highly effective ligand in enantioselective cyclization of *ortho*-allyl phenol affording a desired cyclized product with 91% yield and 97% ee (Scheme 4b).[8b]



Scheme 4. Enantioselective Oxypalladation

Although BOXAX ligand was highly effective for the enantioselective cyclization of *ortho*-allyl phenol, the scope of successful reactions was limited to oxygen addition onto tetra substituted alkene. Zhang and co-workers have developed a unique class of axially chiral bisoxazoline

ligand that afford high level of enantioselectivity for *ortho*-allyl phenol cyclization with low ligand loading (Scheme 4c).[8c] All these examples proceeds via 5-*exo*-*trig* Wacker-type cyclization.

Asymmetric Pd(0)/Pd(II) catalyzed reactions were associated with the most valuable methods for C-C, C-N and C-O bond formation. However, it is expected to have a highly potent Pd catalyst for a broad range of enantioselective catalysis.

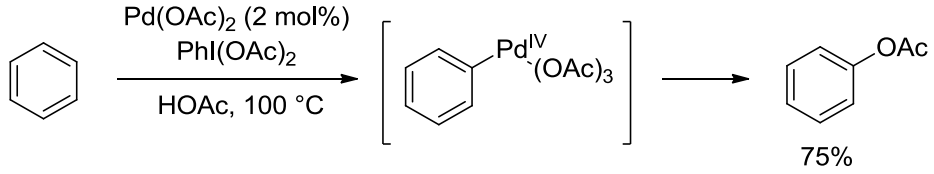
1.1.3 Pd(II)/Pd(IV) Catalysis

The most common form of catalysis for palladium is through a Pd(0)/Pd(II) catalytic cycle, and this is represented by many of the popular cross coupling reactions such as the Suzuki and Sonogashira. Mechanistic analysis has revealed that nearly all of these processes involve catalysis by 'low-valent' palladium (that is, Pd(0) or Pd(II) oxidation states). In contrast to Pd(0)/Pd(II) catalysis, potential Pd(II)/Pd(IV) catalysis received wide interest in Pd-catalysis due to the unique reactivity of Pd(IV) complexes.

Catalysis by high valent palladium is defined as a catalytic reaction in which the metal is oxidized to form a high-valent organometallic intermediate during the catalytic cycle by the action of strong oxidant. Recently, catalytic reactions involving Pd(IV) intermediates have attracted tremendous interest in synthetic chemistry due to the following issues: the synthetic accessibility of Pd(IV) organometallic complexes, the ability of these species to participate in catalytic asymmetric carbon-carbon, carbon-heteroatom bond forming reactions over more-common Pd(II) catalysis.[9]

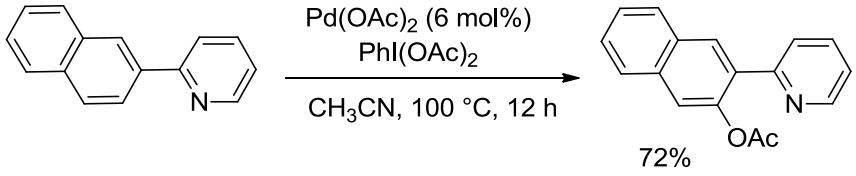
Relatively speaking, Pd(II)/Pd(IV) chemistry is a novel field of catalysis. The unique reactivity of Pd(IV) intermediate has increasingly been recognized and exploited in catalysis over the past decade. The existence of Pd(IV) intermediate was not evidenced until 1985, Bäckvall and co-workers proposed the intermediacy of Pd(IV) in catalysis without supporting the viability of such species.[10a] In 1986, White and co-workers were reported the preparation of Pd(IV) complex supported with first X-ray structural analysis in organopalladium(IV) chemistry.[10b] The organometallic Pd(IV) complex [$PdMe_3$(bpy)I] was prepared through the reaction of [$PdMe_2$(bpy)] with CH_3I in acetone, which was isolated and characterized by ^1H NMR and X-ray analysis to support the structure. The stability was checked by NMR analysis, which undergoes reductive elimination at 25 °C with generation of ethane and PdMe(bpy)I complex.

These seminal discoveries have inspired extensive efforts to exploit related intermediates in catalysis. Later on, in 1996 Crabtree and co-workers reported successful example of *in situ* generation of Pd(IV) intermediate in arene acetoxylation by using $PhI(OAc)_2$ as a powerful oxidant (eq. 4).[11]



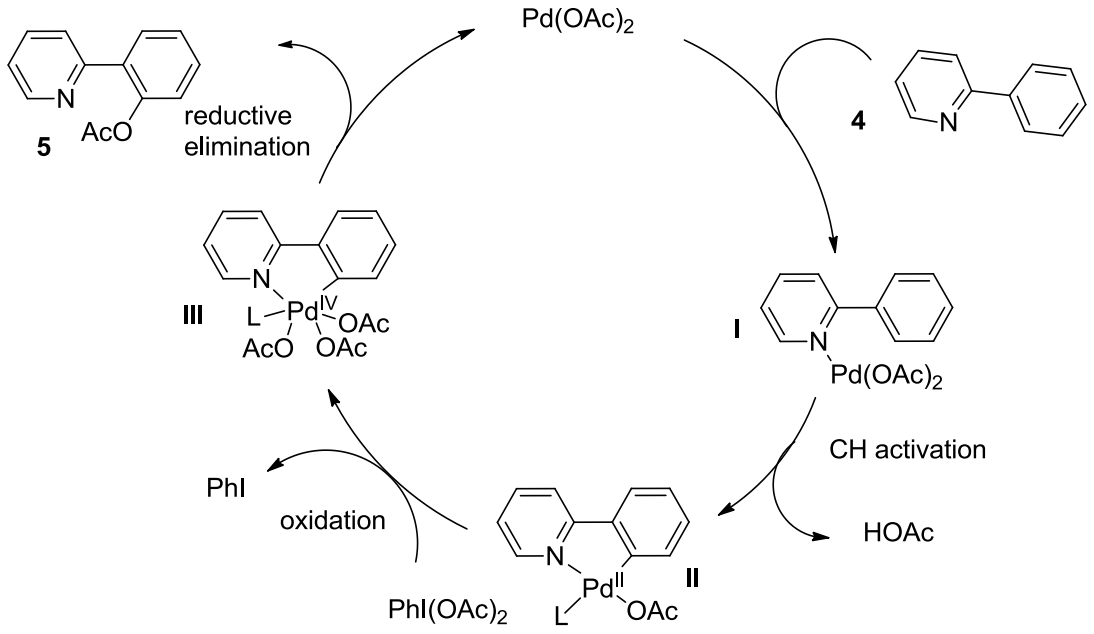
(4)

Though numerous Pd(II)/Pd(IV) catalyzed reactions have been published to date, better understanding of this mode of catalysis is still poor. In recent years, the work reported by Sanford and coworkers that has acquired this mechanistic design more attention. In their first publications in this field, presented a new chelate-assisted carbon–hydrogen (C–H) bond oxygenation with pyridine, pyrazole, azobenzene and imine directing groups (eq. 5).[12a]



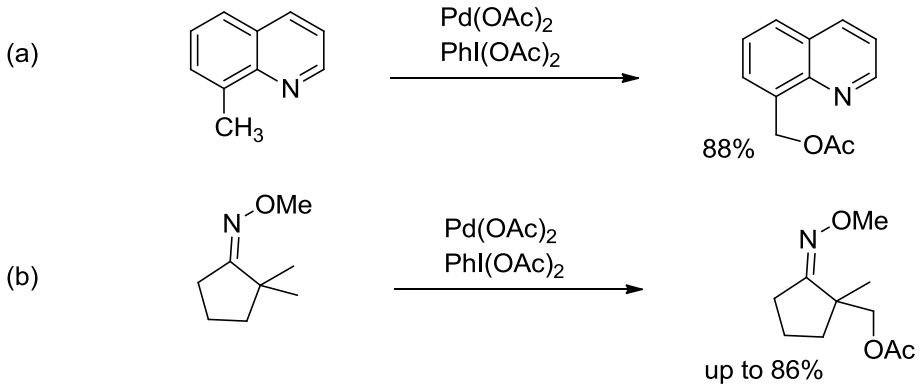
(5)

The mechanism proposed was a general Pd(II)/Pd(IV) catalytic cycle (Scheme 5) with 2-phenylpyridine **4** as a representative substrate. This cycle involves the coordination of pyridine N atom to the palladium to form an N-chelated palladium intermediate **I**. Next, the intermediate **I** undergo ligand directed C-H activation to generate a cyclopalladated intermediate **II**. This palladacycle intermediate undergo two-electron oxidation by the action of strong oxidant hypervalent iodine to generate Pd(IV) species **III**. And finally high valent Pd-intermediate undergo C-O bond forming reductive elimination to release the product **5**.



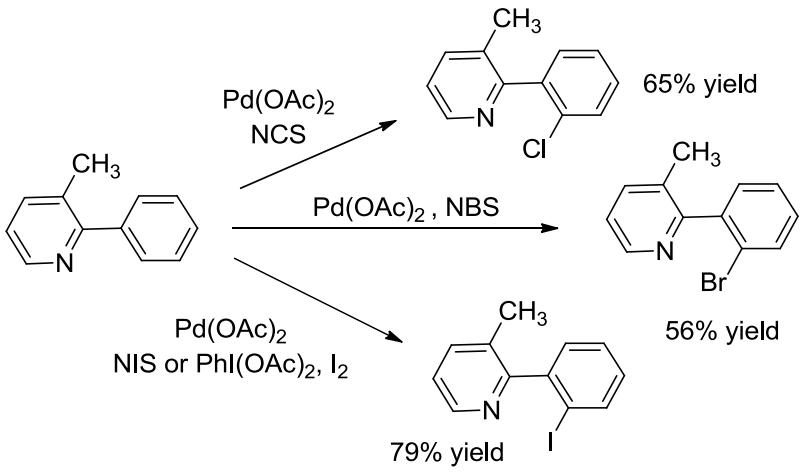
Scheme 5. Pd(II)/Pd(IV) catalytic cycle proposed by Sanford in chelate-assisted C-H bond oxygenation

The choice of appropriate oxidizing agent is a key to success of the Pd(II)/Pd(IV) catalysis. Iodosobenzene diacetate has been found to be very effective for adding an acetate group. It has been proposed that, this is by oxidation of Pd(II) intermediate (**II**) to a Pd(IV) species (**III**), which triggers reductive elimination, giving the *ortho*-acetoxylated product **5**. The acetoxylation reaction can be applied to benzylic[12a] and aliphatic[12b] C-H bonds (Scheme 6).



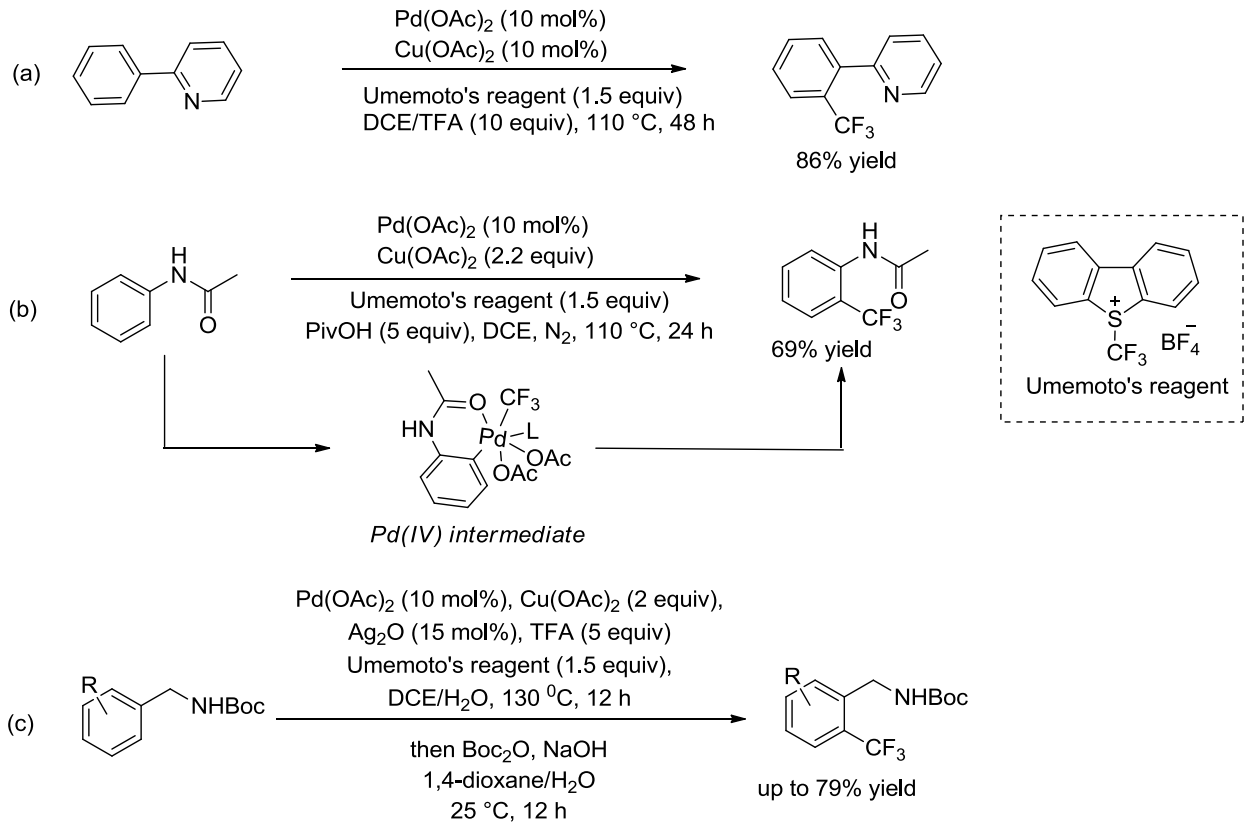
Scheme 6. Pd(II)/Pd(IV) catalyzed C_{sp3}-H bond activation

To promote the oxidation of Pd(II)-complex into Pd(IV)-complex, usually hypervalent iodine regents are suitable, where as other inorganic oxidant such as Oxone, $K_2S_2O_8$ can also be used, but with low efficacy. Along with these oxidants, use of other nucleophiles can install the other functionality. While *N*-halosuccinimides are very effective for C-halogen bond formation (Scheme 7).[13]



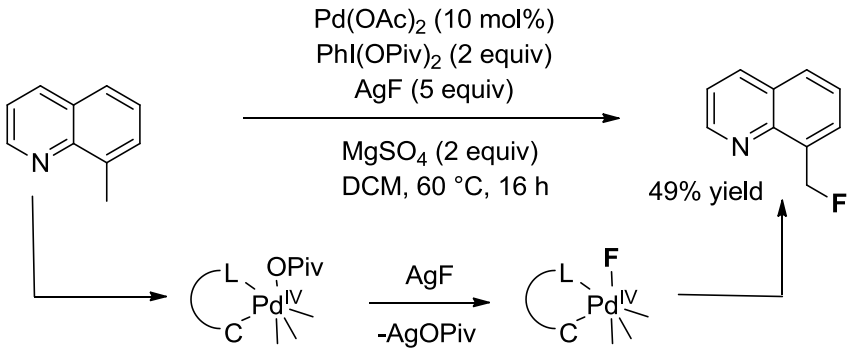
Scheme 7. Pd(II)/Pd(IV) catalyzed C-halogen bond formation

The Pd(II)/Pd(IV) catalysis is highly useful in the C-H functionalization, because C-heteroatom bonds can be formed in presence of oxidant which can act as a nucleophilic source. So, the oxidant can oxidize the Pd(II) into Pd(IV) intermediate by addition of nucleophilic anion and subsequent reductive elimination affords the new functionality on carbon center. The ligand directed trifluoromethylation of C_{sp2}-H bond were achieved by Yu and coworkers, by utilizing electrophilic CF_3^+ source such as Umemoto's trifluoromethylating reagent as an oxidant. They have reported the successful *ortho*-trifluoromethylation of 2-phenylpyridine (Scheme 8a)[14a] and benzylamine (Scheme 8b)[14b] respectively. Recently Shi and coworkers developed *ortho*-trifluoromethylation of *N*-aryl acetanilide using Umemoto's reagent as a trifluoromethylating source and as oxidant (Scheme 8c).[14c]



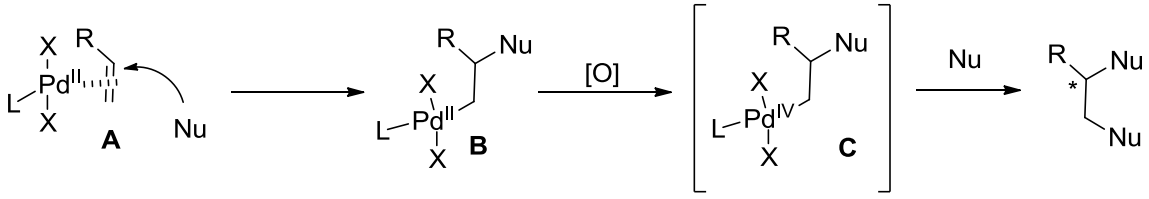
Scheme 8. Pd(II)/Pd(IV) catalyzed C-H *ortho*-trifluoromethylation

The first example of Pd(IV)-catalyzed C_{sp3}-H fluorination of 8-methylquinoline using nucleophilic fluoride source such as AgF, was reported by Sanford and coworkers (Scheme 9).[15] The literature shows numerous protocols for Pd-catalyzed C-H fluorination which required electrophilic F+ source such as *N*-fluoropyridinium salt and Selectfluor, which are often more expensive and also generate large quantity of organic waste. In their work, AgF was used as an oxidant and fluorine source as well. The reaction proceeds in the same way as mentioned in trifluoromethylation.



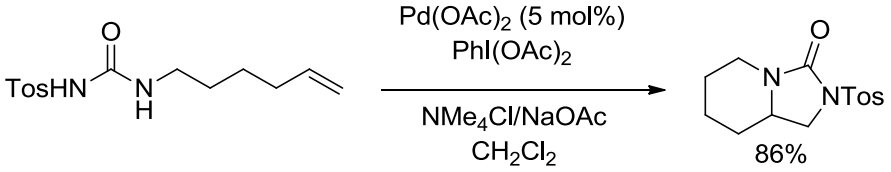
Scheme 9. Pd(II)/Pd(IV) catalyzed C_{sp3}-H fluorination

The Pd(II)/Pd(IV) catalyzed C-H functionalization is highly step economic process as explained in earlier discussion. Being electrophilic species, palladium(II) salts tend to react with π-nucleophiles such as olefins and alkynes. A typical reaction with alkenes starts with the complexation of the olefin by the Pd(II) salt, as shown in Scheme 10. The resulting π-olefin complex **A** can undergo an intermolecular or intramolecular nucleophilic attack, usually at the more substituted vinylic carbon, to give a σ-alkylpalladium(II) complex **B**. The Pd(II) complex **B**, then oxidized into Pd(IV) intermediate **C**, which is highly active to undergo for further functionalization by another nucleophile (inter- or intramolecularly) to generate stereogenic center. Palladium-catalyzed vicinal oxidation is an attractive synthetic tool that can be used to transform simple and readily available alkenes into valuable products. In one step, functionalized molecules can be generated by methods such as diamination, aminoalkoxylation, and dialkoxylation of olefins.



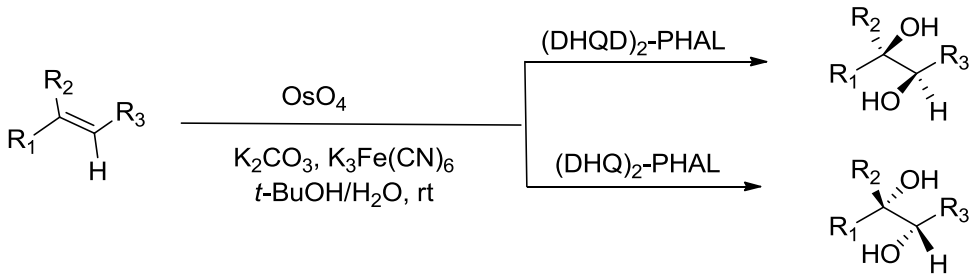
Scheme 10. General procedure for olefin difunctionalization

Hence, Pd(II)/Pd(IV) catalysis is step economical process in olefin difunctionalization for the synthesis of complex molecules. In one of the first examples published on diamination of alkenes, Muniz showed the intramolecular reaction of a 1,3-diamine with a pendant olefin to yield a five-, six-membered fused bicyclic heterocycle (eq. 6).[16] This reaction was carried out with a palladium (II) catalyst and in the presence of a strong hypervalent iodide oxidant ($PhI(OAc)_2$).



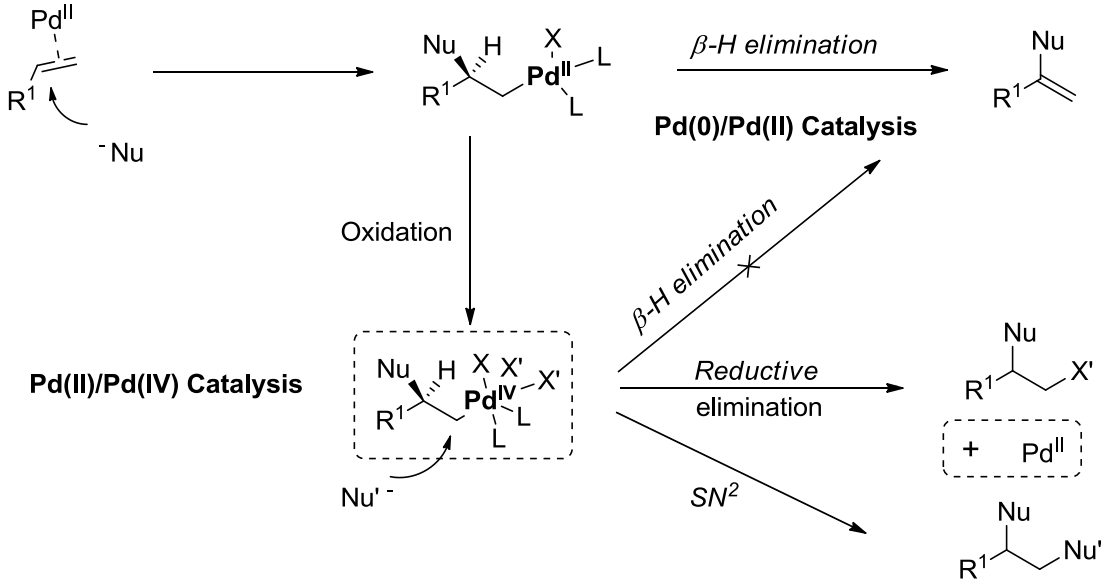
(6)

The traditional approach for olefin difunctionalization is Sharpless asymmetric dihydroxylation. Even though, catalytic variants of this reaction are developed, it has major disadvantages. This method requires catalytic amount of expensive and extremely toxic OsO_4 and stoichiometric $K_3Fe(CN)_6$ which limits its applicability in synthetic organic chemistry (eq. 7).[17] Hence, Pd catalyzed asymmetric difunctionalization of olefin is getting attention due to its versatility.



(7)

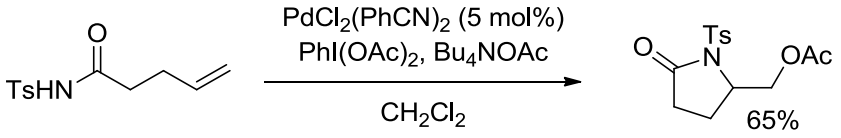
The Pd(II)/Pd(IV) catalysis can realize unprecedented transformations complementary to the conventional Pd(0)/Pd(II) catalysis because of the unique reactivity of Pd(IV) complexes and in a higher oxidation state as such complexes should undergo reductive elimination or S_N2 type reaction more readily to stabilize the metal (Scheme 11)



Scheme 11. Pd(0)/Pd(II) versus Pd(II)/Pd(IV) Catalysis

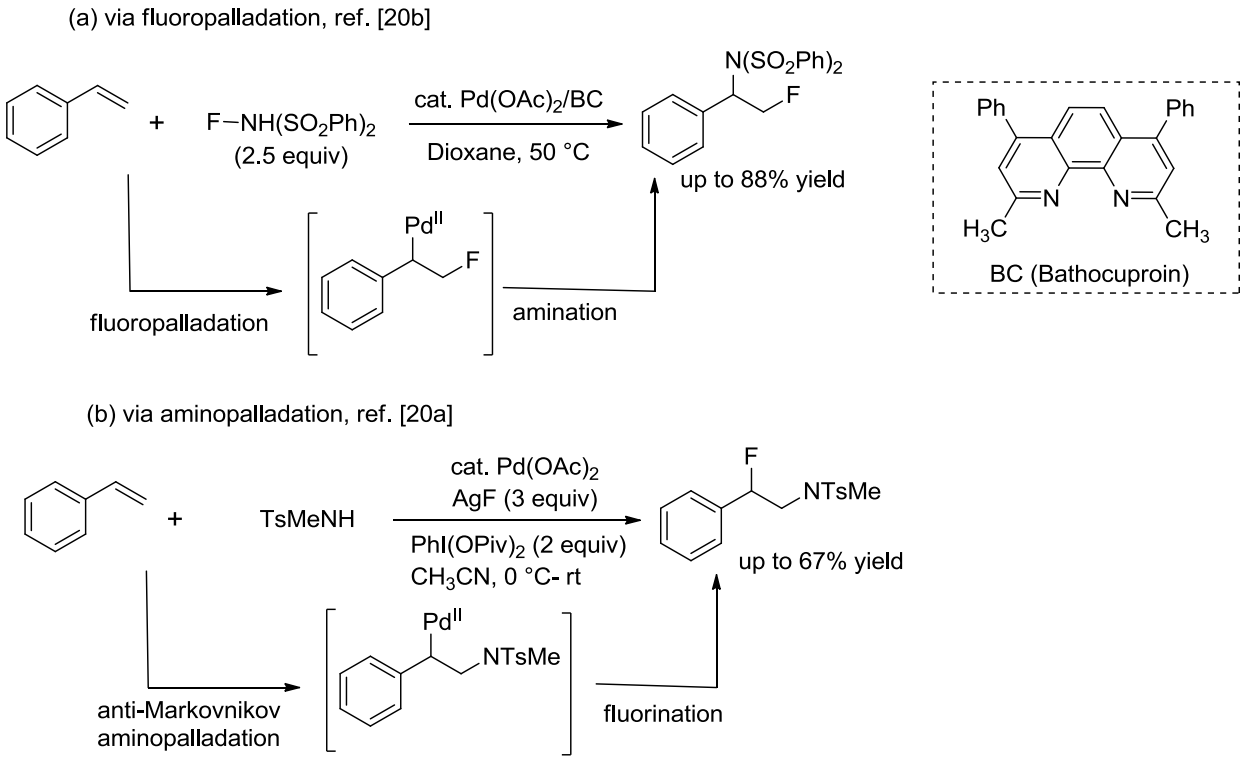
The new approach in palladium catalyzed olefin difunctionalization was developed by Sigman and co-workers, through the formation of a quinone methide intermediate. The quinone methide intermediate allows for attack by a second equivalent of nuceophile thus, a sequential intramolecular-intermolecular process allow for the selective formation of two distinct carbon-heteroatom bonds by employing nucleophile tethered alkene substrate.[18]

In addition to diamination, palladium catalysts have been valuable in olefin amino-oxygenation. In 2005, Sorensen's group developed an intramolecular amino-oxygenation which can furnish five to seven membered aliphatic nitrogen heterocyclic compounds from a range of nitrogen nucleophiles and substituted alkenes.[19] This mild, palladium(II)-catalyzed transformation can proceed in high regio and stereo control, making it a useful method in organic synthesis. In eq. 8, the cyclization of an amide substrate to the corresponding five-membered lactam is shown. The oxygen heteroatom added across the double bond is in form of an acetate group.



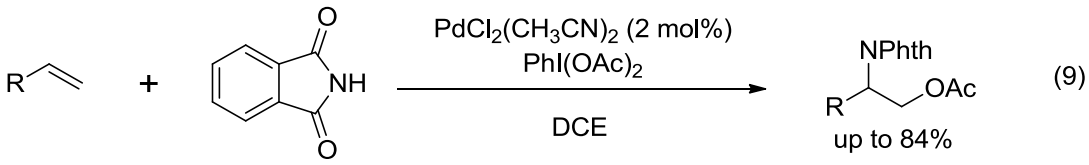
(8)

Simple unactivated alkenes can also be functionalized via oxidative aminopalladation with fluorine source. Recently, Liu and co-workers have reported successful fluoropalladation and aminopalladation in order to C-N/C-F bond formation of unactivated alkene such as styrene (Scheme 12).[20a-c] They have reported a $Pd(OAc)_2$-catalyzed intramolecular aminofluorination of unactivated alkenes, where the C_{sp3}-Pd bond generated via intramolecular aminopalladation was oxidatively cleaved by $PhI(OPiv)_2$/AgF resulting in C-F bond formation.



Scheme 12. Pd-catalyzed aminofluorination of styrenes.

Similar to Sorensen's work, Stahl showed that intermolecular amino-oxygenation was also possible with terminal alkenes (eq. 9).[21] Phthalimide was used as the nitrogen nucleophile in all of the reported cases, with particularly good reactivity with allyl ethers due to a presumed chelating effect with the oxygen heteroatom. It is important to note that in both the amino-oxygenations developed by Sorensen and Stahl a Pd(II)/Pd(IV) catalytic cycle is the proposed reaction mechanism.



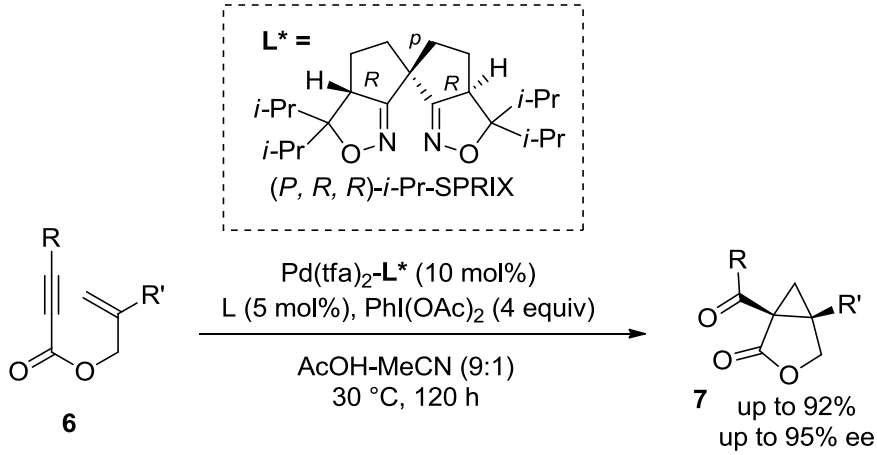
Alkene difunctionalization, the formation of two new bonds from an alkene starting material, is a powerful synthetic method which rapidly increases molecular complexity. Such a transformation has the potential to set two new chiral centers, and thus methods to accomplish highly enantioselective and/or diastereoselective transformations catalytically are highly desirable.

Palladium has become a popular metal of choice for alkene difunctionalization, likely due to its propensity to coordinate and activate alkene substrates for nucleophilic attack.[22]

1.1.4 Enantioselective Pd(II)/Pd(IV) Catalysis

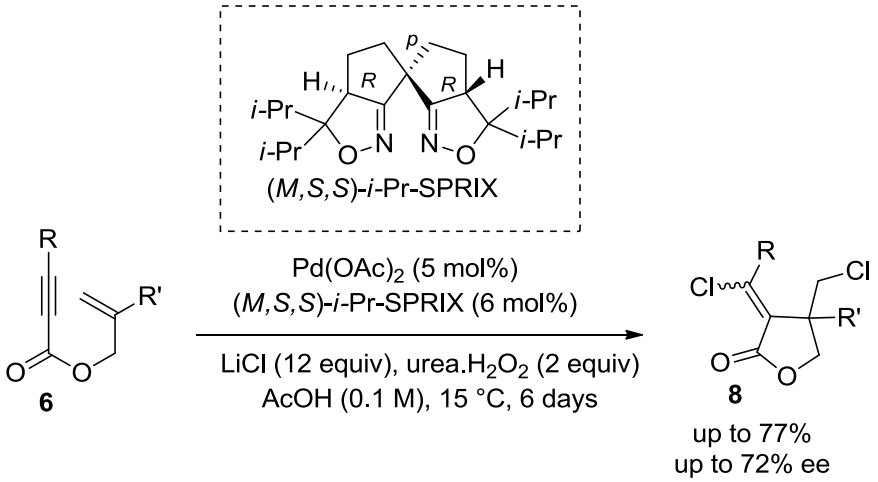
Compared to the impressive development of enantioselective reactions through the Pd(0)/Pd(II) catalytic cycle, only minimal attention has been devoted to exploring asymmetric Pd(II)/Pd(IV) catalysis. The Pd(II)/Pd(IV) catalysis enormously being applied in diversification of alkenes and alkynes as well as in C-H functionalization. For the enantioselective Pd(II)/Pd(IV) catalysis, selection of appropriate ligand is crucial, because particular ligand must survive in oxidative reaction condition and could create effective chiral environment. In 2007, Tse and Sanford groups independently reported an exquisite Pd(II)/Pd(IV) catalytic cyclization of enynes **6** affording lactones **7** with a bicyclo[3.1.0]hexane skeleton in racemic version.[23a-b] Since such a molecule in optically pure form has been utilized successfully for the synthesis of an antiherpetic agent, a protein kinase C-β-inhibitor (JTT-010), and an anticonvulsant drug (pregabalin), **7** promises to be a versatile building block for biologically active molecules.

Sasai et al. reported the first example of asymmetric Pd(II)/Pd(IV) catalysis, in which enantioselective oxidative cyclization of enyne **6** catalyzed by the Pd-SPRIX complex affording lactone **7** in up to 92% yield and 95% ee (Scheme 13).[24a] The high affinity of SPRIX ligands for palladium(II) centers, and their notable stability under oxidative conditions made quite valuable in these reactions. Most impressively, in this system two chiral quaternary carbon centers were set in up to 95% ee.



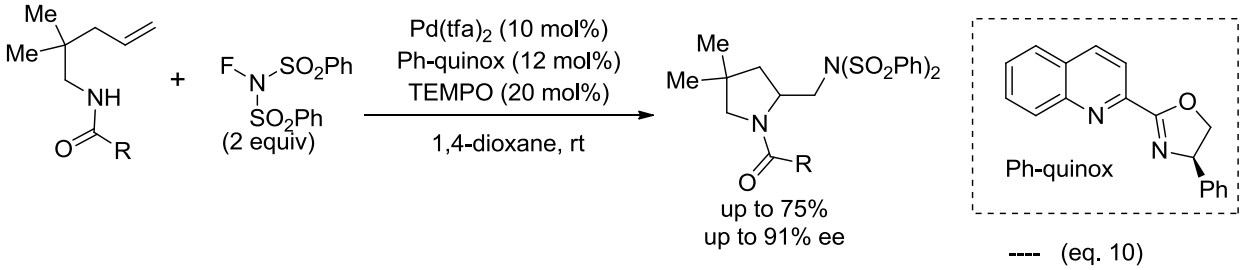
Scheme 13. First enantioselective Pd(II)/Pd(IV) catalysis promoted by SPRIX ligand

Later on, another example of enantioselective Pd(II)/Pd(IV) catalysis was introduced by our group in 2011. In this report enantioselective chlorinative Pd(II)/Pd(IV) catalysis using 1,6-enyne substrates **6** was developed by applying chiral ligand *i*-Pr-SPRIX and H_2O_2 as an oxidant, which led to optically active α-methylene-γ-lactones **8** in up to 77% yield and up to 72% ee (Scheme 14).[24b] The detailed explanation of SPRIX ligand is provided in the next section (Section 1.2).

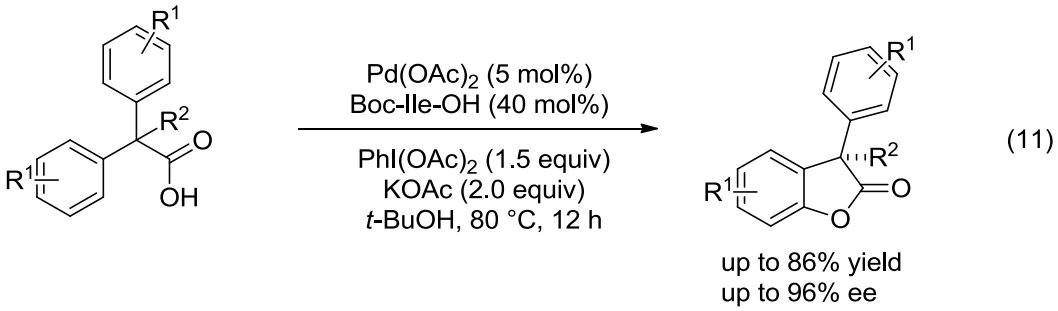


Scheme 14. Enantioselective chlorinative Pd(II)/Pd(IV) catalysis promoted by SPRIX ligand

Very recently, Michael and co-workers reported enantioselective Pd-catalyzed vicinal diamination of unactivated alkenes using *N*-fluorobenzenesulfonimide as both an oxidant and a source of nitrogen using chiral oxazoline as ligand (eq. 10). [25]



Very recently, Yu and coworkers reported the first example of Pd(II)-catalyzed enantioselective C-H activation/C-O cyclization of arylacetic acid to afford chiral benzofuranones by using amino acid ligand, which proceeds through Pd(II)/Pd(IV) redox cycle (eq. 11).[26] The enantioselective Pd(II)/Pd(IV) catalysis is developing which is emerged with only few examples reported above, due to the efficient synthetic method for optically active materials, more attention is required to explore this new approach.



(11)

1.2 Spiro Bis(isoxazoline) Ligand [SPRIX]

In 1900, Baeyer[27] introduced the name "spirocyclane" for bicyclic rings attached to common quaternary carbon atom (spiro carbon atom). The synthesis of spiro compounds has attracted considerable attention because of its involvement in many natural products.[28] Along with usefulness in biological activity, spiro compounds can also be utilized as ligand due to their structural properties by installing heteroatoms on rigid spiro skeleton. Due to the tetrahedral structure of the spiro carbon atom and perpendicular orientation of the two rings, the rotation of the two rings in bicyclic spiro compounds is therefore restricted and as a result gives rise to central chirality with substituents on the rings (Figure 1).

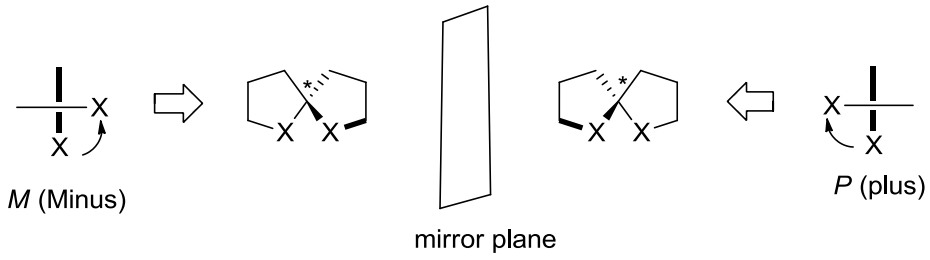
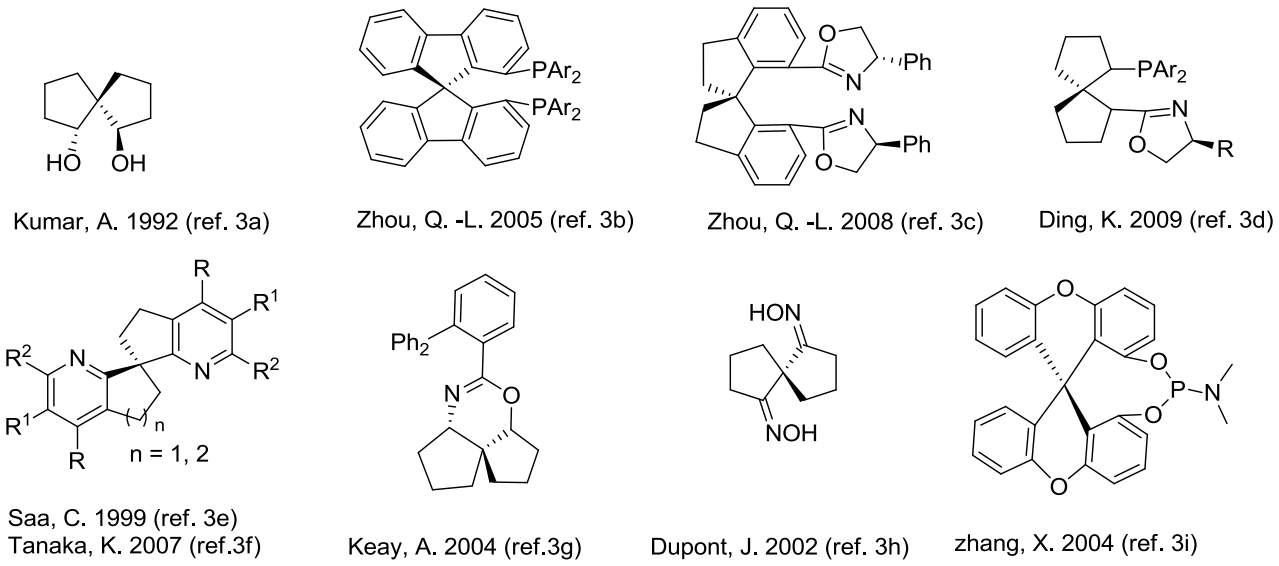


Figure 1. Spirane chirality

In spiro molecules, two rings connect at a quaternary center through σ-bond, which makes racemization of such compounds virtually impossible, hence can be utilized as a chiral ligand for asymmetric synthesis under various reaction conditions. The construction of spiro cyclic framework containing heteroatom (nitrogen, phosphorus, and sulfur), which acts as Lewis base

for coordination with metal, make it practically useful as a chiral ligand. Recently a variety of chiral spiro-type ligands were developed and applied for asymmetric reactions (Figure 2). [29]

The oxazoline and isoxazoline rings has a rigid five-membered rings containing two heteroatoms (nitrogen and oxygen) which serves as Lewis bases, and could acts as ligands for transition metals. The oxazoline ligands were common in transition metal catalysis, where as isoxazoline ligands found to be rare.

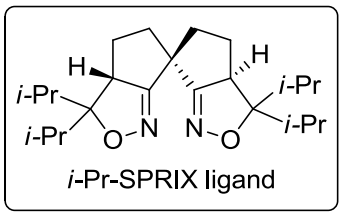


Kumar, A. 1992 (ref. 3a) | Zhou, Q. -L. 2005 (ref. 3b) | Zhou, Q. -L. 2008 (ref. 3c) | Ding, K. 2009 (ref. 3d)

Saa, C. 1999 (ref. 3e)
Tanaka, K. 2007 (ref.3f) | Keay, A. 2004 (ref.3g) | Dupont, J. 2002 (ref. 3h) | zhang, X. 2004 (ref. 3i)

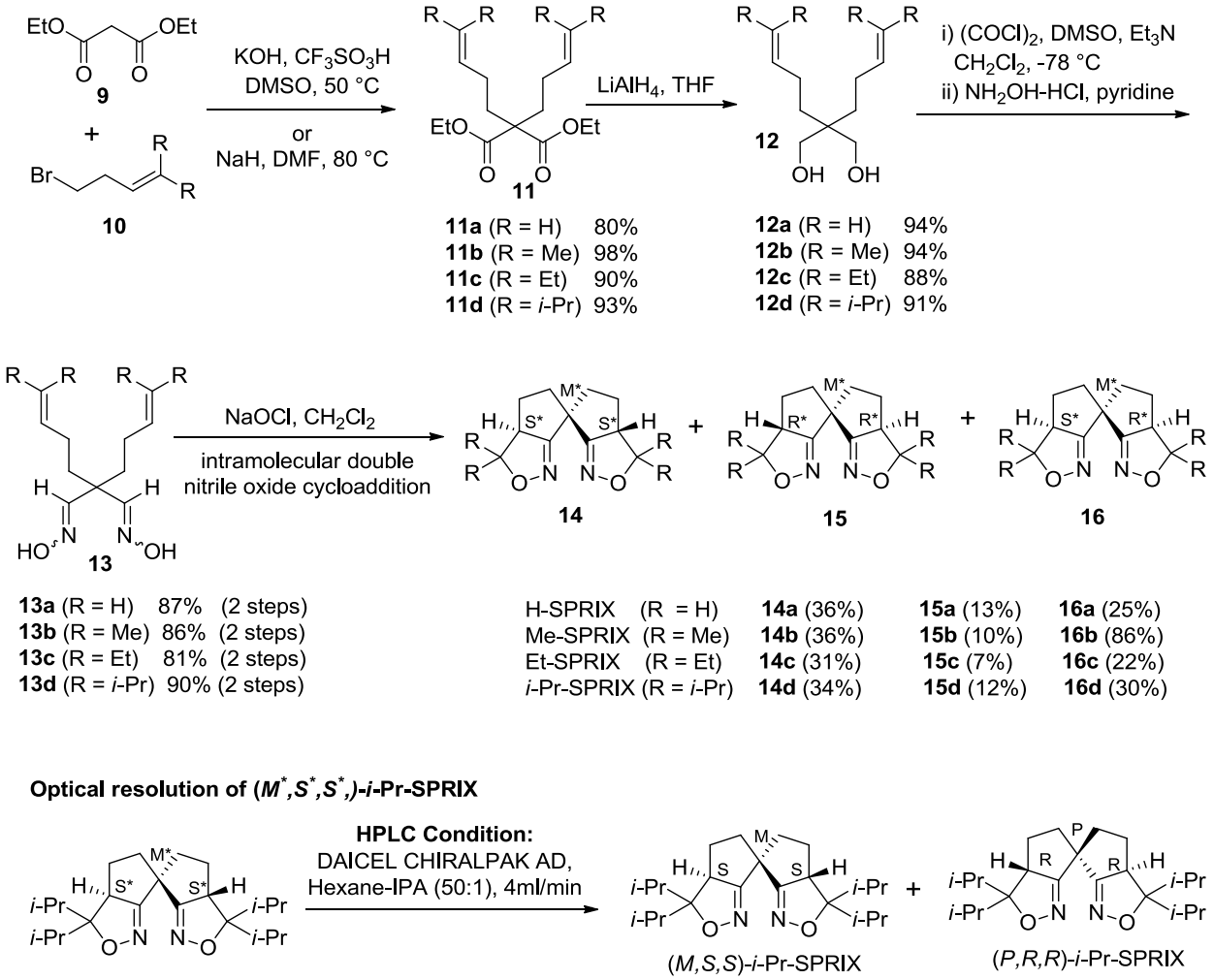
Figure 2. Reported ligands bearing spiro skeleton

In 1999, our group has reported the first design and synthesis of chiral spiro bis(isoxazoline) ligand (SPRIXs) bearing a chiral spiro skeleton and two isoxazoline rings. The general synthetic route for the preparation of various racemic SPRIX ligands [30a] is shown in Scheme 15, which later obtained in enantiomerically pure form by optical resolution with a chiral stationary phase column (Daicel Chiralpak AD). Judicious placement of substituents (H, Me, Et, *i*-Pr) on the isoxazoline rings organizes the most appropriate asymmetric environment around the metal to achieve high levels of asymmetric induction. The *i*-Pr-SPRIX ligand was found to be more effective in case of asymmetric induction compared to other substituents on isoxazoline ring. The coordination ability of SPRIX ligand with various metals such as Cu(II), Co(II), Pd(II), Ag(II) and Ni(II) salts were studied and confirmed by X-ray crystallographic analysis.[31]



i-Pr-SPRIX ligand

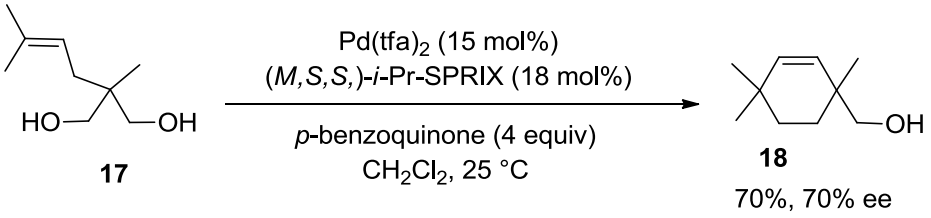
The *i*-Pr-SPRIX ligand was more effective in various kinds of enantioselective oxidative reactions due to following reasons; (A) Isoxazoline ring - The basic unit on the SPRIX skeleton is isoxazoline ring which have low sigma donor ability compared to oxazoline ring, which exert unique reactivity on metal center. (B) Rigid-spiro skeleton - which play vital role in chelation and maintaining the chirality in transition state. (C) The bulky *i*-Pr-group at 5–position create effective chiral environment. (D) Stability - significantly stable in acidic, basic and oxidative condition (Acidic conditions: MeOH-aq 1M HCl (1:1) at



Scheme 15. Syntheis of SPRIX and optical resolution

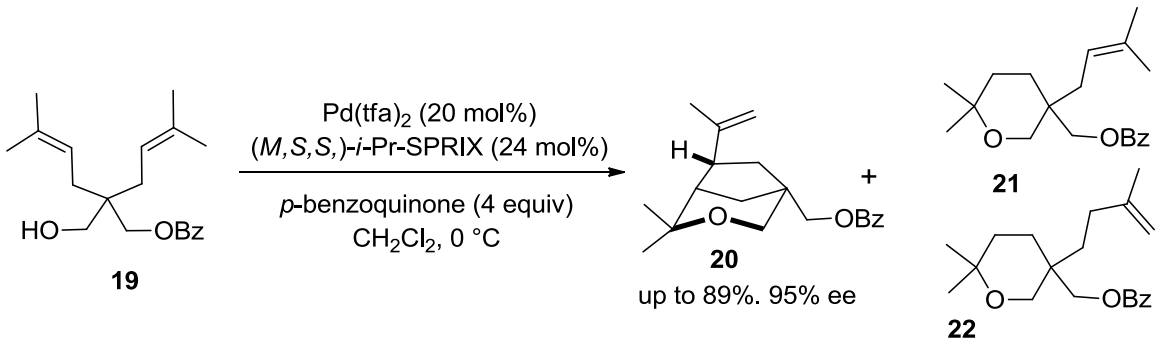
rt overnight, Basic conditions: MeOH-aq 1M NaOH (1:1) at rt overnight, and Oxidative conditions: MeOH-35% aq H_2O_2 (1:1) at rt overnight). The above mentioned crucial electronic, structural and chemical properties make SPRIX ligand as a successful chiral ligand in asymmetric reactions. So far, our group employed the SPRIX ligand for the palladium catalyzed asymmetric transformations and representative examples are mentioned below.

The first example of asymmetric Wacker-type cyclization of aliphatic alkenyl alcohol **17** was achieved in the presence of Pd(II)-SPRIX catalyst and *p*-benzoquinone as a reoxidant to give 6-*endo* cyclized product **18** in 70% yield and 70% ee (Scheme 16).[30b]



Scheme 16. Pd-SPRIX Catalyzed Asymmetric Wacker-type Cyclization

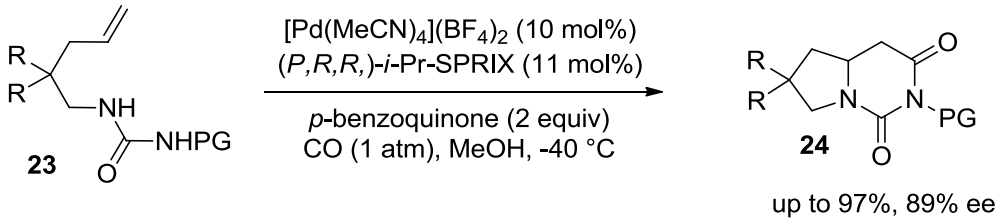
In addition, when dialkenyl alcohol **19** was used as a substrate in the presence of Pd(II)-(*M,S,S*)-*i*-Pr-SPRIX catalyst at 0 °C, the reaction proceeded *via* oxy-palladation which provided bicyclic product **20** as a single diastereomer in 95% ee along with small amount of monocyclic product **21** and **22** (Scheme 17).[30b]



Scheme 17. Pd-SPRIX Catalyzed Asymmetric Tandem Cyclization

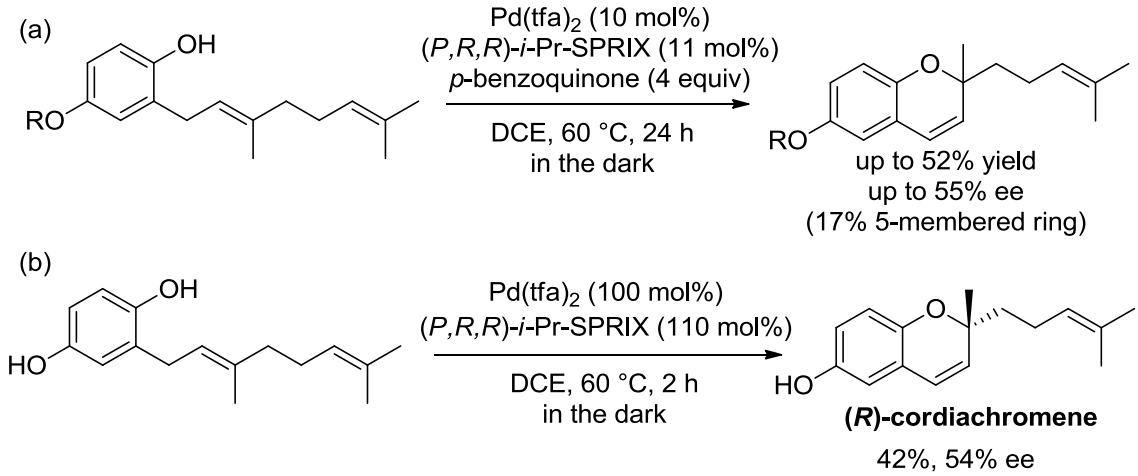
The enantioselective synthesis of tetrahydropyrrolo[1,2-*c*]pyrimidine-1,3-diones **24** starting from alkenylurea derivatives **23** was achieved through intramolecular oxidative aminocarbonylation reactions catalyzed by Pd(II)-SPRIX complexes. In the presence of catalytic amount of $[Pd(MeCN)_4](BF_4)_2$, (*P,R,R*)-*i*-Pr-SPRIX and *p*-benzoquinone (2 equiv) as an oxidant under

carbon monoxide atmosphere, a wide variety of alkenylureas were successfully transformed into the products with excellent yields (up to 97%) and high enantioselectivity (up to 89%) (Scheme 18). [30c]



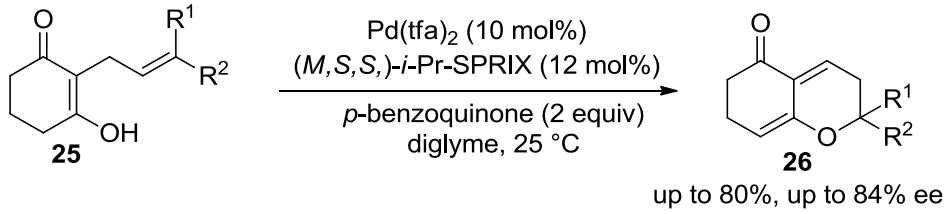
Scheme 18. Pd-SPRIX Catalyzed Aminocarbonylation of Alkenylurea

Our group (Sasai et al.) have investigated the synthetic utility of asymmetric oxypalldation of *ortho*-allyl phenol in order to synthesis of the benzopyran derivatives. They have developed the Pd-SPRIX catalyzed enantioselective Wacker-type cyclization of 2-geranylphenol affording a optically active benzopyran in up to 68% yield and 55% ee respectively (Scheme 19a).[30d] This process was applied for the synthesis of natural product (*R*)-cordiachromene (Scheme 19b).[30d] In their work, it was discovered that, under catalytic condition, substrate oxidized into a benzoquinone derivative, where as stoichiometric mixture consisting of $Pd(tfa)_2$, Spiro Bis-isoxazoline (SPRIX) afforded six-membered ring in 42% yield and 54% ee. The six-membered ring (6-*endo*-trig) was formed preferentially to the five-membered ring (5-*exo-trig*), a feature observed in other oxycyclization by using SPRIX ligand.



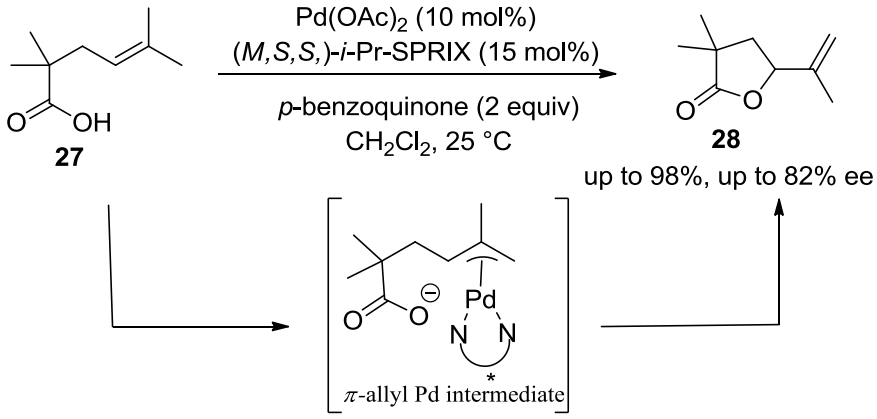
Scheme 19. Application of SPRIX in asymmetric synthesis of (*R*)-cordiachromene

An enantioselective intramolecular Wacker-type cyclization of 2-alkenyl-1,3-diketones **25** catalyzed by a Pd(II)-SPRIX complex was reported.[30e] The reaction proceeded in a 6-*endo-trig* mode to give the desired chromene derivatives **26** with moderate to good enantioselectivity (Scheme 20).



Scheme 20. Enantioselective Intramolecular Wacker-Type Cyclization

Recently, enantioselective cyclization of 4-alkenoic acids **27** via an oxidative allylic C-H esterification by using Pd-SPRIX catalyst was reported, in which the reaction proceeded via a π-allyl Pd intermediate generated by an allylic C-H activation to give γ-lactone derivatives **28** with moderate to good enantioselectivities (Scheme 21).[30f]



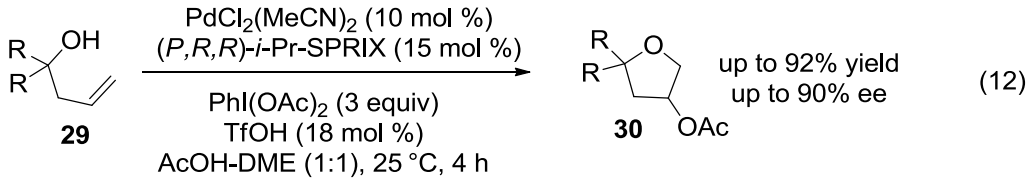
Scheme 21. Enantioselective Cyclization of 4-Alkenoic Acids

1.3 Outline of this Thesis

The thesis is divided into three chapters. This thesis describes the development of novel enantioselective cyclative functionalization of alkenes and alkynes catalyzed by Pd-SPRIX. Previously our group reported the design and synthesis of chiral spiro bis(isoxazoline) ligand [SPRIX] and its application in asymmetric catalysis. The crucial characteristic structural and chemical properties of SPRIX played vital role in asymmetric catalysis compared to other chiral ligands. By taking the advantage of these unique properties of SPRIX, it had been applied in various types of cyclative reactions under acidic and oxidative conditions.

The **chapter 1** of this thesis explains concise introduction about Pd-catalysis and SPRIX ligand. The detailed information about asymmetric Pd(0)/Pd(II) catalyzed reactions is well described. The importance of Pd(II)/Pd(IV) over Pd(0)/Pd(II) catalysis is explained with numerous examples supported by reaction pathways or mechanisms. This chapter also deals with recent progress in Pd-SPRIX catalyzed enantioselective reactions along with its scope and limitations.

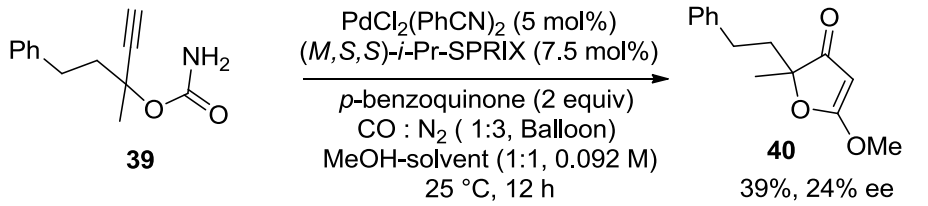
In the **chapter 2**, development of an novel asymmetric cyclative acetoxylation of homoallyl alcohols **29**, which is a rare example of enantioselective catalytic reactions involving Pd(IV) intermediates is explained. The reaction proceeded by treatment of **29** with 10 mol % of $PdCl_2(MeCN)_2$, 15 mol % of (*P,R,R*)-*i*-Pr-SPRIX, and 18 mol % of TfOH in the presence of 3 equiv of $PhI(OAc)_2$ in a 1:1 mixture of AcOH–dimethoxyethane (DME) at 25 °C for 4 h to afford **30** in moderate to good yields with up to 90% ee (eq. 12). Since the chiral 3-oxy-tetrahydrofuran skeleton is found in a variety of biologically active compounds, its asymmetric synthesis is demanding. The detailed optimization study of this reaction found that the addition of catalytic amount of triflic acid (TfOH) served as a key role for achieving high enantioselectivity.



(12)

The **Chapter 3** is related to the application of SPRIX ligand in asymmetric carbonylative cyclization of propargyl carbamates **39** in order to synthesis the chiral 5-methoxy-3(*2H*)-furanone **40**. 3(2H)-Furanones are structural motifs that are widely present in natural products and medicinally important agents. Due to the importance of the chiral furanones in biologically

active compounds, the asymmetric construction of furanones or its derivatives is demanding and challenging task. The extreme optimization of reaction conditions revealed that (*M,S,S*)-*i*-Pr-SPRIX ligand could induce low enantioselectivity and moderate yield of **40** (eq. 13).



(13)

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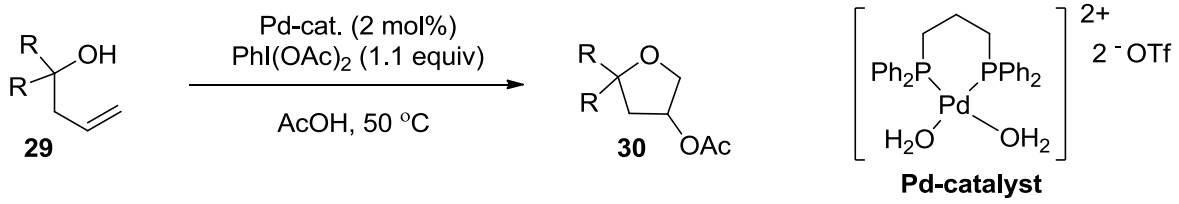
Chapter 2

Enantioselective Pd(II)/Pd(IV) Catalysis Utilizing SPRIX Ligand: Effective Construction of Chiral Acetoxylated Tetrahydrofurans

2.1 Background:

The successful application of SPRIX ligand in Pd(II)/Pd(IV) oxidative catalysis proved the efficiency of SPRIX as an effective chiral ligand in oxidative reaction condition. To further develop an enantioselective Pd(II)/Pd(IV) catalysis, I focused on olefin oxidation reported by Song and Dong, in which terminal and internal olefins were diacetoxylated in presence of palladium and hypervalent iodine reagent [$PhI(OAc)_2$]. In their work, palladium catalyst required the phosphine based ligand as well as a non-coordinating counterion for increased activity. Under the same reaction condition, the olefin substrate having nucleophilic group within the molecule, such as homoallyl alcohols **29** were cyclized in a formal 5-endo-trig mode to give acetoxylated tetrahydrofuran derivatives **30** (Scheme 2.1).[1,2]



Scheme 2.1 Intramolecular Pd-catalyzed cyclization of homoallyl alcohol (Song & Dong's report)

In their report, only few substrates were studied using achiral ligand. Untill now, there is no report on enantioselective cyclization of alkenyl alcohols. Since the chiral 3-oxy-tetrahydrofuran skeleton is found in a variety of biologically active compounds such as amprenavir (Figure 2.1),[3] its asymmetric construction promises to be a versatile synthetic transformation. Due to the importance of asymmetric synthesis of tetrahedrofuran derivatives, I sought to develop an efficient enantioselective construction of chiral 3-oxy-tetrahedrofuran skeleton by utilizing SPRIX ligand.

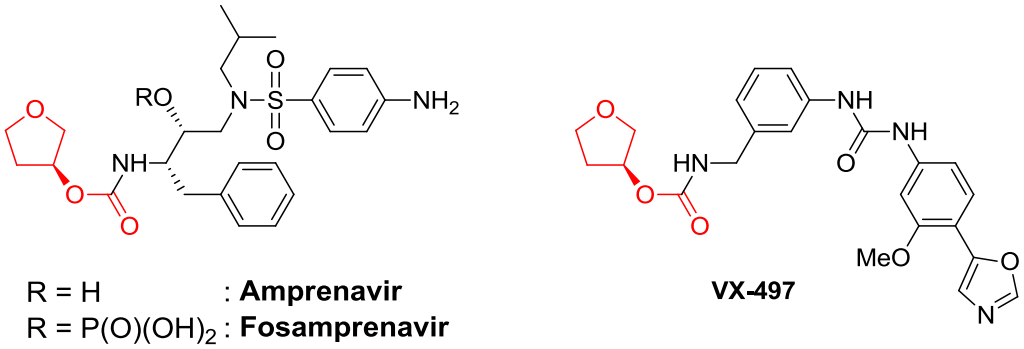
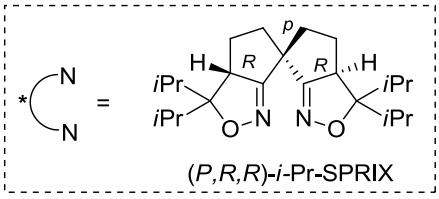


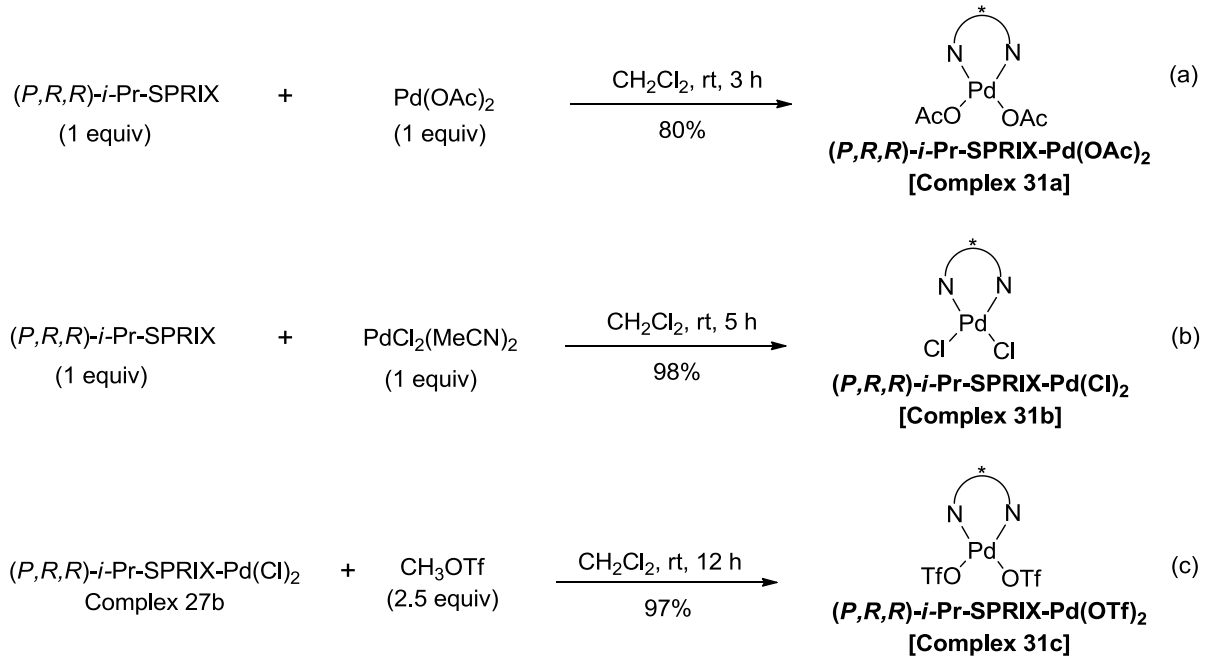
Figure 2.1 Representative examples of drug molecules bearing chiral THF-skeleton

2.2 Result and Discussion

2.2.1 Initial attempt

In my initial attempt, 1,1-diphenyl-3-buten-1-ol (**29a**) was chosen as a model substrate and various kinds of Pd-SPRIX complexes were prepared (scheme 2.2.1a-c). The isolated Pd-SPRIX complexes were used to check the catalytic activity.

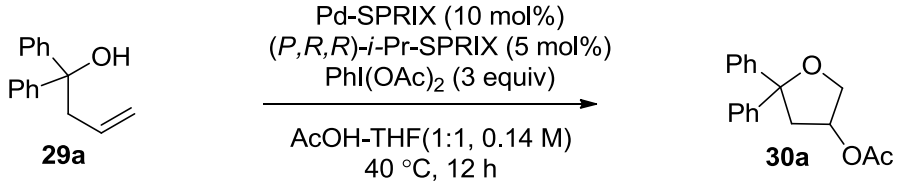




Scheme 2.2.1 Preparation of Pd-SPRIX complex

In order to investigate the catalytic activity of freshly prepared Pd-SPRIX complexes shown in scheme 2.2.1, the model substrate **29a** was treated with $Pd(OAc)_2$-SPRIX complex (**31a)** (10 mol%), (*P,R,R*)-*i*-Pr-SPRIX (5 mol%), and $PhI(OAc)_2$ (3 equiv) in AcOH-THF (1:1) solvent at 40 ^oC for 12 h, which furnished the desired 5,5-diphenyltetrahydrofuran-3-yl acetate **30a** in 48% yield with 11% ee (Table 2.2.1, entry 1). The use of $PdCl_2$-SPRIX complex (**31b)** improved the yield up to 56% and 16%ee (entry2). Where as $Pd(OTf)_2$-SPRIX complex afforded the desired product **30a** with much better yield (60%) although enantiopurity remained almost same (14%) (entry 3).

Table 2.2.1 Initial attempt



Entry	**Pd-SPRIX**	Yield (%)[a]	Ee(%)[b]
1	$Pd(OAc)_2$-SPRIX (**31a)**	48	11
2	$PdCl_2$-SPRIX (**31b)**	56	16
3	$Pd(OTf)_2$-SPRIX (**31c)**	60	14

[a] Isolated yield. [b] Determined by HPLC analysis (Chiralpak AD-H column)

The results depicted in the table 2.2.1 indicate that the activity of $Pd(OTf)_2$-SPRIX complex (**31c**) was good in terms of reaction yield as compared to complex **31a** and **31b**. So, the $Pd(OTf)_2$-SPRIX complex was chosen for further optimization of reaction conditions.

2.2.2 Optimization study

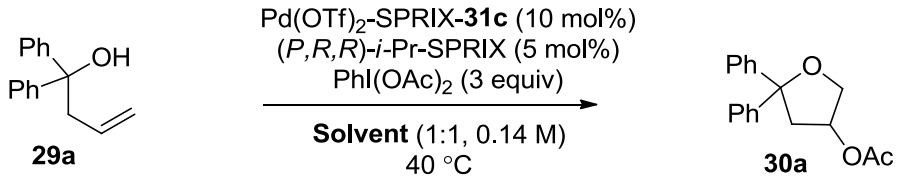
2.2.2.1 Effect of solvent:

Optimizations of the reaction condition were started with screening of various solvents; the results are listed in table 2.2.2.1. When acetic acid was used as sole solvent, the desired product **30a** was afforded in 66% yield and 28% ee over a period of 18 h (entry 1). The reactions were performed in mixture of acetic acid and co-solvents (1:1 ratio). Aprotic solvents such as toluene, acetone, and acetonitrile were tested (entry 2-4) and had no significant effect on reaction outcome, the elevated yield (75%) was observed in AcOH-toluene but enantiopurity was dropped to 16% (entry 2). In the mixture of AcOH-DCM the reaction proceeded with slightly

improved ee (34%) but with moderate yield (entry 5). The combination of acetic acid with ethereal solvents found to be efficient compared to other solvents (entry 6-8). Use of 1,2-dimethoxy ethane (DME) as a co-solvent with acetic acid in 1:1 ratio was found to mediate the reaction in good efficiency (entry 7) yielding the cyclized product **30a** in 68% and 40% ee. Where as, methyl *tert*-butyl ether as a co-solvent also gives similar effect (72% yield, 41%ee, entry 8)

Thus, a systematic solvent-screening was conducted in the hope of realizing the desired oxidative cyclization of homoallylic alcohol **29a** in high efficiency. Pleasingly, solvent had found no significant role in Pd(II)/Pd(IV) catalysis, but mixture of AcOH-DME or AcOH-MTBE realizes good choice of solvents for further optimization.

Table 2.2.2.1 Solvent screening



Entry	**Solvent**	Time (h)	Yield (%)[a]	Ee(%)[b]
1	AcOH	18	66	28
2	AcOH-Toluene	12	75	16
3	AcOH-Acetone	12	66	21
4	AcOH-MeCN	36	54	22
5	AcOH-DCM	12	63	34
6	AcOH-Et_2O	12	72	34
7	AcOH-DME	12	68	40
8	AcOH-MTBE	12	72	41

[a] Isolated yield. [b] Determined by HPLC analysis (Chiralpak AD-H column)

2.2.2.2 Initial screening of reaction parameters (Pd, solvent, additives, temp.)

In the presence of $Pd(OTf)_2$-SPRIX complex in AcOH-MTBE solvent, at 45 °C, desired product **30a** was obtained in 72% yield and 41% ee (Table 2.2.2.2, entry 1). Further lowering the reaction temperature to 30 ^{o}C, yield and ee was raised to 77% & 60% respectively (entry 2). Due to the hygroscopic nature of $Pd(OTf)_2$-SPRIX complex (**31c**), handling and storage of such complex renders the application. Hence, some other palladium catalysts were examined as depicted in the table 2.2.2b. When 10 mol% of $Pd(tfa)_2$ was used as catalyst (instead of using $Pd(OTf)_2$-SPRIX complex) along with 15 mol% of (*P,R,R*)-*i*-Pr-SPRIX, reaction become very sluggish, even after 60 h, only trace amount of **30a** was observed (entry 3).

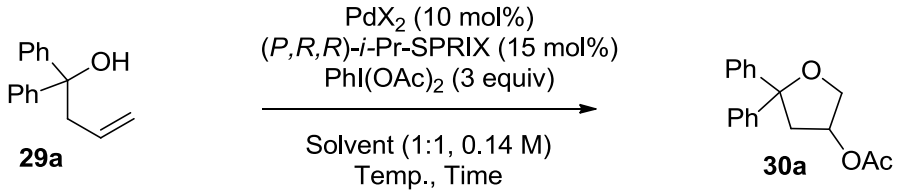


Table 2.2.2.2

Entry	Pd-Source	Solvent	Additive	Temp (°C)	Time (h)	Yield (%)[a]	Ee (%)[b]
1[c]	$Pd(OTf)_2$	AcOH-MTBE	-	40	12	72	41
2[c]	$Pd(OTf)_2$	AcOH-MTBE	-	30	22	77	60
3	$Pd(tfa)_2$	AcOH-MTBE	-	30	60	trace	ND
4	$Pd(OAc)_2$	AcOH-MTBE	-	30	40	48	6
5	$PdCl_2(MeCN)_2$	AcOH-MTBE	-	30	12	>99	22
6	$PdCl_2(MeCN)_2$	AcOH-DME	-	30	22	>99	25
7	$PdCl_2(MeCN)_2$	AcOH-DME	-	25	22	92	26
8	$PdCl_2(MeCN)_2$	AcOH-DME	MS 4A	25	4	93	26
9	$PdCl_2(MeCN)_2$	AcOH-DME	TfOH[d]	25	4	88	36

[a] Isolated yield. [b] Determined by HPLC analysis (Chiralpak AD-H column). [c] $Pd(OTf)_2$-SPRIX complex **31c** (10 mol%) and (*P,R,R*)-*i*-Pr-SPRIX (5 mol%) was used. [d] 10 mol% of TfOH was used.

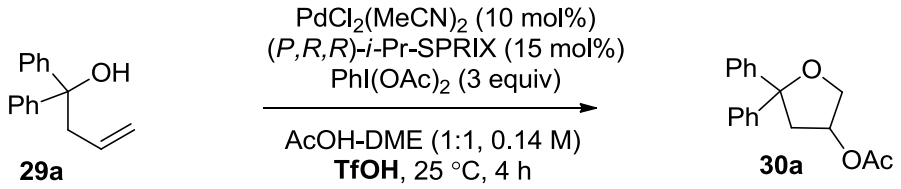
No better result was obtained in case of $Pd(OAc)_2$, which gives moderate yield and very poor enantioselectivity (entry 4). Use of $PdCl_2(MeCN)_2$ was found to be effective affording the desired product quantitatively but with lower ee value (entry 5), compared to entry 2. Similar reaction outcome was observed when 1,2-dimethoxyethane was used as solvent with slightly improved enantioselectivity (25%, entry 6). The reaction at reduced temperature (at 25 °C) provided the desired product with 92% yield and 26% ee (entry 7). Addition of molecular sieves dose not affect the selectivity as well as yield (entry 8). However, addition of trifluoromethanesulfonic acid (TfOH) as an additive drastically improved the reaction rate and the enantioselectivity: in the presence of 10 mol% of TfOH, **29a** was completely consumed after 4 h to give **30a** in 88% yield with 36% ee compared to entry 7 (entry 8). This result indicates that, the non-coordinating counterion plays vital role in catalysis. Motivated form this result, further optimization was continued with fine tuning of TfOH amount.

2.2.2.3 Effect of TfOH

Motivating results obtained by use of 10 mol% of TfOH as an additive which accelerates the reaction rate with slight improvement in enantioselectivity, allows for further investigating the proper amount of triflic acid. I studied the effect of various amount of triflic acid starting from 1 mol% to 100 mol% as shown in table 2.2.2.3. Increasing the amount of TfOH from 1 mol% to 18 mol% (Table 2.2.2c, entry 1-5), yield and selectivity was increased tremendously up to 92% and 90% respectively (entry 5). Further increasing the amount of TfOH in 20 mol% and 50 mol%, both the yield and selectivity were dropped (entry 6&7). In presence of 100 mol% of TfOH, only 20% yield with 56% ee was observed due to the decomposition of starting material in highly acidic condition (entry 8).

This result shows that, the around 2 mole equivalents of trifluoromethanesulfonic acid (TfOH, 18 mol%) to $PdCl_2(MeCN)_2$ was required for high asymmetric induction and yield as well.

Table 2.2.2.3 Amount of TfOH



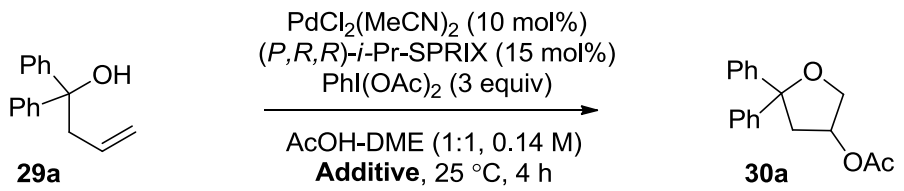
Entry	TfOH (mol %)	Yield (%)[a]	Ee (%)[b]
1	1	48	20
2	5	56	15
3	10	88	36
4	15	93	80
5	18	92	90
6	20	92	85
7	50	40	54
8	100	20	56

[a] Isolated yield. [b] Determined by HPLC analysis (Chiralpak AD-H column).

2.2.2.4 Screening of Additives

It has been observed that, 18 mol% of TfOH improves the yield and enantioselectivity dramatically in oxidative cyclization of homoallylic alcohol. When the reaction was performed in absence of TfOH under the same reaction condition, the desired product **30a** was furnished with only 33% yield and 27% ee (Table 2.2.2.4, entry 1). For further improvement in the result, different kinds of additive were examined. Other additives such as silver salts had no positive effect (entry 3-5). Methyl triflate which is an ester moiety of TfOH gives poor selectivity compared to TfOH (entry 6); probably the free acidic proton in TfOH is essential for high reactivity. Trimethylsilyltriflate and triflimide also promote the reaction affording the cyclized product **30a** with moderate yield and enantioselectivity (entry 7&8). None of these additive improved reaction outcome, hence trifluoromethanesulfonic acid remained the best additive to promote the oxidative cyclization of homoallyl alcohol **29a** in to the acetoxylated tetrahedrofuran **30a** in 92% yield and 90% ee.

Table 2.2.2.4 Effect of additives



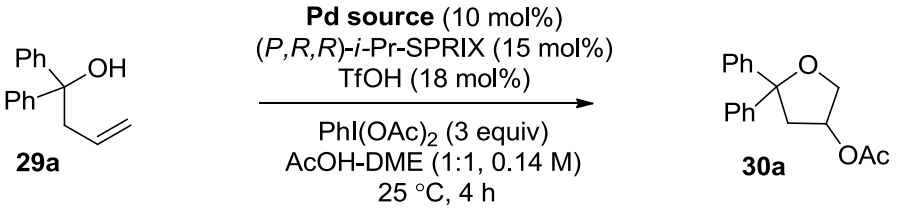
Entry	**Additive** (18 mol %)	Yield (%)[a]	Ee (%)[b]
1	None	33	27
2	TfOH	92	90
3	AgOTf	57	48
4	$AgBF_4$	74	50
5	$AgPF_6$	73	11
6	MeOTf	67	54
7	TMSOTf	65	70
8	Tf_2NH	72	70

[a] Isolated yield. [b] Determined by HPLC analysis (Chiralpak AD-H column).

2.2.2.5 Screening of Pd source in presence of TfOH

The extensive optimization resulted into the finding of TfOH (18 mol%), in presence of $PdCl_2(MeCN)_2$ (10 mol%), shows high catalytic activity, affording the cyclized product **30a** in excellent yield and enantioselectivity (Table 2.2.2.5, entry 1). Where as, reactivity of other palladium sources were not studied in presence of triflic acid. Encouraged by this result, examination of various Palladium sources were carried out (Table 2.2.2.5). The $PdCl_2(PhCN)_2$ and $[PdCl(\pi\text{-allyl})]_2$ could promote the reaction in good yield and enantioselectivity, but less effective as compared to $PdCl_2(MeCN)_2$ (entry 2&3). Next, I examined number of palladium sources (entry 4-12), but none of these palladium catalyst shows good activity and in most of the cases starting material was recovered.

Table 2.2.2.5



Entry	**Pd source**	Yield (%)[a]	Ee (%)[b]
1	$PdCl_2(MeCN)_2$	92	90
2	$PdCl_2(PhCN)_2$	82	74
3	$[PdCl(\pi\text{-allyl})]_2$	80	72
4	$PdCl_2(cod)$	66	57
5	$Pd(OAc)_2$	73	35
6	$Pd(OCOCF_3)_2$	43	7
7	$Pd(acac)_2$	48	24
8	$Pd(hfacac)_2$	56	32
9	$Pd(NO_3)_2$	68	41
10	$PdCl_2$	26	4
11	$PdBr_2$	31	14
12	$Pd_2(dba)_2{\cdot}CHCl_3$	64	14

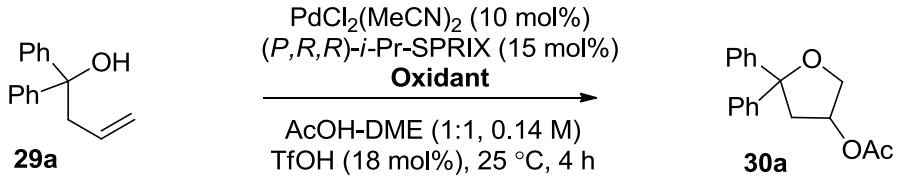
[a] Isolated yield. [b] Determined by HPLC analysis (Chiralpak AD-H column).

2.2.2.6 Oxidant screening

In the Pd(II)/Pd(IV) catalysis, the efficient oxidant is required to oxidize the Pd(II) species in to Pd(IV) intermediate. Recent literature report shows the hypervalent iodine(III) is a best choice of oxidant in Pd(II)/Pd(IV) catalysis.[6] In order to study the effect of other oxidants, reactions were performed with different hypervalent iodine as shown in table 2.2.2.6. The 3 mole equivalents of Bis(trifluoroacetoxy)iodo benzene [$PhI(OCOCF_3)_2$] give only moderate yield and ee (entry 2). Where as PhI(OH)(OTs) afforded the product **30a** in 32% yield and 55% ee (entry 3). The mildly nucleophilic iodosobenzene oxidant promotes this reaction, affording the desired product **30a**

with 54% yield and 72% ee (entry 4). *p*-Benzoquinone, a routine oxidant for the Pd(0)/Pd(II) catalysis, did not engage in the cyclative acetoxylation at all, confirming the Pd(II)/Pd(IV) catalytic system operating in this transformation. Not other than $PhI(OAc)_2$ (PIDA) oxidant was found to be effective in this oxidative transformation. The amount of $PhI(OAc)_2$ also affects the outcome of the reaction. When 1 mole equivalent of $PhI(OAc)_2$ was used, the product **30a** was obtained in low yield and selectivity (entry 6). In contrast, increasing the amount of $PhI(OAc)_2$ more than 3 mole equivalent, does not give satisfactory result (entry 8). So, the 3 mole equivalent of $PhI(OAc)_2$ remained the appropriate quantity for better result.

Table 2.2.2.6 Effect of oxidants



Entry	**Oxidant**	Amount (mol equiv)	Yield (%)[a]	Ee (%)[b]
1	$PhI(OAc)_2$	3	92	90
2	$PhI(OCOCF_3)_2$	3	52	55
3	PhI(OH)(OTs)	3	32	55
4	PhIO	3	54	72
5	*p*-benzoquinone	3	ND	ND
6	$PhI(OAc)_2$	1	72	69
7	$PhI(OAc)_2$	2	90	86
8	$PhI(OAc)_2$	4	85	73

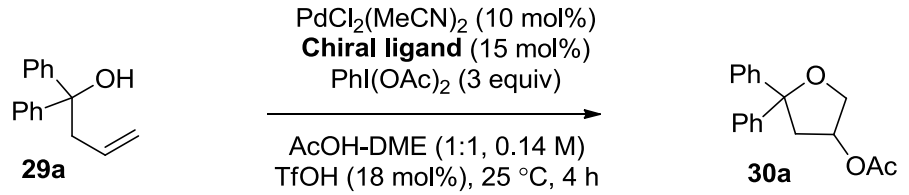
[a] Isolated yield. [b] Determined by HPLC analysis (Chiralpak AD-H column).

2.2.2.7 Screening of other chiral ligand

After extensive study of various reaction parameters, I obtained the optimized reaction condition in which, model substrate **29a** was treated with $PdCl_2(MeCN)_2$ (10 mol%), (*P,R,R*)-*i*-Pr-SPRIX (15 mol%), $PhI(OAc)_2$ (3 equiv) and TfOH (18 mol%) in AcOH-DME (1:1, 0.14 M) co-solvent

system at 25 ^{o}C, after 4 h afforded the cyclized product **30a** in 92% yield and 90% ee. In the enantioselective Pd(II)/Pd(IV) catalysis, chiral ligands play a vital role.

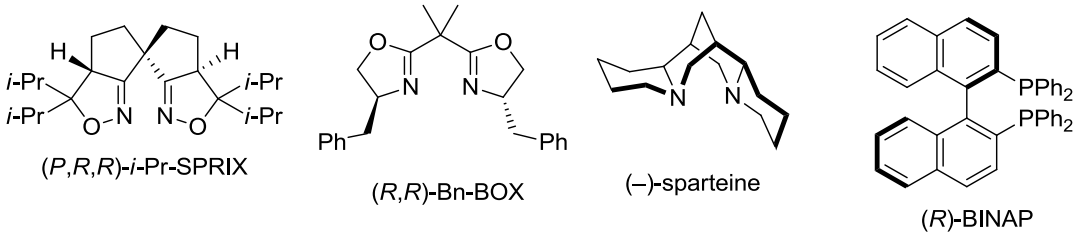
Table 2.2.2.7 Effect of chiral ligands



Entry	**Chiral ligand**	Yield (%)[a]	Ee(%)[b]
1	None	64	Racemic
2	(*P,R,R*)-*i*-Pr-SPRIX	92	90
3	(*R,R*)-Bn-BOX	NR	-
4	(-)-Sparteine	NR	-
5	(*R*)-BINAP	NR	-

[a] Isolated yield. [b] Determined by HPLC analysis (Chiralpak AD-H column). NR = No Reaction

Structure of chiral ligands



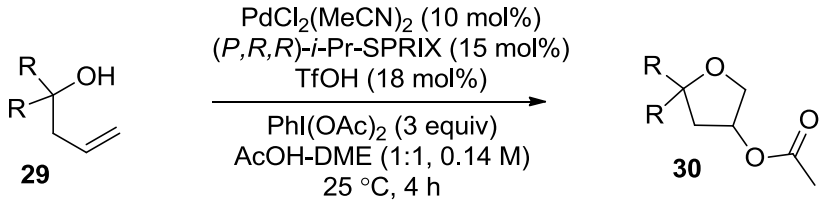
The background reaction, in absence of ligand, proceeds to give **30a** in 64% yield with no enantioselectivity (Table 2.2.2.7, entry 1). Enantiopure SPRIX ligand not only induces the enantioselectivity, but also increases the catalytic activity through the coordination with palladium center and effectively activates the olefin (entry 2). The commercially available chiral ligands such as (*R,R*)-Bn-BOX, (-)-Sparteine and (*R*)-BINAP failed to promote this reaction under the identical reaction condition (entry 3-5). The complete failure of these ligands could be reasoned that, they were not survived under oxidative and acidic condition or could not participate in olefin activation, whereas *i*-Pr-SPRIX ligand is stable under similar condition.

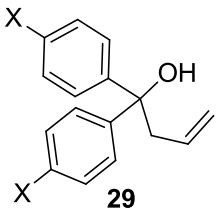
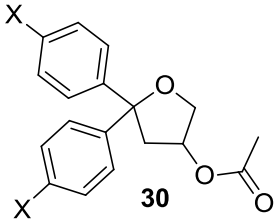
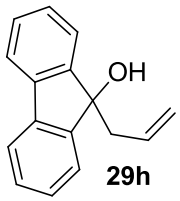
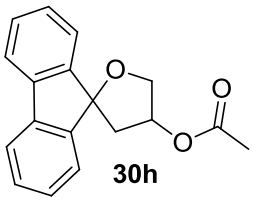
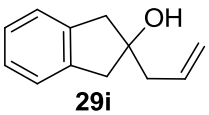
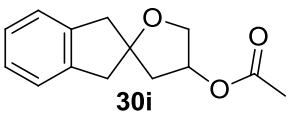
These results clearly demonstrate the high stability of *i*-Pr-SPRIX under such oxidative and acidic conditions, which has proven to be crucial for this Pd(II)/Pd(IV) catalysis.

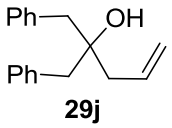
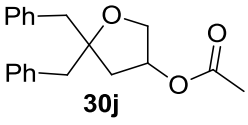
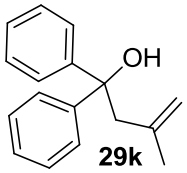
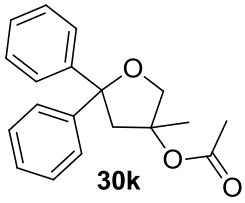
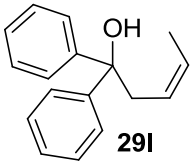
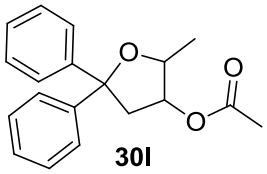
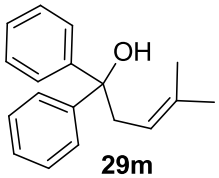
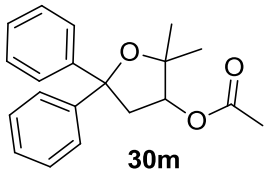
2.2.3 Scope and limitations

After identifying the optimized condition, I explore the scope of this asymmetric cyclative acetoxylation with various homoallyl alcohols **29** (Table 2.2.3).

Table 2.2.3 Substrate scope for the enantioselective cyclative acetoxylation of homoallyl alcohols



Entry	Substrate	Product	
		Yield (%)[a]	Ee(%)[b]
			
1	X = H **(29a)**	92 **(30a)**	90
2	= F **(29b)**	86 **(30b)**	88
3	= Cl **(29c)**	83 **(30c)**	79
4	= Br **(29d)**	79 **(30d)**	78
5	= CF_3 **(29e)**	70 **(30e)**	44
6	= Me **(29f)**	30 **(30f)**	90
7	= OMe **(29g)**	–[c] **(30g)**	–
8[d]			49
		85	
9[e]			37
		75	

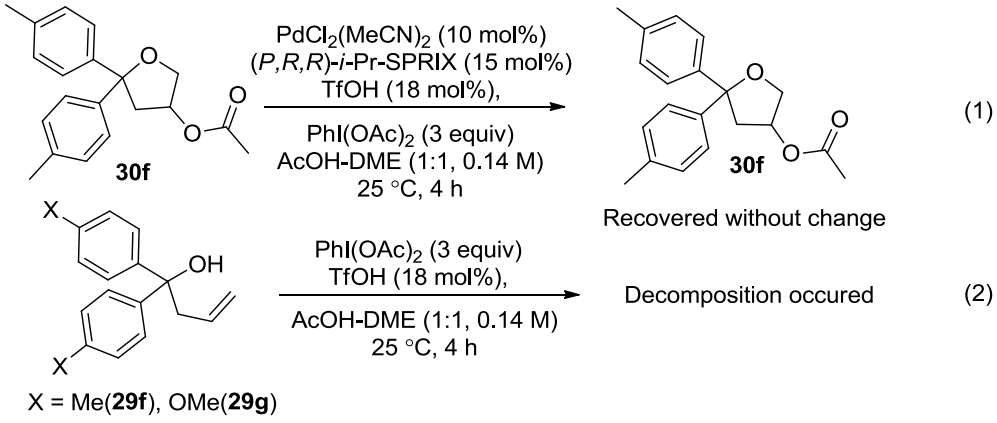
Entry	Substrate	Product	
		Yield (%)[a]	Ee(%)[b]
10[f]	 29j	 30j	55
		55	
11	 29k	 30k	Racemic
		56	
12	 29l	 30l	–
		Trace	
13	 29m	 30m	–
		Trace	

[a] Isolated yield. [b] Determined by HPLC analysis (Chiralpak AD-H column. [c] A complex mixture was obtained. [d] Reaction was carried out at −10 °C for 96 h. [e] Reaction was carried out at −10 °C for 50 h. [f] Reaction was carried out at −10 °C for 12 h.

The reaction of **29b** bearing 4-fluorophenyl groups gave optically active **30b** efficiently (86% yield, 88% ee) (entry 2). Other halo substituents at the para positions of phenyl ring were also tolerated: chloride product **30c** and bromide product **30d** were obtained in 83% and 79% yields with 79% ee and 78% ee, respectively (entries 3 and 4). In the reaction of **29e** having electron-withdrawing 4-trifluoromethylphenyl rings, the enantioselectivity significantly dropped to 44% ee (entry 5). On the other hand, the acetoxy tetrahydrofuran with electron-donating groups was produced in a highly enantioenriched form, albeit in low yield. Thus, product **30f** having 4-tolyl groups was obtained in 30% yield with 90% ee, whereas the reaction of **29g** having 4-anisyl

groups did not provide cyclized product **30g**, resulting in a complex mixture (entries 6 and 7). Optically active spiro-type product **30h** with a fluorene ring was formed satisfactorily at lower temperature (entry 8). An aliphatic group was also applicable to the substituent at the α-position of the hydroxy group, leading to products **30i** and **30j** in moderate yields (entries 9 and 10). Substituents on the olefin component had a great influence on the chemical yield as well as the selectivity. Treatment of **29k** bearing a crotyl group afforded racemic **30k** in 56% yield, while the reaction of prenyl substrate **29l** hardly proceeded to give a trace amount of **30l** (entries 11 and 12). The substrate **29m** bearing dimethyl groups on terminal end of olefin gives only trace amount of product **30m**. The substitution on olefinic part with methyl groups could not tolerated which might be resulted into decomposition of substrate under the reaction condition, which resulted into the complex mixture and only trace amount of product were isolated.

When the isolated **30f** was subjected to the optimal conditions, no detectable change was observed on TLC and in the crude ^{1}H NMR spectrum (eq.1). By contrast, substrates **29f** and **29g** were completely consumed within 1 h even in the absence of the Pd–*i*-Pr-SPRIX catalyst to give a complex mixture (eq. 2). These results suggested that the low chemical yield of **30f** and no formation of **30g** were ascribed to the decomposition of the substrate under the reaction conditions.



2.2.4 Hammett study

In this Pd(II)/Pd(IV) catalysis, the enantioselectivity was supposed to have a certain relationship with the electron density on the aromatic rings of **29a**–**e** which was resulted in high enantioselectivity of products **30a-e** (Table 2.2.3, entry 1-5), where the electron-rich substrate gave a better selectivity compared to the electron-poor substrate. By taking the % ee values of **30a-e** and plotting it versus the appropriate Hammett σ parameter, the Hammett Plot was prepared (Figure 2.2.4). The ee values were found to correlate very well (R^2 = 0.9527) to the σ parameter. The Hammett plot yielded a slope, showing that there is a significant electronic effect on the enantioselectivity of reaction. That can be explained as, the electron rich functional groups exert the inductive effect, which result in to the tight coordination of –OH group to the palladium, and the palladium activates the olefin. As a result, the asymmetric environment of *i*-Pr-SPRIX reflects well on the stereochemistry in the enantioselectivity-determining acetoxylation.

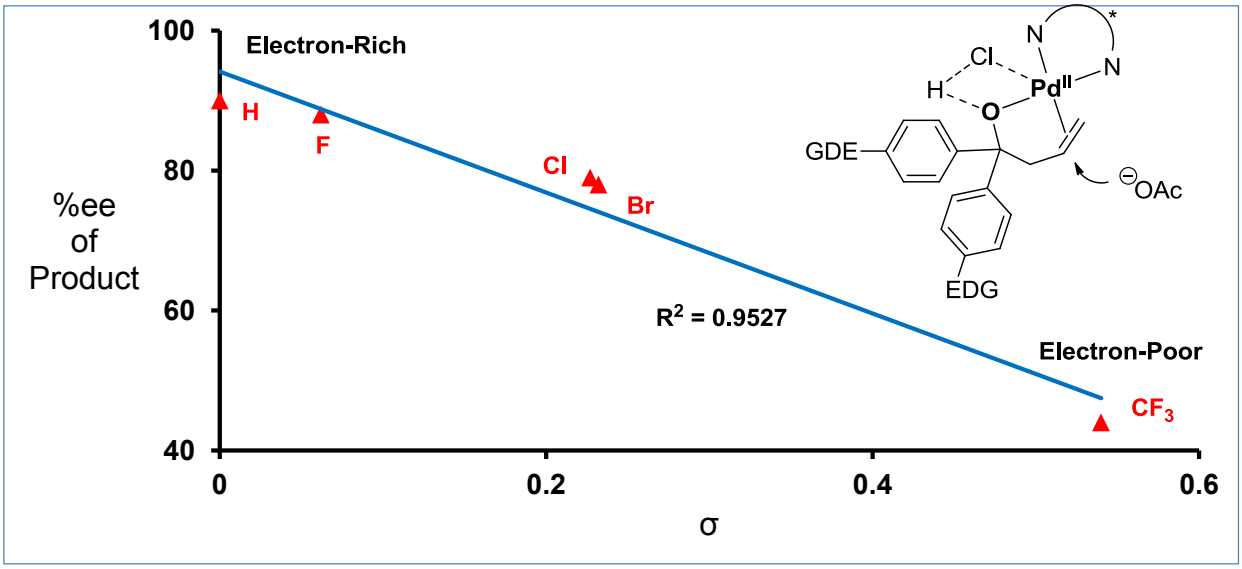
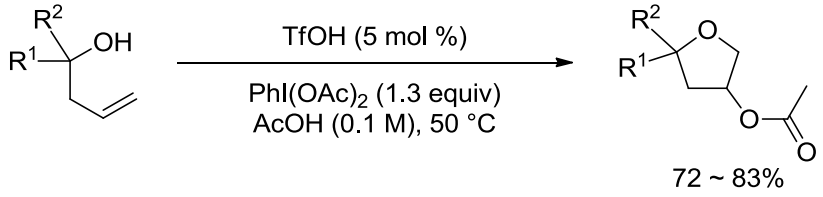


Figure 2.2.4 Substituent effects on the enantioselectivity in the cyclative acetoxylation of **25**.

2.2.5 Control Experiments

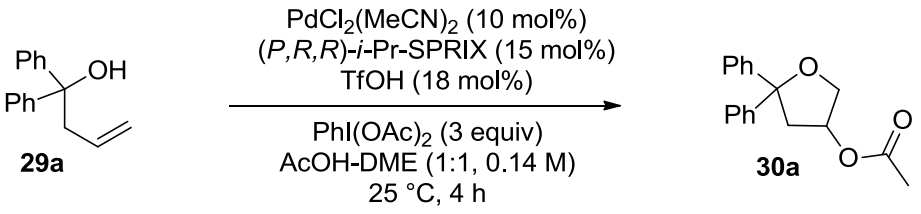
A similar but metal-free cyclative acetoxylation of alkenyl alcohols was reported during the course of this study by Gade et al., in which catalytic TfOH stimulated PhI(OAc)2 to give a reactive cationic iodoso compound (Scheme 2.2.5).[4] The detailed mechanistic study revealed that the strong acid (TfOH) functions as the active catalyst.



Scheme 2.2.5 Metal-free cyclative acetoxylation of alkenyl alcohols (Gade's report)

To make it clear whether the metal complex or the Bronsted acid operated as the catalyst in this catalytic system, I conducted several control experiments using **29a** (Table 2.2.5).

Table 2.2.5 Control experiments



Optimal condition

Entry	**Variation from the optimal conditions**	Yield (%)[a]	Ee(%)[b]
1	None	92	90
2	No *i*-Pr-SPRIX	64	–
3[c]	No $PdCl_2(MeCN)_2$	49	Racemic
4[c]	No *i*-Pr-SPRIX and No $PdCl_2(MeCN)_2$	27	–
5[d]	No *i*-Pr-SPRIX, $PdCl_2(MeCN)_2$ and TfOH	NR	–

[a] Isolated yield. [b] Determined by HPLC analysis (Chiralpak AD-H column). [c] Reaction time was 6 h. [d] Reaction was carried out at 40 °C for 34 h. NR = No Reaction

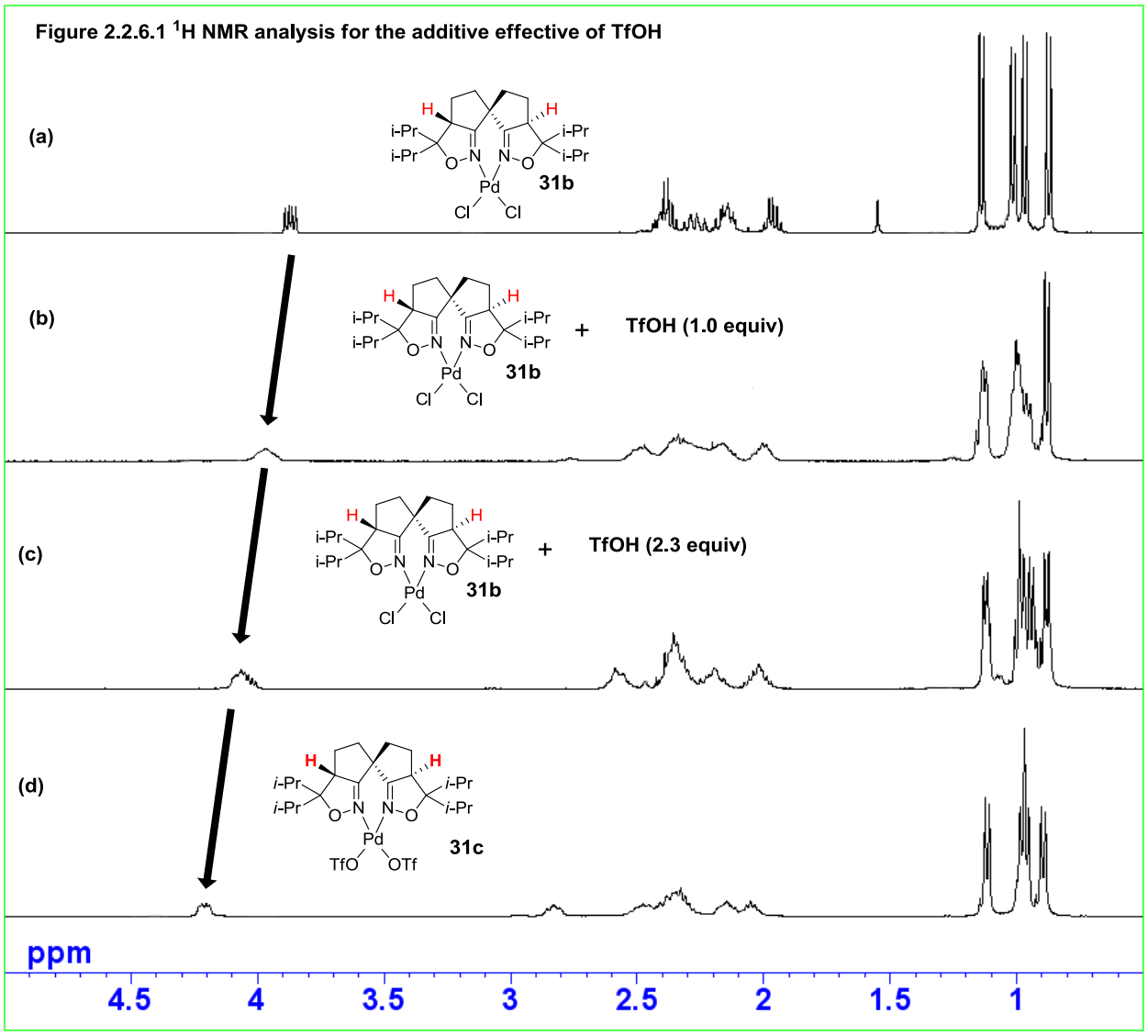
The reaction in the absence of *i*-Pr-SPRIX furnished **30a** in 64% yield under otherwise identical conditions to the optimal (entry 2). Without use of Pd, racemic **30a** was obtained in poor yields

(entries 3 and 4). When neither Pd nor SPRIX nor TfOH was applied to the reaction, no conversion was observed even at higher temperature for a prolonged time, resulting in the full recovery of **29a** (entry 5). These results clearly indicate that the active catalyst in the present work is not TfOH but the Pd–*i*-Pr-SPRIX complex.

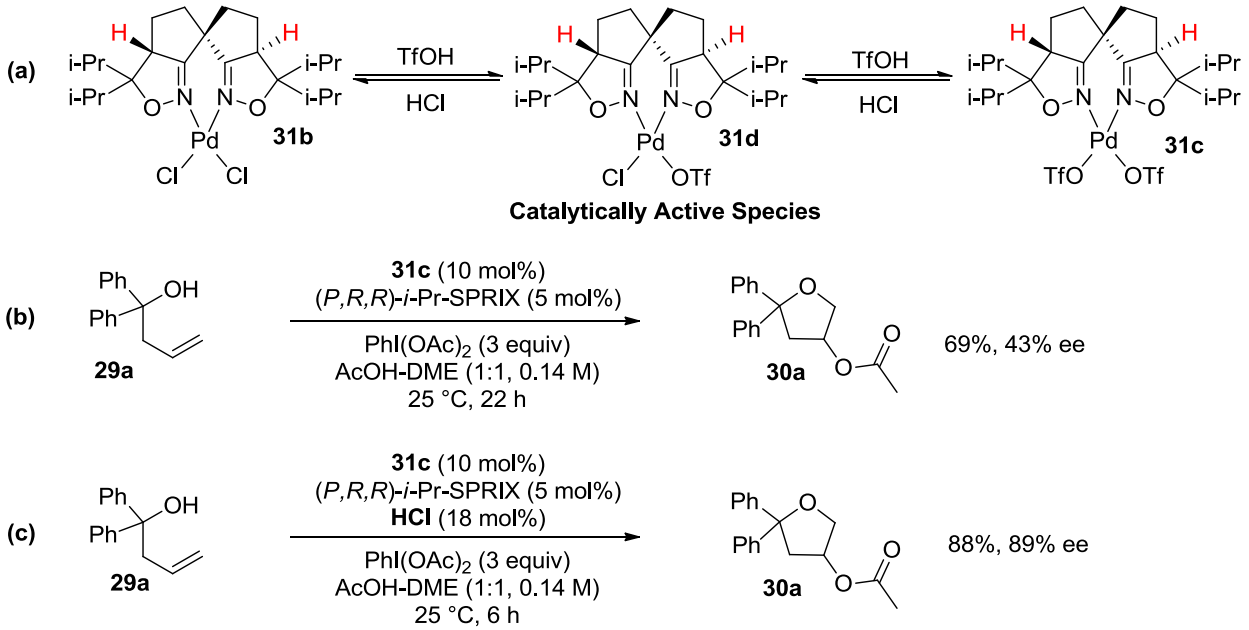
2.2.6 Mechanistic study

2.2.6.1 Role of Triflic acid (TfOH)

The control experiment study shows that, the active catalyst is not TfOH, but Pd-SPRIX plays a catalyst role. The addition of 18 mol% of TfOH is essential for high reaction outcome regarding yield and enantioselectivity. Without TfOH, the reaction proceeds to give poor yield and enantiopurity.



To investigate the exact role of triflic acid (TfOH) in this enantioselective Pd(II)/Pd(IV) catalysis, I performed the ^{1}H NMR measurements study by carrying out experiments. In which, effect of triflic acid on Pd-SPRIX complex were studied by ^{1}H NMR analysis (Figure 2.2.6.1a-d). The ^{1}H NMR of $PdCl_2$-(*i*-Pr-SPRIX) (**31b**) recorded which shows a sharp double doublet at 3.86 ppm, assignable to the bridgehead protons of *i*-Pr-SPRIX (Figure 2.2.6.1a). When, 1 equivalent of TfOH was added to the **31b**, the bridgehead proton signals of *i*-Pr-SPRIX were broadened and shifted to the lower field at 3.96 ppm (Figure 2.2.6.1b). Further addition of 2.3 equivalent of TfOH, the characteristic signal shifted to lower field indicating broad multiplet at 4.04 ppm (Figure 2.2.6.1c). In order to clarify this phenomenon, ^{1}H NMR of $Pd(OTf)_2$-(*i*-Pr-SPRIX) **31c** was recorded. The spectrum of **31c** showed a double doublet at 4.21 ppm for the corresponding bridgehead protons. The above observations suggest that TfOH triggers anion exchange to provide an equilibrium among chloride complex **31b**, triflate complex **31c**, and their intermediary complex **31d** (Scheme 2.2.6.1a).[5]

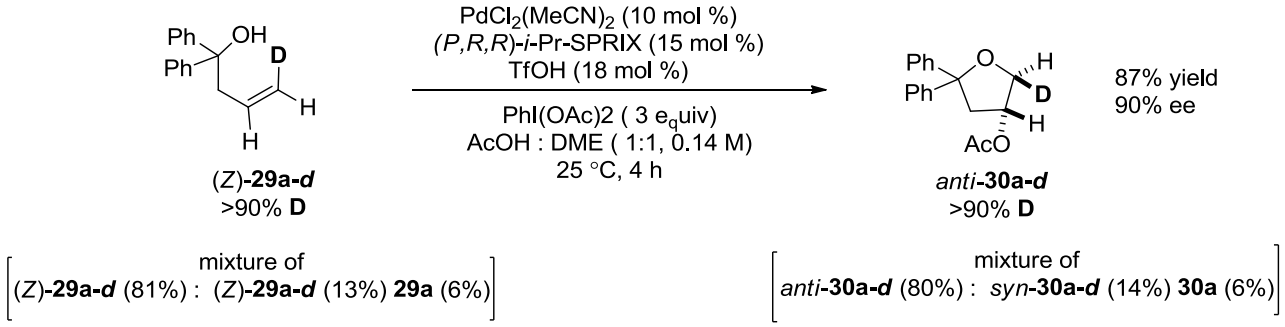


Scheme 2.2.6.1 (a) Equilibrium among Pd-SPRIX complexes **31b, 31d** and **31c**. (b) Reaction of **29a** catalyzed by **31c** (c) Reaction of **29a** catalyzed by **31c** in the presence of catalytic HCl.

Complex **31c**, however, turned out to exhibit only moderate catalytic activity. Under optimal conditions but without TfOH, the reaction of **29a** catalyzed by **31c** was so sluggish as to produce **30a** with 69% yield in 43% ee after 22 h (Scheme 2.2.6.1). I found that the addition of 18 mol% of HCl (as a diethyl ether solution) to the above reaction restored the chemical yield (88%) and the enantioselectivity (89% ee), which were reminiscent of the output under optimal conditions (Scheme 2.2.6.1c). Presumably, **31d** would be involved as the real active catalyst in this reaction.

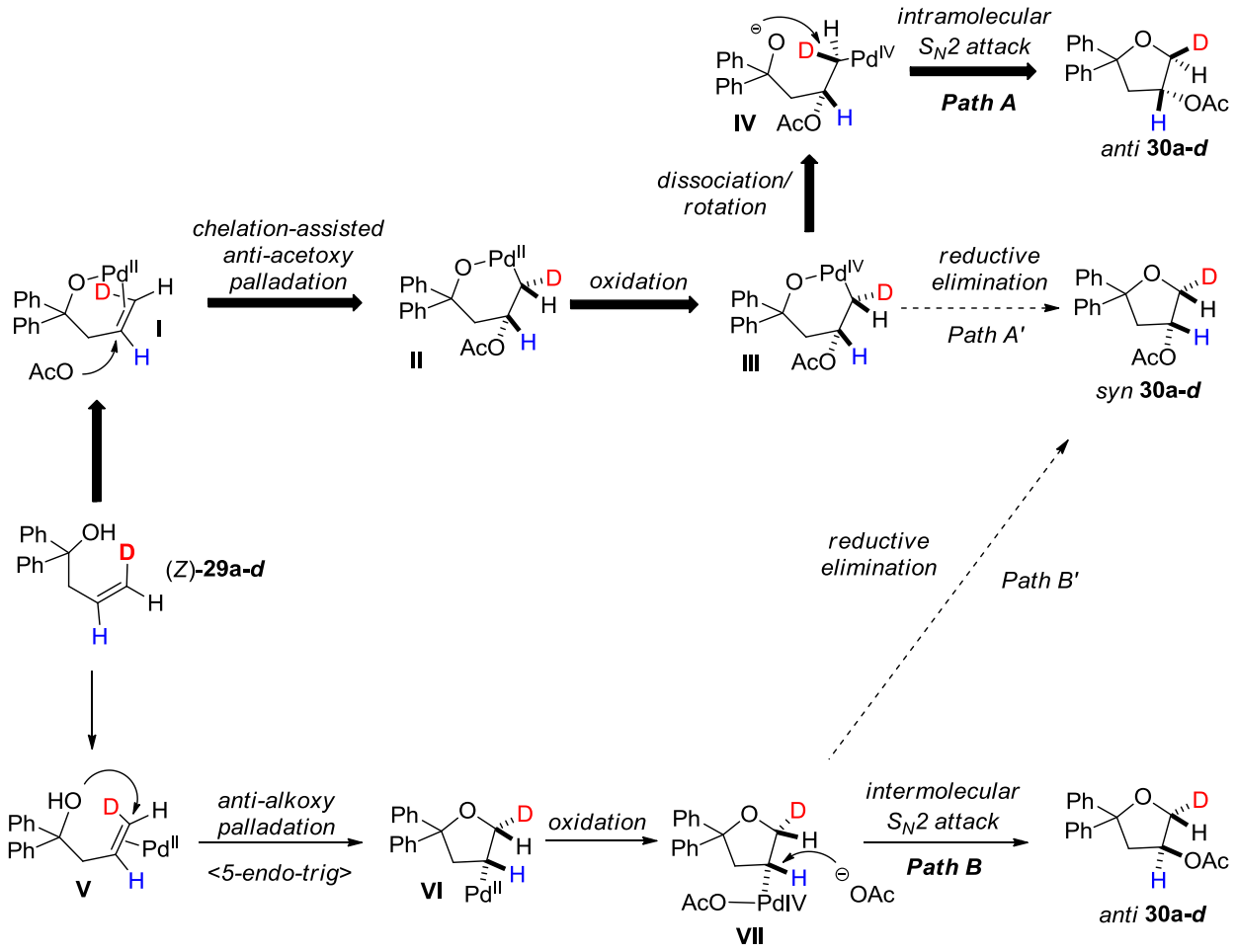
2.2.6.2 Deuterium labeling experiment (insight into mechanism)

To probe the underlying mechanism, deuterium labeling experiment was carried out. The deuterium labelled substrate **29a-*d*** was prepared with >90% isotopic purity in isomeric form as (*Z*)-**29a-*d***(81%) : (*E*)-**29a-*d***(13%) **: 29a**(6%). When, the substrate (*Z*)-**29a-*d*** (mixture) was subjected under optimal condition, the desired product **30a-*d*** was obtained in 87% yield with 90% ee (Scheme 2.2.6.2). The product was found to consist in which the -OAc and *D* were *anti* to each other. The coupling constant between the two hydrogen atoms was found 2.2Hz. Relative configuration of the major product, *anti*-**30a-*d***, was determined by the comparison of chemical shifts[6] and coupling constant[7] in the ^{1}H NMR spectrum with reported values and was eventually established by NOE.



Scheme 2.2.6.2 Enantioselective cyclative acetoxylation of (*Z*)-**29a-*d*** promoted by Pd/SPRIX/TfOH catalyst.

Since the isomeric ratio was not changed throughout the process, i.e. from the substrate ((*Z*)-**29a-*d*** *:* (*E*)-**29a-*d*** = 81:13) to the product (*anti*-**30a-*d*** : *syn*-**30a-*d*** = 80:14), this Pd(II)/Pd(IV) catalysis is thought to proceed in a stereospecific manner. Thus, treatment of substrate (*Z*)-**29a-*d*** with the catalytic system afforded only *anti*-**30a-*d***. There are two possibilities for the formation of *anti*-**30a-*d*** from (*Z*)-**29a-*d*** (Scheme 2.2.6.3). One is initiated by *anti*-acetoxypalladation through the coordination of the alkoxy moiety, which is followed by the oxidation of alkyl–Pd(II) species **II** to Pd(IV) intermediate **III**. Then, dissociation of the alkoxy ligand and rotation of the C–C bond take place to result in intermediate **IV**. Finally, intramolecular S_N2 attack of the alkoxy (or alcohol) nucleophile furnishes *anti*-**30a-*d*** (path A). The other pathway involves cyclization via *anti*-alkoxypalladation, oxidation, and S_N2 attack of an external acetoxy anion (path B).



Scheme 2.2.6.3 Stereochemical pathway of enantioselective cyclative acetoxylation of (*Z*)-**29a-*d***.

From Pd(IV) intermediates **III** or **VII**, no direct reductive elimination leading to *syn*-**30a-*d*** occurs (paths A′ and B′). Although path B cannot be ruled out at the present time, path A is preferable for the following reasons:

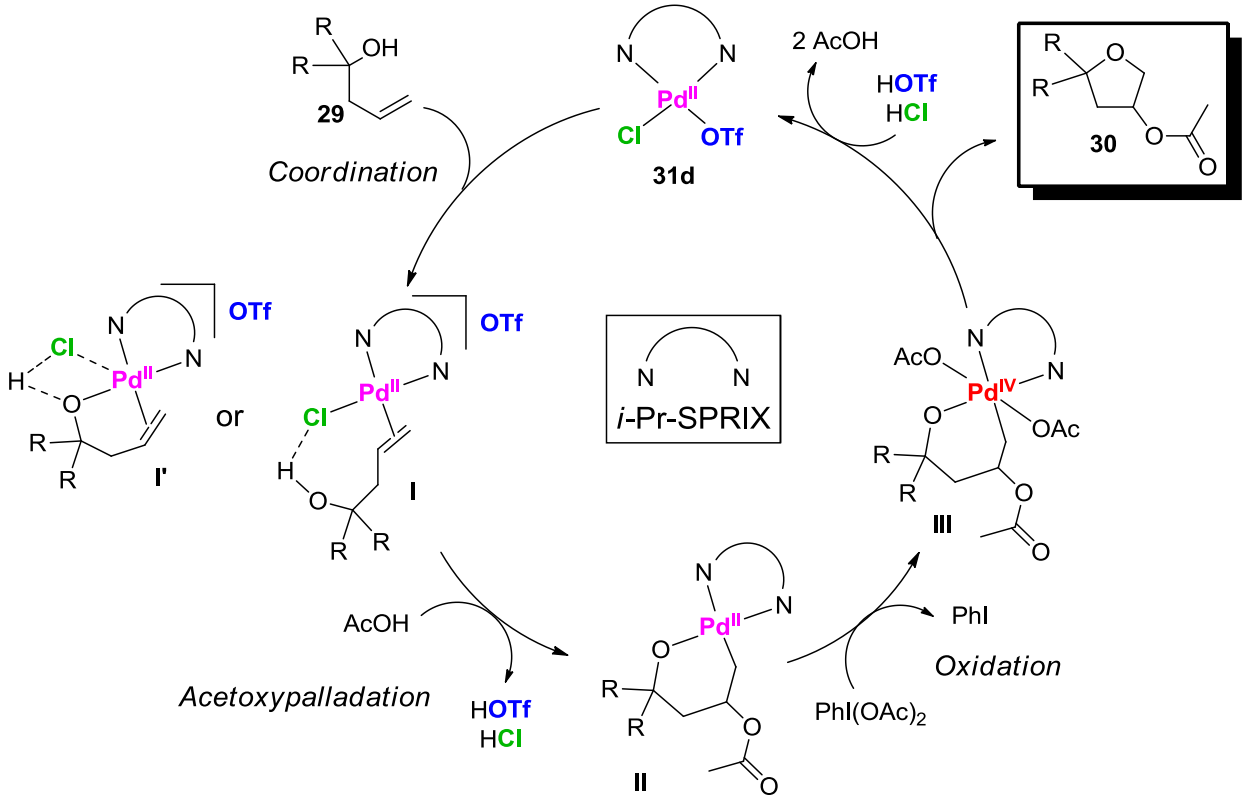
1. The relationship between the electronic property of the aromatic substituent and the enantioselectivity is better explained.

2. Path B contains 5-endo-trig-type cyclization, which is classified as an unfavorable process according to the Baldwin's rule.

3. The use of TfOH drastically accelerates the reaction: In addition to the generation of the catalytically active species, TfOH may also facilitate the dissociation step.

2.2.6.3 Plausible catalytic cycle

On the basis of these mechanistic studies such as ^{1}H NMR analysis and deuterium labeling experiment, the plausible mechanism is outlined in scheme 2.2.6.4.



Scheme 2.2.6.4 Plausible catalytic cycle

The asymmetric cyclative acetoxylation of **29** probably proceeds along the mechanism proposed previously.[8,9] The reaction is initiated by coordination of the C–C double bond to Pd catalyst **31d** derived from $PdCl_2(MeCN)_2$, *i*-Pr-SPRIX, and TfOH. At this stage, the hydroxyl functionality is believed to participate in chelate coordination by way of alkoxide complex **I** or hydrogen-bonding complex **I′**. (vide infra). A subsequent nucleophilic attack of acetate on the activated olefin affords palladacycle **II**, which is oxidized by the action of $PhI(OAc)_2$ to Pd(IV) intermediate **III**. Finally, C–O bond formation in **III** leads to products **30** and the regeneration of catalytically active **31d**.[10]

In this Pd(II)–Pd(IV) catalysis, the enantioselectivity was supposed to have a certain relationship with the electron density on the aromatic rings of **29a–e**, where the electron-rich substrate gave a better selectivity compared to the electron-poor substrate. It is speculated that for electron-rich substrates, the asymmetric environment of *i*-Pr-SPRIX reflects well on the stereochemistry in the enantioselectivity-determining acetoxylation by the tight coordination in the intermediate I or I′.

2.3 Summary

In summary, I have developed an asymmetric cyclative acetoxylation of **29**, which is a rare example of enantioselective catalytic reactions involving Pd(IV) intermediates.[11] The detailed study on mechanistic pathways and involvement of catalytically active species were explained well with experimental proof. Chiral ligand *i*-Pr-SPRIX is found to be crucial for obtaining optically active 3-oxy-tetrahydrofurans **30**. This asymmetric Pd(II)/Pd(IV) catalytic process can be helpful in construction of pharmaceutically relevant building blocks.

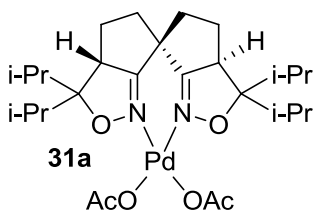
2.4 Experimental and characterization section

General information

NMR spectra were recorded at 25 °C on JEOL ECS400 (400 MHz for ^{1}H, 100 MHz for ^{13}C and 376 MHz for ^{19}F) or BRUKER Avance III 700 (700 MHz for ^{1}H). Chemical shifts are reported in δ ppm referenced to an internal tetramethylsilane standard for ^{1}H NMR. Chemical shifts of ^{13}C NMR are given relative to $CDCl_3$ (δ 77.0). ESI and APCI mass spectra were recorded on a Thermo Fisher, LTQ ORBITRAP XL. IR spectra were obtained using a JASCO FT/IR-4100 instrument. Optical rotations were measured with a JASCO P-1030 polarimeter. HPLC analyses were performed on JASCO HPLC system (JASCO PU 2080 pump and MD-2010 UV/Vis detector). Anhydrous diethyl ether, acetic acid, and dimethoxyethane were purchased from Kanto Chemicals and were used without further purification. Other solvents were purified prior to use by standard techniques. *i*-Pr-SPRIX was prepared according to the method reported by our laboratory. Complex **27c** was prepared from **27b** and MeOTf.[12] All other chemicals were purchased from commercial suppliers and used as received. All reactions were performed with standard Schlenk technique under a nitrogen atmosphere. Column chromatography was conducted on Kishida Silica Gel (spherical, 63–200 μm).

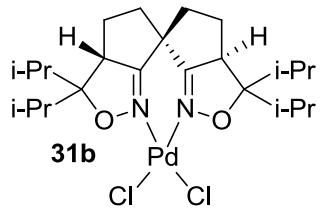
2.4.1 General procedure for the preparation of Pd-SPRIX complexes

A mixture of Pd salt (1.0 equiv) and (*P,R,R*)-*i*-Pr-SPRIX (1.0 equiv) in CH_2Cl_2 was stirred at 25 °C for several hours. Half amount of CH_2Cl_2 was removed in *vacuo*, and the complex was precipitated by addition of diethyl ether (Et_2O). After filtration, Pd-SPRIX complex was obtained.

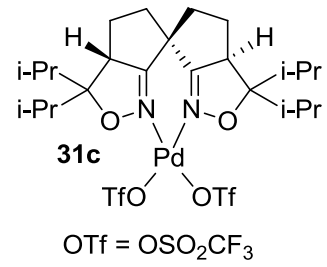


31a

Pd(OAc)$_2$-*i*-Pr-SPRIX (31a). According to general procedure, $Pd(OAc)_2$ (6 mg, 0.0266 mmol), (*P,R,R*)-*i*-Pr-SPRIX (10 mg, 0.0266 mmol) in CH_2Cl_2 (1 mL) were used. After a reaction time of 3 h, the titled compound was obtained in 80% yield (12.8 mg) as light yellow powder. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 0.85 (d, *J* = 6.7 Hz, 6H), 0.93 (d, *J* = 6.7 Hz, 6H), 0.96 (d, *J* = 6.7 Hz, 6H), 1.15 (d, *J* = 6.7 Hz, 6H), 1.86 (s, 6H), 1.93 (sep, *J* = 6.7 Hz, 2H), 2.08-2.13 (m, 4H), 2.26-2.31 (m, 6H), 3.77-3.80 (m, 2H). ^{13}C NMR (125.8 MHz, CD_2Cl_2): δ 16.3, 16.9, 17.0, 17.2, 19.4, 21.6, 31.8, 31.9, 36.4, 45.6, 48.5, 103.2, 166.1, 176.8.



$PdCl_2$-*i*-Pr-SPRIX (31b). According to general procedure, $PdCl_2(MeCN)_2$ (20.7 mg, 0.08 mmol), (*P,R,R*)-*i*-Pr-SPRIX (30 mg, 0.08 mmol) in CH_2Cl_2 (2 mL) were used. After a reaction time of 5 h, the titled compound was obtained in 98% yield (43.3 mg) as light yellow powder. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 0.87 (d, *J* = 6.7 Hz, 6H), 0.96 (d, *J* = 6.7 Hz, 6H), 1.00 (d, *J* = 6.7 Hz, 6H), 1.13 (d, *J* = 6.7 Hz, 6H), 1.96 (sep, *J* = 6.7 Hz, 2H), 2.08-2.15 (m, 2H), 2.16-2.29 (m, 4H), 2.36 (sep, *J* = 6.7 Hz, 2H), 2.42-2.46 (m, 2H), 3.88 (dd, *J* = 5.5 Hz, *J* = 11.7 Hz, 2H). ^{13}C NMR (125.8 MHz, CD_2Cl_2): δ 16.4, 17.0, 17.0, 18.0, 19.0, 31.6, 31.7, 36.8, 45.4, 48.8, 103.1, 167.1.

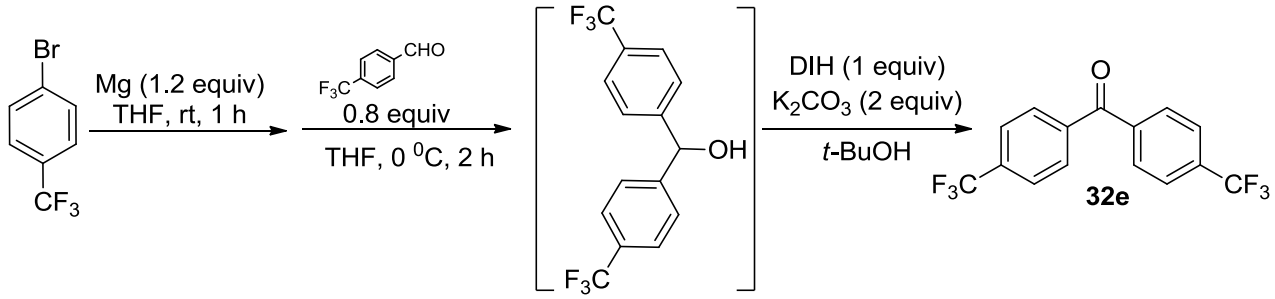


$Pd(OTf)_2$-*i*-Pr-SPRIX (31c). To a CH_2Cl_2 (2 mL) solution of $PdCl_2$-*i*-Pr-SPRIX **(31b)** (44 mg, 0.079 mmol) was added CH_3OTf (0.021 mL, 0.19 mmol) and stirred at 25 °C for 12 h.[14] The dark yellow solution was evaporated to dryness and crude material washed with diethyl ether several times to get dark yellow powder as a titled compound. ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.5, 17.1, 17.5, 18.0, 18.2, 20.0, 32.1, 36.8, 46.8, 48.4, 107.7, 120.6 (q, J_{CF} = 300 Hz), 170.4. ^{19}F NMR (376 MHz, $CDCl_3$): δ –77.99

2.4.2 Experimental Procedure for the Synthesis of Starting Material

All the starting materials were prepared from commercial available ketones (except 8e).

2.4.2.1 General procedure for the synthesis of bis-(4-(trifluoromethyl) phenyl) methanone (32e).

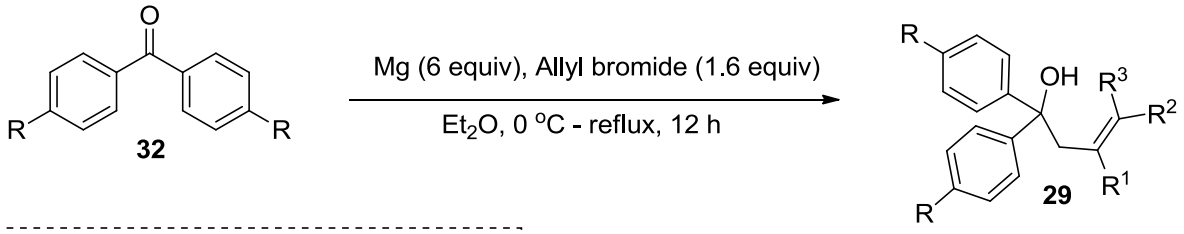


Bis-(4-(trifluoromethyl)phenyl)methanone (**32e**) was prepared by reported procedure[13]. A solution of 1-bromo-4-(trifluoromethyl)benzene (1 g, 4.44 mmol) in dry THF (3 mL) was added dropwise to Mg turnings (130 mg, 5.33 mmol) in THF (5 mL) at room temperature and then, the

mixture was stirred at room temperature for 1 h. A solution of 4-(trifluoromethyl) benzaldehyde (620 mg, 3.55 mmol) in THF (4 mL) was added to the reaction mixture at 0 ^{o}C and the obtained mixture was stirred at room temperature for 2 h. The DIH (1,3-Diiodo-5,5-Dimethylhydantoin) (1.68 g, 4.44 mmol), K_2CO_3 (1.22 g, 8.88 mmol) and *t*-BuOH (13 mL) were added and the obtained mixture was stirred for 20 h at refluxing conditions. The reaction mixture was quenched with sat. aq. Na_2SO_3 (10 mL) and was extracted with $CHCl_3$ (3x25 mL). The organic layer was washed with brine and dried over Na_2SO_4. Purification by short chromatography (silica gel: hexane/$CHCl_3$ = 1:1) yielded *p*- Bis-(4-(trifluoromethyl)phenyl)methanone **32e** as white solid in 98% yield.

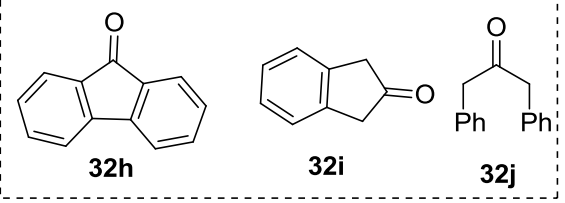
2.4.2.2 General procedure for the synthesis of starting materials (29a-29m)

To an oven-dried two-necked flask equipped with a condenser was added preheated magnesium turnings (6 equiv) followed by dry diethyl ether (5 mL) and one crystal of iodine at room temperature. To this mixture was added allyl bromide (1 equiv) dropwise at 0 °C, which was refluxed for 1 h. The reaction mixture was then cooled to 0 °C, to which a solution of ketone **32** (0.623 equiv) in diethyl ether was added dropwise at that temperature (for **32b**, **32c**, and **32d**: a solution of the Grignard reagent was added to a solution of ketone to avoid formation of diaryl methanol byproduct). The reaction mixture was refluxed for 12 h. To the mixture was added sat. aq. NH_4Cl to quench the reaction, which was extracted three times with diethyl ether. The organic layer was dried over Na_2SO_4 and evaporated under vacuum to dryness. The crude material was then chromatographed on silica gel using hexane-ethyl acetate solvent.



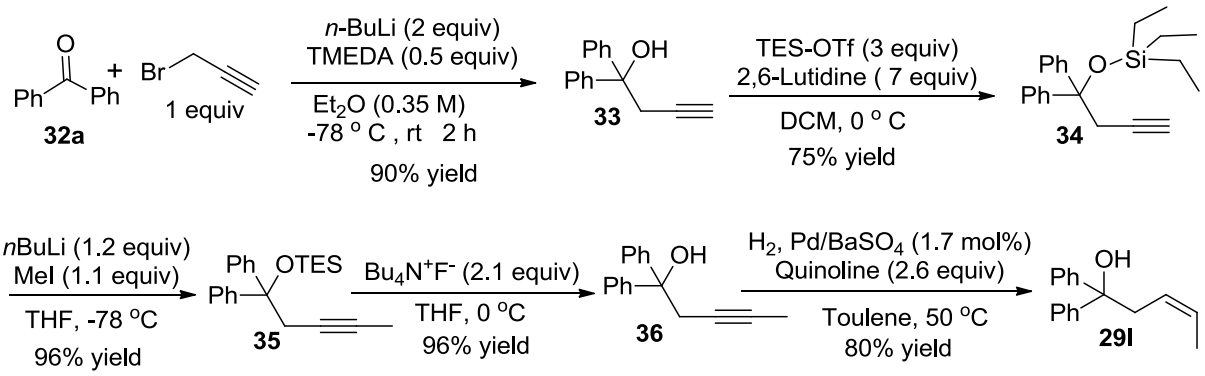
R, R^2, R^3 = H, R^1 = Me **(29K)**
R, R^1 = H, R^2, R^3 = Me **(29m)**

R = H **(32a)**, R = CF_3 **(32e)**
R = F **(32b)**, R = Me **(32f)**
R = Cl **(32c)**, R = OMe **(32g)**
R = Br **(32d)**,



32h **32i** **32j**

2.4.2.3 General procedure for the synthesis of starting material (29l)



1,1-diphenylbut-3-yn-1-ol (33): To a solution of dry diethyl ether (15 mL) and *n*-BuLi 8.44 mL, 21.9 mmol) was cooled to -78 °C and TMEDA (0.821 mL, 5.48 mmol) was added followed by dropwise addition of propargyl bromide (0.91 mL, 12.0 mmol) and resulting mixture stirred for 20 min at this temperature. After this time white precipitate formed. A solution of benzophenone **32a** (2 g, 10.97 mmol) in diethyl ether (10 mL) was added dropwise over 5 min and the reaction mixture was allowed to warm to room temperature over 2 h and quenched with aq. NH_4Cl and organic material was extracted with ethyl acetate. The organic layers were dried over anhydrous Na_2SO_4, and evaporated to dryness. The crude material was chromatographed on short silica gel column to get titled compound **33** in pure form (90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.04 (t, *J* = 2.76 Hz, 1H), 2.96 (s, 1H), 3.16 (d, *J* = 2.28 Hz, 2H), 7.22-7.45 (m, 10H).

(1,1-diphenylbut-3-yn-1-yl)oxy-triehtylsilane (34): To a solution of 1,1-diphenylbut-3-yn-1-ol **33** (1.53 g, 6.88 mmol) in CH_2Cl_2 (7 mL) was added 2,6-lutidine (5.6 mL, 48.1 mmol) and triethyl silyltriflate (4.66 mL, 20.6 mmol) at 0 ^{0}C. The reaction mixture was stirred for 3 h at room temperature and quenched with aq. NH_4Cl and organic material was extracted with ethyl acetate. The organic layers were dried over anhydrous Na_2SO_4, and evaporated to dryness. The crude material was chromatographed on short silica gel column with hexane to afford 1,1-diphenylbut-3-yn-1-yl)oxy-triehtylsilane **34** in pure form (75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ = -0.02-0.03 (q, *J* = 7.8 Hz, 6H), 0.45 (t, *J* = 7.8 Hz, 9H), 1.5 (t, *J* = 2.72 Hz, 1H), 2.74 (d, *J* = 2.76 Hz, 2H), 6.79-6.97 (m, 10H).

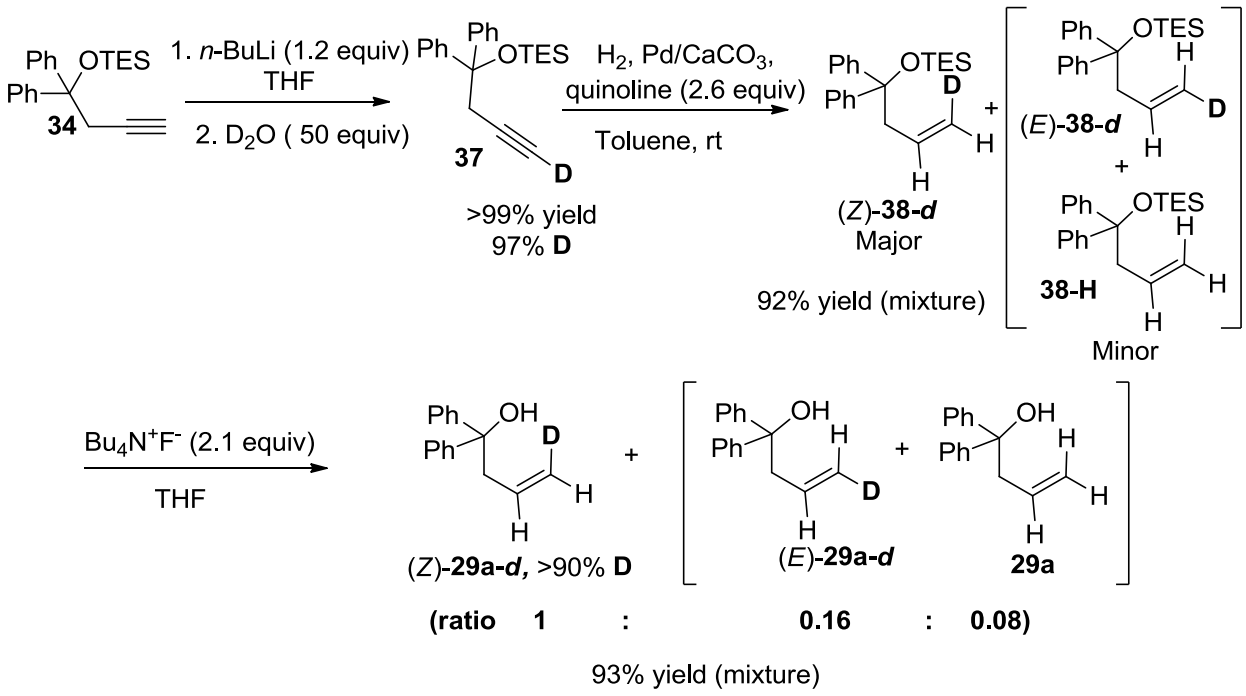
1,1-diphenylpent-3-yn-1-yl-oxy-triethylsilane (35): To a flame dried two neck round bottom flask equipped with a magnetic stirring bar and three way cock with nitrogen balloon, was added a solution of terminal alkyne **34** (0.690 g, 2.05 mmol) in dry THF (13 mL). The solution was cooled to -78 °C followed by adding *n*-BuLi (2.6M in hexane, 0.946 mL, 2.46 mmol) dropwise.

The reaction was stirred at -78 ^{o}C for 30 min. Into this reaction mixture, MeI (0.14 mL, 2.25 mmol) was added rapidly and allowed to warm at room temperature slowly and stirred for 2 h. The reaction mixture was then quenched with aq. NH_4Cl and organic material was extracted with ethyl acetate. The organic layers were dried over anhydrous Na_2SO_4, and evaporated to dryness. The crude material was chromatographed on silica gel column to afford title compound **35** in 96% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.40-0.46 (q, *J* = 7.8 Hz, 6H), 0.87 (t, *J* = 8.2 Hz, 9H), 1.66 (t, *J* = 2.32 Hz, 3H), 3.06-30.7 (q, *J* = 2.28 Hz, 2H), 7.19-7.38 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.5, 6.2, 7.0, 33.7, 75.8, 79.2, 79.9, 126.8, 127.15, 127.4.

1,1-diphenylpent-3-yn-1-ol (36): To a solution of **35** (0.712 g, 2.03 mmol) in THF (5 mL) was added 1M solution of TBAF in THF (4.26 mL, 4.26 mmol) at 0 ^{o}C. The resulting mixture was stirred for 1 h at room temperature. After the completion of reaction, H_2O was added and extracted with ether several times. The combined extracts were dried over Na_2SO_4 and evaporated to leave crude product, which was purified by column chromatography to afford a product **36** in pure form. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.72 (t, *J* = 4.68 Hz, 3H), 3.08 (q, *J* = 2.28 Hz, 2H), 7.21-7.46 (m, 10H).

(Z)-1,1-diphenylpent-3-en-1-ol (29l): To a flame-dried 30 mL round bottom flask with a stir bar under N_2 atmosphere was added Lindlar's catalyst (71.8 mg, 1.7 mol%). The atmosphere was purged with N_2, and then toluene (2 mL), quinoline (0.6 mL, 2.6 equiv), and a solution of alkyne **36** (0.46 gm, 1.94 mmol, 1.0 equiv) in toluene (8 mL) were added in that order. The N_2 line was replaced with a H_2 balloon, and the heterogeneous mixture was stirred vigorously and progress of reaction was monitored by TLC. After the completion of reaction, diluted with dichloromethane, filtered through a celite pad, concentrated in *vacuo* and the crude product was chromatographed on short silica gel column with hexane to afford a entitle compound **29l** (0.37 g, 80% yield).

2.4.2.4 General procedure for the synthesis of starting material ((*Z*)-29a-*d*)



1,1-diphenylbut-3-yn-1-yl)oxy-4-D-triehtylsilane (37): To a flame dried two neck round bottom flask equipped with a magnetic stirring bar and three way cock with nitrogen balloon, was added a solution of terminal alkyne **34** (0.926 g, 2.75 mmol) in dry THF (13 mL). The solution was cooled to -78 ^{o}C followed by adding *n*-BuLi (2.6M in hexane, 1.26 mL, 3.3 mmol) dropwise. The reaction was stirred at -78 ^{o}C to -30 ^{o}C for an additional 1 h, D_2O (2.75 mL) was added to quench the reaction. The mixture was then separated; the organic layer was dried over anhydrous Na_2SO_4 and concentrated to dryness, affording the terminal deuterated alkyne product **37** with 97% deuterium incorporation, in quantitative yield, which was subjected directly to the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.39-0.45 (q, *J* = 16.04 Hz, 6H). 0.87 (t, *J* = 7.8 Hz, 9H), 3.16 (s, 2H), 7.22-7.39 (m, 10H).

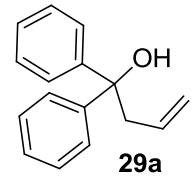
***(Z)*- Deuterium labeled (1,1-diphenylbut-3-en-1-yl)oxy-triehtylsilane (38):** To a flame-dried 30 mL round bottom flask with a stir bar under N_2 atmosphere was added Lindlar's catalyst (96.2 mg, 37 mg per mmol alkyne). The atmosphere was purged with N_2, and then toluene (2 mL), quinoline (0.798 mL, 2.6 equiv), and a solution of alkyne **37** (875 mg, 2.6 mmol 1.0 equiv) in toluene (8 mL) were added in that order. The N_2 line was replaced with a H_2 balloon, and the heterogeneous mixture was stirred vigorously and progress of reaction was monitored by TLC. After the completion of reaction, diluted with dichloromethane, filtered through a celite pad, concentrated in *vacuo* and the crude product was chromatographed on short silica gel column

with hexane to afford a terminal *cis*-deuterated olefin as major compound along with traces of *trans*-deuterated and non deuterated byproducts in non-separable mixture (92% yield, mixture of (Z)-**38a-*d* :** (*E*)-**38-*d* : 38-H**) ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.35-0.41 (q, *J* = 16.04 Hz, 6H). 0.85 (t, *J* = 8.24 Hz, 9H), 3.10-3.12 (broad dd, *J* = 6.44 Hz, *J* = 0.92 Hz, 2H), 4.89 (d, *J* = 10.56 Hz, 1H), 5.6-5.67 (m, 1H), 7.18-7.33 (m 10H).

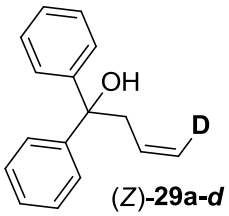
(*Z*)-Deuterium labeled-1,1-diphenylbut-3-en-1-ol (29a-*d*): To a solution of **38** (mixture of three compounds) (812 mg, 2.39 mmol) in THF (5 mL) was added 1M solution of TBAF in THF (5.5 mL, 5.5 mmol) at 0 ^{o}C. The resulting mixture was stirred for 1 h at room temperature. After the completion of reaction, H_2O was added and extracted with ether several times. The combined extracts were dried over Na_2SO_4 and evaporated to leave crude product, which was purified by column chromatography (silica gel, EtOAc/Hexane=1/100) to give (*Z*)-Deuterium labeled-1,1-diphenylbut-3-en-1-ol **29a-*d*** in 93% yield (in a ratio (Z)-**29a-*d*** : (*E*)-**29a-*d*** : **29a = 1 : 0.16 : 0.08**).

Characterization of starting materials:

1,1-Diphenyl-3-buten-1-ol (29a): Colorless oil; yield: 2.00 g (86%). IR (KBr): 3553, 3058, 2345, 1492, 1447, 1344, 1166, 991, 726, 699, 620 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 2.55 (s, 1H), 3.08 (dt, *J* = 7.3 Hz, *J* = 1.4 Hz, 2H), 5.16–5.27 (m, 2H), 5.61–5.71 (m, 1H), 7.20–7.24 (m, 2H), 7.29–7.33 (m, 4H), 7.43–7.46 (m, 4H). ^{13}C NMR (100 MHz, CDCl3): *δ* 46.6, 76.9, 120.5, 125.9, 126.8, 128.1, 133.3, 146.4. HRMS (APCI): *m/z* $[M–OH]^+$ calcd for $C_{16}H_{15}$: 207.1173; found: 207.1163.



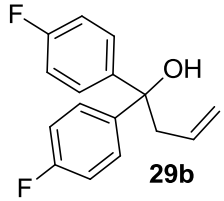
29a



(*Z*)-**29a-*d***

(*Z*)-**29a-*d***: ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 2.55 (s, 1H), 3.10–3.12 (br dd, *J* = 6.9 Hz, *J* = 0.9 Hz, 2H), 5.16 (d, *J* = 10.1 Hz, 1H), 5.61–5.70 (m, 1H), 7.20–7.46 (m, 10H).

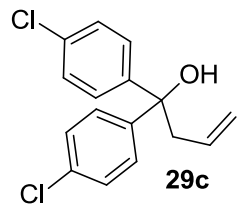
1,1-Bis(4-fluorophenyl)but-3-en-1-ol (29b): Colorless oil; yield: 2.46 g (93%). IR (KBr): 3548, 3077, 2980, 1896, 1602, 1508, 1344, 1227, 1160, 1013, 927, 835, 565 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 2.56 (s, 1H), 3.02 (dt, *J* = 7.3 Hz, *J* = 1.4 Hz, 2H), 5.19–5.27 (m, 2H), 5.57–5.67 (m, 1H), 6.96–7.02 (m, 4H), 7.36–7.41 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 46.8, 77.2, 115.0 (d, $J_{C\text{-}F}$ = 21.0 Hz), 121.0, 127.6 (d, $J_{C\text{-}F}$ = 8.6 Hz), 132.8, 142.1 (d, $J_{C\text{-}F}$ = 2.9 Hz), 161.7 (d,



29b

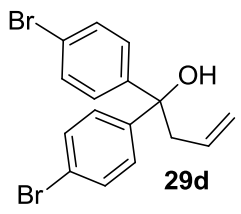
$J_{C\text{-}F}$ = 244 Hz). HRMS (APCI): *m/z* $[M–OH]^+$ calcd for $C_{16}H_{13}F_2$: 243.0985; found: 243.0976.

1,1-Bis(4-chlorophenyl)but-3-en-1-ol (29c): Colorless oil; yield: 2.84 g (95%). IR (KBr): 3631, 3548, 3076, 2925, 1903, 1638, 1489, 1401, 1093, 1012, 820, 755, 526 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.50 (s, 1H), 3.01 (dt, J = 7.3 Hz, J = 1.4 Hz, 2H), 5.19–5.27 (m, 2H), 5.56–5.66 (m, 1H), 7.59–7.29 (m, 4H), 7.33–7.37 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.4, 76.2, 121.2, 127.3, 128.4, 132.5, 132.9, 144.6. HRMS (APCI): *m/z* $[M–OH]^+$ calcd for $C_{16}H_{13}Cl_2$: 275.0394; found: 257.0384.



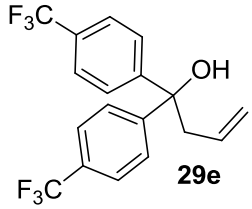
29c

1,1-Bis(4-bromophenyl)but-3-en-1-ol (29d): Colorless oil; yield: 2.72 g (70%). IR (KBr): 3547, 3076, 2924, 2372, 1904, 1485, 1397, 1163, 1074, 1008,746 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.55 (s, 1H), 3.00 (dt, J = 7.3 Hz, J = 1.4 Hz, 2H), 5.20–5.28 (m, 2H), 5.56–5.66 (m, 1H), 7.27–7.31 (m, 4H), 7.42–7.45 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.3, 76.2, 121.1, 121.3, 127.7, 131.3, 132.4, 145.0. HRMS (APCI): *m/z* $[M–OH]^+$ calcd for $C_{16}H_{13}Br_2$: 362.9383; found: 362.9374.85



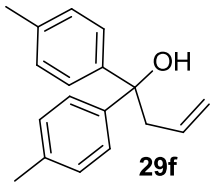
29d

1,1-Bis(4-(trifluoromethyl)phenyl)but-3-en-1-ol (29e): Colorless oil; yield: 2.20 g (60%). IR (KBr): 3553, 3081, 2934, 1617, 1413, 1326, 1125, 1016, 833, 509 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.60 (s, 1H), 3.10 (dt, J = 7.3 Hz, J = 1.4 Hz, 2H), 5.24–5.32 (m, 2H), 5.56–5.67 (m, 1H), 7.56–7.61 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.6, 76.6, 122.2, 122.9, 125.7 (q, $J_{C\text{-}F}$ = 3.8 Hz), 126.5, 129.8 (q, $J_{C\text{-}F}$ = 97.0 Hz), 132.3, 149.8. HRMS (APCI): No corresponding peaks were observed.



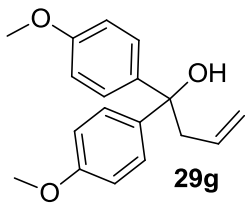
29e

1,1-Bis(4-methylphenyl)but-3-en-1-ol (29f): Colorless oil; yield: 1.93 g (75%). IR (KBr): 3554, 3024, 2921, 2345, 1638, 1510, 1439, 1163, 992, 815, 566 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.50 (s, 1H), 2.31 (s, 6H), 3.04 (dt, J = 7.3 Hz, J = 1.4 Hz, 2H), 5.15–5.26 (m, 2H), 5.62–5.72 (m, 1H), 7.10–7.13 (m, 4H), 7.31–7.34 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 46.7, 77.2, 120.2, 125.8, 128.8, 133.6, 136.3. 143.7. HRMS (APCI): *m/z* $[M–OH]^+$ calcd for $C_{18}H_{19}$: 235.1486; found: 235.1477.



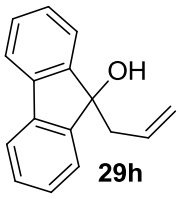
29f

1,1-Bis(4-methoxyphenyl)but-3-en-1-ol (29g): Colorless oil; yield: 2.54 g (85%). IR (KBr): 3503, 3073, 3002, 2934, 2835, 2050, 1509, 1440, 1345, 1247, 1177, 1034, 830, 577 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.50 (s, 1H), 3.00 (dt, J = 7.3 Hz, J = 1.4 Hz, 2H), 3.70 (s, 6H), 5.12–5.23 (m, 2H), 5.60–5.71 (m, 1H), 6.80–6.83 (m, 4H), 7.30–7.33 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.9, 55.3, 76.4, 113.3, 120.0, 127.1, 133.6, 139.0, 158.2. HRMS (APCI): m/z $[M–OH]^+$ calcd for $C_{18}H_{19}O_2$: 267.1385; found: 267.1373.



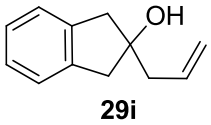
29g

9-Allyl-9H-fluoren-9-ol (29h): Colorless crystals; yield: 2.20 g (97%). IR (KBr): 3307, 3075, 2831, 1913, 1839, 1448, 1065, 997, 916, 768, 578 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.10 (s, 1H), 2.84 (dt, J = 7.3 Hz, J = 1.4 Hz, 2H), 4.94–4.99 (m, 2H), 5.55–5.65 (m, 1H), 7.28–7.39 (m, 4H), 7.53–7.63 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.0, 81.5, 118.7, 119.9, 123.8, 127.8, 128.9, 132.6, 134.3, 148.2. HRMS (APCI): m/z $[M–OH]^+$ calcd for $C_{16}H_{13}$: 205.1017; found: 205.1006.



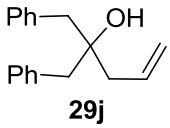
29h

2-Allyl-2,3-dihydro-1H-inden-2-ol (29i): Brown oil. Yield: 800 mg (45%). IR (KBr): 3401, 3072, 2902, 1639, 1481, 1275, 916, 740, 599 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.89 (s, 1H), 2.52 (br d, J = 7.4 Hz, 2H), 2.95 (d, J = 16.0 Hz, 2H,) 3.09 (d, J = 16.0 Hz, 2H), 5.19–5.24 (br m, 2H), 5.92–6.03 (m, 1H), 7.15–7.22 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.9, 46.4, 81.4, 119.0, 124.9, 126.5, 133.9, 141.1. HRMS (APCI): m/z $[M–OH]^+$ calcd for $C_{12}H_{13}$: 157.1017; found: 157.1007.



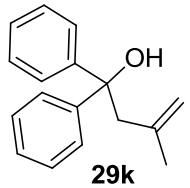
29i

2-Benzyl-1-phenylpent-4-en-2-ol (29j): Colorless oil; yield; 1.98 g (77%). IR (KBr): 3568, 3475, 3062, 2977, 1638, 1494, 1364, 1058, 916, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.44 (s, 1H), 2.00 (dt, J = 7.3 Hz, J = 1.4 Hz, 2H), 2.70 (s, 4H,) 5.00–5.05 (m, 1H), 5.10–5.13 (m, 1H), 5.82–5.92 (m, 1H), 7.15–7.25 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.0, 45.5, 73.7, 118.9, 126.4, 128.1, 130.7, 134.0, 137.2. HRMS (APCI): m/z $[M–OH]^+$ calcd for $C_{18}H_{19}$: 235.1486; found: 235.1476.



29j

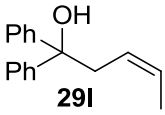
3-Methyl-1,1-diphenylbut-3-en-1-ol (29k): White solid; yield: 616 mg (45%). IR (KBr): 3058, 2345, 1638, 1491, 1447, 1056, 901, 741 35 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 3H), 2.89 (s, 1H), 3.11 (s, 2H), 4.80–4.81 (m, 1H), 4.94–4.96 (m, 1H), 7.18–7.22 (m, 2H), 7.27–7.32 (m, 4H). 7.45-7.48 (m, 4H). ^{13}C



29k

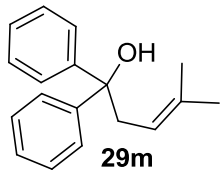
NMR (100 MHz, $CDCl_3$): δ 24.2, 49.8, 75.8, 116.7, 125.8, 126.7, 128.0, 142.2, 146.9. HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{17}H_{18}NaO_3$: 261.1255; found: 261.1248.

(Z)-1,1-diphenylpent-3-en-1-ol (29l): Colorless oil; yield: 0.37g (86%). ^1H NMR (400 MHz, $CDCl_3$): δ 1.66-1.68 (m, 3H), 2.51 (s, 1H), 3.08 (d, J = 7.32 Hz, 2H), 5.27–5.34 (m, 1H), 5.66-5.74 (m, 1H), 7.19–7.24 (m, 2H), 7.29–7.33 (m, 4H), 7.43–7.47 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.2, 34.4, 77.6, 124.5 (2C), 125.9, 126.7 (2C), 128.1, 129.5 (2C), 146.6 (2C).



29l

4-Methyl-1,1-diphenylpent-3-en-1-ol (29m): Pale green oil; yield: 1.35 g (98%). IR (KBr): 3537, 2914, 1662, 1492, 1376, 1266, 1168, 1054, 753, 643 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.69 (s, 6H), 2.56 (s, 1H), 3.02 (d, J = 7.32 Hz, 2H), 5.02–5.07 (m, 1H), 7.20–7.24 (m, 2H), 7.29–7.33 (m, 4H), 7.44–7.47 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.2, 26.1, 40.7, 77.6, 118.3, 125.9, 126.6, 128.0, 137.9, 146.9. HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{18}H_{20}NaO$: 275.1411; found: 275.1402.



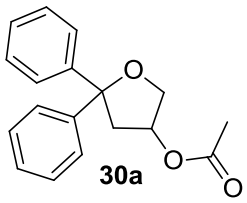
29m

2.4.3 Experimental Procedure for the Pd-Catalyzed Cyclization of homoallyl alcohols

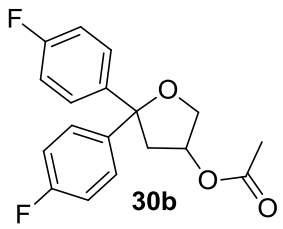
A solution of $PdCl_2(MeCN)_2$ (4.6 μmol, 10 mol%) and (*P,R,R*)-*i*-Pr-SPRIX (6.6 μmol, 15 mol%) in dry CH_2Cl_2 (0.5 mL) was stirred at 25 °C for 2 h. The volatiles were then removed by evaporation to afford Pd–*i*-Pr-SPRIX complex as a yellow powder. Into the vessel containing the complex was added a solution of TfOH (8.2 μmol, 18 mol%) in DME (0.15 mL) [prepared by mixing 1.5 mL of DME and 7.2 μL of TfOH] and the resulting mixture was stirred for 5 min at 25 °C. To this suspension was added $PhI(OAc)_2$ (0.137 mmol, 3 equiv) followed by alkenyl alcohol substrates **29** (0.046 mmol) dissolved in AcOH (0.15 mL), which was stirred at 25 °C for 4 h unless otherwise mentioned. After completion of the reaction, the solvents were evaporated under reduced pressure. The residue was purified by column chromatography on silica gel by using hexane/ethyl acetate = 99.3/0.7 to afford 3-acetoxy-tetrahydrofurans **30**.

Characterization of 3-acetoxy-tetrahydrofurans (30):

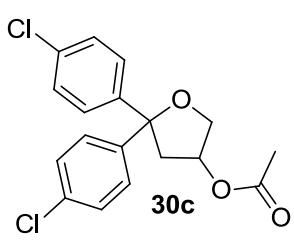
5,5-Diphenyltetrahydrofuran-3-yl acetate (30a): Colorless wax; yield: 11.5 mg (92%); 90% ee [HPLC (Chiralpak AD-H, hexane/EtOH = 99.5/0.5, flow rate = 1 mL/min, λ = 220 nm): 10.8 min (minor), 13.7 min (major)]; $[\alpha]_D^{22}$ +16.92 (*c* 0.26, $CHCl_3$). IR (KBr): 3058, 2963, 2372, 2345, 1737, 1448, 1365, 1238, 1082, 1049, 1020, 701, 535 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.91 (s, 3H), 2.73 (dd, J = 13.8 Hz, J = 3.2 Hz, 1H), 3.04 (dd, J = 13.8 Hz, J = 7.3 Hz, 1H), 4.01 (dd, J = 10.5 Hz, J = 2.8 Hz, 1H), 4.17 (dd, J = 10.5 Hz, J = 5.9 Hz, 1H), 5.26–5.30 (m, 1H), 7.17–7.24 (m, 2H), 7.27–7.33 (m, 4H), 7.41–7.43 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 44.9, 71.7, 75.2, 87.8, 125.6, 127.7, 126.8, 127.0, 128.1, 128.3, 145.0, 145.6, 170.8. HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{18}H_{18}NaO_3$: 305.1153; found: 305.1174.



5,5-Bis(4-fluorophenyl)tetrahydro-furan-3-yl acetate (30b): Colorless wax; yield: 12.2 mg (86%); 88% ee [HPLC (Chiralpak AD-H, hexane/EtOH = 99.5/0.5, flow rate = 1 mL/min, λ = 220 nm): 15.3 min (minor), 19.9 min (major)];$[\alpha]_D^{25}$ +20.22 (*c* 0.267, $CHCl_3$). IR (KBr): 2964, 2878, 2372, 2345, 1738, 1602, 1508, 1408, 1366, 1234, 1159, 1076, 1014, 835, 561, 540 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.92 (s, 3H), 2.70 (dd, J = 13.7 Hz, J = 3.2 Hz, 1H), 2.9 (dd, J = 13.7 Hz, J = 6.8 Hz, 1H), 4.0 (dd, J = 10.5 Hz, J = 2.7 Hz, 1H), 4.15 (dd, J = 10.5 Hz, J = 5.9 Hz, 1H), 5.26–5.30 (m, 1H), 6.95–7.02 (m, 4H), 7.33–7.38 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 45.1, 71.8, 75.1, 87.1, 114.9 (d, $J_{C\text{-}F}$ = 31.4 Hz), 115.4 (d, $J_{C\text{-}F}$ = 30.5 Hz), 127.4 (d, $J_{C\text{-}F}$ = 3.8 Hz), 127.5 (d, $J_{C\text{-}F}$ = 2.9 Hz), 140.7 (d, $J_{C\text{-}F}$ = 2.8 Hz), 141.2 (d, $J_{C\text{-}F}$ = 2.8 Hz), 160.6 (d, $J_{C\text{-}F}$ = 15.2 Hz), 163.0 (d, $J_{C\text{-}F}$ = 15.2 Hz), 170.7. HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{18}H_{16}F_2NaO_3$: 341.0965; found: 341.0955.

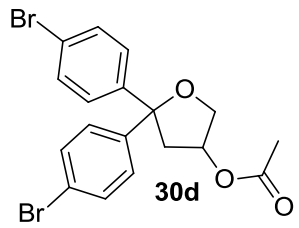


5,5-Bis(4-chlorophenyl)tetrahydro-furan-3-yl acetate (30c): Colorless wax; yield: 13.0 mg (83%); 79% ee [HPLC (Chiralpak AD-H, hexane/EtOH = 99.5/0.5, flow rate = 1 mL/min, λ = 227 nm): 20.0 min (minor), 26.1 min (major)]; $[\alpha]_D^{24}$ +9.68 (*c* 0.95, $CHCl_3$). IR (KBr): 2928, 2372, 2345, 1738, 1490, 1237, 1092, 1012, 831, 537 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.91 (s, 3H), 2.70 (dd, J = 13.7 Hz, J = 3.2 Hz, 1H), 2.9 (dd, J = 13.7 Hz, J = 6.8 Hz, 1H), 4.0 (dd, J = 10.5 Hz, J = 2.7 Hz, 1H),



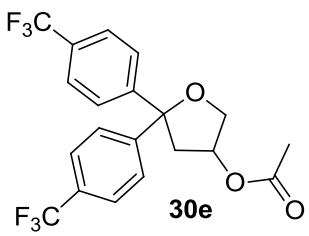
4.15 (dd, J = 10.5 Hz, J = 5.5 Hz, 1H), 5.25–5.30 (m, 1H), 7.25–7.28 (m, 4H), 7.30–7.34 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 44.8, 71.9, 75.0, 87.0, 127.0, 127.0, 128.3, 128.6, 132.9, 133.2, 143.3, 143.8, 170.7. HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{18}H_{16}C_{l2}NaO_3$: 373.0374; found: 373.0364.

5,5-Bis(4-bromophenyl)tetrahydro-furan-3-yl acetate (30d): Colorless wax; yield: 15.4 mg (79%); 78% ee [HPLC (Chiralpak AD-H, hexane/EtOH = 99.5/0.5, flow rate = 1 mL/min, λ = 221 nm): 24.2 min (minor), 34.8 min (major)]; $[\alpha]_D^{23}$ +10.25 (*c* 1.12, $CHCl_3$). IR (KBr): 2973, 2877, 2372, 2345, 1737, 1486, 1365, 1238, 1077, 1008, 821, 738, 534 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.91 (s, 3H), 2.68 (dd, J = 13.7 Hz, J = 3.2 Hz, 1H), 2.92 (dd, J = 13.7 Hz, J = 6.8 Hz, 1H), 4.0 (dd, J = 10.5 Hz, J = 2.8 Hz, 1H), 4.14 (dd, J = 10.5 Hz, J = 5.9 Hz, 1H), 5.25–5.30 (m, 1H), 7.24–7.28 (m, 4H), 7.40–7.45 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 44.7, 71.9, 74.9, 87.1, 121.0, 121.3, 127.4, 127.4, 131.3, 131.5, 143.8, 144.2, 170.7. HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{18}H_{16}Br_2NaO_3$: 460.9363; found: 460.9358.



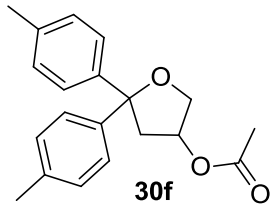
30d

5,5-Bis(4-(trifluoromethyl)phenyl)-tetrahydrofuran-3-yl acetate (30e): Colorless wax; yield: 13 mg (70%); 44% ee [HPLC (Chiralpak AD-H, hexane/EtOH = 99.5/0.5, flow rate = 1 mL/min, λ = 221 nm): 11.6 min (minor), 16.2 min (major)]; $[\alpha]_D^{24}$ +2.14 (*c* 0.28, $CHCl_3$). IR (KBr): 2936, 2372, 2345, 1741, 1617, 1412, 1367, 1325, 1238, 1165, 1122, 1069, 1016, 847, 606, 522 cm^{-1}. 1H NMR (400 MHz, $CDCl_3$): δ 1.87 (s, 3H), 2.82 (dd, J = 13.7 Hz, J = 2.7 Hz, 1H), 2.98 (dd, J = 13.7 Hz, J = 6.8 Hz, 1H), 4.04 (dd, J = 10.5 Hz, J = 2.7 Hz, 1H), 4.19 (dd, J = 10.5 Hz, J = 5.5 Hz, 1H), 5.28–5.32 (m, 1H), 7.53–7.59 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.7, 44.8, 72.2, 74.8, 87.2, 122.5, 122.6, 125.3 (q, $J_{C\text{-}F}$ = 3.8 Hz), 125.6 (q, $J_{C\text{-}F}$ = 3.8 Hz), 125.95, 125.98, 129.4 (q, $J_{C\text{-}F}$ = 32.4 Hz), 129.7 (q, $J_{C\text{-}F}$ = 32.4 Hz), 148.5, 148.9, 179.6. HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{20}H_{16}F_6NaO_3$: 441.0901; found: 441.0894.

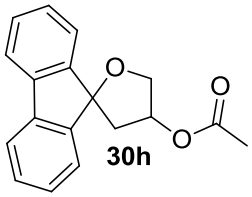


30e

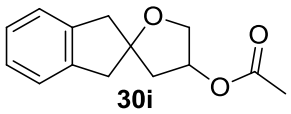
5,5-Bis(4-methylphenyl)tetrahydro-furan-3-yl acetate (30f): Colorless wax; yield: 4.1 mg (30%); 90% ee [HPLC (Chiralpak AD-H, hexane/EtOH = 99.7/0.3, flow rate = 1 mL/min, λ = 219 nm): 20.3 min (minor), 23.9 min (major)]; $[\alpha]_D^{23}$ +11 (*c* 0.218, $CHCl_3$). IR (KBr): 2923, 2372, 2345, 1737, 1509, 1439, 1325, 1238, 1075, 1019, 813, 564, cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.93 (s, 3H), 2.29 (s, 3H), 2.30 (s, 3H), 2.65 (dd, *J* = 13.7 Hz, *J* = 3.7 Hz, 1H), 3.02 (dd, *J* = 13.7 Hz, *J* = 6.9 Hz, 1H), 4.0 (dd, *J* = 10.5 Hz, *J* = 2.8 Hz, 1H), 4.1 (dd, *J* = 10.5 Hz, *J* = 6.0 Hz, 1H), 5.23–5.28 (m, 1H), 7.07–7.11 (m, 4H), 7.26–7.29 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.92, 20.94, 20.94, 44.9, 71.5, 75.4, 87.7, 125.6, 125.7, 128.7, 129.0, 136.3, 136.6, 142.2, 142.9, 170.9. HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{20}H_{22}NaO_3$: 333.1466; found: 333.1463.



4',5'-Dihydro-3'H-spiro[fluorene-9,2'-furan]-4'-yl acetate (30h): The reaction was performed at –10 °C for 96 h. Pale yellow solid; yield: 10.6 mg (85%); 50% ee [HPLC (Chiralpak AD-H, hexane/EtOH = 98/2, flow rate = 1mL/min, λ = 298 nm): 17.3 min (minor), 24.5 min (major)]; $[\alpha]_D^{24}$ –10.68 (*c* 0.5, $CHCl_3$). IR (KBr): 3061, 2930, 2858, 2345, 1737, 1449, 1375, 1236, 1152, 1070, 1048, 759, 505 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.22 (s, 3H), 2.54 (dd, *J* = 14.6 Hz, *J* = 3.6 Hz, 1H), 2.85 (dd, *J* = 14.6 Hz, *J* = 3.2 Hz, 1H), 4.35 (dd, *J* = 10.5 Hz, *J* = 3.2 Hz, 1H), 4.50 (dd, *J* = 10.5 Hz, *J* = 3.6 Hz, 1H), 5.70–5.74 (m, 1H), 7.26–7.43 (m, 5H), 7.59–7.60 (m, 2H), 7.07–7.70 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 42.6, 74.3, 75.9, 77.2, 89.8, 119.8, 119.9, 123.2, 124.4, 128.1, 128.2, 129.0, 129.1, 139.6, 147.8, 148.7, 170.7. HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{18}H_{16}NaO_3$: 303.0997; found: 333.0991.

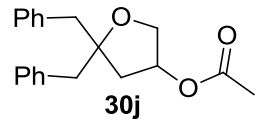


1',3',4,5-Tetrahydro-3H-spiro[furan-2,2'-inden]-4-yl acetate (30i): The reaction was performed at –10 °C for 50 h. Colorless wax; yield: 7.7 mg (75%); 37% ee [HPLC (Chiralpak AD-H, hexane/EtOH = 98/2, flow rate = 1 mL/min, λ = 216 nm): 12.5 min (major), 17.1 min (minor)]; $[\alpha]_D^{24}$ –56 (*c* 0.05, $CHCl_3$). IR (KBr): 3022, 2940, 2372, 2345, 1737, 1480, 1432, 1365, 1240, 1150, 1098, 1057, 1022, 742, 506 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.10 (s, 3H), 2.18 (dd, *J* = 14.2 Hz, *J* = 2.3Hz, 1H), 2.35 (dd, *J* = 14.2 Hz, *J* = 6.8 Hz, 1H), 3.03 (d, *J* = 16.0 Hz, 1H), 3.10 (d, *J* = 16.4 Hz, 1H), 3.16 (d, *J* = 16.0 Hz, 1H), 3.23 (d, *J* = 16.4 Hz, 1H), 3.89 (dd, *J* = 10.5 Hz, *J* = 2.3 Hz, 1H), 4.14 (dd, *J* = 10.5 Hz, *J* = 5.0 Hz, 1H), 5.33–5.38 (m, 1H), 7.12–7.20 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 42.4, 45.0, 45.2, 72.3, 75.4, 90.9,



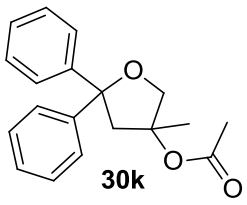
124.5, 124.6, 126.57, 126.61, 140.9, 141.3, 170.9. HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{14}H_{16}NaO_3$: 255.0997; found: 255.0990.90

5,5-Dibenzyltetrahydrofuran-3-yl acetate (30j): The reaction was performed at –10 °C for 12 h. Colorless wax; yield: 7.6 mg (55%); 54% ee [HPLC (Chiralpak IC, hexane/EtOH = 99.7/0.3, flow rate = 0.5 mL/min, λ = 219 nm): 21.0 min (major), 25.8 min (minor)]; $[\alpha]_D^{24}$ –13.45 (*c* 0.055, $CHCl_3$). IR (KBr): 3027, 2922, 2863, 2372, 2345, 1737, 1453, 1244, 1108, 1082, 1052, 1021, 701, 517 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.92 (s, 3H), 1.94 (dd, J = 14.2 Hz, J = 2.7 Hz, 1H), 2.10 (dd, J = 14.2 Hz, J = 3.2 Hz, 1H), 2.71 (d, J = 13.8 Hz, 1H), 2.88 (d, J = 13.8 Hz, 1H), 2.94 (d, J = 13.8 Hz, 1H), 2.98 (d, J = 13.8 Hz, 1H), 3.73 (d, J = 3.7 Hz, 2H), 4.84–4.89 (m, 1H), 7.20–7.32 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 38.5, 44.8, 46.1, 72.2, 75.4, 85.8, 126.3, 126.4, 127.99, 128.03, 130.75, 130.84, 137.3, 137.7, 170.7. HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{20}H_{22}NaO_3$: 333.1466; found: 333.1459.



30j

3-Methyl-5,5-diphenyltetrahydrofuran-3-yl acetate (30k): Colorless wax; yield: 6.1 mg (56%); racemic [HPLC (Chiralpak As-H, hexane, flow rate = 1 mL/min, λ= 221 nm): 18.3 min, 22.86 min]. IR (KBr): 3058, 2345, 1735, 1490, 1448, 1368, 1242, 1058, 738, 701, 494 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.55 (s, 3H), 1.68 (s, 3H), 2.73 (d, J = 13.8 Hz, 1H), 3.39 (d, J = 13.8 Hz, 1H), 3.95 (d, J = 10.1 Hz, 1H), 4.26 (d, J = 10.1 Hz, 1H), 7.14–7.21 (m, 2H), 7.27–7.31 (m, 4H), 7.41–7.46 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 22.4, 50.7, 77.3, 87.2, 87.9, 125.4, 125.4, 126.5, 126.8, 128.1, 128.3, 146.0, 146.1, 170.6. HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{19}H_{20}NaO_3$: 319.1310; found: 319.1301.



30k

2.5 References

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2. A similar reaction using Pd–NHC catalysts (NHC = N-heterocyclic carbine ligand) has been reported. See: Wang, W.; Wang, F.; Shi, M. *Organometallics,* **2010**, *29*, 928.
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9. A similar reaction using Pd–NHC catalysts (NHC = N-heterocyclic carbene ligand) has been reported. See: Wang, W.; Wang, F.; Shi, M. *Organometallics*, **2010**, *29*, 928.
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13. Dohi, S.; Moriyama, K.; Togo, H. *Tetrahedron* **2012,** 68, 6557-6564.)

Chapter 3

Carbonylation of Propargyl Carbamates with Palladium-SPRIX Catalysis: Towards Efficient Synthesis of 5-Methoxy-3(2*H*)-furanones

{This research was performed in collaboration with Prof. K. Kato, Toho University, Chiba, Japan.}

3.1 Introduction

3(2H)-Furanones are structural motifs that are widely present in natural products and medicinally important agents (figure 3.1). Due to the importance of the chiral furanones in biologically active compounds, the asymmetric construction of furanones or its derivatives are demanding and challenging task.

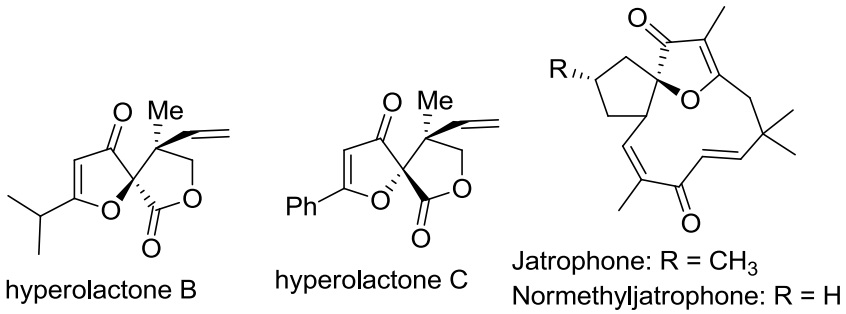
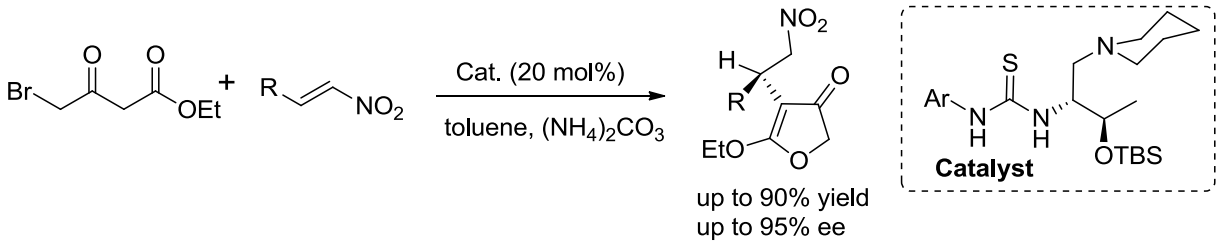


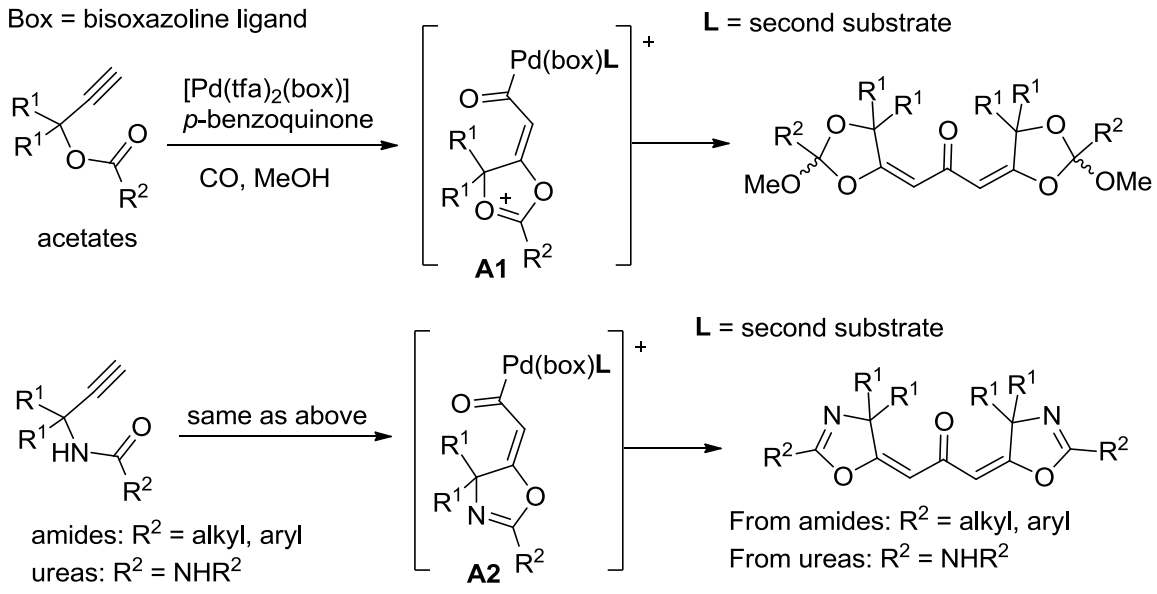
Figure 3.1 Representative examples of chiral furanone motifs

A number of approaches towards the synthesis of 3(2H)-Furanones have been established including metal-mediated cyclization of alkynyl substrates, [1a-e] transformations from furans, [1f-g] cyclization of dienes or alkynes,[1h-k] and cycloisomerization of allenes.[1l] However, most of the above reactions require the employment of specific substrates and the reaction conditions are often harsh. Organocatalytic asymmetric synthesis of 3(2H)-Furanone derivatives was reported by Lu and coworkers by using α-halo-1,3-diketone and nitroolefin (scheme 3.1).[2]



Scheme 3.1.Organo catalyzed asymmetric approach towards furanone derivatives

The transition metal catalyzed reaction of unsaturated systems has recently proven to be a powerful method for the construction of a variety of carbo- and heterocycles. Recently Kato and coworkers reported the cyclization/carbonylation/cyclization-coupling reaction (CCC-coupling reaction) of propargyl acetates, amides, ureas,[3a-b] γ-propynyl-1,3-diketones[3c], N-propargyl anilines, and *o*-alkynylphenols[3d] catalyzed by palladium(II) bisoxazoline (box) complexes (scheme 3.1.1)

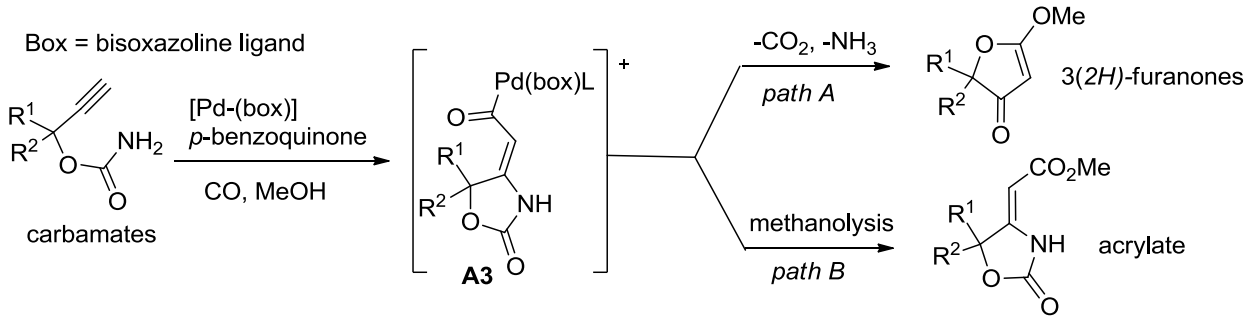


Scheme 3.1.1. CCC-coupling reaction (Kato and et al previous work)

The symmetrical ketones bearing two heterocycle were obtained in presence of palladium and box ligand. In this reaction, box ligand play crucial role in second coordination of the triple bond to the intermediate **A1** or **A2** by enhancing the π-electrophilicity of palladium(II), and thus leading to the dimerization. In short, box ligand suppresses the methanolysis of acyl palladium intermediate **A1** and **A2**.

Hypothesis:

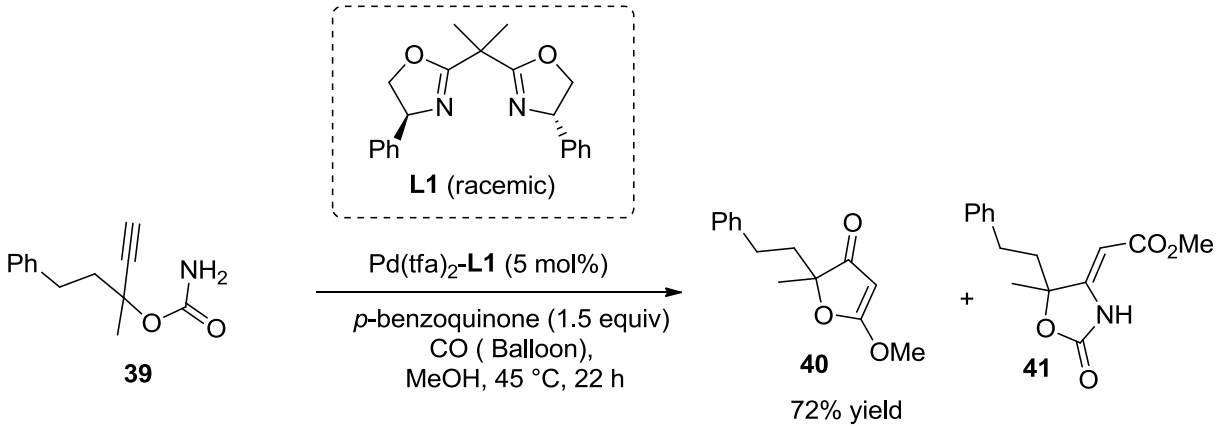
This concept can be utilized for carbamate substrate under (box-Pd^{II})-catalyzed carbonylation condition, which could expect new type of cascade reaction. As shown in scheme 3.1.2, acyl palladium intermediate **A3** should be produced and methanolysis should be suppressed. If the rate of decarboxylation of **A3** is fast compared to that of CCC-coupling reaction, a new product is expected (path A).



Scheme 3.1.2. Pd-box catalysis of carbamate

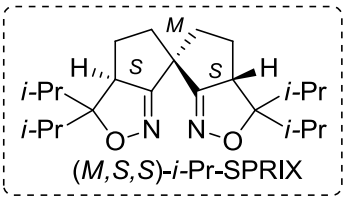
3.2 Result and Discussion

Kato and coworkers performed the reaction of carbamate **39** in presence of [$Pd(tfa)_2$-**L1**], *p*-benzoquinone and CO (1atm) in methanol solvent at 45°C, according to hypothesis, the reaction resulted in a new reaction pathway to afford the 5-methoxy-3(*2H*)-furanones **40** in 72% yield without detection of acrylate product **41** (scheme 3.2).



Scheme 3.2 Pd-box catalyzed carbonylation of carbamate **39**

Pd-SPRIX catalyzed carbonylative cyclization of carbamate:



The successful application of SPRIX ligand in activation of olefin as well as alkyne, motivated for its further application in carbonylative cyclization of carbamates. In order to develop asymmetric catalysis in this reaction, enantiopure SPRIX [(*M,S,S*)-*i*-Pr-SPRIX] ligand was supposed to be effective due its rigid structure and coordinating ability to palladium. For the development of enantioselective cyclization of carbamate using (*M,S,S*)-*i*-Pr-SPRIX towards synthesis of chiral compound **40**, starting material 3-methyl-5-phenylpent-1-yn-3-yl carbamate **39** was selected as a model substrate.

Optimization study

3.2.1 Pd source screening

Initial optimization study was started with palladium source screening by using model substrate 3-methyl-5-phenylpent-1-yn-3-yl carbamate **39** (racemic). The reaction was performed in presence of palladium (10 mol%), racemic SPRIX (15 mol%), *p*-benzoquinone (2 equiv), CO:N_2 (1:1), in methanol at 25 °C for 12 h (Table 3.2.1). When carbamate was treated with $PdCl_2(MeCN)_2$ the desired product 5-methoxy-3(*2H*)-furanone **40** was afforded in 17% yield along with acrylate **41** in 3% yield (Table 3.2.1. entry 1).

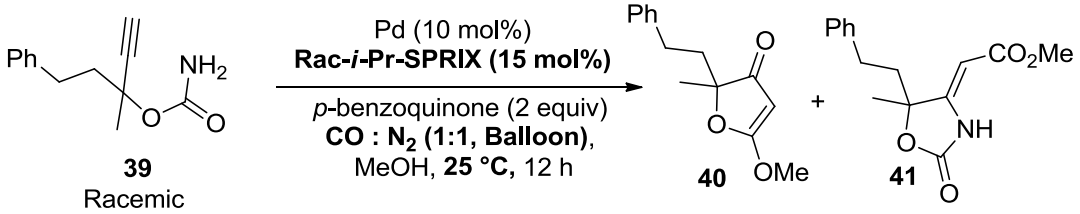


Table 3.2.1

Entry	**Pd source**	Yield (%)[a]	
		40	**41**
1	$PdCl_2(MeCN)_2$	17	3
2	$Pd(MeCN)_4(BF)_4$	14	13
3	$PdCl_2(PhCN)_2$	28	12
4	$Pd(OTf)_2$	7	8
5[b]	**$PdCl_2(PhCN)_2$**	**28 (17% ee)**	**12**

[a] Isolated yield. [b] Reaction were performed by using (*M,S,S*)-*i*-Pr-SPRIX

Various palladium sources were tested under similar condition such as $Pd(MeCN)_4(BF)_4$, $PdCl_2(PhCN)_2$ and $Pd(OTf)_2$ (entry 2-4). Among these palladium tested, $PdCl_2(PhCN)_2$ was effective which yielded corresponding product **40** in 28% and **41** in 12% respectively (entry 3). When reaction was performed by using enantiopure (*M,S,S*)-*i*-Pr-SPRIX and $PdCl_2(PhCN)_2$, the furanone compound **40** was afforded in 17% enantiopurity. These results explain the ability of SPRIX ligand compared to box ligand in carbonylative cyclization of carbamates.

3.2.2 Effect of concentration of CO

Optimization study was continued with $PdCl_2(PhCN)_2$ and (*M,S,S*)-*i*-Pr-SPRIX. Our previous experience in carbonylation reactions catalyzed by Pd-SPRIX shows that carbon monoxide interfere the Pd-SPRIX complex by ligand exchange. So, the reactions were performed by using mixture of carbon monoxide and nitrogen (Table 3.2.2). In the absence of CO, reaction could not be promoted and starting material was recovered (entry1). Where as, in presence of only CO, desired product **40** was obtained in 18% yield with 9% of **41** (entry 2). Next, the reactions were performed by applying various

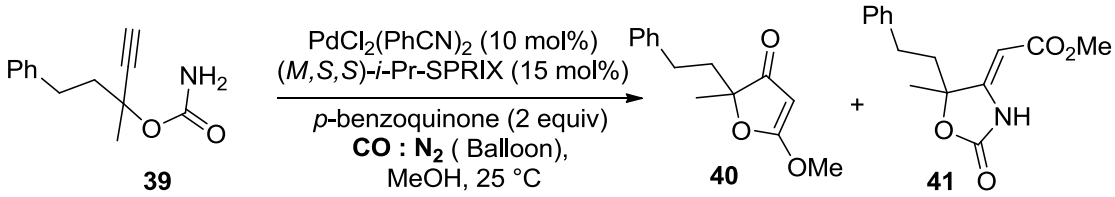


Table 3.2.2

Entry	**CO/N_2**	Time (h)	Yield (%)[a]		Ee of **40** (%)[b]
			40	**41**	
1	**-**	12	NR	NR	
2	100/0	8	18	9	17 (In all cases)
3	1/1	12	28	12	
4	1/2	12	28	4	
5	**1/3**	**12**	**30**	**5**	
6	1/6	12	17	8	

[a] Isolated yield. [b] Determined by HPLC analysis (Chiralpak AD-H)

combinations of CO and N_2 (entry 3-6). When reaction was performed in presence of CO:N_2 in 1:3 ratio, 5-methoxy-3(2H)-furanone **40** was obtained in 30% yield and 17% ee along with acrylate **41** in only 5% (entry 5). Where as decreasing the concentration of CO, the yield of desired product **40** decreased (entry 6).

3.2.3 Temperature effect

Effect of temperature was studied as shown in table 3.2.3. The reaction was sluggish at lower temperature, when the reaction was promoted at 0 °C for longer reaction time (96 h), giving the desired product **40** in 24% yield and 12% ee (entry 1). At -20 °C, reaction could not complete within 100 h, and only 66% conversion was observed (entry 2).

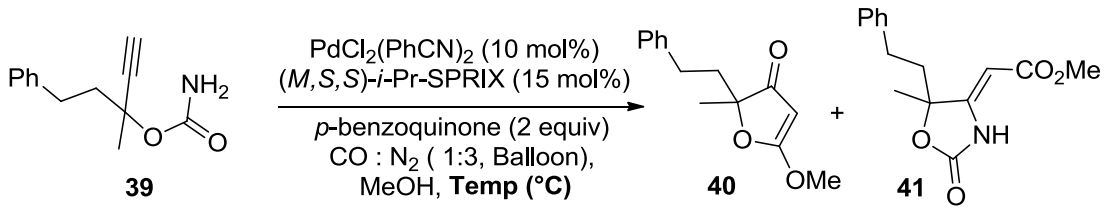


Table 3.2.3

Entry	**Temp. (°C)**	Time (h)	Conversion	Yield (%)[a]		Ee of **40** (%)[b]
				40	**41**	
1	0	96	100%	24	8	12
2	-20	100	66%	4	ND	12
3	**25**	**12**	**100%**	**30**	**5**	**17**
4	45	4	100%	19	5	20

[a] Isolated yield. [b] Determined by HPLC analysis (Chiralpak AD-H)

At higher temperature (45 °C), reaction was faster and consumption of starting material was 100%, but only 19% of 3-(*2H*)-furanone **40** was obtained with 20% ee (entry 4). The appropriate temperature was found to be 25 °C, which gives desired product **40** in 30% yield and 17% ee along with negligible amount of acrylate product **41** (entry 3).

3.2.4 Catalyst loading

I performed further optimization of the reaction conditions in regards to the ligand/metal ratio and amount of catalyst (Table 3.2.4). When reaction was performed in presence of high catalyst

loading such as 30-20 mol% in various metal/ligand ratios, the desired product was not observed (entry 1-3). The reason is, under the particular concentration, Pd-SPRIX complexation was not occurred effectively, and only palladium could promote the reaction affording trace amount of undesired product **41**. At lower catalyst loading such as 10 mol% palladium and 20 mol% SPRIX, the reaction completed in 6 h, affording the product **40** in 28% yield and 14% ee (entry 4). The better reaction outcome was observed by lowering the metal/ligand ratio (entry 5-7).

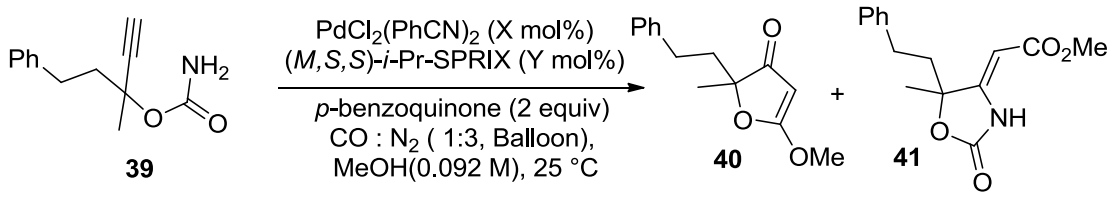


Table 3.2.4

Entry	**Pd/Ligand (mol%)**	Time (h)	Yield (%)[a]		Ee of **40** (%)[b]
			40	**41**	
1	30/35	4	Not observed	3	-
2	20/35	1.5	Not observed	Trace	-
3	20/25	4	Not observed	4	-
4	10/20	6	28	7	14
5	10/15	8	30	5	17
6	5/15	12	20	6	20
7	**5/7.5**	**18**	**25**	**4**	**20**
8	2/6	>12	Reaction is very sluggish, almost no reaction		

[a] Isolated yield. [b] Determined by HPLC analysis (Chiralpak AD-H)

The catalyst loading could be lowered to 5 and 7.5 mol% of palladium and SPRIX, which could catalyze efficiently the reaction to afford the product **40** in 25% yield and 20% ee in 18h. Where as very low catalyst loading (Pd/SPRIX: 2/6) makes the reaction very sluggish even reaction was allowed to run for more than 12 h, and starting material was recovered (entry 8). The results depicted in table 3.2d indicate that an excess amount of Pd-SPRIX retards the reaction.

3.2.5 Effect of co-solvent

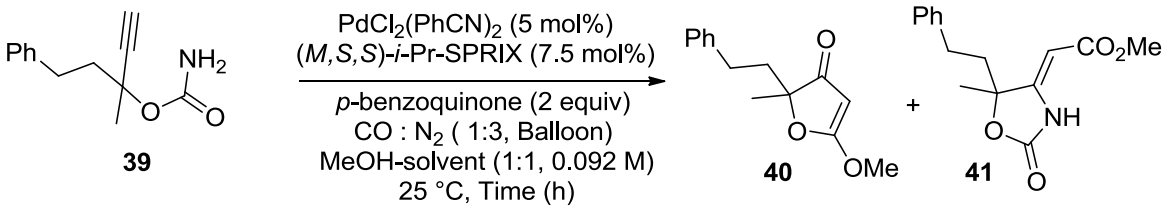


Table 3.2.5

Entry	**Solvent**	Time (h)	Yield (%)[a]		Ee of **40** (%)[b]
			40	**41**	
1	MeOH	12	25	4	20
2	MeOH-DME	12	35	ND	18
3	MeOH-Toluene	12	42	Trace	13
4	MeOH-THF	12	28	5	16
5	MeOH-Et_2O	12	25	3	15
6	MeOH-CPME	12	26	6	12
7	MeOH-Diglyme	12	38	ND	16
8	MeOH-DCM	12	24	11	12
9	MeOH-Benzene	6	29	5	12
10	MeOH-Dioxane	24	30	3	16
11	MeOH-Acetone	24	32	7	20
12	**MeOH-MeCN**	**24**	**39**	**6**	**24**

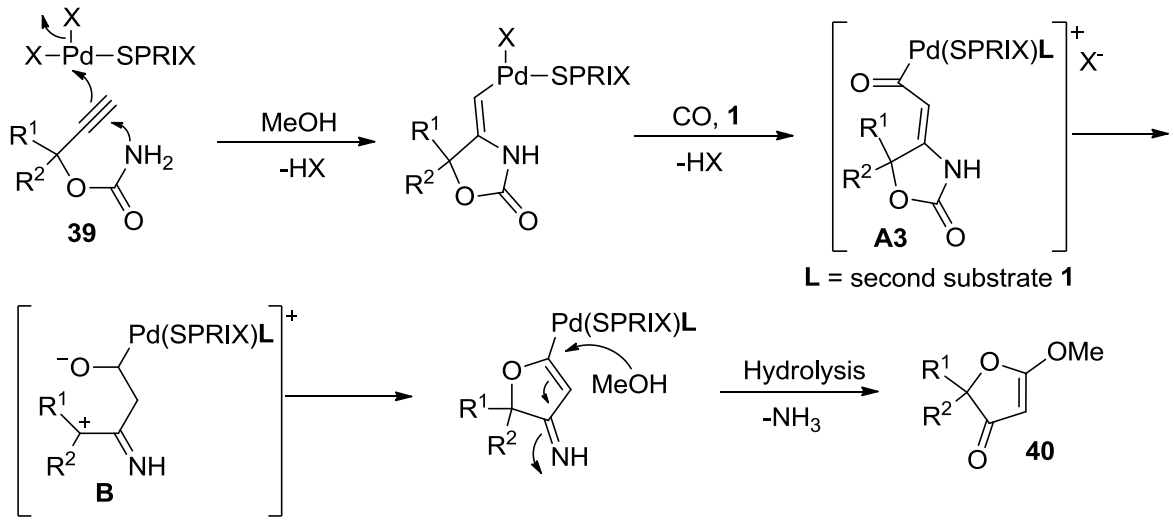
[a] Isolated yield. [b] Determined by HPLC analysis (Chiral Pack AD-H)

Methanol as a solvent is necessary for methoxide source, and optimization study were performed using MeOH as a sole solvent. In order to further optimize reaction conditions, reactions were carried out in methanol and co-solvent systems (Table 3.2e). Various co-solvents with methanol in 1:1 ratio were tested (table 3.2e, entry 1-12). Mixed solvent system showed positive effect on reaction outcome. The reaction in MeOH-DME gives desired product **40** with improved yield (35%, 18% ee) and undesired product **41** was not detected (entry 2). The mixed MeOH-toluene solvent system increases the yield up to 42% but enantioselectivity remained only 13% (entry 3).

Other ethereal and chlorinated co-solvents were screened, but none of these improved yield or selectivity (entry 4-11). The acetonitrile as co-solvent shows better result, which affords 5-methoxy-3(*2H*)-furanone **40** in 39% yield and 24% ee (entry 12).

3.3 Mechanism

A plausible mechanism for the reaction of propargyl carbamate **39** is shown in scheme 3.3. The triple bond of the substrate coordinates to palladium (II) and undergoes nucleophilic attack by the intramolecular nucleophilic nitrogen atom followed by CO insertion to produce the acyl palladium intermediate **A3**. Next, a rapid decarboxylation may take place to generate zwitterionic intermediate **B,** which then cyclizes and is followed by addition of methanol and subsequent hydrolysis of the imine moiety, thus producing the 5-methoxy-3(*2H*)-furanone **40**. The box ligand promotes coordination of the second substrate (L) to acyl palladium intermediate **A3**, thus preventing the methanolysis. In addition, the cationic Pd^{II} center in **A3** is more electrophilic and thus stimulates the rapid decarboxylation.



Scheme 3.3 Plausible reaction mechanism

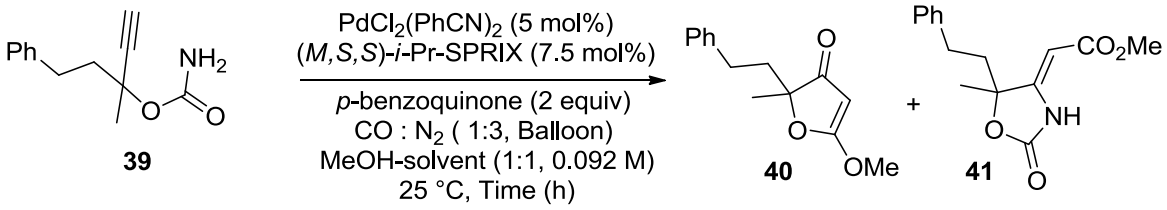
3.4 Summary

Enantioselective Pd-SPRIX catalyzed carbonylation of propargyl carbamate **39** was attempted in order to synthesis the chiral 5-methoxy-3(*2H*)-furanone **40**. The extreme optimization of reaction conditions revealed that (*M,S,S*)-*i*-Pr-SPRIX ligand could induce low enantioselectivity and moderate yield. As compared to box ligand, SPRIX found to be not as effective as bisoxazoline ligand regarding the yield of desired product **40**.

Kato and coworkers developed a cyclization/carbonylation/decarboxylation/cyclization sequence of the propargyl carbamate **39** catalyzed by [(box)Pd^{II}] complexes to obtain the 5-methoxy-3(*2H*)-furanones **40** in moderate to excellent yield.[4]

3.5 Experimental section

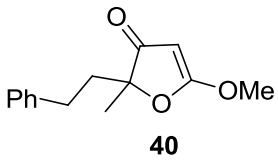
Typical procedure for the Pd-SPRIX catalyzed synthesis of 5-methoxy-3(*2H*)-furanones (40)



In to a oven dried Schlenk tube, was added $PdCl_2(PhCN)_2$ (5 mol%, 0.88 mg), (M,S,S)-i-Pr-SPRIX (7.5 mol%, 1.3 mg), methanol (0.5 mL) **or** MeOH/co-solvent (1:1) and stirred at 25^o C for 2h under N_2 atm. To this solution was added solution of SM **39** (0.046 mmol, 10 mg) in methanol (0.6 mL) and *p*-benzoquinone (2 equiv, 10 mg). The Schlenk tube was fitted with three-way stopcock connected to a balloon filled with carbon monoxide. The apparatus was purged with CO by pumping-filling via the three way stopcock and the reaction mixture was stirred at 25 °C for 12 h unless otherwise mentioned. After completion of reaction, the mixture was diluted with CH_2Cl_2 (8 mL) and washed with 3% NaOH (6 mL). The aqueous layer was extracted with CH_2Cl_2 (8 mL) twice and the combined organic layers were dried over Na_2SO_4 and concentrated in *vacuo*. The crude product was purified by column chromatography on silica gel to afford pure **40**.

Characterization

5-methoxy-2-methyl-2-phenethylfuran-3(2H)-one (40):



40

Orange color oil ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.47 (s, 3H), 2.02-2.16 (m, 2H), 2.54-2.66 (m, 2H), 3.94 (s, 3H), 4.78 (s, 1H), 7.15-7.19 (m, 3H), 7.24-7.32 (m, 2H); ^{13}C NMR (100 MHz): δ 22.0, 29.4, 38.0, 57.9, 78.9, 93.2, 126.1, 128.3 (2C), 128.4 (2C), 141.0, 184.0, 201.5; HRMS-EI: m/z [M+] calcd for $C_{14}H_{16}O_3$: 232.1100; found: 232.1099; IR (KBr): 3027, 2930, 2865, 1699, 1589, 1392 cm-1

3.6 References

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