Development of Aza-Wacker-Type Reaction Promoted by Pd-SPRIX Catalyst

A Doctoral Thesis

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By

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Contents

Abbreviation

Ac	Acetyl
Acac	Acetylacetonate
Aq.	Aqueous
Ar	Aryl
Atm	Atmospheric
b.p.	Boiling point
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
BOX	Bis(oxazoline)
BQ	Benzoquinone
br	Broad singlet
c	Concentration
^{o}C	Degree Celsius
calcd	Calculated
cod	1,5-Cyclooctadiene
d	Doublet
DCM	Dichloromethane
DCE	Dichloroethane
dd	Doublet of doublets
DMAP	4-(*N*,*N*-Dimethylamino)pyridine
dt	Doublet of triplets
ee	Enantiomeric excess
EDG	Electron donating group
Equiv	Equivalent
eq.	Equation
ESI	Electrospray ionization
Et	Ethyl
EWG	Electron withdrawing group
F_6-acac	Hexafluoroacetylacetonate
h	Hour
HPLC	High performance liquid chromatography

HRMS	High resolution mass spectrometry
IPA	Isopropyl alcohol
i-Pr	Isopropyl
J	Coupling constant
KIE	Kinetic isotope effect
$LiAlD_4$	Lithium aluminium deuteride
$LiAlH_4$	Lithium aluminium hydride
L	Ligand
M	Molar
m	Multiplet
m.p.	Melting point
Me	Methy
min	Minute
mol	Mole
nm	Nanometer
NMR	Nuclear magnetic resonance
Ph	Phenyl
Py	Pyridine
q	Quartet
RT	Room temperature
s	Singlet
sat.	Saturated
SPRIX	Spiro bis(isoxazoline)
t	Triplet
td	Triplet of doublet
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFA	Trifluoroacetic Acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
Ts	Tosyl
t_R	Retention time

Chapter 1

1. Background

1.1. Nitrogen-Containing Molecules

Nitrogen-containing molecules are ubiquitous in pharmaceutical and naturally occurring substrates.[1] They are also useful for dyes[2] and electroluminescent materials.[3] In 2014, Prof. J. T. Njardarshon complained a database of Food and Drug Administrator of USA (FDA) approved drug. After eliminating biologics (146), combination drug (253), peptides (23) and drug duplications (537), they left with 1035 small-molecule drugs and they observed 874 drugs containing at least one nitrogen atom (84%) whereas 613 (59%) small-molecule drugs containing *N*-heterocycles (Figure 1.1.1).[4] This number slightly increased when they considered those drugs which are approved only as a part of combination. Out of such 51 drugs 36 contained at least a nitrogen atom and 27 contained a nitrogen heterocycles. As a result, the total number of small-molecule drugs containing nitrogen atom increased to 910 from 874 whereas the number of drugs containing nitrogen heterocycles rose to 640 out of 1086 total drugs. This data clearly indicates the importance of *N*-containing organic compounds. So, it is highly desirable to develop a very easy and straightforward methodology to construct C–N bond.

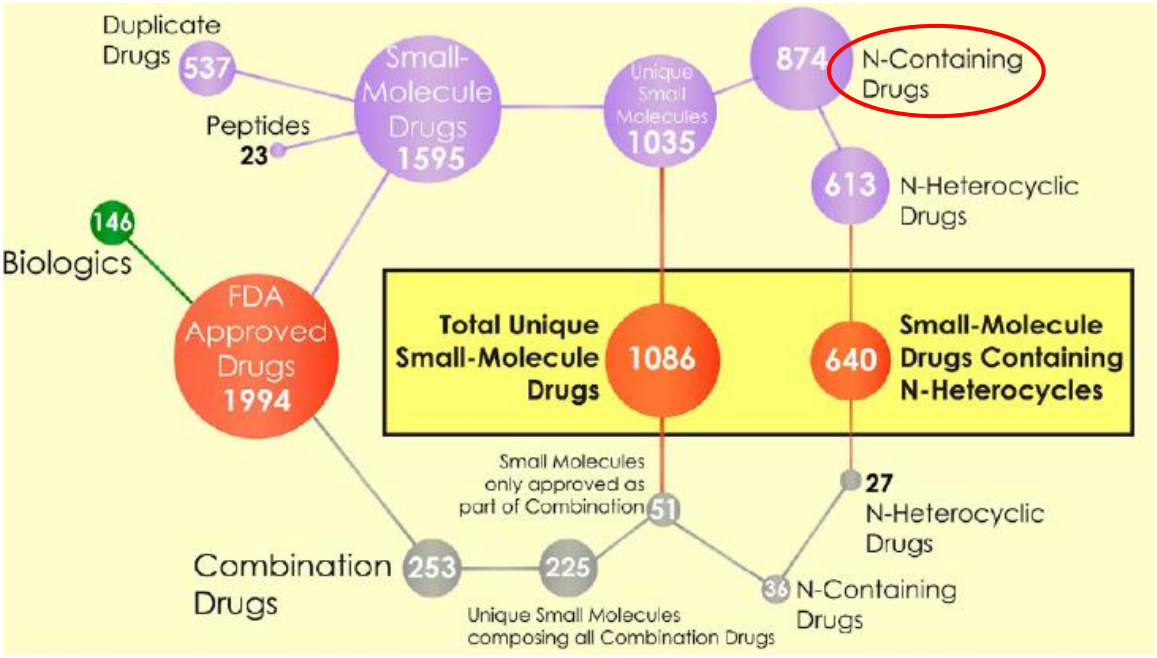
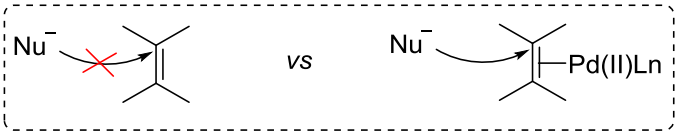


Figure 1.1.1. Breakdown of FDA Approved Drugs[a]

[a] Vitaku, E.; Smith, D. T.; Njardatshon, J. T. *J. Med. Chem.* **2014**, *57*, 10257.

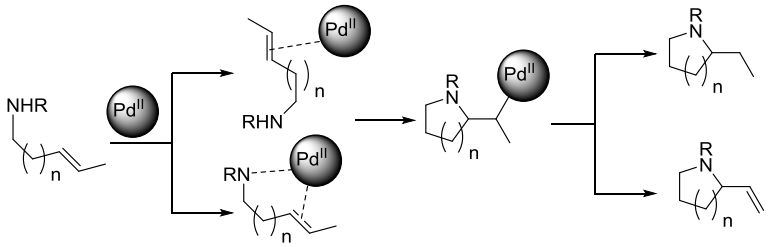
1.2. Aza-Wacker-Type Reaction

Oxidative coupling reactions of olefins by using transition metal catalysts are an important transformation in synthetic organic chemistry and nowadays these coupling reactions are one of the most efficient methods for introducing several functional groups directly connected to carbon–carbon double bonds of alkenes.[5] Synthesis of nitrogen-containing compounds such as enamines *via* oxidative coupling reaction using transition metal such as palladium catalysis in presence of an external oxidant, known as aza-Wacker-Type reaction, has now been seems to be a highly useful and straightforward methodology.[6] In principle, nitrogen atom of an amine and a carbon–carbon double bond of an alkene both represent electron-rich nature. As a result, the direct reaction between them demands very high activation energy. Interestingly, transition metal (such as palladium) coordination induces electrophilicity to the C=C and allows olefin to undergo reaction with the nitrogen nucleophile (Scheme 1.2.1).[7]



Scheme 1.2.1. Difference in Reactivity in Presence of Palladium

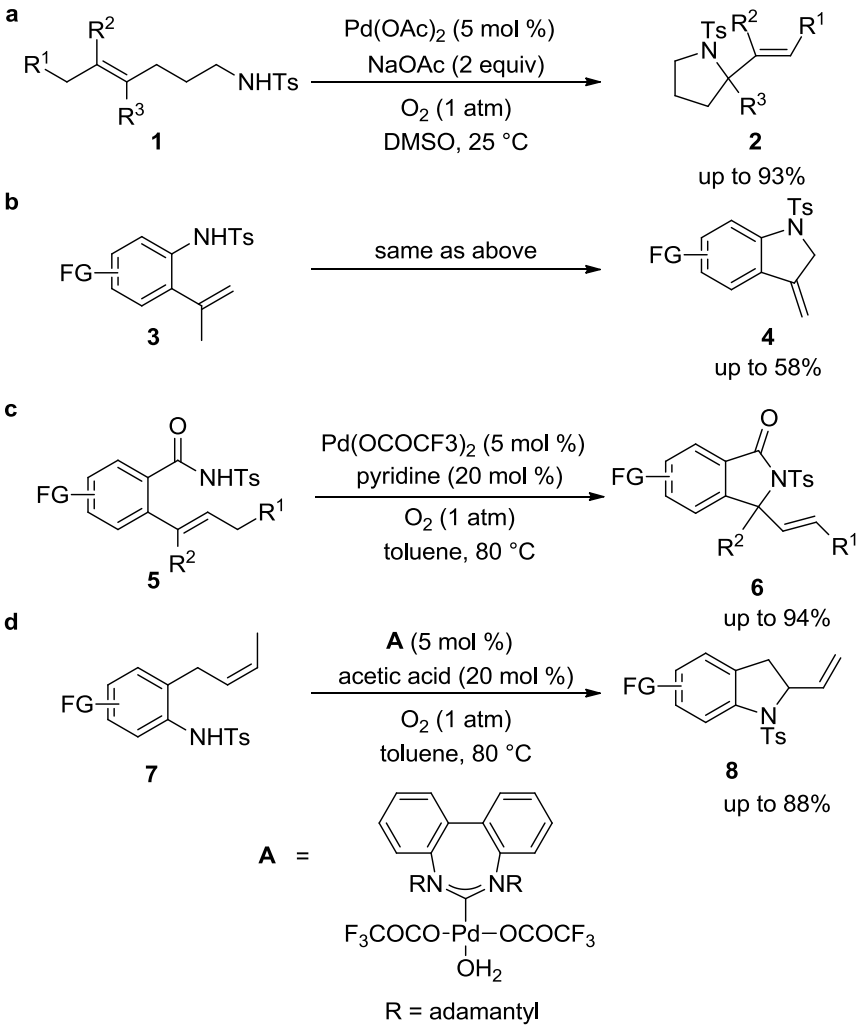
Aza-Wacker-Type reaction proceeds only when strongly electron-withdrawing groups such as amides, sulfonamides or carbamates are used as the nitrogen source.[8] The aza-Wacker-type reaction may proceed *via* two different pathways namely i) *syn*-aminopalladation, ii) *anti*-aminopalladation. When the reactions proceed through initial nitrogen palladium interaction followed by the coordination of olefin with palladium then the process is known as *syn*-aminopalladation. Alternatively, initial olefin palladium interaction followed by the nucleophilic addition of nitrogen motif is known as *anti*-aminopalladation.[9] After the nucleophilic addition, the generated amino-palladium compound may undergo protodemetallation to result hydroamination or it may undergo ß-hydride elimination to give aza-Wacker-type product (Scheme 1.2.2).[10]



Scheme 1.2.2. Mechanistic Background of Aminopalladation for Heterocycle Synthesis

Depending on the substitution pattern, aza-Wacker-type reaction can provide enamides or allylic amines.[11]

In 1996, Larock and his co-workers reported cyclization of substrate **1** based on aza-Wacker-type reaction by using a convenient catalytic system consisting of $Pd(OAc)_2$ as a pre-catalyst, molecular oxygen as an external oxidant, sodium acetate as a base and DMSO as solvent (Scheme 1.2.3).[12a] A variety of tosylamide substrates underwent efficient intramolecular cyclization to provide the corresponding 5-membered allyl amides in yield varying from 40% to 93%. Interestingly, an indene derivative with an exocyclic double bond was obtained *via* 5-*endo-cyclization* using this aza-Wacker-type reaction (**4**). Stahl and his co-workers further improved the catalytic reactivity of palladium by using pyridine (10 mol %) as a ligand with a combination of $Pd(OAc)_2$ (5 mol %).[12b] Utilizing the effect of ligand acceleration, Stoltz and co-worker showed that aza-Wacker-type cyclization proceed efficiently from *N*-tosylbenzamide derivatives **5**.[12c] Later on, Stahl and his coworker employed carbene as a ligand in palladium catalyzed aza-Wacker-type reaction.[12d]

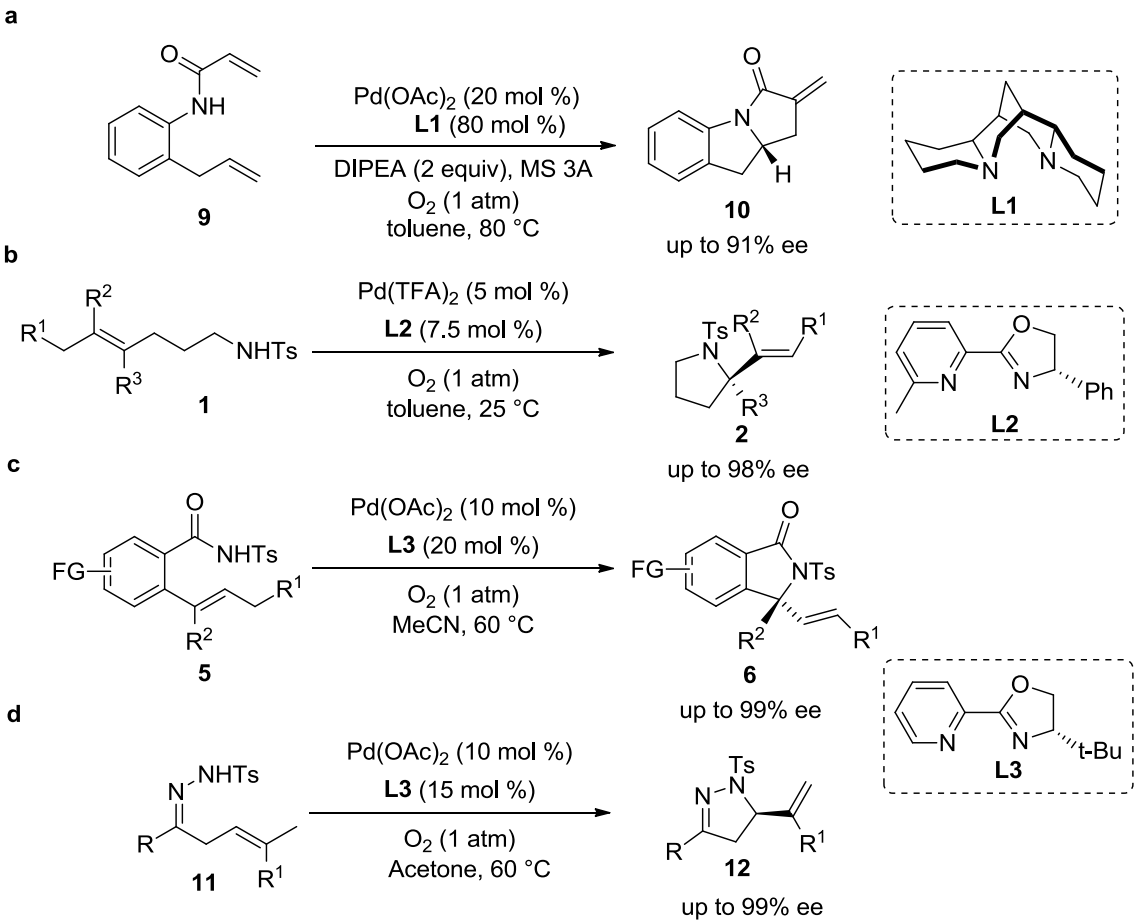


Scheme 1.2.3. Aza-Wacker-Type Cyclization

On the other hand, asymmetric synthesis is a powerful tool to obtain optically pure products in recent synthetic transformation. Among the approaches of asymmetric transformation, transition metal-catalyzed enantioselective reactions are most useful strategy. The chiral ligands which coordinate with transition metal provide the asymmetric induction. Till now numerous numbers of chiral ligands are developed for the transition metal catalyzed asymmetric transformation.

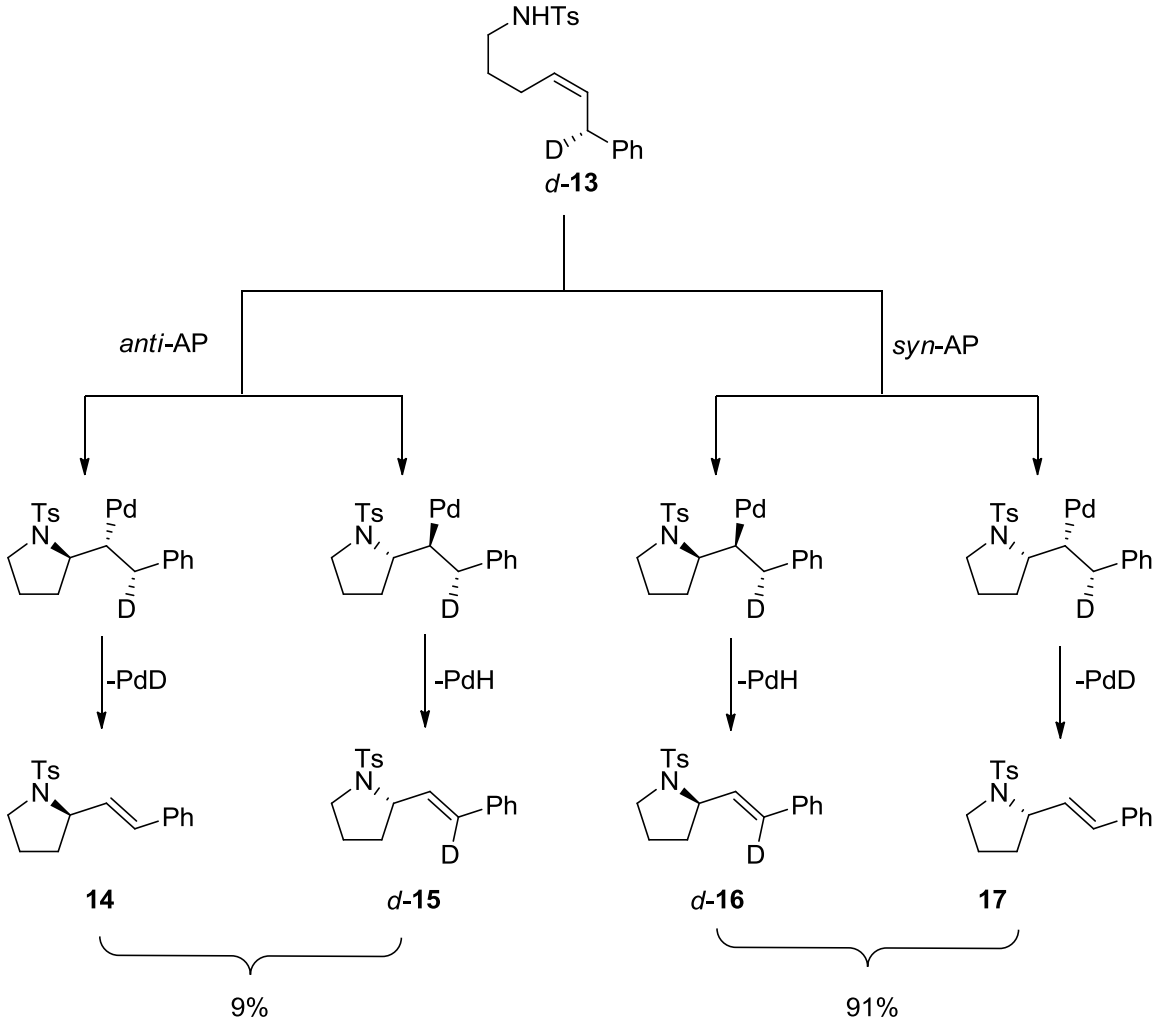
1.3. Enantioselective Aza-Wacker-Type Reaction

Enantioselective aza-Wacker-type cyclization was first reported by Yang in 2006 where (–)-sparteine worked as ligand and they obtained up to 91% enantioselectivity with up to 78% yield (scheme 1.3.1).[13a] In 2011, synthesis of 1-tosyl-2-vinylpyrrolidine **2** was reported by Stahl in enantioselective manner. They used pyridine based oxazoline type ligand **L2** (Ph-PYOX) for the enantioinduction.[13d] Zhang also observed high enantioselectivity by using, **L3** (*t*-Bu-PYOX) ligand in 5-membered cyclization.[13e] Recently, Zhang reported *N*-Ts hydrazone **11** as a nucleophile to synthesize enantioenriched 5-membered *N*-heterocyles **12**.[13g]



Scheme 1.3.1. Representative Examples of Enantioselective Aza-Wacker-Type Cyclization

The mechanistic investigation by Stahl suggests that the reaction follow the *syn*-aminopalladation pathway.[12e-f] The treatment of *d*-**13** under the palladium catalysis results the formation of *d*-**16** and **17** as main products (Scheme 1.3.2). The observed product ratio suggests that *anti*-aminopalladation is 10 times less selective than the *syn*-aminopalladation (*syn*-AP/*anti*-AP = 91:9).



Scheme 1.3.2. Mechanistic Pathways for Intramolecular Oxidative Amination

1.4. Spiro-Type Compounds as Ligand

In 1990, Adlof von Bayear proposed the name "spirocyclane" for the bicyclic hydrocarbons attached through a common carbon atom.[14] These spiro-type compounds are common in natural products and biological molecules. The two rings of spiro compounds are perpendicular to each other and connected through a quaternary carbon center *via* σ-bond. The perpendicular nature and the tetrahedral geometry restrict the rotation of the rings and generate a central chirality with the substitution on rings. As a result, spiro type molecules can work as a chiral ligand by installation of a suitable coordination site on rigid skeleton.

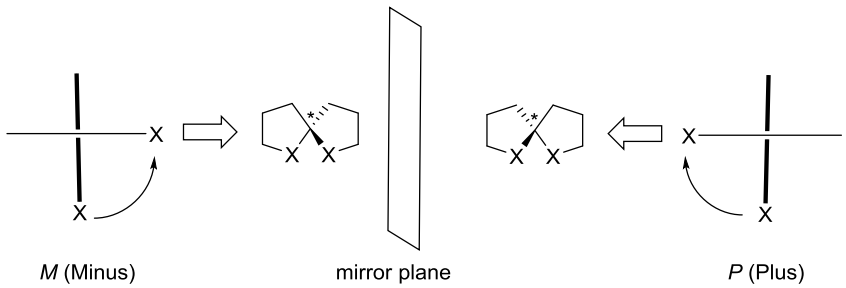


Figure 1.4.1. Chirality on Spiro Type Molecules

The spiro type molecules containing heteroatom such as nitrogen, oxygen, sulfur or phosphorus which can act as a Lewis base for the coordination with Lewis acidic metal center are practically very useful as a chiral ligand. There are several reports of this type ligand in transition metal catalysis (Figure 1.4.2)

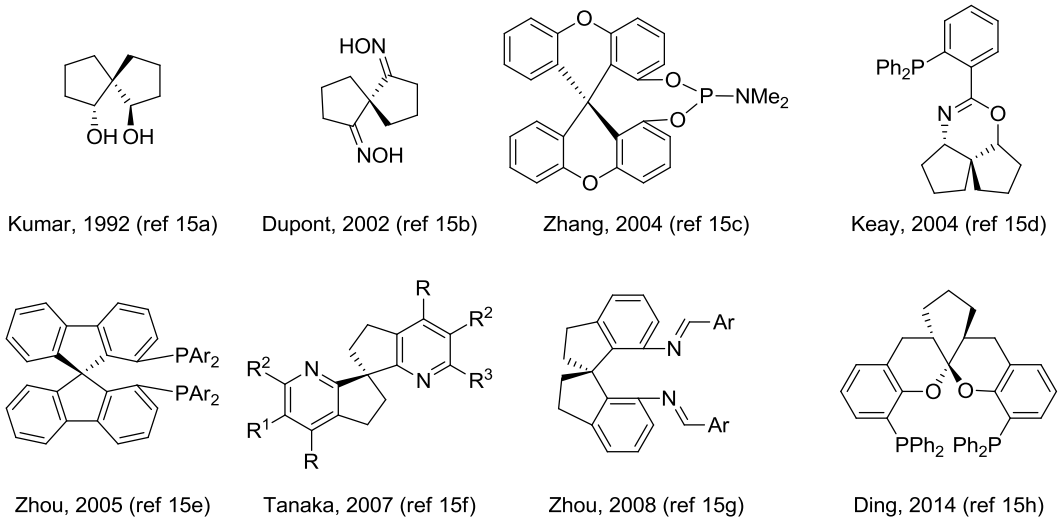
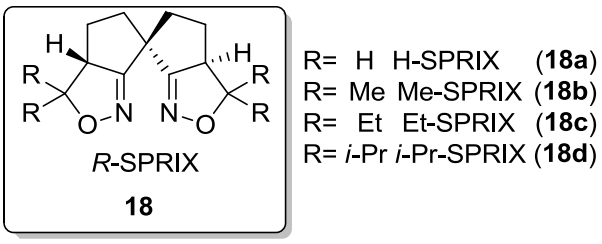
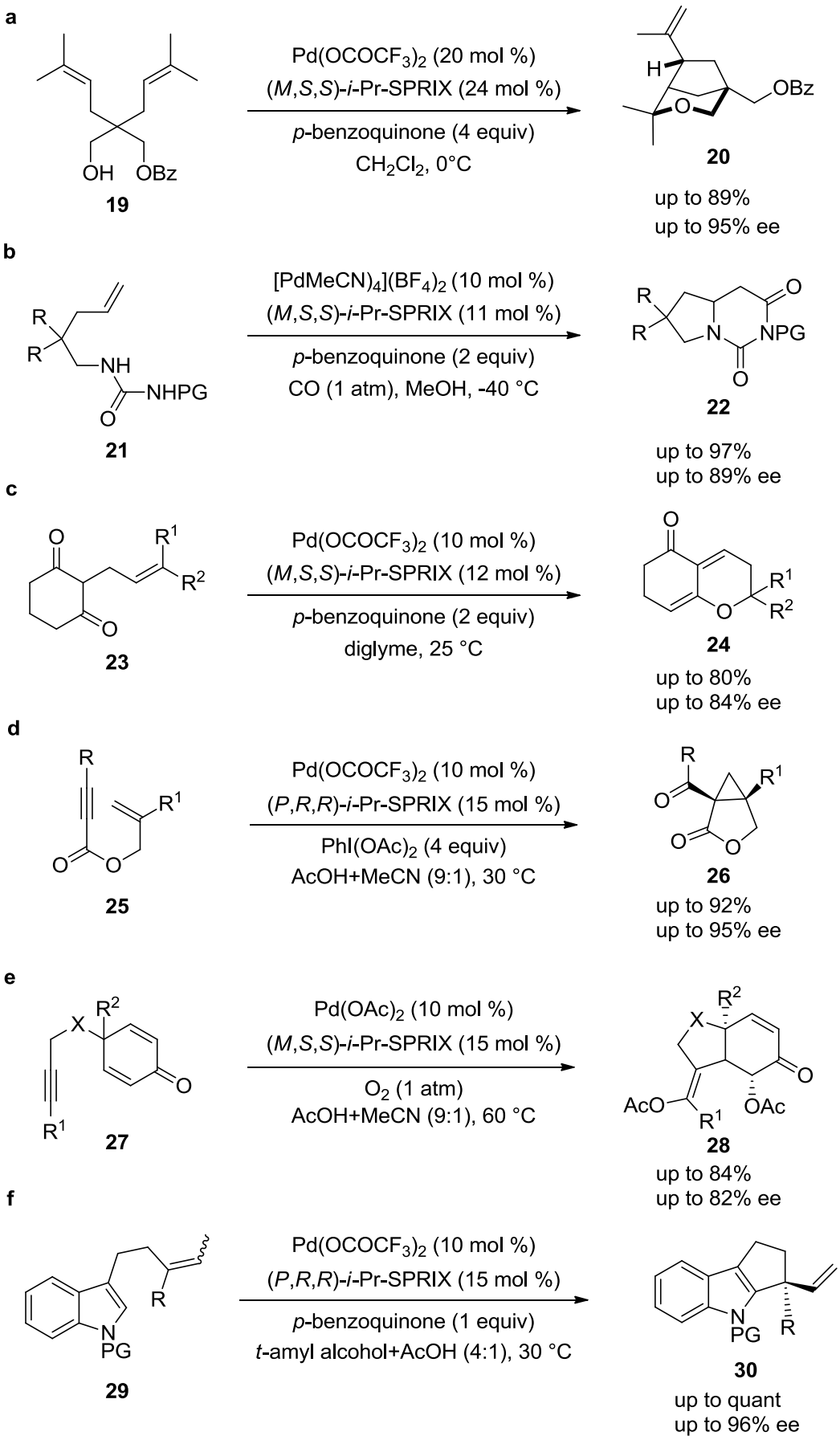


Figure 1.4.2. Examples of Spiro Type Ligands

In 1999, our group developed chiral H-SPRIX (spiro bis(isoxazoline)) ligand[16] (**18a**, R = H) containing a rigid spiro skeleton.[17a] This was the first report of transition metal catalysis using isoxazoline as a ligand. One the basis of a good affinity of SPRIX toward the palladium center, our group demonstrated the most effective spiro bis(isoxazoline) ligand *i*-Pr-SPRIX (**18d**, R = *i*-Pr) for the tandem enantioselective Wacker-type cyclization of alkenyl alcohol **19**



affording a bicyclic ether molecule **20** with up to 95% ee as a single diastereomer (Scheme 1.4.1).[16b] SPRIX is highly stable under acidic basic as well as oxidative reaction conditions.

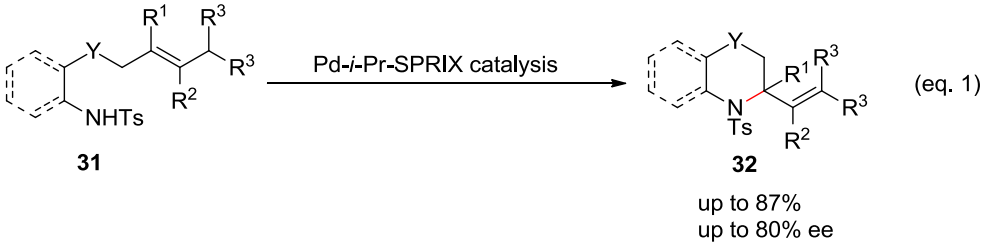


Scheme 1.4.1. Enantioselective Cyclization Promoted by SPRIX

The most importantly SPRIX has weak σ-donor ability compared to the well-known ligands such as oxazoline, sparteine, BINAP.[17d,18] The benefit of this weak σ-donor ability is the preservation of Lewis acidity of the metal atom. This preserved Lewis acidity of metal assists to increase electrophilicity of the olefin *via* olefin-metal coordination and it may overcome many unsolved olefin activation problems. Later on, *i*-Pr-SPRIX ligand was applied in various asymmetric transformation and provided excellent reactivity and selectivity (Scheme 1.4.1).[17] In 2009, our group reported Pd–SPRIX catalyzed *N*-heterocycle (**22**) synthesis by using aminocarbonylation reaction and up to 89% enantioselectivity was observed.[17d] Oxygen heterocycle **24** was also efficiently constructed in an enantioselective form by utilizing Pd–SPRIX catalyst *via* enol-Wacker reaction in 2010.[17e] Moreover, Pd–*i*-Pr-SPRIX allowed Pd(II)/Pd(IV) catalysis with high enantioselectivity in order to synthesize bicyclic compound **26**.[17c] A novel palladium-enolate *umpolung* reaction involving unusual nucleophilic attack on enolate was developed by using *i*-Pr-SPRIX ligand. When alkynyl cyclohexadienone **27** was treated with a catalytic amount of Pd–*i*-Pr-SPRIX complex in acetic acid solvent, then unusual diacetoxylated product **28** was observed under the oxygen atmosphere.[17g] In addition, recently our group reported the carbon-carbon bond forming Fujiwara-Moritani reaction of 3-alkenylindol **30** with excellent enantioselectivity (up to 96% ee).[17h]

All of these reported examples suggest the versatility or efficiency of the Pd–*i*-Pr-SPRIX catalysis. More importantly, *i*-Pr-SPRIX ligand allowed the construction of heterocyclic compounds *via* the generation of new carbon-heteroatom bond. On the other side, although several aza-Wacker-type cylization were reported but there are a few reports of intermolecular aza-Wacker-type reactions or enantioselective 6-membered aza-Wacker-type cyclization. So, I envisioned that the unique properties of SPRIX and its ability to generate the carbon-heteroatom bond will allow me to construct a new carbon–nitrogen bond in intermolecular as well as intramolecular fashion to obtain allylamine derivatives or 6-membered *N*-heterocycles in enantioselective manner, respectively.

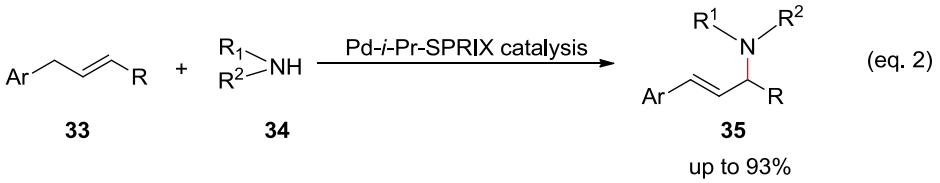
In **Chapter 2** of this thesis, I discuss about the construction of enantioselective 6-membered *N*-heterocycles having chiral center at α-position to nitrogen atom. The reaction of **31** in presence of a catalytic amount of Pd–*i*-Pr-SPRIX provided the desired *N*-heterocycle **32** (eq. 1).



31 **32** (eq. 1)

up to 87%
up to 80% ee

The **Chapter 3** is related to the Pd–*i*-Pr-SPRIX catalyzed intermolecular carbon–nitrogen bond formation to generate allylamine derivatives *via* aza-Wacker-type reaction. The reaction between olefin **33** and a nitrogen nucleophile **34** proceeded well in presence of a catalytic amount of Pd–*i*-Pr-SPRIX to provide the allylamine derivatives **35** with excellent regioselectivity (eq. 2).



33 **34** **35**

up to 93%

(eq. 2)

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Chapter 2

Enantioselective Synthesis of *N*-Heterocyles *via* Aza-Wacker-Type Cyclization

2.1. Introduction

Nitrogen-containing heterocyclic molecules are key building blocks used to develop a compound having biological or pharmaceutical interest. A huge number of *N*-heterocyclic building blocks have applications in pharmaceutical science, agricultural science, and drug discovery. Along with these applications, *N*-heterocyclic compounds also have genuine uses as ligands, bases, dyestuffs, antioxidants, copolymers.[1a-e] Approximately 60% of total small-molecule drug contains at least one nitrogen heterocycle. Among the nitrogen heterocycles, 379 small-molecule drugs contains 6-member *N*-heterocycles whereas 250 drugs contains 5-membered *N*-heterocycles (Figure 2.1.1).[1f] The 6-membered *N*-heterocyclic drugs can be sub-divided into two different categories such as i) non-aromatic heterocycles (273) and ii) aromatic heterocycles (106).

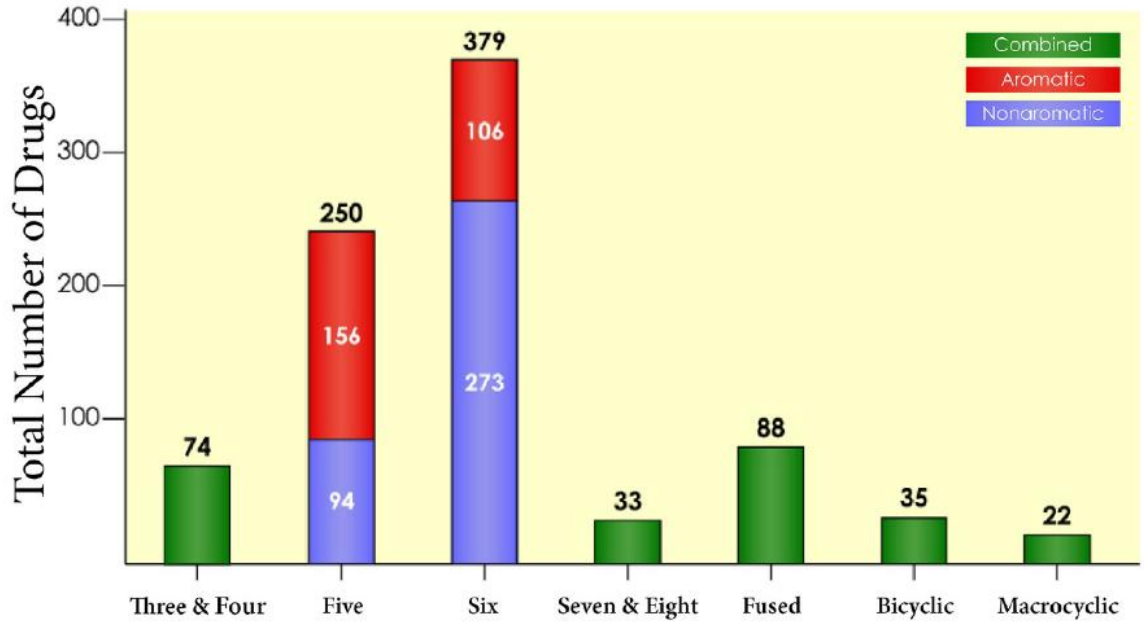
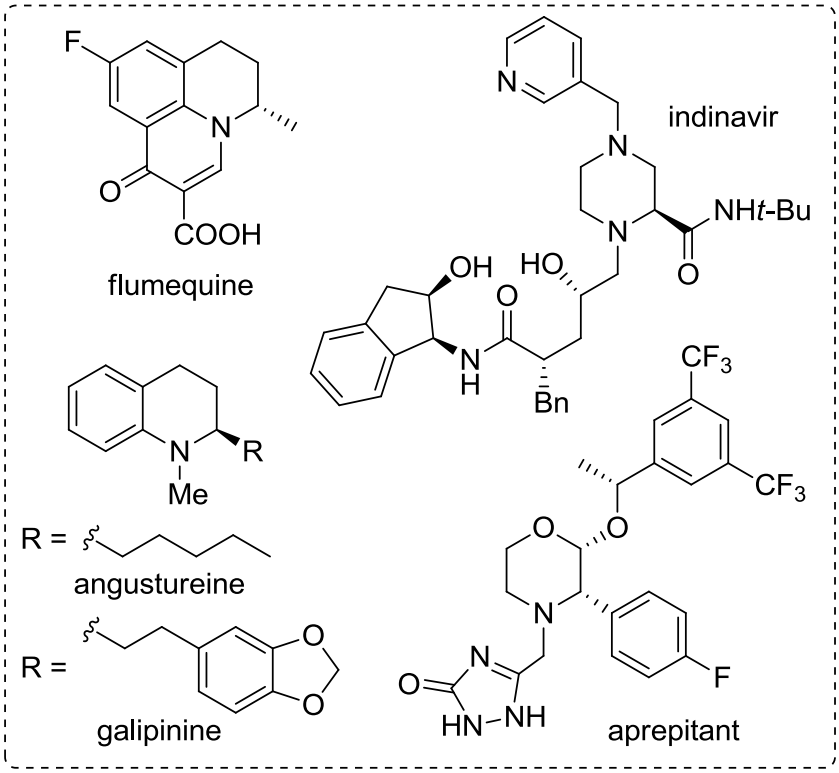


Figure 2.1.1. Distribution of *N*-Heterocycles in Drug[b]

[b] Vitaku, E.; Smith, D. T.; Njardatshon, J. T. *J. Med. Chem.* **2014**, *57*, 10257.

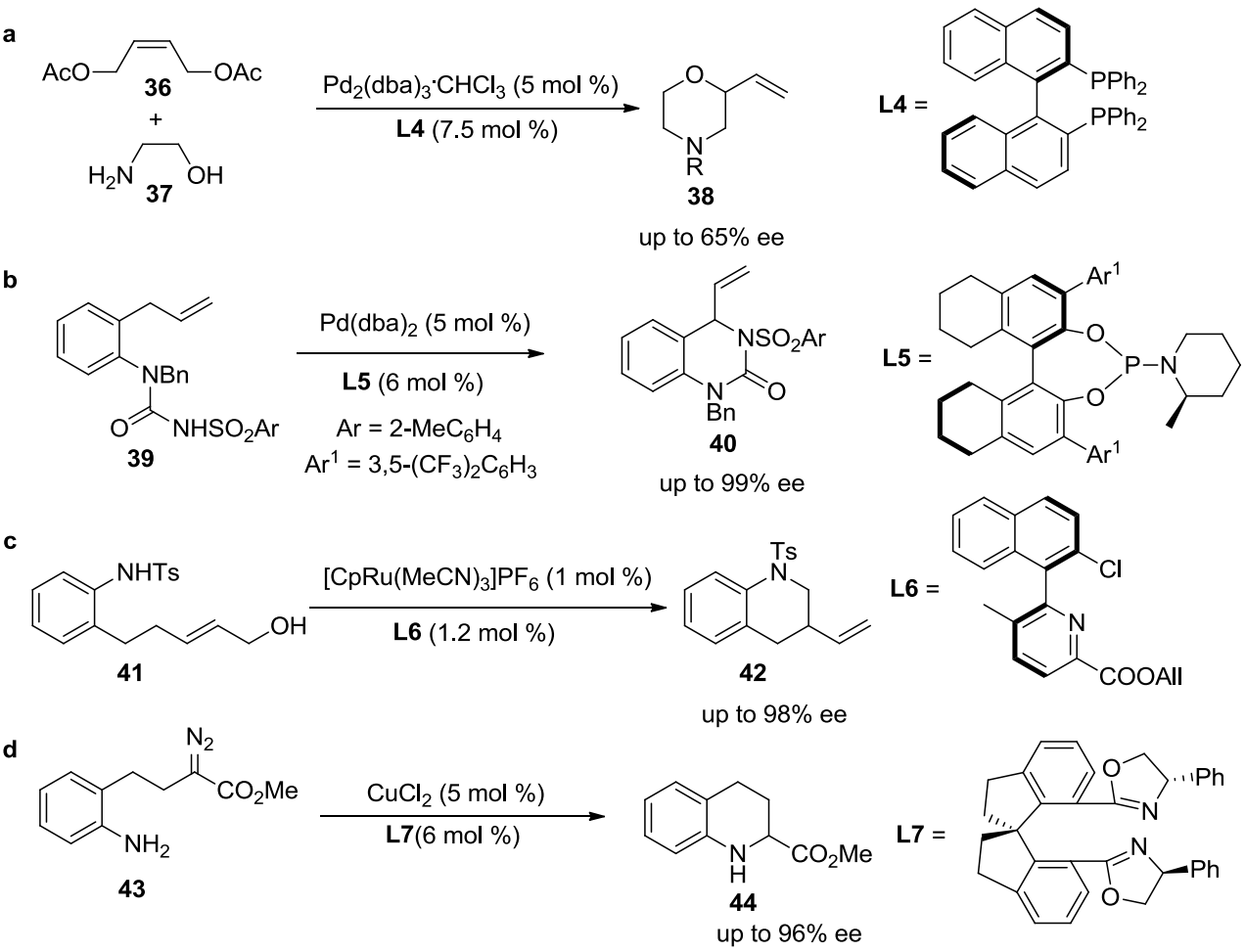
Piperidine and piperazine ring containg *N*-heterocycles are most frequently observed in small-molecule drugs whereas the morpholine is also applicable as a drug candidate.[1f] *N*-heterocycles having a chiral center at the α-position of the nitrogen atom are broadly found in

natural products and biologically active compounds, e.g. flumequine,[2] indivavir,[3] angustureine,[4a,b] galipinine,[4c,d] and aprepitant[5] (Scheme 2.1.1). Hence, several methodologies have been developed for the synthesis of optically active 6-memebered *N*-heterocyclic skeletons.[6]



Scheme 2.1.1. Biologically Active *N*-Heterocyclic Compounds

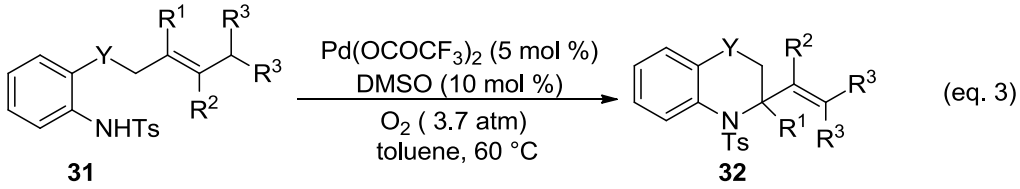
In 1994, Hayashi and his co-workers reported asymmetric synthesis of morpholine and piperazine derivatives by using Tsuji-Trost reaction (Scheme 2.1.2.a).[6a] When they treated a diacetate compound **36** with amino alcohol derivatives **37** in presence of $Pd_2(dba)_3$-(*R*)-BINAP catalyst then they obtained morpholine **38** with up to 65% ee. Later on, palladium catalyzed asymmetric allylic amination reaction *via* the allylic C–H activation was also reported by Gong and his co-workers.[6i] Other transition metals are also used for the construction of enantioenriched 6-membered *N*-heterocycles. For example, ruthenium pre-catalyst in presence of **L6** as a chiral ligand provided 1,2,3,4-tetrahydroquinoline derivatives **42** with very high ee whereas Cu-catalysis provided the tetrahydroquinoline-2-carboxylic acid **44** in enantioselective manner in presence of **L7** ligand.[6e,h]



Scheme 2.1.2. Asymmetric Synthesis of 6-Membered *N*-Heterocycles

On the other hand, Pd-catalyzed enantioselective C–N bond-forming oxidative cyclization, so-called aza-Wacker-type reaction, is anticipated to be a highly useful and straightforward methodology.[7] Although a number of examples have been reported for the enantioselective 5-membered cyclization *via* oxidative amination,[8] the aza-Wacker-type cyclization leading to 6-membered nitrogen heterocycles has hardly been reported.[9,10]

In 2012, Stahl and his co-workers reported aza-Wacker-type cyclization of alkenyl sulfonamide substrates **31** that produced 6-membered *N*-heterocyclic compounds **32** in a racemic form (eq.3).[9d] This cyclization proceeded smoothly in presence of DMSO ligand under O_2 atmosphere. Herein, I describe, to the best of my knowledge, the first example of enantioselective aza-Wacker-type cyclization producing 6-membered nitrogen heterocycles.



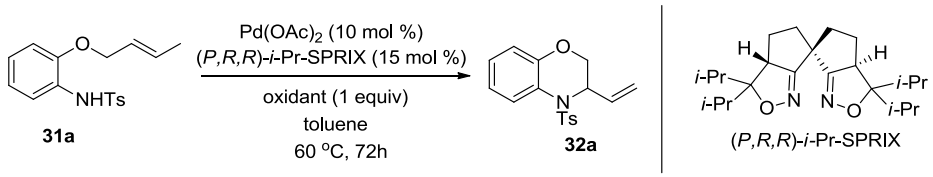
(eq. 3)

2.2. Results and Discussion

2. 2. 1. Effect of Oxidant

I examined reaction conditions of enantioselective cyclization from a model-substrate, (*E*)-*N*-(2-but-2-en-1-yloxy)phenyl)tosylamide ((*E*)-**31a**), to the desired product, 4-tosyl-3-vinyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (**32a**) (Table 2.2.1). At first, (*P*,*R*,*R*)-*i*-Pr-SPRIX was tested under Stahl's reaction conditions instead of the achiral DMSO ligand. Unfortunately, no reaction with palladium trifluoroacetate and only a trace amount of **32a** with palladium acetate were observed (entries 1 and 2). I assumed that molecular oxygen was unable to re-oxidize Pd(0)–SPRIX complex to catalytically active Pd(II)–SPRIX complex.

Table 2.2.1. Optimization of Oxidant



Entry	Oxidant	Yield (%)	Ee (%)[b]
1[c]	O_2 (4 atm)	NR[d]	---
2	O_2 (4 atm)	Trace	---
3	*p*-Benzoquinone (BQ)	Trace	---
4	H_2O_2 (aq)	50	7
5	$2Na_2CO_3 \cdot 3H_2O_2$	Trace	racemic
6	$PhI(OAc)_2$	21	57
7	$K_2S_2O_8$	52	60
8	$K_2S_2O_8$[e]	52	60
9	Oxone	60	64
10[f]	Oxone	40	28

[a]All reactions were carried out in 0.0315 mmol scale at 0.1M toluene under N_2. [b]Determined by HPLC (CHIRALCEL OJ-H column). [c]$Pd(OCOCF_3)_2$ (10 mol %). [d]No reaction. [e]$K_2S_2O_8$ (2 equiv). [f]18-crown-6-ether (15 mol %).

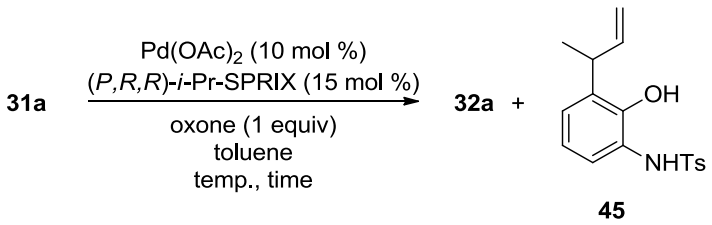
Hence, several other stronger oxidants were tested for this enantioselective cyclization. *p*-Benzoquinone is known to work as an oxidant in Wacker-type oxidation reaction but failed to provide the desired product in aza-Wacker-type transformation of **31a** to **32a** (entry 3). Hydrogen peroxide (H_2O_2) provided the desired product with poor enantioselectivity (entry 4) whereas sodium percarbonate ($2Na_2CO_3 \cdot 3H_2O_2$) furnished the cyclization only in trace amount (entry 5). When $PhI(OAc)_2$ and $K_2S_2O_8$ were used as oxidant, **32a** was obtained in 21% yield with 57% ee and 52% yield with 60% ee, respectively (entries 6 and 7). No

improvement of reactivity as well as enantioselectivity was obtained by increasing the oxidant amount (2 equivalent, entry 8). Oxone was found to be the best oxidant to give **32a** in 60% yield with 64% ee (entry 9). Addition of 18-crown-6 ether (15 mol %) was supposed to increase the solubility of oxone in toluene and transform the heterogeneous catalysis to homogeneous but it failed to improve the reactivity for this transformation (entry 10).

2. 2. 2. Effect of Temperature

Next I examined the effect of reaction temperature. When the reaction was carried out at 60 °C desired product was observed with 60% yield and no side-product was observed (Table 2.2.2, entry 1). Calisen rearrangement product **45** was observed at higher reaction temperature (120 °C and 90 °C) leading to decrease in yield of **32a** (entries 2 and 3). Only trace amount of product was obtained upon lowering the reaction temperature to 50 °C or 40 °C with very poor conversion leading to the recovery of **31a** (85% to 90%, entries 4 and 5). So, the optimized reaction temperature was determined to be 60 °C.

Table 2.2.2. Temperature Screening



Entry	Temp(^{o}C).	Time (h)	Yield (%)	Ee (%)[b]	Conversion
1	60	72	60	69	60
2	120	65	62	38	95
3	90	72	51	52	78
4	50	72	trace	---	10
5	40	72	trace	---	10

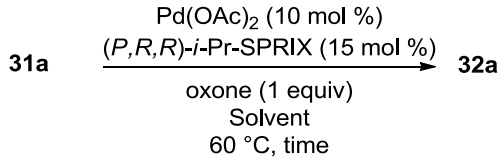
[a]All reactions were carried out in 0.0315 mmol scale at 0.1M toluene under N_2. [b]Determined by HPLC (CHIRALCEL OJ-H column).

2.2.3 Effect of Solvent

After having the optimized oxidant and temperature in hand, I proceeded for the screening of solvent. All solvents except ether-type solvents provided good reactivity and selectivity (Table 2.2.3). A little improvement of reactivity was observed in acetonitrile (MeCN) without significant loss of enantioslectivity (entry 2). Ether-type solvents were not suitable for this

transformation. In tetrahydrofuran (THF) and 1, 4-dioxane desired product was obtained in trace amount (entries 3 and 4). Halogenated solvents were better than the other solvents. In dichloroethane (DCE), tetrachloroethane (TCE), and 1,2-dichlorobenzene cyclization product **32a** was observed in 71%, 41%, and 81% with 66%, 64%,and 60% ee, respectively (entries 5, 6 and 7). Finally, chlorobenzene was the best solvent where 84% yield with 69% ee was acquired (entry 8).

Table 2.2.3. Solvent Screening:



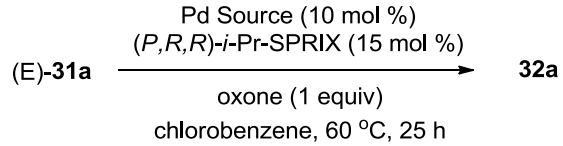
Entry	Solvent	Time (h)	Yield (%)	Ee (%)
1	toluene	72	60	64
2	MeCN	72	71	60
3	THF	48	Trace	---
4	1,4-dioxane	48	Trace	---
5	$ClCH_2CH_2Cl$	20	71	66
6	$Cl_2CHCHCl_2$	72	41	64
7	*o*-$C_6H_4Cl_2$	32	81	60
8	C_6H_5Cl	25	84	69

[a]All reactions were carried out in 0.0315 mmol scale at toluene (0.1M) under N_2 atmosphere

2.2.4 Effect of Palladium Source

Next, I turned my attention to the screening of Palladium salts. Palladium acetate efficiently provided the 6-membered *N*-heterocycle **32a** *via* 6-*exo*-*trig* cyclization with 84% yield and 69% ee (entry 1, Table 2.2.4). Palladium trifluoroacetate, $Pd(TFA)_2$ and palladium acetylacetonate, $Pd(acac)_2$ were also able to provide the desired product in enantioselective manner with moderate yield (entries 2 and 3). When halogen anion like chloride or bromide was present then the reactivity dropped significantly (entries 4 and 5). Allylpalladium chloride dimer efficiently provided the heterocycle but unfortunately only 26% ee was observed (entry 6). Other palladium sources such as bis(acetonitrile)palladium dichloride and tetrakis(acetonitrile)palladium tetrafluoroborate provided poor reactivity (entries 7 and 8). Slow reaction was observed with lower catalyst loading (5 mol %) whereas the selectivity was unaltered (entry 9). Based on these experimental results described in Table 2.2.4 palladium acetate was chosen as the optimum palladium source.

Table 2.2.4. Effect of Palladium Source:

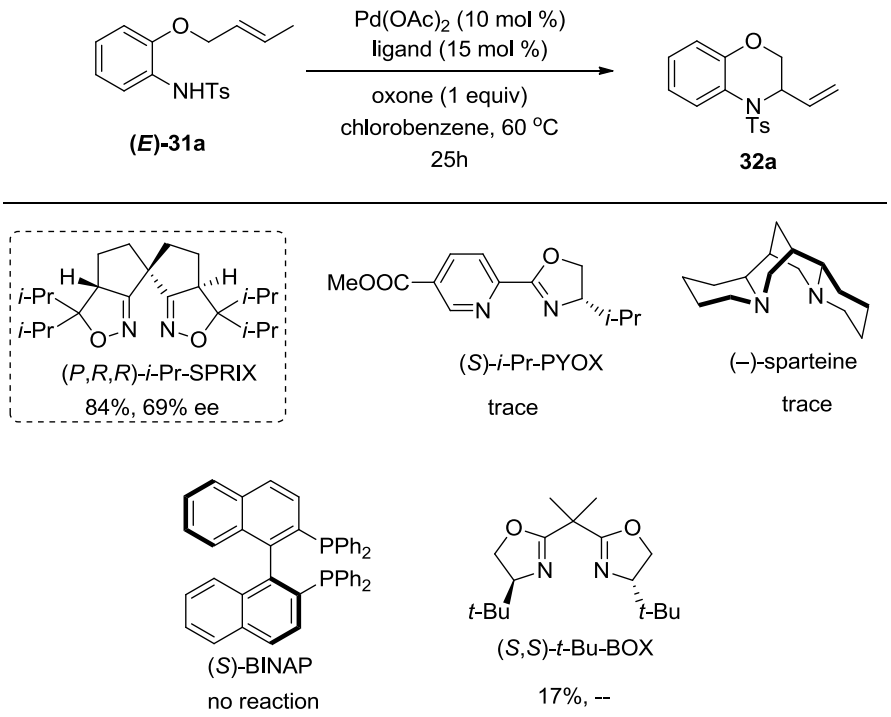


Entry	Pd Source	Yield (%)	Ee (%)[b]
1	$Pd(OAc)_2$	84	69
2	$Pd(OCOCF_3)_2$	64	66
3	$Pd(acac)_2$	50	66
4	$PdCl_2$	16	--
5	$PdBr_2$	13	--
6[c]	$[PdCl(allyl)]_2$	75	26
7	$PdCl_2(MeCN)_2$	23	60
8	$[Pd(MeCN)_4](BF_4)_2$	40	60
9[d,e]	$Pd(OAc)_2$	39	68

[a]All reactions were carried out in 0.0315 mmol scale at 0.1M toluene under N_2. [b]Determined by HPLC (CHIRALCEL OJ-H column). [c]$[PdCl(allyl)]_2$ (5 mol %). [d]$Pd(OAc)_2$ (5 mol %). [e](*P*,*R*,*R*)-*i*-Pr-SPRIX (8 mol %).

2.2.5. Importance of Isoxazoline Ligand

In order to show the superiority of SPRIX ligand for this enantioselective transformation, different kinds of commercially available chiral ligands were evaluated under the optimized reaction conditions. The replacement of (*P*,*R*,*R*)-*i*-Pr-SPRIX ligand by (–)-sparteine, and (*S*)-*i*-Pr-PYOX ligands which are known to provide the 5-membered enantioselective Wacker-type cyclization, were inefficient to provide **32a** (Scheme 2.2.1). Similarly, no reaction was observed with (*S*)-BINAP. In presence of (*S*,*S*)-*t*-Bu-BOX the cyclization was significantly suppressed and as a result, only 17% yield of **32a** was obtained. High σ-donating ability of these ligands which may destroy the Lewis acidity of the metal is responsible for the poor reactivity. Additionally, phosphine-type ligands including (*S*)-BINAP were not suitable for oxidative cyclization because phosphorous atoms could be easily oxidized to the corresponding phosphine oxide under the reaction conditions.

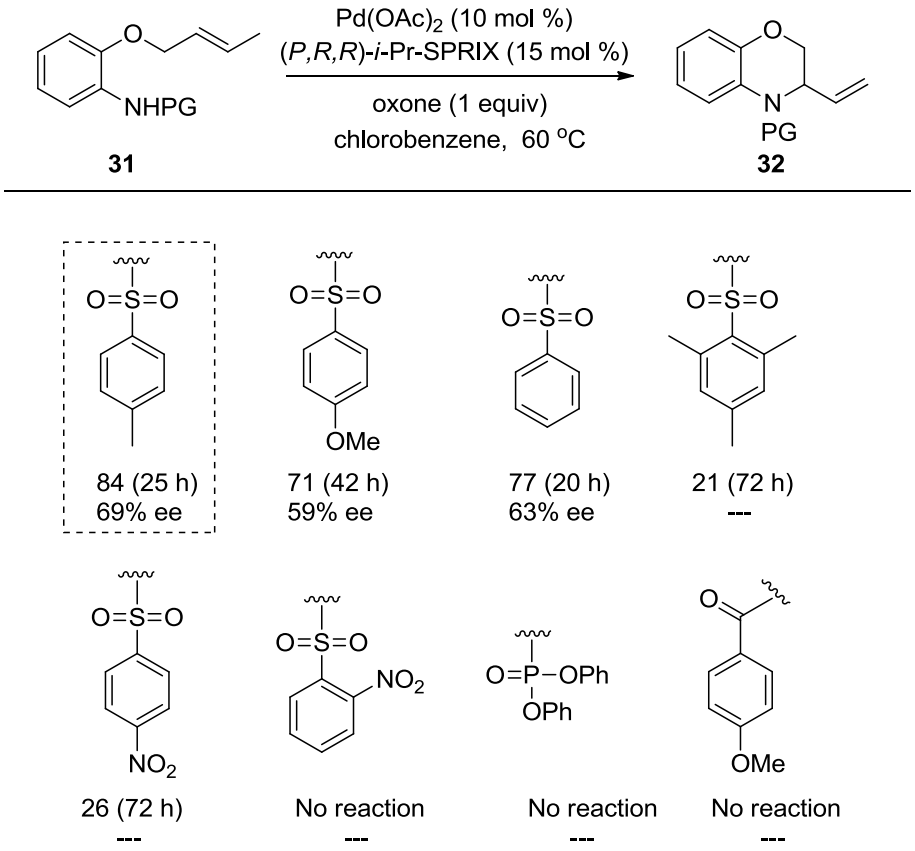


Scheme 2.2.1. Effect of Ligand

More importantly, a background reaction in the absence of *i*-Pr-SPRIX ligand hardly proceeded to provide a trace amount of **32a**. These results clearly indicate a great advantage of Pd–SPRIX catalyst for the enantioselective aza-Wacker-type cyclization of **31a**.

2.2.6. Effect of Protecting Group:

Next, the effect of the nucleophilic moiety was examined. A protecting group on the nitrogen atom turned out to be crucial for this cyclization (Scheme 2.2.2). The sulfonyl group bearing an electron donating substituent, for example *p*-toluenesulfonyl, and *p*-methoxybenzenesulfonyl groups, provided good reactivity as well as good enantioselectivity. The protecting group bearing simple benzenesulfonyl group also provided the desired cyclization efficiently. On the other hand, when an electron withdrawing substituent like nitro group was attached with sulfonyl motif, the corresponding product was hardly obtained. This cyclization was also sensitive to steric factor of the protecting group. Substrate having 2,4,6-trimethylbenzenesulfonyl group provided 21% yield of the desired product. The sulfonyl functionality was essential for this transformation in order to maintain the nucleophilicity of the *N*-center. Hence, no reaction proceeded with carbonyl or phophoryl protecting groups. Steric bulkiness may also be one reason of no reactivity in case of diphenyl phosphoryl protection. In conclusion, *p*-toluenesulfonyl protecting group provided the best reactivity and selectivity.

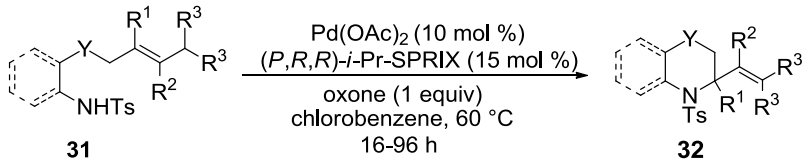


Scheme 2.2.2. Effect of Protecting Group

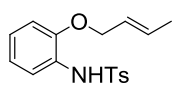
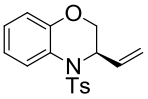
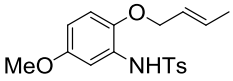
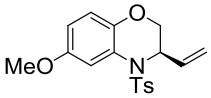
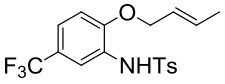
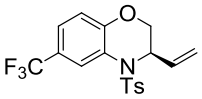
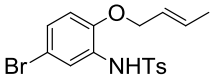
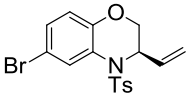
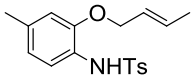
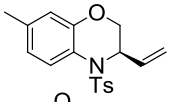
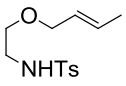
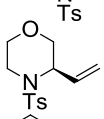
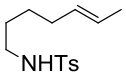
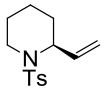
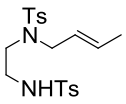
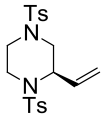
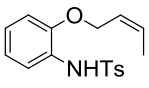
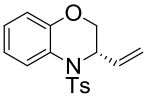
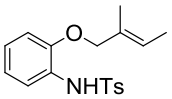
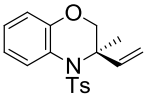
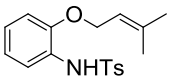
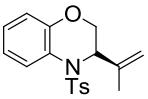
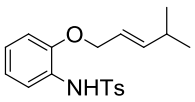
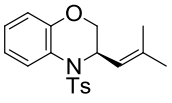
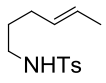
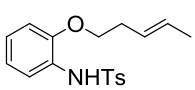
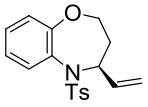
2.3. Substrate Scope and Limitations

After having the optimal reaction conditions in hand, I investigated the scope of this enantioselective aza-Wacker-type reaction with a variety of alkenyl sulfonamide substrates **31** (Table 2.3.1). The change in electronic nature on the phenylene ring by introduction of MeO, CF_3, and Br functionalities at the 5-position had no significant effect on the product outcome (entries 2–4). Similarly, Me group at the 4-position did not restrict the aza-Wacker-type cyclization to provide **32e** in 87% yield with 54% ee (entry 5). The phenylene linker was not indispensable for the starting material in this cyclization. Optically active morpholine (**32f**), piperidine (**32g**) and piperazine (**32h**) products were obtained successfully (entries 6–8). Substitution pattern on the olefin moiety showed a crucial effect on the chemical yield and enantioselectivity. Comparable reactivity to (*E*)-**31a** was observed for *cis*-alkene substrate (*Z*)-**31a** but the major enantiomer of product **32a** was opposite to that derived from (*E*)-**31a** (entries 1 and 9). Substrates **31i** and **31j** having tri-substitution on alkene exhibited poor reactivity, which led to low yields of **32i** and **32j** (entries 10 and 11). Installation of a bulky substituent at the olefin terminus turned out to be beneficial for the enantioinduction. Substrate **31k** bearing *i*-Pr group on the olefin component was thus converted smoothly to desire *N*-heterocycle **32k** in 79% yield with 80% ee (entry 12). Surprisingly, the reaction of

Table 2.3.1. Substrate Scope of Aza-Wacker-Type Cyclization



31 **32**

Entry	Starting Material		Product		Yield (%)[b]	Ee (%)[c]
1		**(*E*)-31a**		(*R*)-**32a**	84	69
2		**31b**		**32b**	77	53
3		**31c**		**32c**	51	43
4		**31d**		**32d**	64	36
5		**31e**		**32e**	87	54
6		**31f**		**32f**	68	30
7		**31g**		**32g**	63	68
8		**31h**		**32h**	71	61
9		**(*Z*)-31a**		(S)-**32a**	74	77
10		**31i**		**32i**	33	12
11		**31j**		**32j**	12[d]	n.d.[e]
12		**31k**		**32k**	79	80
13		**31l**		**32l**	48	38
14		**31m**		**32m**	n.r.[f]	–

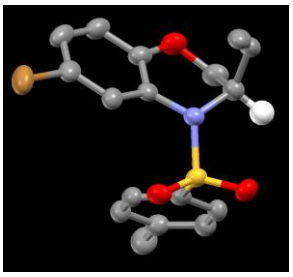
[a] chlorobenzene (0.1M) [b] isolated yield. [c]determined by HPLC. [d]NMR yield. [e]n.d.: not determined. [f]n.r.: no reaction.

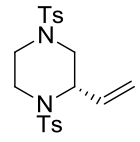
(*E*)-*N*-(hex-4-en-1-yl)tosylamide (**31l**), which was known to provide pyrrolidine in the presence of PYOX-type ligand,[8d] generated piperidine product **32l** in 48% yield with 38% ee

via 6-*endo-trig* cyclization (entry 13). This result clearly displays the unique property of the SPRIX ligand in the Pd-catalyzed oxidative cyclization. This current methodology was unable to generate benzo[*b*][1,4]oxazepine product **32m** (entry 14).

2.4. Determination of Absolute Configuration

The absolute configuration of **32d** was unambiguously determined to be *R* by X-ray crystallographic analysis. This enantiocontrol was further supported by comparing the optical rotation of **32h** with the reported value for (*S*)-**32h** with 60% ee.[6a] The stereochemistry of other products was deduced on the basis of these results.





(*S*)-**32h**

Lit. $[\alpha]_D^{20}$ +8.8 (60% ee)

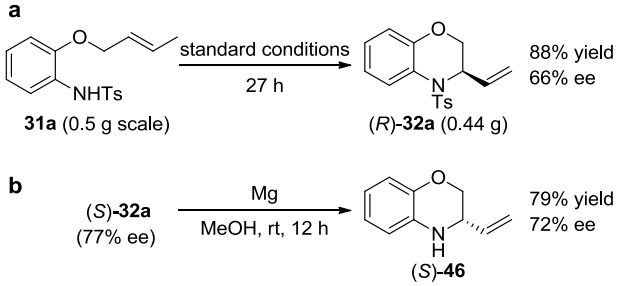
observed. $[\alpha]_D^{25}$ -6.4 (61% ee)

Figure 2.4.1. X-Ray Structure of **32d** (left side) and Comparison of Optical Rotation Value of **32h** (right side).

2.5. Gram-scale Reaction and Detosylation of 32a

The present reaction promoted by Pd–SPRIX complex was easily transferable to gram-scale synthesis in enantioselective manner. When the reaction of (*E*)-**31a** (0.50 g) was performed under the standard conditions, product (*R*)-**32a** was obtained in 88% yield (0.44 g) with 66% ee (Scheme 2.5.1a). The Ts group was easily removable from the nitrogen atom in order to generate an unprotected heterocyclic amine **46**. For example, the detosylation of (*S*)-**32a** with 77% ee proceeded smoothly by treating with Mg and MeOH to generate deprotected benzoxazine product (*S*)-**46** in 79% yield without significant loss in ee (Scheme 2.5.1b).[6d]

Scheme 2.5.1. Gram-Scale Reaction and Detosylation of 34a.

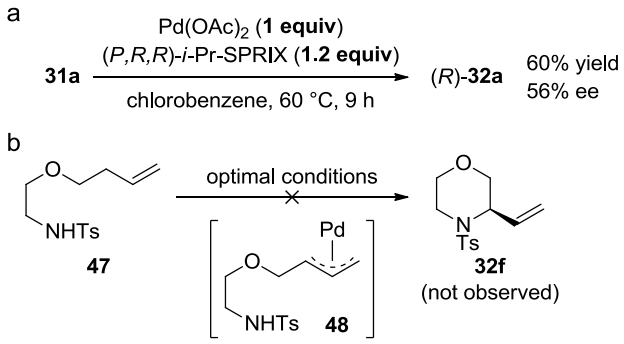


2.6. Mechanistic Study

Oxidative amination of olefin may proceed *via* three different reaction pathways, such as conventional aza-Wacker-type reaction, Pd(II)/Pd(IV) catalysis or allylic amination. To gain

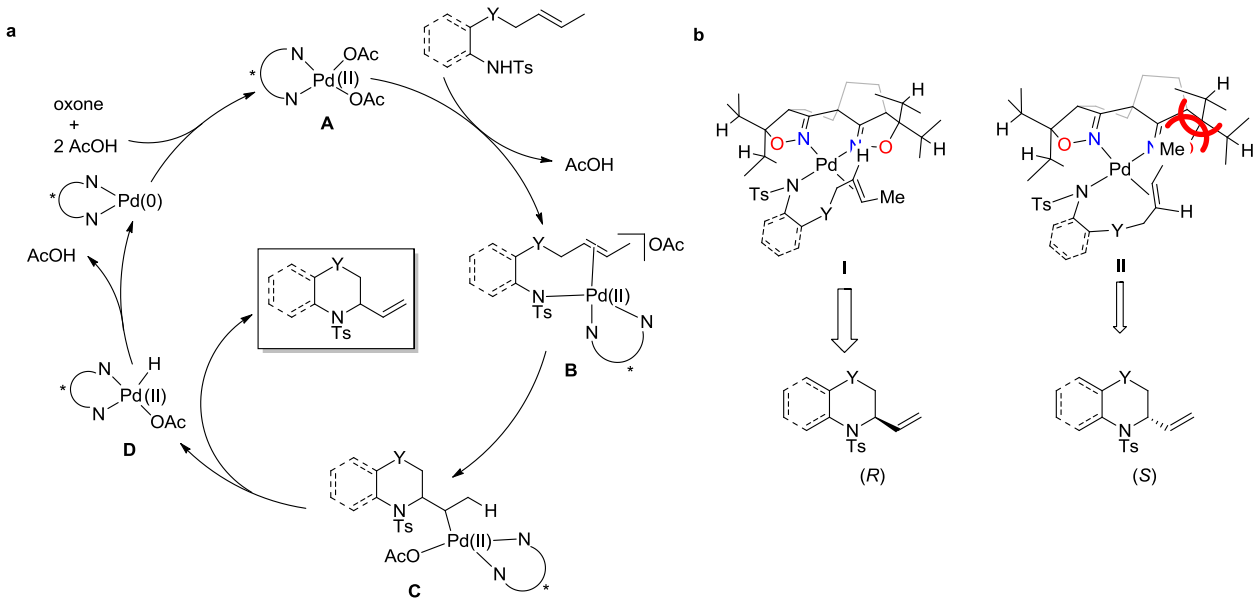
insight in the reaction mechanism, control experiments were performed. When the reaction of **31a** was carried out in the presence of stoichiometric amount of $Pd(OAc)_2$ in absence of any oxidant, aimed product (*R*)-**32a** was generated in 60% yield with 56% ee (Scheme 2.6.1a). Since the desired enantioselective cyclization proceeded in absence of Oxidant, the possibilities of Pd(II)/Pd(IV) catalysis can be excluded. Oxidative allylic amination *via* the C–H activation is one more possibility. If oxidative allylic amination is responsible for this catalytic system then product **32f** would also be formed from homoallyl ether substrate **47** which is an olefinic isomer of **31f**, *via* the π-allyl Pd intermediate **48** (Scheme 2.6.1b). The generation of **32f**, however, was not observed at all in the ^{1}H NMR of the crude reaction mixture. From these experimental results, I conclude that the oxidative cyclization of **31** catalyzed by Pd–SPRIX complex proceeds through the conventional Wacker-type mechanism.

Scheme 2.6.1. Preliminary Mechanistic Study



A plausible mechanistic cycle is shown in Scheme 2.6.2.a. Initially the coordination of substrate **31** with Pd–SPRIX complex **A** leads to chelate complex **B** *via* ligand exchange of acetate with the sulfonamide and the olefin. Although the exact reaction mechanism for the next C–N bond formation is not clear yet, I believe that *syn*-aminopalladation is most favorable pathway.[11] After the generation of alkyl–Pd intermediate **C** β-hydride elimination gave the desired *N*-heterocyclic products **32** and Pd–H intermediate **D**. Reductive elimination of one equivalent AcOH from intermediate **D** produced a Pd(0) intermediate **E**. Oxidation of Pd(0)–SPRIX intermediate to a catalytically active Pd(II)–SPRIX complex took place in the presence of oxone and acetic acid. The *syn*-aminopalladation from **B** to **C**, i.e. the olefin insertion into Pd-N bond is supposed to be the enantio-determining step. (*P*,*R*,*R*)-*i*-Pr-SPRIX ligand create a C_2-symmetric environment around the palladium center, where the *i*-Pr groups locate in the first and third quadrants.[12] There are two different stereochemical models for intermediate **B** (Scheme 2.6.2.b). One is intermediate **I**, where the olefin moiety of **31** coordinates to the Pd–*i*-Pr-SPRIX catalyst in such a manner that the terminal part of olefin

could avoid the steric repulsion with *i*-Pr groups of ligand. On the other hand, model **II** has an unfavorable interaction between the alkene terminus and the axial *i*-Pr substituent of the ligand. Thus the stereo-determining step *syn*-aminopalladation takes place preferentially from model **I** to furnish products **32** in a (*R*)-form. The observed higher enantioselectivity by introducing a bulky *i*-Pr substituent at the terminus of olefin (**31k**, Table 2.3.1) can be explained *via* the model **II** which lead to a greater steric repulsion with the ligand.



Scheme 2.6.2. **a**) Plausible Reaction Mechanism and **b**) Stereochemical Model

2.7. Conclusion

I developed a new efficient Pd–(*P*,*R*,*R*)-*i*-Pr-SPRIX catalyzed methodology for enantioselective oxidative amination of olefin in presence of an internal sulfonamide nucleophile. The use of other known chiral ligand failed to provide desired cyclization, which proved the superiority of SPRIX as ligand for this olefin oxidation. The control experiments suggested that the reaction followed the Pd(0)/Pd(II) catalysis like a conventional Wacker-type oxidation of olefin. This cyclization allowed us to generate a vast number of *N*-heterocyclic compounds having chiral center α-position to nitrogen with good to moderate enantioselectivity. This product would be an important intermediate for the natural product or pharmaceutical product synthesis.

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Chapter 3

Efficient Construction of Allyl Amine Derivatives *via* Intermolecular Aza-Wacker-Type Reaction

3.1. Introduction

Allylamines are highly versatile building blocks[1] in the modern synthetic organic chemistry to produce various kinds of heterocycles, biologically active compounds and pharmaceutically important molecules (Figure 3.1.1).[2] The presence of allylamine derivatives in many commercially available drugs, such as naftifine (antifungal drug),[3] terbinafine (antifungal drug),[4] flunarizine (calcium channel blocker)[5] proved the versatility of these compounds (Figure 3.1.2). Mitochondrial targeting agent gramicidine S can be synthesized easily from the allylamine derivative JP4-039.[6] Interestingly, simple (*E*)-4-phenylbut-3-en-2-amine also showed biological activities like dopamine transporter (DAT), norepinephrine transporter (NET).[7]

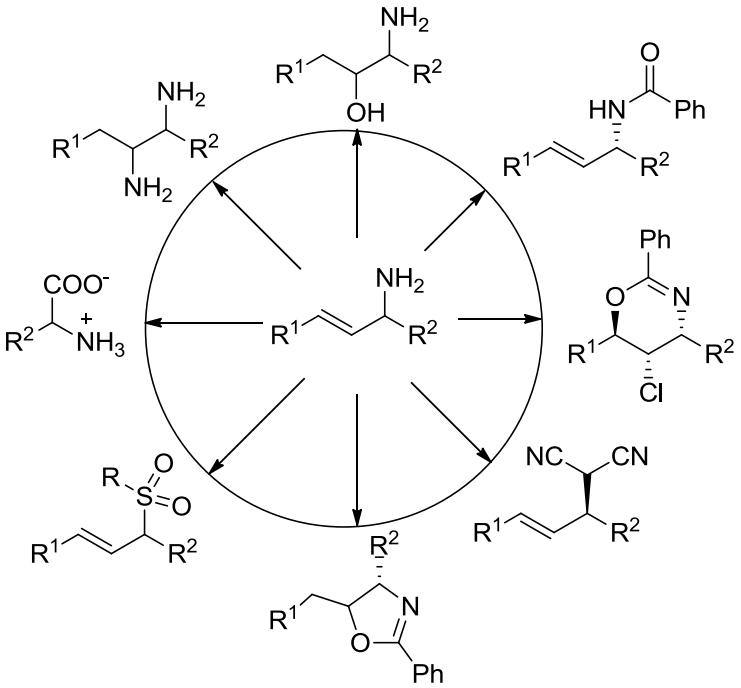


Figure 3.1.1. Synthetic Transformations of Allylamine Building Blocks

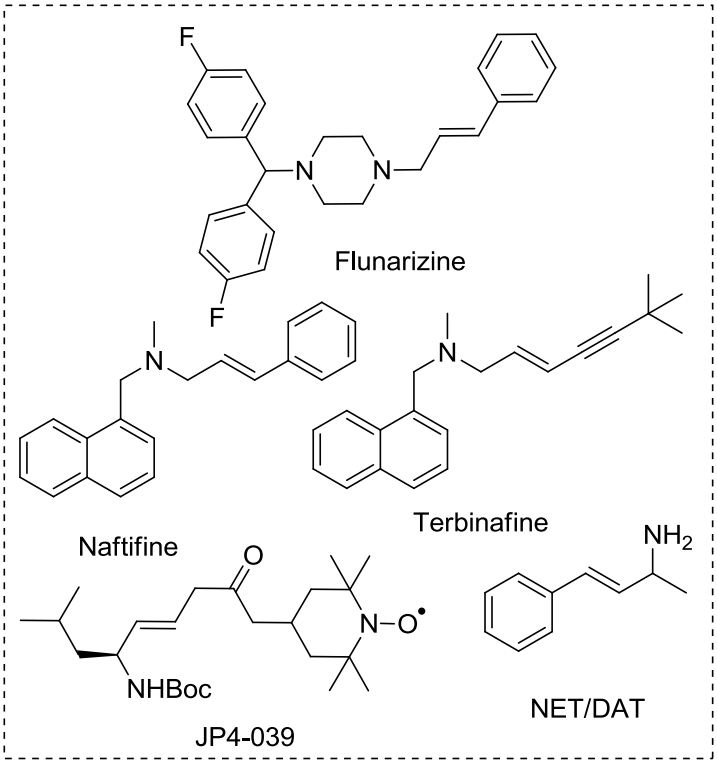
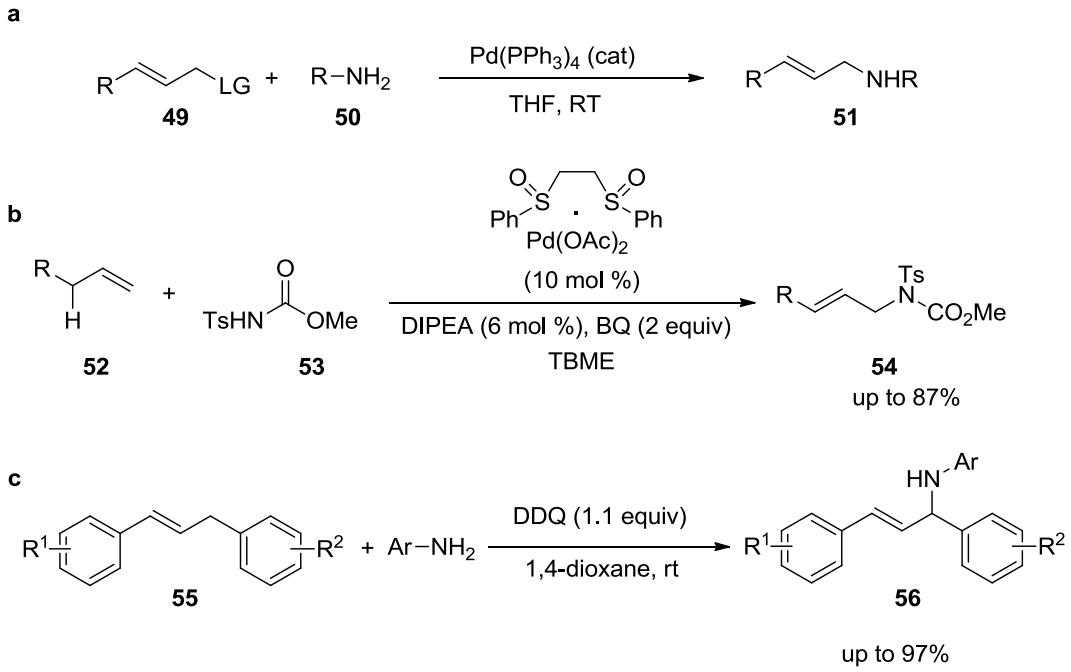


Figure 3.1.2. Representative Examples of Biologically Active Allylamine Derivatives

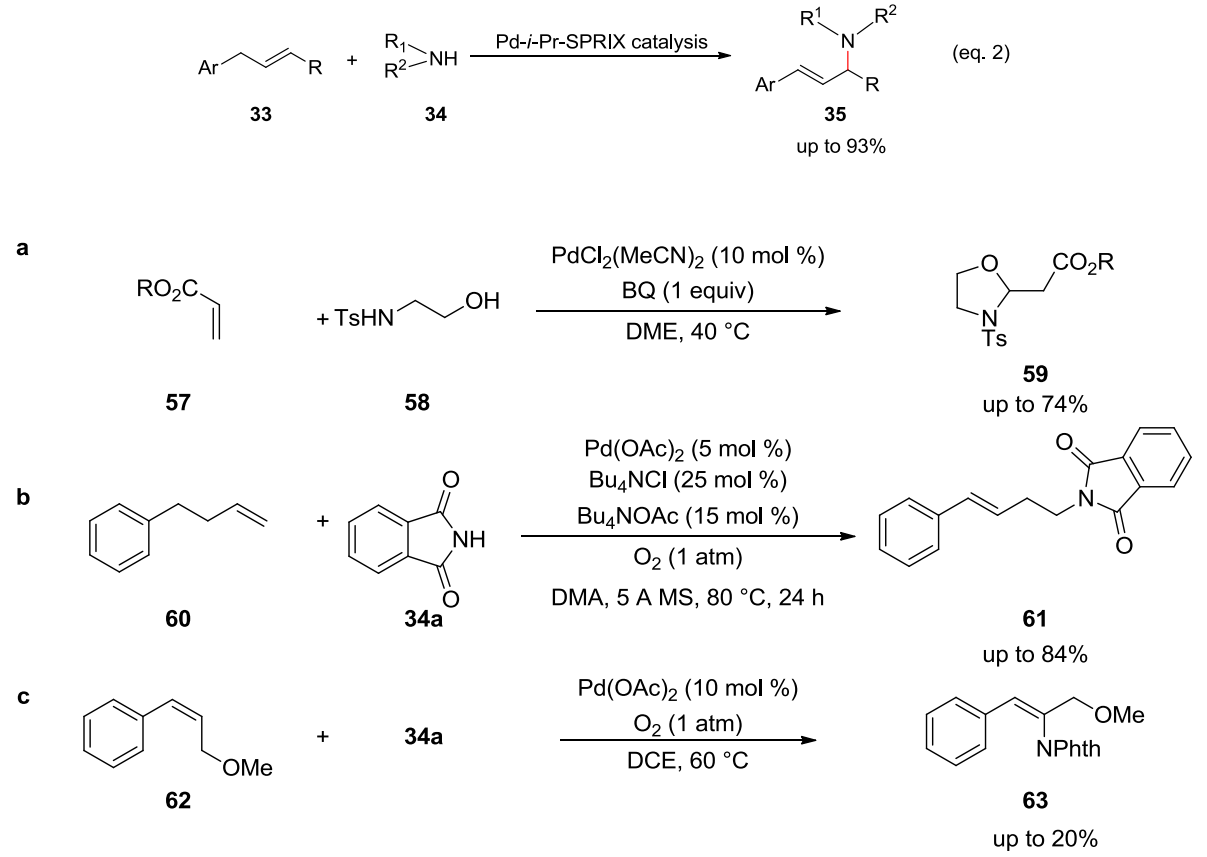
A common route to synthesize allylic amine is the palladium catalyzed Tsuji-Trost reaction (Scheme 3.1.1. a).[8] Tsuji-Trost reaction demands a pre-functionalized olefin having a leaving group attached at the allylic position in order to generate π–allyl-palladium intermediate. Transition metal catalyzed C–H functionalization is a well-known and powerful tool to construct a carbon-heteroatom bond. Allylamine derivatives also can be synthesized *via* C–H functionalization. The synthesis of allylamine derivatives *via* C–H functionalisation is limited to terminal olefin.[9] White reported allylic C–H amination reaction of terminal olefin **52** by utilizing the sulfoxide ligand on palladium catalysis (Scheme 3.1.1. b).[10] In 2012, Bao and his co-workers introduced transition metal-free cross dehydrogenative coupling (CDC) reaction of 1,3 diarylpropanes **55** with anilines **56** under mild conditions (Scheme 3.1.1 c).[11] The mechanistic study of CDC reaction revealed that the coupling proceeded through radical intermediate. As a result, poor regioselectivity and poor substrate scope was observed. In spite of several methodologies available for the synthesis of allylamine derivatives, a robust methodology is required.



Scheme 3.1.1. Representative Methodologies for the Synthesis of Allylamine Derivatives

On the other side, allylamine derivatives can be synthesized *via* an intermolecular aza-Wacker-type reaction. Booker-Milburn and his co-workers reported first intermolecular aza-Wacker-type reaction of an activated olefin **57** in order to synthesize oxazolidine derivative **59** (Scheme 3.1.2. a).[12] The necessity of activated olefin highly limits the reaction. Recently, Hull and his co-workers published an anti-Markovnikov oxidative amination of but-3-en-1-ylbenzene (**60)** to produce styrene-type product **61** through the aza-Wacker-type reaction (Scheme 3.1.2. b).[13] The reported intermolecular aza-Wacker-type reactions are restricted to the terminal olefin. Stahl and his co-workers failed to use internal olefin in oxidative amination reactions (Scheme 3.1.2. c).[14] When they treated (*Z*)-(3-methoxyprop-1-en-1-yl)benzene (**62**) with phthalimide (**34a**) in presence of a catalytic amount of palladium salts under the oxygen atmosphere then they observed maximum 20% yield of the amination product.

Since the weak coordination ability of SPRIX is able to maintain the Lewis acidity of the metal center, I envisioned that Pd–SPRIX complex might able to increase the electrophilicity of the internal olefin by virtue of olefin-metal coordination. As a result, the olefin might allow the nitrogen nucleophile to undergo nucleophilic addition to provide allylamine derivatives *via* intermolecular aza-Wacker-type reaction. Herein, I reported an efficient synthetic route to allylamine derivatives based on the aza-Wacker-type reaction of internal olefin substrates (eq. 2)



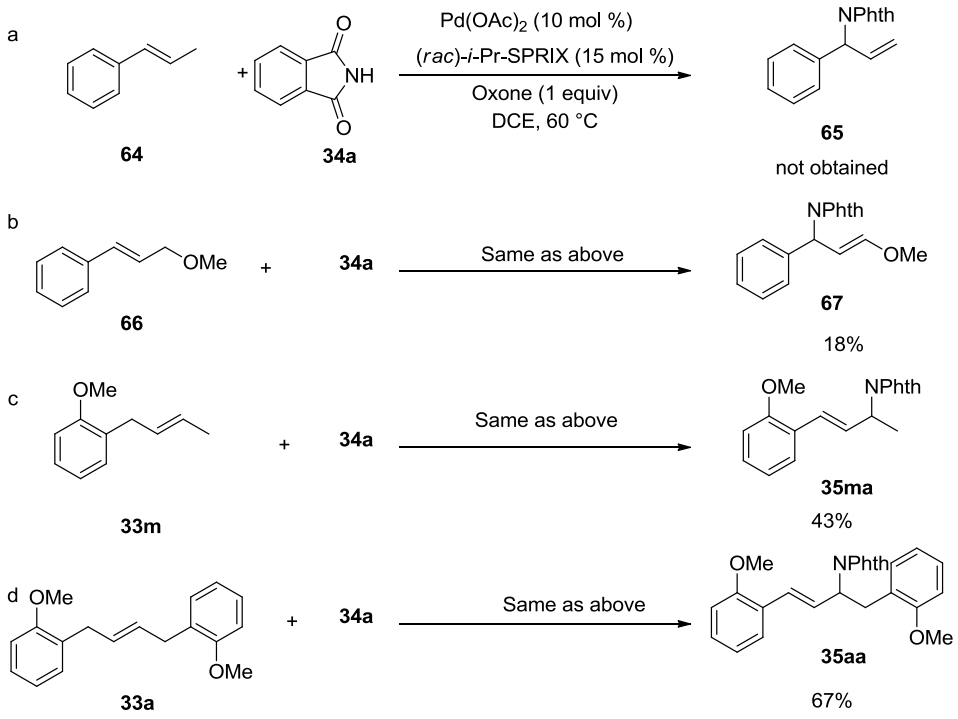
Scheme 3.1.2. Intermolecular Aza-Wacker-Type Reactions

3.2. Results and discussion

3. 2. 1. Effect of Olefin Structure

The choice of appropriate olefin for the investigation of reaction conditions for oxidative amination was very crucial. When simple (*E*)-prop-1-en-1-ylbenzene (**64)** was treated under the optimal conditions of the 6-membered cyclizaion (except the use of DCE instead of chlorobenzene), no desired amination was observed (Scheme 3.2.1.a). Gratifyingly, installation of a methoxy group on the substrate turned out to be effective to produce allylamine derivative **67** with 18% yield. I assumed that the methoxy substituent might work as a directing group to improve the reactivity. On the other hand, conjugated double bond like styrene has high bond dissociation energy compared with an isolated double bond because of the resonance stabilization. So, the use of a non-conjugated olefin as a starting material which will be transformed to a conjugated olefin in product (styrene-type) may provide better reactivity. Interestingly, improved reactivity was indeed observed from (*E*)-1-(but-2-en-1-yl)-2-methoxybenzene (**33m)** (Scheme 3.2.1.c). Further improvement in reactivity was observed by using a symmetric olefin **33a**. As a result, I chose alkene **33a** as the best candidate for the

intermolecular aza-Wacker-type reaction and started to find an appropriate nitrogen nucleophile.

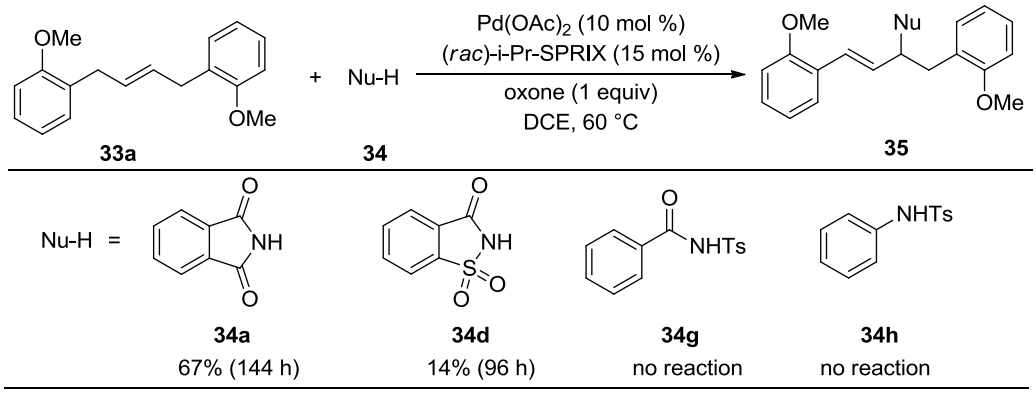


Scheme 3.2.1. Initial Trials to Find out Suitable Olefin Reaction Partner

3.2.2. Effect of Nitrogen Nucleophiles

After having the suitable olefinic reaction partner, I focused my attention to find out appropriate nucleophile for the aza-Wacker-type reaction. The treatment of phthalimide **34a** with olefin **33a** under the Pd–SPRIX catalysis provided 67% desired product (Scheme 3.2.2). Other nucleophiles, such as saccharine (**34d**) provided only 14% yield of desired allylamine derivatives whereas *N*-tosylbenzamide (**34g**) and 4-methyl-*N*-phenylbenzenesulfonamide (**34h**) failed to generate allylamine derivatives. So, I chose the phthalimide as the appropriate nucleophile for the optimization of reaction parameters.

Scheme 3.2.2. Effect of Nitrogen Nucleophiles[a]

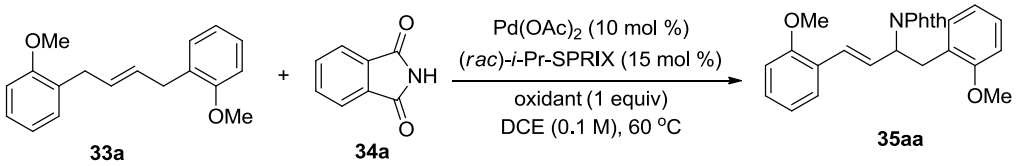


[a] All reactions were performed in the presence of 3 equiv **33a**, 1 equiv **34**, 10 mol % of $Pd(OAc)_2$, 15 mol % of (*rac*)-*i*-Pr-SPRIX, and 1 equiv of oxidant in DCE (0.1 M) at 60 °C under a nitrogen atmosphere.

3.2.3. Effect of Oxidant

After the choice of reaction partners as (*E*)-1,4-bis(2-methoxyphenyl)but-2-ene (**33a**) and phtahlimide (**34a**), I started to optimize the oxidant (Table 3.2.1). Oxone provided the desired product **35aa** in 67% yield (entry 1). Unfortunately, the reaction was very slow and took 6 days to provide 67% NMR yield. Replacement of oxone by potassium persulfate provided quite similar yield with respect to oxone but reaction was slightly accelerated (entry 2). Molecular oxygen was inefficient for this reaction (entry 3). Hypervalent iodine ($PhI(OAc)_2$) and aqueous hydrogen peroxide (H_2O_2) provided only a trace amount of **35aa** (entries 4 and 5). Other oxidants such as *p*-benzoquinone (BQ) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) were also unable to promote the reoxidation of Pd(0) to catalytically active Pd(II) intermediate (entries 6 and 7). Further reaction acceleration was observed by increasing the oxidant loading to 3 equiv (entries 2 and 8). Finally, 3 equiv of potassium persulfate provided the champion result for the amination reaction (entry 8).

Table 3.2.1. Screening of Oxidant for Aza-Wacker-Type Reaction[a]



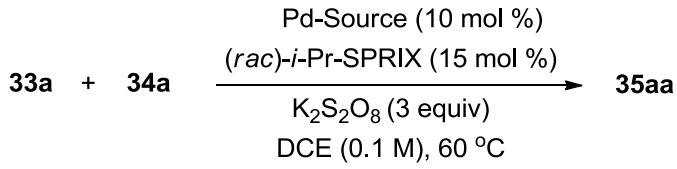
Entry	Oxidant	Time (h)	Yield (%)
1	Oxone	144	67
2	$K_2S_2O_8$	96	65
3	O_2 (1 atm)	24	n.r
4	$PhI(OAc)_2$	24	trace
5	H_2O_2 (aq.)	24	trace
6	*p*-Benzoquinone (BQ)	24	trace
7	DDQ	24	trace
8[b]	$K_2S_2O_8$	80	69

[a] All reactions were performed in the presence of 3 equiv **33a**, 1 equiv **34a**, 10 mol % of $Pd(OAc)_2$, 15 mol % of (*rac*)-*i*-Pr-SPRIX, and 1 equiv of oxidant in DCE (0.1 M) at 60 °C under a nitrogen atmosphere.[b] $K_2S_2O_8$ (3 equiv)

3.2.4. Effect of Palladium Source

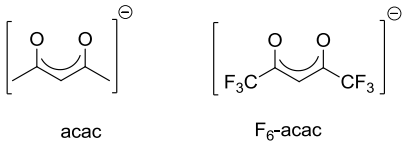
Electrophilicity of the palladium salts plays a pivotal role in this transformation. Palladium acetate and palladium trifluoroacetate afforded comparable reactivity whereas $PdCl_2$ and $PdBr_2$ weren't able to furnish the aimed product (entries 1-4, Table 3.3.2). Strong coordination of chloride and bromide to palladium compared to acetate and trifluoroacetate makes the formation of a vacant site on the complex difficult. As a result, the substrate hardly interacts with the reactive metal center which led to poor reactivity of $PdCl_2$ or $PdBr_2$. Bis(acetonitrile)dichloropalladium or bis(benzonitrile)palladium dichloride were not effective for this oxidative amination of olefin (entries 5 and 6). Allylpalladium chloride dimer was able to furnish the desired transformation (entry 7). Electrophilic palladium source such as tetrakis(acetonitrile)palladium tetrafluoroborate was also capable to generate **35aa** in 56% yield (entry 8). Palladium acetylacetonate promoted the reaction to give 66% chemical yield whereas more electrophilic palladium hexafluoroacetylacetonate reduced the reaction time to 60 hours from 96 hours without any loss of chemical yield (entries 9 and 10). At the end of the palladium salt screening, $Pd(F_6\text{-acac})_2$ was chosen as the best candidate for the next steps.

Table 3.2.2. Screening of Palladium Source[a]



Entry	Pd-Source	Time (h)	Yield (%)
1	$Pd(OAc)_2$	80	69
2	$Pd(OCOCF_3)_2$	120	61
3	$PdCl_2$	30	trace
4	$PdBr_2$	30	n.r.[b]
5	$PdCl_2(MeCN)_2$	24	trace
6	$PdCl_2(PhCN)_2$	24	trace
7[c]	$[PdCl(allyl)]_2$	120	59
8	$[Pd(MeCN)_4](BF_4)_2$	96	56
9	$Pd(acac)_2$	96	65
10	$Pd(F_6\text{-acac})_2$	60	66

[a]All reactions were performed in the presence of 3 equiv **33a**, 1 equiv **34a**, 10 mol % of Pd-Source, 15 mol % of (*rac*)-*i*-Pr-SPRIX, and 1 equiv of oxidant in DCE (0.1 M) at 60 °C under a nitrogen atmosphere. [b] n.r. No reaction. [c] $[PdCl(allyl)]_2$ (5 mol %)



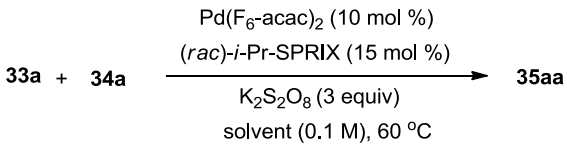
acac F_6-acac

3.2.5. Effect of Solvent

After having optimized palladium source and oxidant I turned my attention to find out the best solvent (Table 3.2.3). In all halogenated solvents such as 1,2-dichloroethane, benzotrifluoride, chlorobenzene and carbon tetrachloride, **35aa** was observed with similar yields (entries 1-4). Maximum yield of **35aa** was obtained in toluene but high reaction retardation was observed compared to DCE (entries 1 and 5) whereas in acetonitrile **35aa** was obtained with 45% yield (entry 6). Ethereal solvents, DMF, and DMA were not suitable for

this transformation (entries 7-10). In terms of reaction rate stimulation, DCE and benzotrifluoride had quite similar effect (entries 1 & 2). I chose DCE as the best candidate for the next set of optimization because it is more cost effective compare to benzotrifloride.

Table 3.2.3. Solvent Optimization[a]



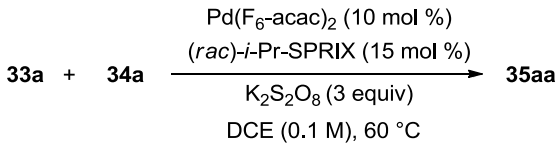
Entry	Solvent	Time (h)	Yield (%)
1	DCE	60	66
2	Benzotrifluoride	60	68
3	Chlorobenzene	72	64
4	CCl_4	96	64
5	Toluene	144	72
6	MeCN	120	45
7	1,4-dioxane	24	n.r.[b]
8	THF	24	trace
9	DMF	24	n.r.
10	DMA	24	n.r.

[a]All reactions were performed in the presence of 3 equiv **33a**, 1 equiv **34a**, 10 mol % of $Pd(F_6\text{-acac})_2$, 15 mol % of (*rac*)-*i*-Pr-SPRIX, and 3 equiv of $K_2S_2O_8$ in solvent (0.1 M) at 60 °C under a nitrogen atmosphere. [b] n.r. No reaction.

3.2.6. Effect of Starting Materials' Ratio

Next, I focused my attention to find the appropriate starting materials ratio (Table 3.2.4). Initially, I treated 3 equiv of **33a** with 1 equiv of **34a** in presence of a catalytic amount of Pd–SPRIX complex (entry 1). When 2 equiv of **33a** was tested under the catalytic conditions **35aa** was obtained with unaltered reactivity whereas 1 equiv of **33a** furnished slightly lower yield (entries 2 & 3). Finally, I found 1.2 equiv of **33a** was sufficient enough to provide the **35aa** without any loss in yield (entry 4). Next I examined the effect of excess amount of nucleophile **34a** (entry 5). When I treated 5 equiv of **34a** with 1 equiv of **33a** no improvement in chemical yield of **35aa** was observed.

Table 3.2.4. Effect of Starting Materials' Ratio[a]



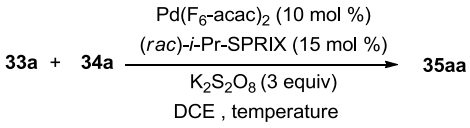
Entry	**33a** (x equiv)	Yield (%)
1	3	66
2	2	65
3	1	54
4	1.2	65
5[b]	1	60

[a]All reactions were performed in the presence of X equiv **33a**, 1 equiv **34a**, 10 mol % of $Pd(F_6\text{-acac})_2$, 15 mol % of (*rac*)-*i*-Pr-SPRIX, and 3 equiv of $K_2S_2O_8$ in DCE (0.1 M) at 60 °C under a nitrogen atmosphere.[b] **34a** : 5 equiv

3.2.7. Effect of Reaction Temperature

The increase in reaction temperature led to very high acceleration of reaction with the improvement in chemical yield (Table 3.2.5). When reaction was carried out at 90 °C full conversion of phthalimide was observed within 20 h to provide 93% NMR yield whereas the isolated yield was 88% (entry 2). On the other hand, sluggish reactivity was observed at lower temperature (entry 3).

Table 3.2.5. Reaction Temperature Screening[a]



Entry	Temp (°C)	Time (h)	Yield (%)
1	60	60	65
2	90	20	93 (88[b])
3	30	120	28

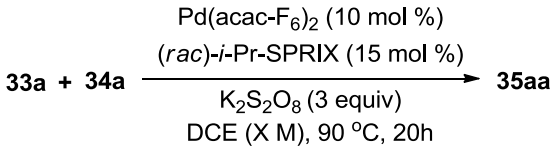
[a]All reactions were performed in the presence of 1.2 equiv **33a**, 1 equiv **34a**, 10 mol % of $Pd(F_6\text{-acac})_2$, 15 mol % of (*rac*)-*i*-Pr-SPRIX, and 3 equiv of $K_2S_2O_8$ in DCE (0.1 M) under a nitrogen atmosphere. *b*: isolated yield

3.2.8. Effect of Reaction Concentration

Next, I examined the effect of reaction concentration (Table 3.2.6). When the reaction was carried out in 0.1 M scale then the desired product was obtained in 93% NMR yield (entry 1). High reaction concentration such as 1 M provided slightly reduced yield of **35aa** (entry 2). Low concentration (0.01 M) further reduced the chemical yield of allylamine derivatives

35aa (entry 3). Finally, 0.1 M concentration was chosen as the best conditions for intermolecular aza-Wacker-type reaction.

Table 3.2.6. Concentration Dependence[a]



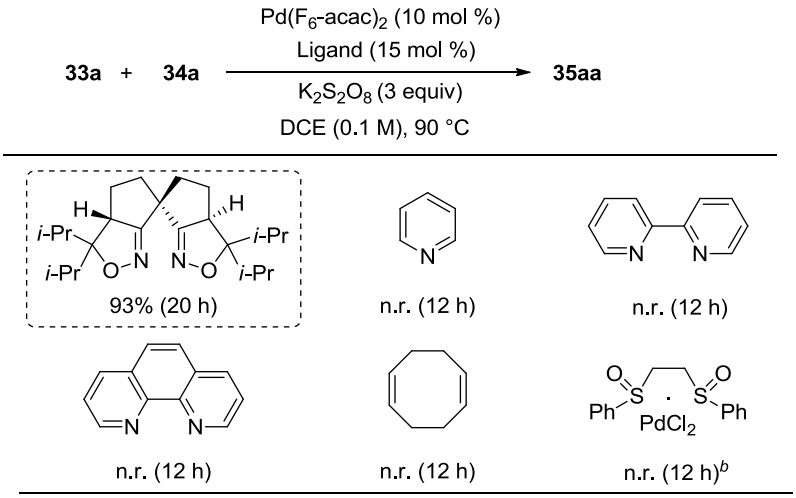
Entry	x M	Yield (%)
1	0.1	93
2	1	85
3	0.01	73

[a]All reactions were performed in the presence of 1.2 equiv **33a**, 1 equiv **34a**, 10 mol % of $Pd(F_6\text{-acac})_2$, 15 mol % of (*rac*)-*i*-Pr-SPRIX, and 3 equiv of $K_2S_2O_8$ in DCE (X M) under a nitrogen atmosphere.

3.2.9. Importance of SPRIX Ligand

To check the importance of SPRIX, I examined several other ligands for aza-Wacker-type reaction (Scheme 3.2.3). Pd–SPRIX complex provided the aimed product with excellent yield. The reactions by replacing SPRIX from the optimal conditions by pyridine, bipyridine or phenanthroline were unsuccessful with complete recovery of **34a**. The higher σ-donating ability of these ligands might responsible for the failure. The use of cycloocta-1,4-diene (COD) as a ligand also turned out to be ineffective. The bis-sulfoxide-Pd catalyst which is known to promote the allylic C–H amination reaction failed to provide **35aa**. Based on these experimental results, I concluded that SPRIX is playing a very crucial role in this transformation. The week σ-donating ability of SPRIX preserved the Lewis acidity of palladium and as a consequence the olefin activation was possible by Pd–SPRIX complex.

Scheme 3.2.3. Comparison of Reactivity between Different Ligands.

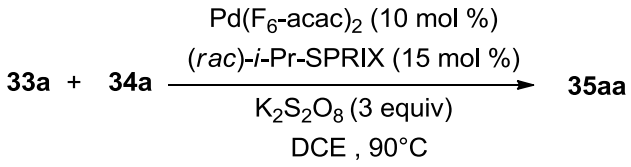


[a] All reactions were performed in the presence of 1.2 equiv **33a**, 1 equiv **34a**, 10 mol % of $Pd(F_6\text{-acac})_2$, 15 mol % of (rac)-*i*-Pr-SPRIX, and 3 equiv of $K_2S_2O_8$ in DCE (0.1 M) at 90 °C under a nitrogen atmosphere. [b] without $Pd(F_6\text{-acac})_2$

3.2.10. Control Experiments

After having the optimized reaction conditions in hand, I performed control experiments in order to understand the necessities of all reagents or in order to understand the involvement of radical intermediate in the reaction (Table 3.2.7). The absence of either palladium hexafluoroacetylacetonate or *i*-Pr-SPRIX was unable to afford the **35aa** (entries 1 and 2). When potassium persulfate was dropped from the reaction system 6% product was observed, suggesting that reaction was stopped after the 1st catalytic cycle due to the absence of Pd(II)-intermediate (entry 3). The presence of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) had no significant effect on the reactivity to furnish 84% chemical yield (entry 4). This result clearly declined the possibilities of generation of radical intermediate in the reaction system.

Table 3.2.7. Control Experiments[a]



Entry	Deviation from Standard Conditions	Yield (%)
1	none	93
2	without $Pd(F_6\text{-acac})_2$	n.r.
3	without *i*-Pr-SPRIX	n.r.
4	without $K_2S_2O_8$	6
5	in presence of 1 equiv TEMPO	84

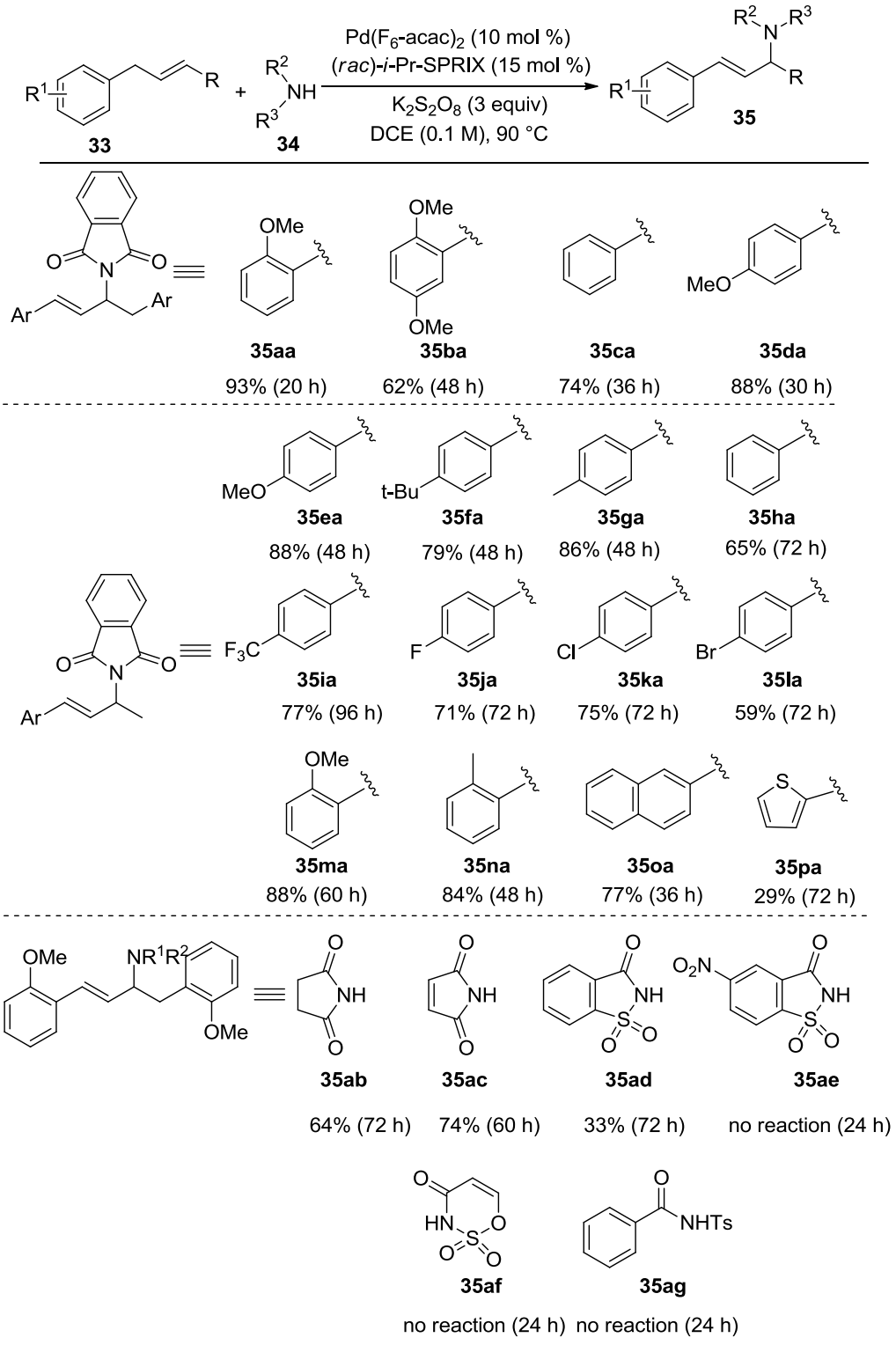
[a] Standard conditions: 1.2 equiv **33a**, 1 equiv **34a**, 10 mol % of $Pd(F_6\text{-acac})_2$, 15 mol % of (*rac*)-*i*-Pr-SPRIX, and 3 equiv of $K_2S_2O_8$ in DCE (0.1 M) at 90 °C under a nitrogen atmosphere.

3.3. Substrate Scope and Limitations

Next, I turned my attention to examine the substrate scope for intermolecular aza-Wacker-type reaction (Table 3.3.1). When allylbenzene substrate **33a** was treated with phthalimide **34a** under the optimized reaction conditions, target allylamine product **35aa** was obtained in 93% NMR yield. Other symmetrical substrates **33b**, **33c** and **33d** having 2,5-dimethoxy, no substituent, and 4-methxoxy substituent were also converted to desired products **35ba**, **35ca** and **35da**, respectively without any difficulties. In the case of unsymmetrical substrates, this intermolecular oxidative amination proceeded well with excellent regioselectivity. Crotylbenzene substrates containing electron-rich substituent such as, MeO, *t*-Bu and Me were underwent the reaction efficiently (**35ea**, **35fa** and **35ga**). On the other hand, simple crotylbenzene **33h** also transformed to **35ha** smoothly. The use of electron deficient crotylbenzene (CF_3 and F) furnished 77% and 71% yields of corresponding allylamine derivatives, respectively (**35ia** and **35ja**). Interestingly, chloro and bromo substitutents were also tolerable under these catalytic conditions (**35ka** and **35la**). Sterically-demanding substrates **33ma** and **33na** having MeO and Me groups at the ortho position generated the aimed products in good yields. Replacement of crotylbenzene with crotylnaphthalene had no significant loss of reactivity (**35oa**). When heteroaromatic ring like thiophene was installed with olefin (**33p**), the target compound **35pa** was observed only in 29% chemical yield. The

strong coordination ability of sulfur towards palladium may responsible for this low reactivity.

Table 3.3.1. Substrate Scope and Limitations[a]



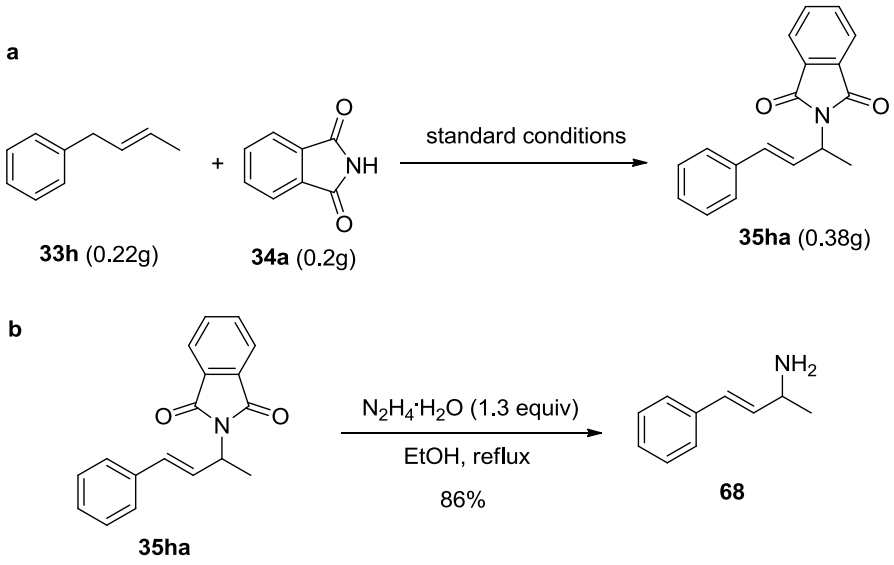
[a] All reactions were performed in the presence of 1.2 equiv **33**, 1 equiv **34**, 10 mol % of $Pd(F_6\text{-acac})_2$, 15 mol % of (*rac*)-*i*-Pr-SPRIX, and 3 equiv of $K_2S_2O_8$ in DCE (0.1 M) at 90 °C under a nitrogen atmosphere.

Instead of phthalimide, different other nucleophiles were also applicable to this transformation. Succinimide (**34b**), maleimide (**3c**) and saccharine (**34d**) afforded the target allylamine successfully. Other nucleophiles such as **34e**, **34f** and **34g** weren't able to provide the reaction.

3.4. Large Scale Reaction and Synthesis of Biologically Active Allyl Amine

The current aza-Wacker-type reaction using Pd–SPRIX complex was easily applicable to large-scale synthesis of allylamine derivatives. When the reaction of **33h** (0.21 g, 1.63 mmol) and phthalimide **34a** (0.2 g, 1.36 mmol) was carried out under the standard conditions, product **35ha** was isolated in 63% yield (0.24 g, 0.85 mmol, Scheme 3.4.1.a). An unprotected allylamine, (*E*)-4-phenylbut-3-en-2-amine (**68**) was readily accessible (Scheme 3.4.1.b). The deprotection of **35ha** proceeded easily by treating with hydrazine monohydrate to furnish free allylamine **68** in 86% yield.[15] Along with its biological activities[7] like dopamine transporter (DAT) or nor-epinephrine transporter (NET), **68** has versatile application in synthetic chemistry as a building block.[1]

Scheme 3.4.1. Gram-Scale Synthesis and Preparation of Unprotected Allylamine



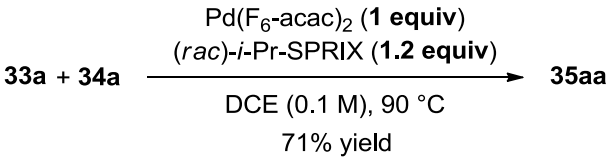
3.5. Reaction Mechanism

Allylamine product **35** generated from substrates **33** and nitrogen nucleophiles **34** might originate through three different pathways, namely i) usual aza-Wacker-type reaction, ii) Pd(II)/Pd(IV) catalysis or iii) C–H activation/allylic amination.

3.5.1. Possibilities of Pd(II)/Pd(IV) Catalysis

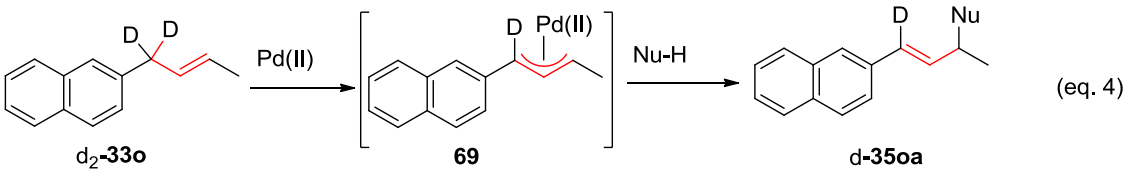
To get a clear idea about the reaction mechanism, I carried out stoichiometric experiment. When the reaction of **33a** and **34a** were performed in the absence of any oxidants using a stoichiometric amount of Pd(F_6-acac)$_2$, **35aa** was produced in 71% yield (Scheme 3.5.1). Therefore, the probability of the generation of Pd(IV) species can be denied for this transformation.

Scheme 3.5.1. Stoichiometric Experiments

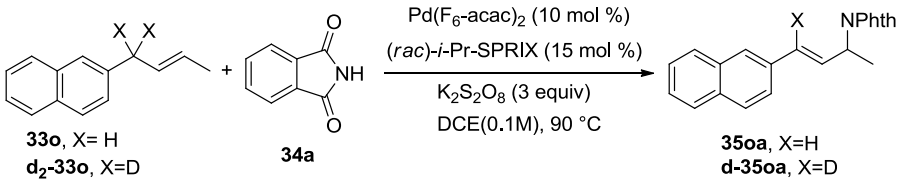


3.5.2. Possibilities of Allylic Amination

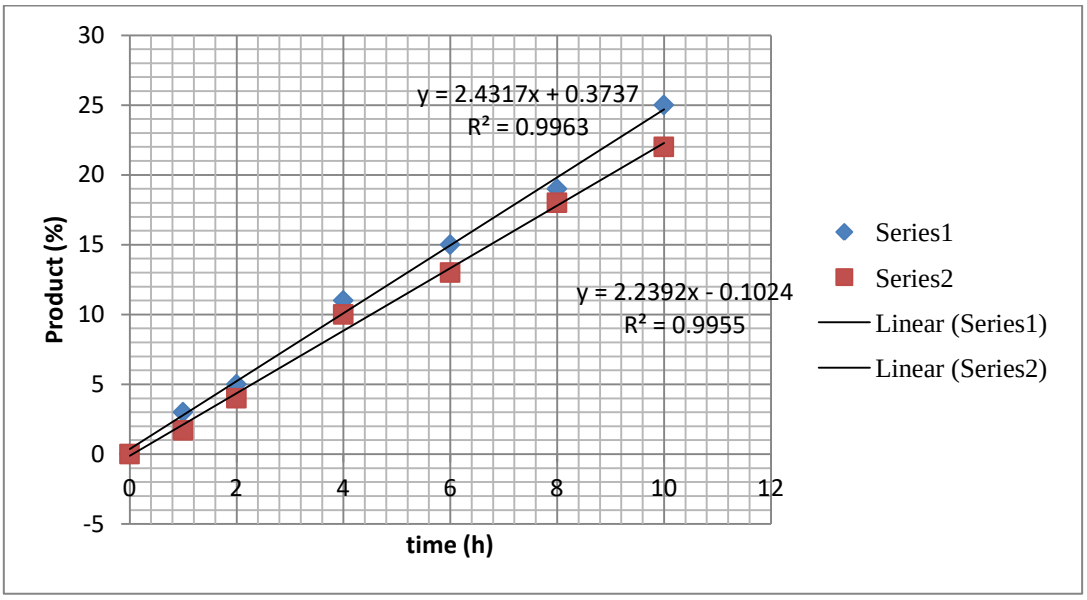
Another plausible pathway is oxidative allylic amination through an allylic C–H bond activation. If allylic amination is responsible for this catalytic system, product *d*-**35oa** should provide high kinetic isotope effect (KIE) because of the C–D bond cleavage in order to generate intermediate **69** (eq. 4). However the observed KIE value was 1.09 which suggests there was no isotope effect (Scheme 3.5.2). White reported C–H allylic amination of a terminal olefin proceeded with KIE 4.0.[10e] Based on these results, I conclude this reaction followed conventional aza-Wacker-type pathway.



Scheme 3.5.2. KIE Measurements



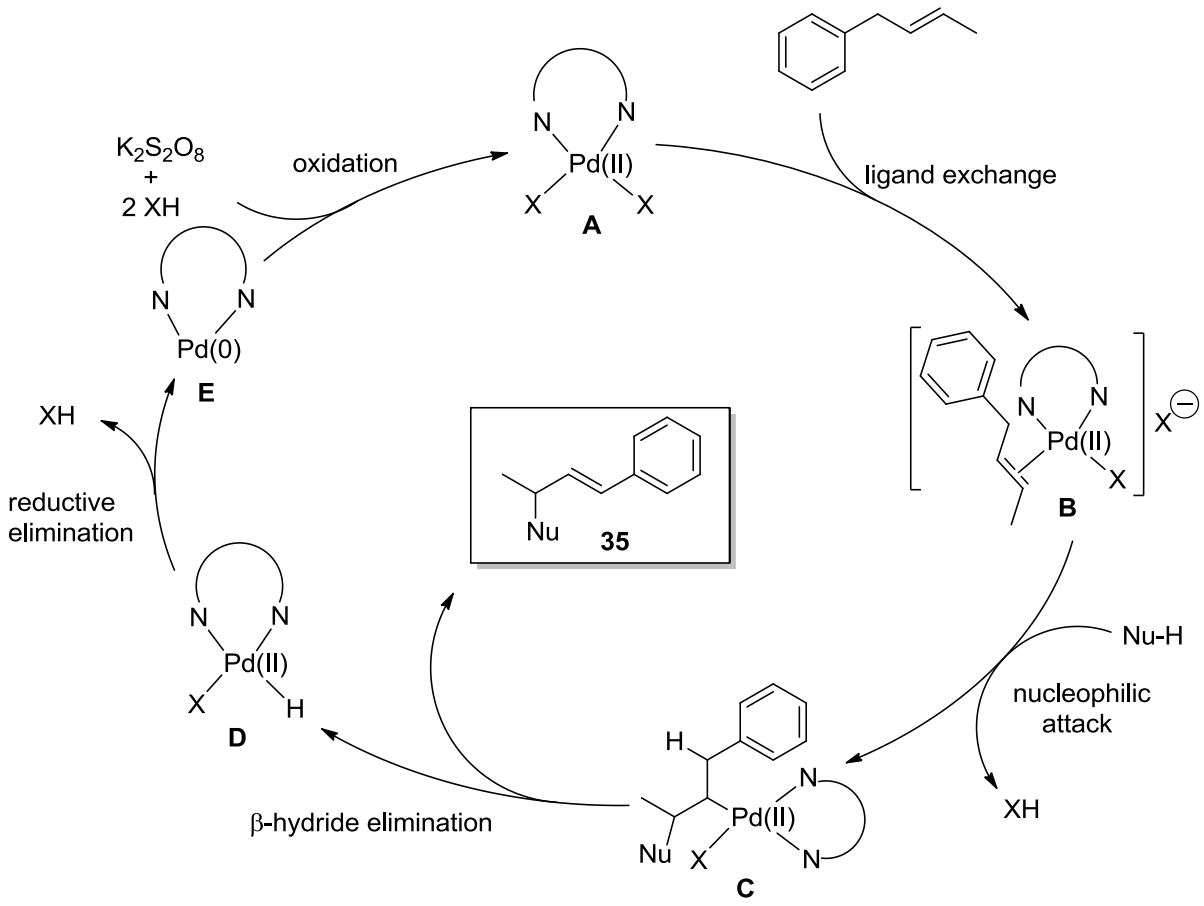
Entry	Time (h)	Yield (%) **35oa**	Yield (%) d-**35oa**
0	0	0	0
1	1	3	1.7
2	2	5	4
3	4	11	10
4	6	15	13
5	8	19	18
6	10	25	22



KIE=slope1/slope2=2.4317/2.2392=1.09

3.5.3. Plausible Reaction Mechanism

A plausible reaction mechanism is shown in Scheme 3.5.3. The initial step of this catalytic system is the coordination of substrate **33** to Pd–SPRIX complex **A**, which leads to a complex **B** *via* ligand exchange of acetylacetonate with alkene. Next step is nucleophilic addition of nitrogen either *via syn*-aminopalladation or *anti*-aminopalladation to generate intermediate **C**. β-Hydride elimination from alkyl–Pd intermediate **C** gave desired allylamine products **35** and Pd–H intermediate **D**. Reductive elimination of one equivalent acetylacetone from intermediate **D** produced Pd(0) intermediate **E**. Potassium persulfate and acetylacetone converted Pd(0)–SPRIX intermediate to a catalytically active Pd(II)–SPRIX complex.

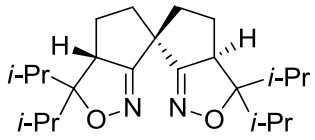
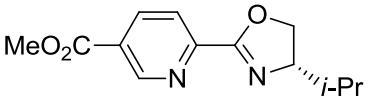
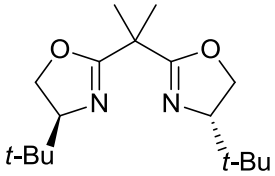
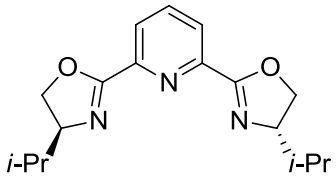
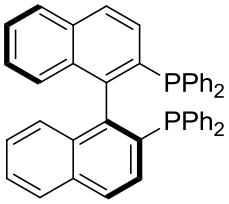
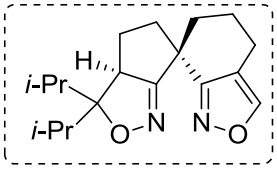


Scheme 3.5.3. Plausible Reaction Mechanism

3.6. Enantioselective Approach

Finally, I tried this reaction in enantioselective manner (Table 3.6.1). The replacement of (*rac*)-*i*-Pr-SPRIX by (*P*,*R*,*R*)-*i*-Pr-SPRIX ligand provided the target product with 11% ee (Scheme 3.6.1). The reaction with *i*-Pr-PYOX as a ligand generated only 9% target compound. Other chiral ligands such as *t*-Bu-BOX and *i*-Pr-PYBOX, which are known to provide enantioselective Wacker-type cyclization, failed to provide **35aa**. Similarly, (*S*)-BINAP was unable to generate **35aa**. Strong coordination abilities of these ligands might destroy the Lewis acidity of the metal. Interestingly, a more weak coordinating chiral ligand possessing isoxazole-isoxazoline coordination site[16] slightly improved the enantioselectivity (25% ee). Further improvement of enantioselectivity was observed by lowering the reaction temperature to 50 °C which provided 39% ee with 50% chemical yield.

Table 3.6.1. Effect of Chiral Ligands towards Enantioinduction[a]

		
93% (18 h) 11% ee	9% (12 h) ---	n.r (12 h) ---
		
n.r (12 h) ---	n.r (12 h) ---	94% (26 h) 25% ee 50% (96 h)[b] 39% ee

[a] All reactions were performed in the presence of 1.2 equiv **33a**, 1 equiv **34a**, 10 mol % of $Pd(F_6\text{-acac})_2$, 15 mol % of Ligand, and 3 equiv of $K_2S_2O_8$ in DCE (0.1 M) at 90 °C under a nitrogen atmosphere. [b] At 50 °C

3.7. Conclusion

Here, I developed a new efficient and straightforward methodology for the generation of allylamine derivatives from easily accessible internal alkenes **33** and nitrogen neucleophiles **34** catalyzed by Pd–(*P*,*R*,*R*)-*i*-Pr-SPRIX complex. The use of other known ligands failed to provide desired transformation which supports the superiority of SPRIX as ligand for this olefin oxidation. Stoichiometric experiments and KIE measurements suggested that the reaction followed the aza-Wacker-type pathway. The synthesis of biologically active molecule, (*E*)-4-phenylbut-3-en-2-amine, was successful. This allylamine product would be an important intermediate for natural product or pharmaceutical product synthesis.

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Experimental

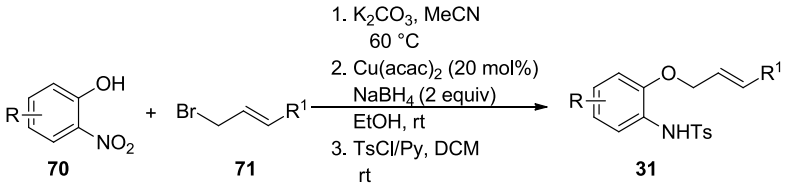
All reactions were performed using standard Schlenk techniques under N_2 atmosphere. Anhydrous dichloromethane, diethyl ether, THF, toluene, and DMF were purchased from Kanto Chemicals and further purified by passage through activated alumina using a Glass Contour solvent purification system. Chlorobenzene and 1,2-dichloroethane were purchased from Kishida and used without further purification. Other solvents were purified prior to use by standard techniques. Phthalimide was purchased from Tokyo Chemical Industries Ltd. All other chemicals were purchased from commercial suppliers and used as received. Reactions were monitored by thin layer chromatography, on glass plates coated with silica gel with fluorescent indicator (Merck). Column chromatography was conducted on Kishida Silica Gel (spherical, 63–200 μm). Melting points were measured using Yanaco melting point apparatus MP-S9 and were uncorrected. All NMR spectra were recorded at 25 °C on JEOL ECS400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) or Bruker AVANCE II (600 MHz for ^{1}H and 150 MHz for ^{13}C{^{1}H} NMR). 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 77.16). ESI mass spectra were recorded on a Thermo Fisher LTQ ORBITRAP XL. HPLC analysis were performed on JASCO HPLC system (JASCO PU 2080 pump and MD-2010 UV/Vis detector) using a mixture of hexane and *i*-PrOH eluents. Optical rotations were measured with JASCO P-1030 polarimeter. Substrates **31a**, **31b**, **31f**, **31g**, **31h**, **31l**, **33a**, **33c-p**, **68** were prepared according to the literature procedure.

Chapter 2

Enantioselective Synthesis of *N*-Heterocyles *via* Aza-Wacker-Type Cyclization

1. Preparation of Substrates

General Procedure



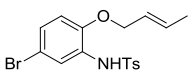
Nitrophenol **70** (1 equiv) and K_2CO_3 (1.1 equiv) were stirred in MeCN at room temperature for 10 minutes. To the red-colored reaction mixture was added allyl bromide **71** (1.3 equiv) slowly, which was heated at 60 °C until the full conversion of **70** (the progress was monitored by TLC). After the consumption of **70,** the reaction was quenched by the addition of water. The mixture was then extracted with EtOAc and washed with 1 M aq. HCl and brine. The organic layer was dried over anhydrous Na_2SO_4, followed by the removal of volatiles under vacuum, to give the desired alkylation product in an almost pure form, which was used in the next step without further purification.

$Cu(acac)_2$ (20 mol %) and $NaBH_4$ (1 equiv) were stirred in EtOH at room temperature for 30 minutes. To this reaction mixture were added an EtOH solution of the above alkylation compound (1 equiv) and an additional equivalent of $NaBH_4$, which was stirred at room temperature until the full conversion of the substrate (the progress was monitored by TLC). The reaction was quenched carefully by the addition of water and then the resulting solid was filtered and washed with EtOAc. The filtrate was concentrated under reduced pressure to a quarter of the original volume. The mixture was partitioned between EtOAc and H_2O, and the organic layer was washed with brine followed by drying over Na_2SO_4. The volatiles were removed under vacuum to give the corresponding aniline derivative, which was used in the next step without further purification.

To a CH_2Cl_2 solution of the aniline derivative (1 equiv) were added TsCl (1.1 equiv) and pyridine (5 equiv) at 0 °C, which was stirred at room temperature. After the complete conversion of the aniline derivative (monitored by TLC), the reaction mixture was quenched

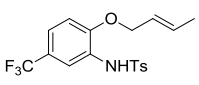
by the addition of 1 M aq. HCl and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. The volatiles were removed under vacuum and the crude mixture was purified by column chromatography on silica gel (hexane/ethyl acetate) to afford **31**.

(*E*)-*N*-(5-Bromo-2-(but-2-en-1-yloxy)phenyl)-4-methylbenzenesulfonamide (31d)



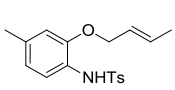
White solid (68%). M.p. 114–116 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74–7.62 (m, 3H), 7.22 (d, J = 8.2 Hz, 2H), 7.13–7.06 (m, 1H), 7.04 (s, 1H), 6.59 (dd, J = 8.7 Hz, 6.9 Hz, 1H), 5.76–5.63 (m, 1H), 5.53–5.39 (m, 1H), 4.48–4.24 (d, J = 6.4 Hz, 2H), 2.38 (s, 3H), 1.79–1.64 (d, J = 6.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 147.5, 144.0, 136.0, 131.8, 129.6, 127.7, 127.6, 127.3, 124.9, 123.5, 113.3, 113.2, 69.6, 21.6, 17.9. HRMS (ESI): calcd for $C_{17}H_{18}NO_3S$: *m*/*z* 418.0083 ([M+Na]$^+$), found: *m*/*z* 418.0077.

(*E*)-*N*-(2-(But-2-en-1-yloxy)-5-(trifluoromethyl)phenyl)-4-methylbenzenesulfonamide (31c)



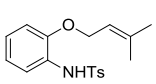
White solid (74%). M.p. 116–119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 2.3 Hz, 1H), 7.66 (dt, J = 8.5 Hz, 1.8 Hz, 2H), 7.29–7.18 (m, 3H), 7.12 (s, 1H), 6.78 (d, J = 8.2 Hz, 1H), 5.81–5.66 (m, 1H), 5.55–5.40 (m, 1H), 4.37–4.35 (d, J = 6.4 Hz, 2H), 2.37 (s, 3H), 1.75 (dd, J = 6.4 Hz, 1.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 150.6, 144.2, 135.9, 132.2, 129.6, 127.4, 126.6, 124.5, 122.3, 117.6, 117.6, 111.5, 69.7, 21.6, 17.9. HRMS (ESI): calcd for $C_{18}H_{18}F_3NO_3S$: *m*/*z* 408.0852 ([M+Na]$^+$), found: *m*/*z* 408.0856.

(*E*)-*N*-(2-(but-2-en-1-yloxy)-4-methylphenyl)-4-methylbenzenesulfonamide (31e)



White solid (79%). M.p. 98–101 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.59 (dd, J = 8.2 Hz, 1.8 Hz, 2H), 7.39 (d, J = 7.8 Hz, 1H), 7.16 (d, J = 8.2 Hz, 2H), 6.88 (s, 1H), 6.68 (d, J = 7.3 Hz, 1H), 6.55–6.45 (m, 1H), 5.73–5.58 (m, 1H), 5.51–5.34 (m, 1H), 4.19–4.18 (d, J = 6.4 Hz, 2H), 2.40 (s, 3H), 2.35 (s, 3H), 1.73 (dd, J = 6.4 Hz, 1.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 148.9, 143.4, 136.4, 135.6, 130.9, 129.3, 127.4, 125.4, 123.4, 121.9, 121.5, 112.7, 69.2, 21.6, 21.5, 17.9. HRMS (ESI): calcd for $C_{18}H_{21}NO_3S$: *m*/*z* 354.1134 ([M+Na]$^+$), found: *m*/*z* 354.1136.

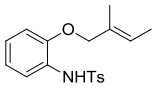
4-Methyl-*N*-(2-((3-methylbut-2-en-1-yl)oxy)phenyl)benzenesulfonamide (31j)



Light reddish solid (83%). M.p. 118–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, J = 8.2 Hz, 2H), 7.52 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 7.17 (d, J = 8.2 Hz, 2H), 7.11–6.94 (m, 2H), 6.87 (td, J = 7.7 Hz, 1.0 Hz, 1H), 6.72 (dd, J = 8.0 Hz, 1.1 Hz, 1H), 5.23 (tt, J = 6.6 Hz, 1.3 Hz, 1H), 4.32 (d, J = 6.9 Hz, 2H), 2.35 (s, 3H), 1.78 (s, 3H), 1.66 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 148.8, 143.6, 138.7, 136.4, 129.4, 127.3, 126.3,

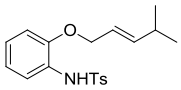
125.2, 121.1, 120.9, 119.1, 111.7, 65.4, 25.8, 21.6, 18.2. HRMS (ESI): calcd for $C_{18}H_{21}NO_3S$: *m*/*z* 354.1134 ([M+Na]$^+$), found: *m*/*z* 354.1136.

(*E*)-4-Methyl-*N*-(2-((2-methylbut-2-en-1-yl)oxy)phenyl)benzenesulfonamide (31i)



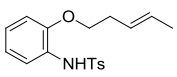
White solid (81%). M.p. 88–90 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.2 Hz, 2H), 7.55 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.17 (d, *J* = 8.2 Hz, 2H), 7.08–6.93 (m, 2H), 6.88 (td, *J* = 8.2 Hz, 1.4 Hz, 1H), 6.72 (dd, *J* = 8.2 Hz, 1.4 Hz, 1H), 5.52–5.37 (m, 1H), 4.20 (s, 2H), 2.35 (s, 3H), 1.64 (dd, *J* = 6.6 Hz, 1.1 Hz, 3H), 1.58 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 148.8, 143.6, 136.5, 130.9, 129.5, 127.3, 126.2, 125.2, 124.2, 121.1, 121.0, 111.8, 74.6, 21.6, 13.6, 13.3. HRMS (ESI): calcd for $C_{18}H_{21}NO_3S$: *m*/*z* 354.1134 ([M+Na]$^+$), found: *m*/*z* 354.1137.

(*E*)-4-Methyl-*N*-(2-((4-methylpent-2-en-1-yl)oxy)phenyl)benzenesulfonamide (31k)



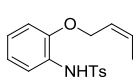
White solid (79%). M.p. 83–84 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (dd, *J* = 6.4 Hz, 1.8 Hz, 2H), 7.53 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.17 (d, *J* = 8.2 Hz, 2H), 7.09–6.95 (m, 2H), 6.88 (td, *J* = 7.7 Hz, 1.1 Hz, 1H), 6.71 (dd, *J* = 8.0 Hz, 1.1 Hz, 1H), 5.71–5.61 (m, 1H), 5.47–5.34 (m, 1H), 4.25 (d, *J* = 6.0 Hz, 2H), 2.35 (m, 4H), 1.02 (d, *J* =6.8Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 148.8, 143.6, 143.2, 136.4, 129.4, 127.4, 126.2, 125.4, 121.5, 121.2, 121.1, 111.9, 69.6, 30.9, 22.1, 21.6. HRMS (ESI) calcd for $C_{19}H_{23}NO_3S$ m/z = 368.1291 [(M+Na)$^+$], found m/z = 368.1293.

(*E*)-4-Methyl-*N*-(2-(pent-3-en-1-yloxy)phenyl)benzenesulfonamide (31m)



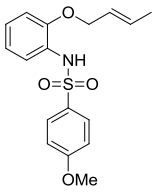
White solid (89%). M.p. 76–79 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (dd, *J* = 6.4 Hz, 1.4 Hz, 2H), 7.53 (dd, *J* = 7.8 Hz, 1.4 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 2H), 7.00 (td, *J* = 7.8 Hz, 1.7 Hz, 2H), 6.88 (td, *J* = 7.7 Hz, 1.1 Hz, 1H), 6.74–6.68 (m, 1H), 5.63–5.51 (m, 1H), 5.44–5.32 (m, 1H), 3.81–3.71 (t, *J* = 6.8 Hz, 2H), 2.36–2.26 (m, 5H), 1.71 (dd, *J* = 6.8 Hz, 1.5 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 148.8, 143.7, 136.4, 129.4, 128.4, 127.3, 126.3, 126.2, 125.4, 121.4, 121.1, 111.7, 68.2, 32.4, 21.6, 18.2. HRMS (ESI): calcd for $C_{18}H_{21}NO_3S$: *m*/*z* 354.1134 ([M+Na]$^+$), found: *m*/*z* 354.1136.

(*Z*)-*N*-(2-(But-2-en-1-yloxy)phenyl)-4-methylbenzenesulfonamide ((*Z*)-31a)



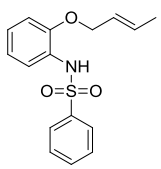
White solid (67%). M.p. 93–95 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.2 Hz, 2H), 7.54 (dd, *J* = 7.8 Hz, 1.4 Hz, 1H), 7.17 (d, *J* = 8.2 Hz, 2H), 7.06–6.96 (m, 2H), 6.89 (td, *J* = 7.8 Hz, 1.1 Hz, 1H), 6.73 (dd, *J* = 8.2 Hz, 0.9 Hz, 1H), 5.79–5.61 (m, 1H), 5.49–5.34 (m, 1H), 4.40 (d, *J* = 6.4 Hz, 2H), 2.35 (s, 3H), 1.66 (dd, *J* = 7.3 Hz, 0.9 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 148.7, 143.6, 136.4, 129.4, 129.2, 127.3, 126.3, 125.3, 124.8, 121.4, 121.2, 111.7, 64.3, 21.6, 13.4. HRMS (ESI): calcd for $C_{17}H_{19}NO_3S$: *m*/*z* 340.0978 ([M+Na]$^+$), found: *m*/*z* 340.0981.

(*E*)-*N*-(2-(but-2-en-1-yloxy)phenyl)-4-methoxybenzenesulfonamide (31n)



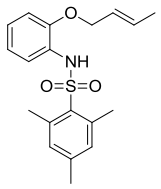
The titled compound was prepared by following the general procedure (replacing TsCl by 4-methoxybenzenesulfonyl chloride). White solid (82%). M.p. 98–100 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 9.2 Hz, 2H), 7.52 (dd, J = 7.8 Hz, 1.4 Hz, 1H), 7.09–6.94 (m, 2H), 6.94–6.80 (m, 3H), 6.71 (dd, J = 8.0 Hz, 1.1 Hz, 1H), 5.77–5.61 (m, 1H), 5.55–5.40 (m, 1H), 4.27 (d, J = 6.4 Hz, 2H), 3.80 (s, 3H), 1.74 (dd, J = 6.4 Hz, 0.9 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 163.0, 148.7, 131.2, 131.0, 129.5, 126.3, 125.4, 125.3, 121.4, 121.1, 113.9, 111.8, 69.3, 55.6, 17.9. HRMS (ESI): calcd for $C_{17}H_{19}NO_4S$: m/z 356.0927 ([M+Na]$^{+}$), found: m/z 356.0930.

(*E*)-*N*-(2-(But-2-en-1-yloxy)phenyl)methanesulfonamide (31o)



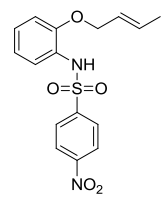
The titled compound was prepared by following the general procedure (replacing TsCl by benzenesulfonyl chloride). White solid (73%). M.p. 81–84 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 7.3 Hz, 2H), 7.57–7.46 (m, 2H), 7.39 (t, J = 7.6 Hz, 2H), 7.07–6.96 (m, 2H), 6.89 (td, J = 7.8 Hz, 0.9 Hz, 1H), 6.70 (dd, J = 8.2 Hz, 0.9 Hz, 1H), 5.75–5.61 (m, 1H), 5.53–5.37 (m, 1H), 4.22 (d, J = 6.4 Hz, 2H), 1.74 (dd, J = 6.4 Hz, 1.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 148.9, 139.2, 132.6, 131.3, 128.8, 127.3, 125.9, 125.6, 125.3, 121.8, 121.1, 111.8, 69.3, 17.9. HRMS (ESI): calcd for $C_{16}H_{17}NO_3S$: m/z 326.0821 ([M+Na]$^{+}$), found: m/z 326.0823.

(*E*)-*N*-(2-(But-2-en-1-yloxy)phenyl)-2,4,6-trimethylbenzenesulfonamide (31p)



The titled compound was prepared by following the general procedure (replacing TsCl by 2,4,6-trimethylbenzene-1-sulfonyl chloride). White solid (51%). M.p. 118–121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 7.19 (s, 1H), 6.96 (td, J = 7.9 Hz, 1.7 Hz, 1H), 6.86 (s, 2H), 6.81 (td, J = 7.7 Hz, 1.2 Hz, 1H), 6.74 (dd, J = 8.2 Hz, 0.9 Hz, 1H), 5.88–5.68 (m, 1H), 5.65–5.43 (m, 1H), 4.34 (d, J = 6.4 Hz, 2H), 2.62 (s, 6H), 2.24 (s, 3H), 1.76 (d, J = 6.4, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 148.4, 142.4, 139.5, 133.8, 131.9, 131.4, 126.3, 125.4, 124.8, 120.9, 120.3, 111.8, 69.3, 23.1, 21.0, 17.9. HRMS (ESI): calcd for $C_{19}H_{23}NO_3S$: m/z 368.1291 ([M+Na]$^{+}$), found: m/z 368.1293.

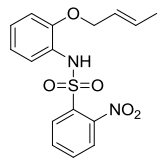
(*E*)-*N*-(2-(But-2-en-1-yloxy)phenyl)-4-nitrobenzenesulfonamide (31q)



The titled compound was prepared by following the general procedure (replacing TsCl by *p*-NsCl). Yellowish solid. M.p. 110–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24-8.18 (m, 2H), 8.88-7.86 (d, J = 6.8 Hz, 2H), 7.56 (m,

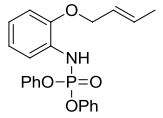
1H), 7.12–7.00 (m, 2H), 6.99–6.88 (m, 1H), 6.78–6.65 (m, 1H), 5.79–5.58 (m, 1H), 5.52–5.29 (m, 1H), 4.23 (d, *J* = 6.4 Hz, 2H), 1.70–1.72 (d, *J* =6.4 HZ, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 149.3, 144.9, 131.7, 128.6, 126.7, 124.9, 124.8, 124.1, 123.9, 122.8, 121.3, 111.8, 69.2, 17.8. HRMS (ESI): calcd for $C_{16}H_{16}N_2O_5S$: *m*/*z* 371.0672 ($[M+Na]^+$), found: *m*/*z* 371.0674.

(*E*)-*N*-(2-(But-2-en-1-yloxy)phenyl)-2-nitrobenzenesulfonamide (31r)



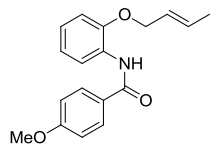
The titled compound was prepared by following the general procedure (replacing TsCl by *o*-NsCl). Yellow solid (54%). M.p. 114–117 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03–7.80 (m, 3H), 7.74–7.51 (m, 3H), 7.08 (td, *J* = 7.8 Hz, 1.4 Hz, 1H), 6.93 (td, *J* = 7.8 Hz, 1.2 Hz, 1H), 6.73 (d, *J* = 8.2 Hz, 1H), 5.72–5.55 (m, 1H), 5.50–5.29 (m, 1H), 4.23 (dd, *J* = 6.4 Hz, 1.1 Hz, 2H), 1.69 (dd, *J* = 6.4 Hz, 1.4 Hz, 3H) $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 149.9, 133.8, 133.6, 132.6, 131.4, 131.0, 126.6, 125.5, 125,2, 125.1, 124.5, 123.7, 121.1, 111.9, 69.3, 17.8. HRMS (ESI): calcd for $C_{16}H_{16}N_2O_5S$: *m*/*z* 371.0672 ($[M+Na]^+$), found: *m*/*z* 371.0675.

(*E*)-Diphenyl (2-(but-2-en-1-yloxy)phenyl)phosphoramidate (31s)



The titled compound was prepared by following the general procedure (replacing TsCl by diphenylphosphinic chloride). White solid (45%). M.p. 68–70 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58–7.49 (m, 1H), 7.31 (t, *J* = 8.0 Hz, 4H), 7.27–7.20 (m, 4H), 7.20–7.13 (m, 2H), 7.03–6.93 (m, 2H), 6.91–6.80 (m, 1H), 6.16–6.01 (m, 1H), 5.86–5.69 (m, 1H), 5.70–5.55 (m, 1H), 4.42 (d, *J* = 6.4 Hz, 2H), 1.74 (dd, *J* = 6.4 Hz, 0.9 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 150.43, 150.37, 147.1, 147.0, 131.3, 129.8, 128.7, 125.6, 125.4, 122.3, 121.2, 120.53, 120.49, 117.0, 112.0, 69.5, 17.9. HRMS (ESI): calcd for $C_{22}H_{22}NO_4P$: *m*/*z* 418.1179 ($[M+Na]^+$), found: *m*/*z* 418.1180.

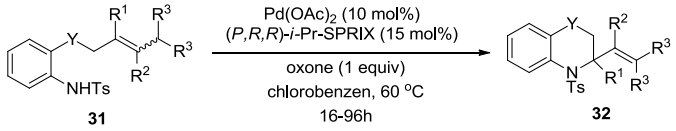
(*E*)-*N*-(2-(But-2-en-1-yloxy)phenyl)-4-methoxybenzamide (31t)



The titled compound was prepared by following the general procedure (replacing TsCl by 4-methoxybenzoyl chloride). White solid (72%). M.p. 70–73 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63–8.39 (m, 2H), 7.85 (tt, *J* = 8.9 Hz, 2.3 Hz, 2H), 7.09–6.87 (m, 5H), 5.96–5.82 (m, 1H), 5.82–5.68 (m, 1H), 4.56 (d, *J* = 6.4 Hz, 2H), 3.88 (s, 3H), 1.78 (dd, *J* = 6.4 Hz, 1.4 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 164.8, 162.4, 147.3, 131.8, 131.1, 128.9, 127.7, 125.7, 123.6, 121.4, 120.5, 119.8, 114.0, 111.7, 70.0, 69.7, 55.6, 17.9. HRMS (ESI): calcd for $C_{18}H_{19}NO_3$: *m*/*z* 320.1257 ($[M+Na]^+$), found: *m*/*z* = 320.1259.

2. Catalysis

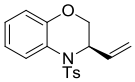
General Procedure



A mixture of $Pd(OAc)_2$ (10 mol %, 3.15 μmol, 0.71mg) and (*P*,*R*,*R*)-*i*-Pr-SPRIX (15 mol%, 4.73 μmol, 1.7 mg) was dissolved in dry dichloromethane (1 mL). After stirring under nitrogen atmosphere at 25 °C for 2 h, the solvent was removed and the resulting yellow Pd complex was kept under vacuum for 10 min. To the dried Pd complex, oxone (1 equiv, 31.5 μmol, 19.4 mg) and alkenyltosylamide substrate **31** (1 equiv, 31.5 μmol) were added. Chlorobenzene (0.3 mL) was added, followed by stirring at 60 °C under nitrogen until the consumption of starting material, monitored by TLC (hexane/ethyl acetate). After the reaction the solid inorganic compounds was filtered off and the solvent was removed under vacuum, and the remaining crude mass was purified by short column chromatography (hexane/EtOAc = 20/1) to give products **32**.

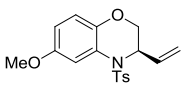
Characterization of Products

4-Tosyl-3-vinyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (32a)



White solid (81%, 25 h). M.p. 82–84 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 8.4 Hz, 1.7 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.05 (td, *J* = 7.8 Hz, 1.4 Hz, 1H), 6.94 (td, *J* = 7.8 Hz, 1.4 Hz, 1H), 6.78 (dd, *J* = 8.2 Hz, 1.4 Hz, 1H), 5.73 (dq, *J* = 17.4 Hz, 5.0 Hz, 1H), 5.40–5.31 (m, 1H), 5.26–5.14 (m, 1H), 4.88 (dt, *J* = 5.0 Hz, 1.8 Hz, 1H), 4.09 (dd, *J* = 11.2 Hz, 1.8 Hz, 1H), 3.35 (dd, *J* = 11.2 Hz, 3.0 Hz, 1H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 146.3, 144.3, 135.6, 132.8, 129.9, 127.3, 126.2, 125.3, 122.5, 121.3, 118.8, 117.3, 65.0, 54.3, 21.6. HRMS (ESI): calcd for $C_{17}H_{17}NO_3S$: *m*/*z* 338.0821 ($[M+Na]^+$), found: *m*/*z* 338.0822. Enantiomeric excess: 69% (HPLC, CHIRALCEL OJ-H column, eluent: *n*-hexane/2-propanol = 10:1 flow rate: 0.7 mL/min, 25 °C, 246 nm) minor peak: t_R = 21.5 min, major peak: t_R = 27.7 min. $[\alpha]_D^{25}$ = –46.7 (*c* 0.3, $CHCl_3$).

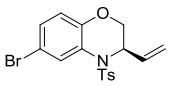
6-Methoxy-4-tosyl-3-vinyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (32b)



White solid (77%, 48 h). M.p. 104-105 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 2.7 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 2H), 6.71–6.60 (m, 2H), 5.72 (dq, *J* = 16.9 Hz, 5.0 Hz, 1H), 5.39–5.31 (m, 1H), 5.20 (dd, *J* = 10.5

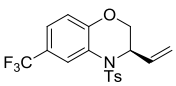
Hz, 0.9 Hz, 1H), 4.88–4.83 (m, 1H), 4.03 (dd, *J* = 11.0 Hz, 1.8 Hz, 1H), 3.79 (s, 3H), 3.25 (dd, *J* = 11.0 Hz, 2.7 Hz, 1H), 2.38 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 153.7, 144.4, 140.3, 135.5, 132.8, 129.9, 127.3, 122.6, 118.7, 117.7, 113.1, 109.2, 64.9, 55.6, 21.7. HRMS (ESI): calcd for $C_{18}H_{19}NO_4S$: m/z 368.0927 ($[M+Na]^+$), found: *m*/*z* 368.0925. Enantiomeric excess: 53% (HPLC, CHIRALCEL OJ-H, eluent: *n*-hexane/2-propanol = 10/1, flow rate: 0.7 mL/min, 25 °C, 231 nm) minor peak: t_R = 28.9 min, major peak: t_R = 49.2 min. $[\alpha]_D^{25}$ = –126.7 (*c* 0.45, $CHCl_3$).

6-Bromo-4-tosyl-3-vinyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (32d)



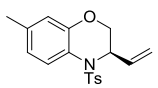
White solid (64%, 52 h). M.p. 99–101 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 2.3 Hz, 1H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.16 (dd, *J* = 8.7 Hz, 2.3 Hz, 1H), 6.67 (d, *J* = 3.7 Hz, 1H), 5.71 (m, 1H), 5.40–5.30 (m, 1H), 5.23 (dd, *J* = 10.5 Hz, 1.4 Hz, 1H), 4.91–4.85 (m, 1H), 4.12 (dd, *J* = 11.0 Hz, 1.4 Hz, 1H), 3.32 (dd, *J* = 11.0 Hz, 3.0 Hz, 1H), 2.42 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 145.4, 144.7, 135.2, 132.4, 130.1, 129.0, 127.6, 127.4, 123.7, 119.1, 118.7, 113.0, 65.0, 53.9, 21.6. HRMS (ESI): calcd for $C_{17}H_{16}BrNO_3S$: *m*/*z* 415.9932 ($[M+Na]^+$), found: *m*/*z* 415.9919. Enantiomeric excess: 36% (HPLC CHIRALPAK AD-3, eluent: *n*-hexane/2-propanol = 50:1, flow rate: 0.7 mL/min, 25 °C, 240 nm) minor peak: t_R = 20.9 min, major peak: t_R = 19.2 min. $[\alpha]_D^{24}$ = +48.6 (*c* 0.4, $CHCl_3$).

4-Tosyl-6-(trifluoromethyl)-3-vinyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (32c)



White solid (51%, 72 h). M.p. 114–117 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.53 (dd, *J* = 6.4 Hz, 1.8 Hz, 2H), 7.33–7.24 (m, 3H), 6.87 (d, *J* = 8.4 Hz, 1H), 5.75–5.64 (m, 1H), 5.37–5.29 (m, 1H), 5.23 (dd, *J* = 10.5 Hz, 1.4 Hz, 1H), 4.92 (tt, *J* = 4.6 Hz, 1.8 Hz, 1H), 4.18 (dd, *J* = 11.4 Hz, 1.4 Hz, 1H), 3.39 (dd, *J* = 11.4 Hz, 3.0 Hz, 1H), 2.41 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 148.7, 144.8, 135.1, 132.2, 130.2, 127.4, 123.7, 122.9, 122.9, 122.6, 119.3, 117.8, 65.3, 53.8, 21.7. HRMS (ESI): calcd for $C_{18}H_{16}F_3NO_3S$: *m*/*z* 406.0701 ($[M+Na]^+$), found: *m*/*z* 406.0697. Enantiomeric excess: 43% (HPLC, CHIRALCEL OD-H, eluent: *n*-hexane/2-propanol = 50:1, flow rate: 0.7 mL/min, 25 °C, 232 nm) minor peak: t_R = 14.7 min, major peak: t_R = 17.8 min. $[\alpha]_D^{25}$ = -32 (*c* 0.5, $CHCl_3$).

7-Methyl-4-tosyl-3-vinyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (32e)



Dense liquid (87%, 16 h). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.2 Hz, 1H), 7.56–7.47 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 8.2 Hz, 2H), 6.80–6.72 (d, *J* = 7.8 Hz, 1H), 6.58 (s, 1H), 5.78–5.66 (m, 1H), 5.40–5.30 (m, 1H), 5.20 (dq, *J* = 10.5 Hz, 0.9 Hz, 1H), 4.84 (tt, *J* = 4.6 Hz, 1.6 Hz, 1H), 4.05 (dd, *J* = 11.2 Hz, 1.8 Hz, 1H), 3.29 (dd, *J* =

11.2 Hz, 3.0 Hz, 1H), 2.39 (s, 3H), 2.26 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 146.1, 144.2, 136.3, 135.6, 132.8, 129.9, 127.4, 125.3, 122.2, 119.8, 118.7, 117.5, 64.8, 54.2, 21.6, 20.9. HRMS (ESI): calcd for $C_{18}H_{19}NO_3S$: *m*/*z* 352.0983 ($[M+Na]^+$), found: *m*/*z* 352.0983. Enantiomeric excess: 54% (HPLC, CHIRALCEL OJ-H, eluent: *n*-hexane/2-propanol = 10:1, flow rate: 0.7 mL/min, 25 °C, 232 nm) minor peak: t_R = 18.7 min, major peak: t_R = 34.8 min. $[\alpha]_D^{25}$ = -62.8 (*c* 0.35, $CHCl_3$).

4-Tosyl-3-vinylmorpholine (32f)

Colorless oil (68%, 48 h). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69–7.63 (d, *J* = 7.8 Hz, 2H), 7.29 (d, *J* = 7.8 Hz, 2H), 5.90–5.78 (m, 1H), 5.28–5.14 (m, 2H), 4.10 (t, *J* = 3.2 Hz, 1H), 3.84–3.73 (m, 2H), 3.66 (dd, *J* = 11.4 Hz, 3.2 Hz, 1H), 3.62–3.53 (m, 1H), 3.39–3.22 (m, 2H), 2.43 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 143.6, 136.0, 133.1, 129.6, 127.8, 118.7, 70.9, 66.6, 56.6, 42.3, 21.6. HRMS (ESI): calcd for $C_{13}H_{17}NO_3S$: *m*/*z* 290.0821 ($[M+Na]^+$), found: *m*/*z* 290.0823. Enantiomeric excess: 30% (HPLC, CHIRALCEL OJ-H, eluent: *n*-hexane/2-propanol = 50:1, flow rate: 1 mL/min, 25 °C, 232 nm) minor peak: t_R = 42.9 min, major peak: t_R = 38.0 min. $[\alpha]_D^{21}$ = –25.8 (*c* 0.85, $CHCl_3$).

1,4-Ditosyl-2-vinylpiperazine (32h)

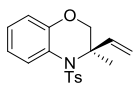
Colorless solid (71%, 30 h). M.p. 179–181 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.61–7.55 (m, 4H), 7.33 (d, *J* = 7.6 Hz, 2H), 7.27–7.23 (m, 2H), 5.72 (dt, *J* = 17.2 Hz, 5.2 Hz, 1H), 5.26 (d, *J* = 17.9 Hz, 1H), 5.22–5.16 (m, 1H), 4.46–4.44 (m, 1H), 3.64 (d, *J* = 12.4 Hz, 2H), 3.57 (dd, *J* = 11.0 Hz, 1.4 Hz, 1H), 3.23 (ddd, *J* = 13.9 Hz, 11 Hz, 2.3 Hz, 1H), 2.59–2.54 (dd, *J* = 7.2 Hz, 2.0 Hz, 1H), 2.47–2.39 (m, 7H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 144.2, 143.2, 136.5, 132.2, 129.9, 129.7, 127.7, 127.5, 119.8, 54.9, 49.8, 45.8, 41.1, 21.6, 21.6. HRMS (ESI): calcd for $C_{20}H_{24}N_2O_4S_2$: *m*/*z* 443.1070 ($[M+Na]^+$), found: *m*/*z* = 443.1070. Enantiomeric excess: 61% (HPLC, CHIRALCEL AD-3, eluent: *n*-hexane/2-propanol = 5:1, flow rate: 1 mL/min, 25 °C, 229 nm) minor peak: t_R = 27.7 min, major peak: t_R = 34.7 min. $[\alpha]_D^{25}$ = –6.4 (*c* 0.65, $CHCl_3$).

1-Tosyl-2-vinylpiperidine (32g)

Colorless oil (63%, 48 h). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71–7.68 (m, 2H), 7.27 (m, 2H), 5.75–5.65 (m, 1H), 5.22–5.09 (m, 2H), 4.60 (m, 1H), 3.71–3.64 (m, 1H), 2.99 (td, *J* = 12.7 Hz, 2.9 Hz, 1H), 2.42 (s, 3H), 1.76–1.59 (m, 2H), 1.55–1.33 (m, 4H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 142.9, 137.9, 135.5, 129.5, 127.4, 117.2, 55.1, 41.7, 29.7, 25.1, 21.5, 19.2. HRMS (ESI): calcd for $C_{14}H_{19}NO_2S$: *m*/*z* 288.1029 ($[M+Na]^+$), found: *m*/*z* 288.1031. Enantiomeric excess: 68% (HPLC, CHIRALPAK IC, *n*-hexane/2-propanol =

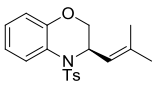
10:1, flow rate: 1 mL/min, 25 °C, 254 nm) minor peak: t_R = 29.0 min, major peak: t_R = 25.0 min. $[\alpha]_D^{18}$ = –32 (*c* 0.50, $CHCl_3$).

3-Methyl-4-tosyl-3-vinyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (32i)



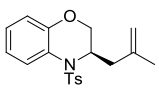
White Solid (33%, 96 h). M.p. 75–78 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (dd, *J* = 8.2 Hz, 1.8 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 7.11–7.05 (m, 1H), 6.93–6.86 (m, 1H), 6.77 (dd, *J* = 8.2 Hz, 1.4 Hz, 1H), 5.92 (dd, *J* = 17.9 Hz, 11.0 Hz, 1H), 5.14–5.03 (m, 2H), 3.83 (d, *J* = 11.4 Hz, 1H), 3.62 (d, *J* = 11.4 Hz, 1H), 2.39 (s, 3H), 1.52 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 148.1, 144.0, 139.7, 137.6, 129.8, 128.3, 127.8, 126.9, 124.5, 120.5, 116.4, 114.9, 70.3, 60.1, 23.8, 21.7. HRMS (ESI): calcd for $C_{18}H_{19}NO_3S$: *m*/*z* 352.0978 ([M+Na]$^+$), found: *m*/*z* 352.0980. Enantiomeric excess: 12% (HPLC, CHIRALCEL OJ-H, eluent: *n*-hexane/2-propanol = 10:1, flow rate: 0.7 mL/min, 25 °C, 246 nm) minor peak: t_R = 20.7 min, major peak: t_R = 27.6 min. $[\alpha]_D^{21}$ = –48 (*c* 0.2, $CHCl_3$).

3-(2-Methylprop-1-en-1-yl)-4-tosyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (32k)



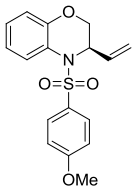
White Solid (79%, 48 h). Present as an inseparable mixture with **32k'** (11%; purified by GPC). M.p. 92–94 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (dd, *J* = 8.2 Hz, 1.4 Hz, 1H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 7.09–7.02 (m, 1H), 6.97–6.89 (m, 1H), 6.80 (dd, *J* = 8.2 Hz, 1.4 Hz, 1H), 5.15–4.97 (m, 2H), 3.88 (dd, *J* = 10.8 Hz, 1.6 Hz, 1H), 3.37 (dd, *J* = 10.8 Hz, 2.5 Hz, 1H), 2.37 (s, 3H), 1.81 (s, 3H), 1.65 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 146.6, 141.1, 137.9, 129.9, 127.3, 126.1, 125.7, 122.7, 121.1, 118.9, 117.2, 66.6, 50.9, 25.8, 21.6, 18.5. HRMS (ESI): calcd for $C_{19}H_{21}NO_3S$: *m*/*z* 366.1134 ([M+Na]$^+$), found: *m*/*z* 366.1136. Enantiomeric excess: 80% (HPLC, CHIRALPAK IG-3, eluent: *n*-hexane/2-propanol = 10:1, flow rate: 0.7 mL/min, 25 °C, 244 nm) minor peak: t_R = 13.5 min, major peak: t_R = 16 min. $[\alpha]_D^{21}$ = –180 (*c* 0.1, $CHCl_3$).

3-(2-Methylallyl)-4-tosyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (32k')



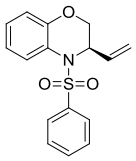
White solid (11%). M.p. 90-93°C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.84 (dd, *J* = 8.2 Hz, 2.1 Hz, 1H), 7.44 (d, *J* = 8.9 Hz, 2H), 7.19 (d, *J* = 7.6 Hz, 2H), 7.11–7.02 (m, 1H), 6.94 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 6.79 (dd, *J* = 8.2 Hz, 1.4 Hz, 1H), 4.84 (s, 1H), 4.65 (s, 1H), 4.43–4.35 (m, 1H), 3.91 (dd, *J* = 11.0 Hz, 1.4 Hz, 1H), 3.19 (dd, *J* = 11 Hz, 2.8 Hz, 1H), 2.37 (s, 3H), 2.27–2.18 (m, 1H), 2.17–2.09 (m, 1H), 1.80 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 146.4, 144.2, 140.8, 135.6, 129.9, 127.3, 126.4, 126.3, 121.9, 121.2, 117.2, 114.5, 63.9, 51.1, 38.8, 22.3, 21.6. HRMS (ESI): calcd for $C_{19}H_{21}NO_3S$: *m*/*z* 366.1134 ([M+Na]$^+$), found: *m*/*z* 366.1138.

(4-Methoxybenzenesulfonyl)-3-vinyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (32n)



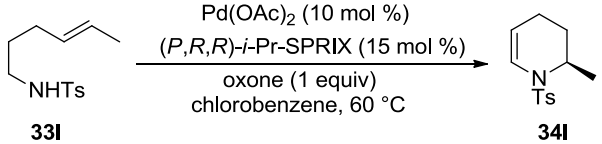
White solid (71%, 42 h). M. p. 97–99 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (dd, J = 8.2 Hz, 1.4 Hz, 1H), 7.56 (dd, J = 6.9 Hz, 1.8 Hz, 2H), 7.10–7.01 (m, 1H), 6.98–6.85 (m, 3H), 6.78 (dd, J = 8.2 Hz, 1.4 Hz, 1H), 5.73 (dq, J = 16.9 Hz, 5.0 Hz, 1H), 5.40–5.31 (m, 1H), 5.20 (dq, J = 10.5 Hz, 0.9 Hz, 1H), 4.88 (qd, J = 3.1 Hz, 1.5 Hz, 1H), 4.10 (dd, J = 11.2 Hz, 1.6 Hz, 1H), 3.83 (s, 3H), 3.38 (dd, J = 11.2 Hz, 3.0 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$); δ 163.4, 146.4, 132.8, 130.2, 129.5, 126.2, 125.4, 122.5, 121.2, 118.8, 117.3, 114.5, 64.9, 55.7, 54.2. HRMS (ESI): calcd for $C_{17}H_{17}NO_4S$: m/z 354.0770 ([M+Na]$^+$), found: m/z 354.0767. Enantiomeric excess: 59% (HPLC, CHIRALCEL OJ-H, eluent: *n*-hexane/2-propanol = 5:1, flow rate: 1.0 mL/min, 25 °C, 232 nm) minor peak: t_R = 24.6 min, major peak: t_R = 35.6 min. $[\alpha]_D^{25}$ = –10 (c 0.5, $CHCl_3$).

4-(Benzenesulfonyl)-3-vinyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (32o)



Colorless oil (77%, 20 h). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (dd, J = 8.2 Hz, 1.8 Hz, 1H), 7.64 (d, J = 7.4 Hz, 2H), 7.57 (t, J = 7.6 Hz, 1H), 7.45 (t, J = 7.8 Hz, 2H), 7.11–7.03 (m, 1H), 7.00–6.92 (m, 1H), 6.78 (dd, J = 8.2 Hz, 1.4 Hz, 1H), 5.74 (dq, J = 16.9 Hz, 5.0 Hz, 1H), 5.36 (dd, J = 16.9 Hz, 1.4 Hz, 1H), 5.22 (dd, J = 10.5 Hz, 1.8 Hz, 1H), 4.93–4.87 (m, 1H), 4.10 (dd, J = 11.2 Hz, 1.6 Hz, 1H), 3.32 (dd, J = 11.2 Hz, 3.0 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 146.3, 138.5, 133.4, 132.7, 129.4, 127.3, 126.3, 125.3, 122.4, 121.3, 118.9, 117.3 65.0, 54.3. HRMS (ESI): calcd for $C_{16}H_{15}NO_3S$: m/z 324.0665 ([M+Na]$^+$), found: m/z 324.0667. Enantiomeric excess: 63% (HPLC, CHIRALCEL OJ-H, eluent: *n*-hexane/2-propanol = 50:1, flow rate: 0.7 mL/min, 25 °C, 242 nm) minor peak: t_R = 27.9 min, major peak: t_R = 18.1 min. $[\alpha]_D^{25}$ = –8.6 (c 1.0, $CHCl_3$).

2-methyl-1-tosyl-1,2,3,4-tetrahydropyridine (32l)

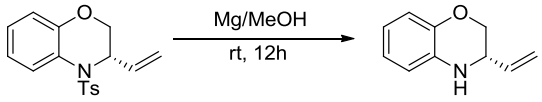


33l **34l**

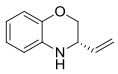
Colorless oil (48%, 48 h). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 8.2 Hz, 2H), 6.61 (d, J = 8.2 Hz, 1H), 4.98 (m, 1H), 4.13-4.03 (m, 1H), 2.40 (s, 3H), 2.06-1.90 (m, 1H), 1.88-1.75 (m, 1H), 1.44-1.40 (m, 1H), 1.14 (d, J = 6.6 Hz, 3H), 1.11-1.00 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 143.3, 136.7, 129.7, 126.9,

123.3, 107.7, 48.6, 25.3., 21.6, 18.3, 16.9. HRMS (ESI): calcd for $C_{13}H_{17}NO_2S$: *m*/*z* 274.0872 ($[M+Na]^+$), found: *m*/*z* 274.0875. Enantiomeric excess: 38% (HPLC, CHIRALPAK IG-3, eluent: *n*-hexane/2-propanol=50:1, flow rate: 0.7 mL/min, 25 °C, 254 nm) minor peak: t_R = 46.1 min, major peak: t_R = 43.5 min. $[\alpha]_D^{25}$ = +53.3 (*c* 0.09, $CHCl_3$).

3-Vinyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (46)



(S)-32a **46**



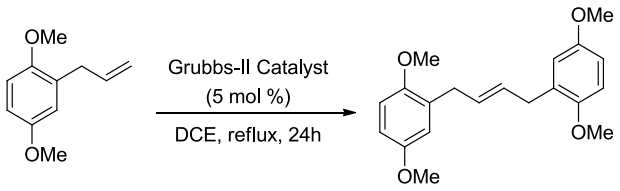
To a solution of (*S*)-**32a** (77% ee, 0.0318 mmol) in MeOH was added pre-activated Mg turning (0.159 mmol), which was stirred at room temperature for additional 12 hours. The reaction mixture was diluted with EtOAc and H_2O, and then extracted with ether. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The volatiles were removed under vacuum and the residue was purified by short column chromatography. Colorless oil (79%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.77 (qd, *J* = 7.6 Hz, 1.4 Hz, 2H), 6.68–6.59 (m, 2H), 5.87-5.78 (m, 1H), 5.38 (dt, *J* = 17.2 Hz, 1.4 Hz, 1H), 5.25 (d, *J* = 10.3 Hz, 1H), 4.21 (dd, *J* = 10.6 Hz, 3.2 Hz, 1H), 3.99–3.94 (m, 1H), 3.89 (dd, *J* = 10.6 Hz, 7.6 Hz, 1H). ^{13}C{^{1}H} NMR 150 MHz, $CDCl_3$): δ 143.7, 135.5, 133.0, 121.6, 118.9, 117.9, 116.6, 115.5, 68.9, 52.6. HRMS (ESI): calcd for $C_{10}H_{11}NO$: *m*/*z* 162.0913 ($[M+H]^+$), found: *m*/*z* 162.0914. Enantiomeric excess: 72% (HPLC, CHIRALCEL OJ-H, eluent: *n*-hexane/2-propanol = 10:1, flow rate: 0.7 mL/min, 25 °C, 277 nm) minor peak: t_R = 20.0 min, major peak: t_R = 18.1 min. $[\alpha]_D^{25}$ = –18.4 (*c* 0.06, $CHCl_3$).

Chapter 3

Efficient Construction of Allyl Amine Derivatives *via* Intermolecular Aza-Wacker-Type Reaction

3. Preparation of Substrates

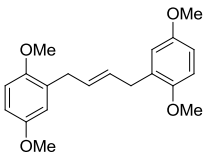
General Procedure



72 **33b**

2-allyl-1,4-dimethoxybenzene **72** (1 equiv) and Grubbs-II catalyst (5 mol %) were stirred in DCE under reflux for 24 hours (monitored by TLC in hexane). The solvent was evaporated under vacuum to give the desired metathesis product in crude form, which was further purified by column chromatography (solvent hexane).

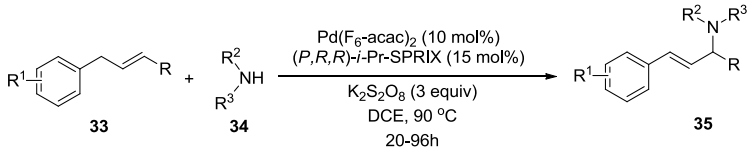
(*E*)-1,4-bis(2,5-dimethoxyphenyl)but-2-ene (33b)



White solid (68%). M.p. 57-59 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 1H), 6.80-6.69 (m, 3H), 6.04-5.91 (m, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.36 (d, J = 6.9 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 153.6, 151.6, 130.8, 129.7, 116.1, 111.4, 111.1, 56.2, 55.7, 33.0. HRMS (ESI): calcd for $C_{20}H_{24}O_4$: *m*/*z* 351.1561 ([M+Na]$^{+}$), found: *m*/*z* 351.1568.

4. Catalysis

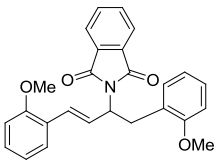
General Procedure



A mixture of Pd(F_6-acac)$_2$ (10 mol %, 6.80 μmol, 3.54mg) and (*P,R,R*)-*i*-Pr-SPRIX (15 mol%, 10.20 μmol, 3.83mg) was dissolved in dry dichloromethane (1 mL). After stirring under nitrogen atmosphere at 30 °C for 2 h, the solvent was removed and the resulting yellow Pd complex was kept under vacuum for 10 min. To the dried Pd complex, $K_2S_2O_8$ (3 equiv, 204.1 μmol, 55.1 mg), nitrogen nucleophile, **34** (1 equiv, 68.03 μmol, 10 mg) and allylbenzene substrate **33** (1.2 equiv, 81.63 μmol) were added. 1,2-dichloroethane (0.7 mL) was added, followed by stirring at 90 °C (chemi-station) under nitrogen until the full consumption of **34**, monitored by TLC (hexane/ethyl acetate). After the reaction the solid inorganic compounds was filtered off and the solvent was removed under vacuum, and the remaining crude mass was purified by short column chromatography (hexane/EtOAc = 5/1) to give products **35**.

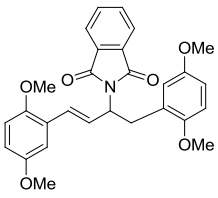
Characterization of Products

(*E*)-2-(1,4-bis(2-methoxyphenyl)but-3-en-2-yl)isoindoline-1,3-dione (35aa)



dense liquid (93%, 20 h). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.74-7.72 (m, 2H), 7.63-7.61 (m, 2H), 7.46 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.22-7.15 (m, 1H), 7.13-7.07 (m, 1H), 7.05 (d, *J* = 5.7 Hz, 1H), 6.97-6.87 (m, 2H), 6.85-6.73 (m, 3H), 6.71 (t, *J* = 7.6 Hz, 1H), 5.31 (td, *J* = 9.1, 5.7 Hz, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 3.46 (dd, *J* = 13.7, 10.3 Hz, 1H), 3.27 (dd, *J* = 13.7, 5.7 Hz, 1H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): *δ* 168.1, 158.2, 156.9, 133.7, 132.0, 131.0, 128.9, 128.0, 127.7, 127.6, 127.1, 126.2, 123.0, 120.6, 120.3, 110.9, 110.2, 55.5, 55.3,54.0, 34.3. HRMS (ESI): calcd for $C_{26}H_{23}NO_4$: *m*/*z* 436.1519 ([M+Na]$^+$), found: *m*/*z* 436.1522.

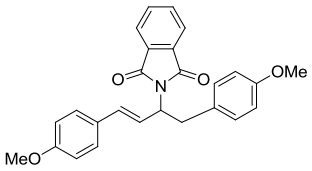
(*E*)-2-(1,4-bis(2,5-dimethoxyphenyl)but-3-en-2-yl)isoindoline-1,3-dione (35ba)



Reddish solid (62%, 48 h). M.p. 42-44 °C. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.74 (m, 2H), 7.64 (m, 2H), 7.01 (d, *J* = 2.7 Hz, 1H), 6.92 (d, *J* = 15.8 Hz, 1H), 6.79-6.72 (m, 3H), 6.68 (d, *J* = 8.2 Hz, 1H), 6.66-6.59 (m, 2H), 5.30 (m, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.72 (s, 3H), 3.56 (s, 3H), 3.47-3.40 (dd, *J*=9.6, 3 Hz, 1H), 3.24 (dd, *J* = 6.4, 3Hz, 1H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): *δ*

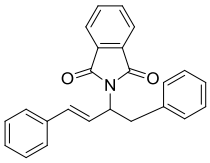
168.1, 153.7, 152.2, 151.4, 133.7, 132.0, 127.8, 127.5, 127.1, 123.0, 116.8, 114.3, 112.8, 112.4, 112.0, 111.2, 56.3, 55.9, 55.8, 55.7, 53.9, 34.4. HRMS (ESI): calcd for $C_{28}H_{27}NO_6$: *m*/*z* 496.1731 ([M+MeOH+Na]$^+$), found: *m*/*z* 496.1724.

(*E*)-2-(1,4-bis(4-methoxyphenyl)but-3-en-2-yl)isoindoline-1,3-dione (35da)



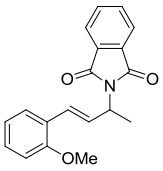
Colorless liquid (88%, 30 h). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.75 (m, 2H), 7.65 (m, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.14-7.07 (d, *J*=8.4 Hz2H), 6.81 (d, *J* = 8.4 Hz, 2H), 6.72 (d, *J* = 8.4 Hz, 2H), 6.53 (d, *J* = 6.9 Hz, 2H), 5.14-5.07 (m, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 3.48-3.41 (dd, *J*=9.6, 4.2 Hz,1H), 3.18 (dd, *J* = 6.9, 4.2 Hz, 1H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): *δ* 168.2, 159.5, 134.4, 133.9, 132.7, 131.9, 130.1, 129.7, 129.1, 127.9, 124.4, 123.7, 123.2, 114.0, 113.9, 55.4, 55.2, 38.1. HRMS (ESI): calcd for $C_{26}H_{23}NO_4$: *m*/*z* 436.1519 ([M+Na]$^+$), found: *m*/*z* 436.1522.

(*E*)-2-(1,4-diphenylbut-3-en-2-yl)isoindoline-1,3-dione (35ca)



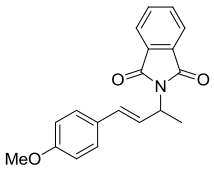
Colorless liquid (74%, 36 h). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.75 (m, 2H), 7.68-7.62 (m, 2H), 7.39-7.33 (m, 2H), 7.31-7.16 (m, 7H), 7.16-7.08 (m, 1H), 6.69 (dd, *J* = 16.4, 7.6 Hz, 1H), 6.57 (d, *J* = 16.4 Hz, 1H), 5.24-5.14 (m, 1H), 3.51 (dd, *J* = 14.0, 4.4 Hz, 1H), 3.28 (dd, *J* = 7.6, 4.4 Hz, 1H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): *δ* 168.1, 136.3, 133.9, 133.3, 131.8, 129.1, 128.6, 128.5, 128.0, 126.7, 123.2, 55.1, 38.9. HRMS (ESI): calcd for $C_{24}H_{19}NO_2$: *m*/*z* 408.1570 ([M+MeOH+Na]$^+$), found: *m*/*z* 408.1564.

(*E*)-2-(4-(2-methoxyphenyl)but-3-en-2-yl)isoindoline-1,3-dione (35ma)



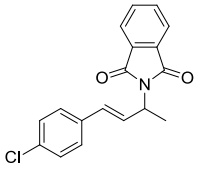
Colorless liquid (88%, 60 h). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.81 (m, 2H), 7.68 (m, 2H), 7.44 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.19 (td, *J* = 7.8, 1.8 Hz, 1H), 6.97-6.80 (m, 3H), 6.65 (dd, *J* =16, 8.1 Hz, 1H), 5.14-5.05 (m, 1H), 3.81 (s, 3H), 1.65 (d, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): *δ* 168.2, 156.8, 133.9, 132.2, 129.0, 128.6, 127.0, 126.9, 125.4, 123.2, 120.7, 110.8, 55.5, 49.6,19.3. HRMS (ESI): calcd for $C_{19}H_{17}NO_3$: *m*/*z* 330.1101 ([M+Na]$^+$), found: *m*/*z* 330.1100.

(*E*)-2-(4-(4-methoxyphenyl)but-3-en-2-yl)isoindoline-1,3-dione (35ea)



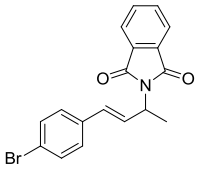
Colorless liquid (88%, 48 h). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.81 (m, 2H), 7.68 (m, 2H), 7.30 (dd, *J* = 6.9, 2.3 Hz, 2H), 6.81 (dt, *J* = 9.5, 2.3 Hz, 2H), 6.58-6.43 (m, 2H), 5.11-5.01 (m, 1H), 3.80-3.76 (s, 3H), 1.65 (d, *J* = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): *δ* 168.1, 133.9, 132.2, 131.6, 127.8, 126.0, 123.2, 114.0, 55.4, 49.2, 19.2. HRMS (ESI): calcd for $C_{19}H_{17}NO_3$: *m*/*z* 362.1363 ([M+MeOH+Na]$^+$), found: *m*/*z* 362.1360.

(*E*)-2-(4-(4-chlorophenyl)but-3-en-2-yl)isoindoline-1,3-dione (35ka)



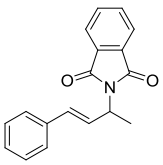
Colorless liquid (75%, 72 h). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.86-7.78 (m, 2H), 7.73-7.66 (m, 2H), 7.31-7.21 (m, 4H), 6.64-6.48 (m, 2H), 5.12-5.02 (m, 1H), 1.65 (d, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): *δ* 168.0, 135.0, 134.0, 133.5, 132.1, 130.8, 128.9, 128.8, 127.9, 123.3, 48.9,19.0. HRMS (ESI): calcd for $C_{18}H_{14}ClNO_2$: *m*/*z* 366.0867 ([M+MeOH+Na]$^{+}$), found: *m*/*z* 366.0864.

(*E*)-2-(4-(4-bromophenyl)but-3-en-2-yl)isoindoline-1,3-dione (35la)



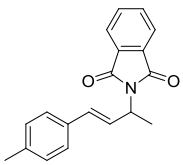
Colorless liquid (59%, 72 h). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.86-7.78 (m, 2H), 7.73-7.66 (m, 2H), 7.40 (d, *J* = 8.2 Hz, 1H), 7.30-7.20 (m, 3H), 6.65-6.47 (m, 2H), 5.12-5.01 (m, 1H), 1.65 (d, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): *δ* 168.0, 135.3, 134.0, 132.1, 131.7, 130.9, 129.0, 128.8, 128.2, 123.3, 48.9, 19.0. HRMS (ESI): calcd for $C_{18}H_{14}BrNO_2$: *m*/*z* 410.0362 ([M+MeOH+Na]$^{+}$), found: *m*/*z* 436.0363.

(*E*)-2-(4-phenylbut-3-en-2-yl)isoindoline-1,3-dione (35ha)



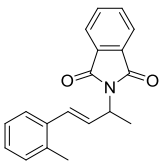
Colorless liquid (65%, 72 h). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.83-7.81 (m, 2H), 7.69-7.67 (m, 2H), 7.40-7.34 (m, 2H), 7.28 (td, *J* = 6.5, 1.7 Hz, 2H), 7.24-7.18 (m, 1H), 6.67-6.55 (m, 2H), 5.13-5.03 (m, 1H), 1.66 (d, *J* = 6.5 Hz, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): *δ* 168.1, 136.5, 134.0, 132.2, 132.1, 128.6, 128.2, 127.9, 126.6, 123.3, 49.1, 19.1. HRMS (ESI): calcd for $C_{18}H_{15}NO_2$: *m*/*z* 332.1257 ([M+MeOH+Na]$^{+}$), found: *m*/*z* 332.1254.

(*E*)-2-(4-(p-tolyl)but-3-en-2-yl)isoindoline-1,3-dione (35ga)



Colorless liquid (86%, 48 h). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.83-7.80 (m, 2H), 7.72-7.66 (m, 2H), 7.26 (d, *J* = 7.8 Hz, 3H), 7.08 (d, *J* = 7.8 Hz, 2H), 6.62-6.51 (m, 2H), 5.13-5.01 (m, 1H), 2.30 (s, 3H), 1.65 (d, *J* = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): *δ* 168.1, 137.8, 134.0, 133.7, 132.2, 132.0, 129.3, 127.1, 126.6, 123.2, 49.2, 21.3, 19.2. HRMS (ESI): calcd for $C_{19}H_{17}NO_2$: *m*/*z* 346.1414 ([M+MeOH+Na]$^{+}$), found: *m*/*z* 346.1411.

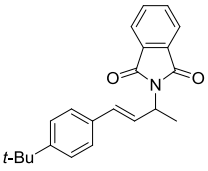
(*E*)-2-(4-(o-tolyl)but-3-en-2-yl)isoindoline-1,3-dione (35na)



Colorless liquid (84%, 48 h). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.83-7.81 (m, 2H), 7.70-7.68 (m, 2H), 7.47-7.40 (m, 1H), 7.12 (td, *J* = 5.8, 3.8 Hz, 3H), 6.81 (d, *J* = 15.6 Hz, 1H), 6.56-6.46 (m, 1H), 5.15-5.05 (m, 1H), 2.31 (s, 3H), 1.66 (d, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): *δ* 168.1, 135.5, 134.0,

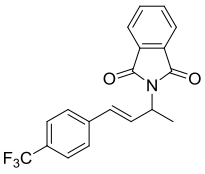
132.2, 130.3, 129.9, 129.5, 127.8, 126.2, 126.0, 123.2, 49.3, 19.8, 19.2. HRMS (ESI): calcd for $C_{19}H_{17}NO_2$: *m*/*z* 346.1414 ([M+MeOH+Na]$^+$), found: *m*/*z* 346.1410.

(*E*)-2-(4-(4-(tert-butyl)phenyl)but-3-en-2-yl)isoindoline-1,3-dione (35fa)



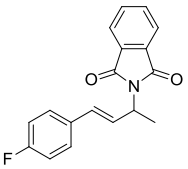
Colorless liquid (79%, 48 h). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.82-7.80 (m, 2H), 7.69-7.67 (m, 2H), 7.31-7.28 (m, 4H), 6.63-6.53 (m, 2H), 5.12-5.01 (m, 1H), 1.64 (d, *J* = 7.3 Hz, 3H), 1.28 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): *δ* 168.0, 151.0, 134.0, 133.6, 132.2, 131.9, 127.4, 126.3, 125.5, 123.2, 49.1, 31.3, 19.1. HRMS (ESI): calcd for $C_{22}H_{23}NO_2$: *m*/*z* 388.1883 ([M+MeOH+Na]$^+$), found: *m*/*z* 388.1881.

(*E*)-2-(4-(4-(trifluoromethyl)phenyl)but-3-en-2-yl)isoindoline-1,3-dione (35ia)



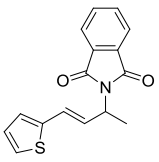
Colorless liquid (77%, 96 h). ^{1}H-NMR (400 MHz, CDCl3) δ 7.84-7.82 (m, 2H), 7.71-7.69 (m, 2H), 7.53 (d, *J* = 8.7 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 2H), 6.71 (dd, *J* = 7.2, 16 Hz, 1H), 6.60 (d, *J* = 16.0 Hz, 1H), 5.15-5.05 (m, 1H), 1.67 (d, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): *δ* 168.0, 140.0, 134.1, 132.1, 130.9, 130.7, 126.8, 125.6, 125.5, 123.3, 48.7, 18.9. HRMS (ESI): calcd for $C_{19}H_{14}F_3NO_2$: *m*/*z* 400.1131 ([M+MeOH+Na]$^+$), found: *m*/*z* 400.1128.

(*E*)-2-(4-(4-fluorophenyl)but-3-en-2-yl)isoindoline-1,3-dione (35ja)



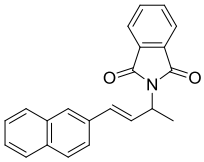
Colorless liquid (71%, 72 h). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.83-7.81 (m, 2H), 7.70-7.68 (m, 2H), 7.36-7.30 (m, 2H), 7.01-6.93 (m, 2H), 6.55-6.53 (m, 2H), 5.11-5.02 (m, 1H), 1.65 (d, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): *δ* 168.1, 134.0, 132.1, 130.9, 128.2, 128.1, 127.9, 123.3, 115.7, 115.4, 49.0, 19.1. HRMS (ESI): calcd for $C_{18}H_{14}FNO_2$: *m*/*z* 350.1163 ([M+MeOH+Na]$^+$), found: *m*/*z* 350.1160.

(*E*)-2-(4-(thiophen-2-yl)but-3-en-2-yl)isoindoline-1,3-dione (35pa)



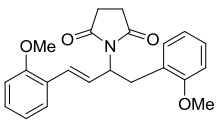
Colorless liquid (29%, 72 h). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.85-7.79 (m, 2H), 7.72-7.67 (m, 2H), 7.13 (d, *J* = 5.5 Hz, 1H), 6.95-6.92 (m, 2H), 6.72 (d, *J* = 15.8 Hz, 1H), 6.49-6.38 (m, 1H), 5.08-5.00 (1H), 1.65 (d, *J* = 7.6 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): *δ* 167.9, 141.3, 134.8, 132.2, 132.0, 130.5, 129.1, 128.3, 127.4, 123.7, 52.1, 19.2. HRMS (ESI): calcd for $C_{16}H_{13}NO_2S$: *m*/*z* 338.0821 ([M+MeOH+Na]$^+$), found: *m*/*z* 338.0818.

(*E*)-2-(4-(naphthalen-2-yl)but-3-en-2-yl)isoindoline-1,3-dione (35oa)



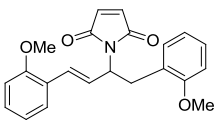
Yellowish Solid (77%, 36 h). M.p. 90-92 °C^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.89-7.80 (m, 2H), 7.80-7.67 (m, 6H), 7.58 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.47-7.36 (m, 2H), 6.77 (dd, *J* = 16.0, 3.7 Hz, 2H), 5.20-5.09 (m, 1H), 1.70 (d, *J* = 6.9 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): *δ* 168.1, 134.0, 133.9, 133.6, 132.2, 132.1, 128.5, 128.3, 128.1, 127.7, 126.7, 126.3, 126.0, 125.9, 123.7, 123.3, 49.2, 19.2. HRMS (ESI): calcd for $C_{22}H_{17}NO_2$: *m*/*z* 382.1414 ([M+MeOH+Na]$^+$), found: *m*/*z* 382.1411.

(*E*)-1-(1,4-bis(2-methoxyphenyl)but-3-en-2-yl)pyrrolidine-2,5-dione (35ab)



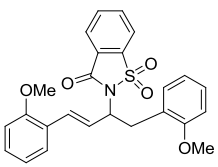
Colorless liquid (64%, 72 h). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.23-7.11 (m, 2H), 7.02 (dd, *J* = 7.6, 1.8 Hz, 1H), 6.98-6.86 (m, 2H), 6.86-6.76 (m, 3H), 6.76-6.64 (m, 1H), 5.21 (td, *J* = 9.3, 5.8 Hz, 1H), 3.83 (d, *J* = 13.7 Hz, 6H), 3.33 (dd, *J* = 13.7, 10.3 Hz, 1H), 3.20 (dd, *J* = 14, 6.4 Hz, 1H), 2.57-2.34 (m, 4H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): *δ* 177.0, 158.0, 157.0, 130.9, 129.0, 128.2, 128.0, 127.0, 126.8, 126.0, 125.4, 120.7, 120.2, 110.9, 110.5, 55.5, 55.4, 54.4, 33.5, 28.9. HRMS (ESI): calcd for $C_{22}H_{23}NO_4$: *m*/*z* 420.1781 ([M+MeOH+Na]$^+$), found: *m*/*z* 420.1775.

(*E*)-1-(1,4-bis(2-methoxyphenyl)but-3-en-2-yl)-1*H*-pyrrole-2,5-dione (35ac)



Colorless liquid (74%, 60 h). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.24-7.12 (m, 2H), 7.00 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.95-6.73 (m, 5H), 6.70-6.58 (m, 1H), 6.49 (s, 2H), 5.20-5.09 (m, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.36-3.25 (dd, *J* =13.6, 3.2 Hz, 1H), 3.18 (dd, *J* = 13.6, 5.6 Hz, 1H) $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): *δ* 170.6, 133.8, 131.0, 129.0, 128.2, 127.5, 127.4, 127.0, 120.9, 120.3, 110.9, 110.3, 55.5, 55.4, 53.6, 34.4. HRMS (ESI): calcd for $C_{22}H_{21}NO_4$: *m*/*z* 418.1625 ([M+MeOH+Na]$^+$), found: *m*/*z* 418.1619.

(*E*)-2-(1,4-bis(2-methoxyphenyl)but-3-en-2-yl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (35ad)



Colorless liquid (33%, 72 h). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.99-7.95 (m, 1H), 7.83-7.72 (m, 3H), 7.43 (d, *J* = 7.3 Hz, 1H), 7.22-7.10 (m, 3H), 6.98 (d, *J* = 16.0 Hz, 1H), 6.85 (td, *J* = 15.2, 7.8 Hz, 3H), 6.78-6.64 (m, 2H), 5.25 (d, *J* = 7.8 Hz, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 3.58-3.41 (m, 2H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): *δ* 170.1, 159.2, 158.3, 140.2, 136.6, 134.9, 130.2, 129.5, 128.9, 127.5, 126.9, 125.8, 123.7, 122.9, 120.9, 114.2, 112.2, 56.3, 56.1, 55.8, 32.3. HRMS (ESI): calcd for $C_{25}H_{23}NO_5S$: *m*/*z* 472.1189 ([M+Na]$^+$), found: *m*/*z* 472.1176

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