

Synthesis and Evaluation of Functionalized Dirhodium(II) Carboxylate Catalysts Bearing Axially Chiral Amino Acid Derivatives

軸性不斉アミノ酸リガンドを有する
官能基化されたロジウムカルボキシレート触媒の
合成と反応開発

2017

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List of abbreviation

Ac	acetyl
AcOEt	ethyl acetate
Alloc	allyloxycarbonyl
aq.	aqueous
Boc	<i>tert</i> -butyloxycarbonyl
<i>t</i> -Bu	<i>tert</i> -butyl
cat.	catalyst
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIPEA	diisopropylethylamine
DPPA	diphenylphosphoryl azide
dr	diastereomeric ratio
DMAP	4-dimethylaminopyridine 4-dimethylaminopyridine
ee	enantiomeric excess
eq	equivalent
EDCI	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide Hydrochloride
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometer
HOBT	1-Hydroxybenzotriazole
IR	infrared
Me	methyl
min	minute
m.p.	melting point
NMR	nuclear magnetic resonance
PTLC	preparative thin-layer chromatography
PMB	<i>p</i> -methoxybenzen
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TS	transition state

Theoretical Section

Foreword

The design and synthesis of novel chiral ligands are one of the most important things to develop unprecedented enantioselective transition metal-catalyzed reactions.

It is well known that metal-ligand interactions can serve both to modulate the electronic properties of the metal, and to influence the steric environment of the metal coordination sphere, thereby allowing some control of reactivity and selectivity. Thus, the design of asymmetric ligands is essential to the development of highly enantioselective and efficient reactions catalyzed by transition metal complex.¹

Dirhodium(II) catalysts, the most efficient catalyst for decomposition of diazo compounds,² play a key role in carbenoid C–H insertion reactions. The dirhodium(II) catalysts adopt an unique three-dimensional structure which are paddlewheel-shaped dimetallic complexes. Four bidentate ligands bridge two rhodium atoms connected by a rhodium-rhodium bond (Scheme 1–1).³

Symmetry is an important factor in chiral rhodium catalyst design in the past decades. Highly symmetric ligands were developed in dirhodium(II) catalysts and amino acids ligated rhodium catalysts with central chirality are the most popular catalysts utilized in asymmetric rhodium carbenoid mediated C–H insertion, cyclopropanation, ylide addition reactions and so on.⁴ Most of the asymmetric inductions were attributed to steric control. Although steric repulsion is one of the most frequent reason in asymmetric induction, distinguishment between similar steric environments around rhodium carbenoid is still an unresolved problem (Scheme 1–6).

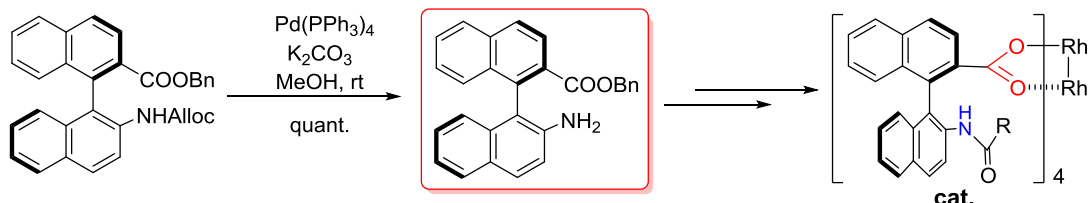
Recently, it has become possible to direct the regioselectivity of C–H activation reaction,⁵ as well as the enantioselectivity of certain addition reactions⁶ by hydrogen bonds in supramolecular metal complexes. Likewise in the case of enzymatic reactions, designed hydrogen bonding in transition metal complexes is known to provide both the required rate acceleration and asymmetric induction. This mode of activation is relatively mild, which makes the activation attractive because it ensures a high functional group tolerance.

The simplest axially chiral amino acids possessing amino and carboxylic acid groups at the C-2 and C-2' positions were prepared before in our lab.⁷ The structure contains an axially chiral binaphthyl skeleton axis and acidic NH proton which is available as a hydrogen bonding donor. As such, they are expected to be suitable for ligand candidates of dirhodium carboxylate catalyst.

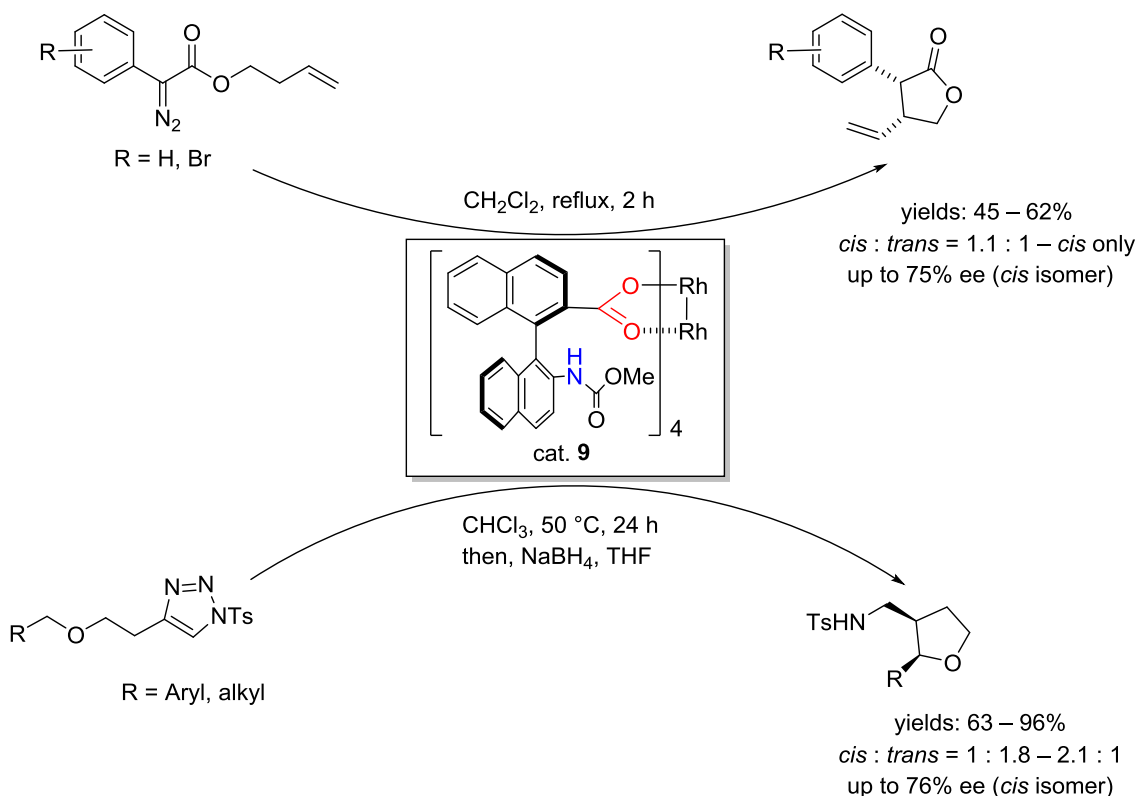
This thesis consists of the design of functionalized dirhodium carboxylate catalysts bearing axially chiral amino acid derivatives and their application to asymmetric intramolecular C–H insertion reactions.

An approach to synthesize optically active *N*-functionalized binaphthyl amino acids upon palladium-catalyzed *N*-Alloc deprotection was described in Chapter 2. With consequent ligand exchange, a series of dirhodium(II) carboxylate catalysts bearing *N*-functionalized axially chiral

amino acid derivatives were synthesized. The conformation of *N*-methoxycarbonyl substituted catalyst **9** was disclosed by X-ray structure analysis.



The ability of its asymmetric induction was investigated in enantioselective intramolecular $\text{C(sp}^3\text{)}\text{-H}$ bond functionalization to afford α -aryl- β -substituted γ -lactones⁸ (Chapter 3). Then I challenged asymmetric synthesis of α,β -disubstituted tetrahydrofurans with triazole substrate, in which precedent catalysts could not give sufficient enantioselectivity. I achieved the first example of moderate enantioselective (up to 78% ee) synthesis of α,β -disubstituted tetrahydrofurans with my catalyst (Chapter 4). Hydrogen bonding interaction between substrate and ligand was effective for this asymmetric induction as we designed. I expect cat. **9** is also applicable and effective for enantioselective reactions with other triazole candidates.



Chapter 1

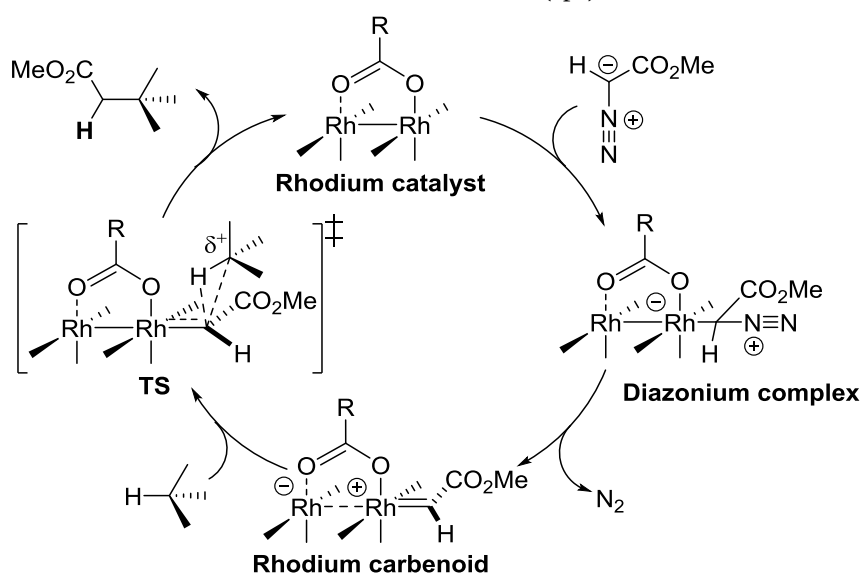
Introduction

1.1 General introduction of rhodium catalyzed C–H insertion

The metal catalyzed carbenoid C–H insertion reactions generated *in situ* from diazo compounds is useful transformation for C–H functionalization. In general, C–H functionalization is particularly attractive strategy available for the synthesis of natural products and pharmaceuticals. Compared to other metal catalysts containing Pd, Ag or Cu complexes, dirhodium(II) complexes are exceptionally active catalyst in the decomposition of diazo compounds.⁹

The dirhodium(II) catalysts are paddlewheel-shaped dimetallic complexes in which four bidentate ligands bridge two rhodium atoms connected by a rhodium-rhodium bond (Scheme 1–1). This structure of dirhodium(II) catalysts brings a 16-electron rhodium center by release of axial ligands. Due to this attribute, rhodium catalyst works as an electrophile to react with diazo group to form a diazonium complex, metalcarbene is produced with release of N₂ from the diazonium complex. In the C–H insertion step, a three-center mechanism was proposed by Nakamura using DFT calculation.¹⁰ The three-center transition state (TS) features significant bond formation between the hydrogen and the carbene carbon, partial positive charge on the carbon of the C–H bond, and partial negative charge on the rhodium center. Carbon-carbon bond formation and carbon–rhodium bond cleavage occur simultaneously to regenerate the catalyst (Scheme 1–1). This type of C–H insertion reactions are generally faster at electron-rich C–H bonds, especially the C–H bonds directly connected to oxygen and nitrogen atoms that can stabilize the developing positive charge.²

Scheme 1–1. Mechanism of the carbenoid insertion into the C(sp³)–H bond



According to mechanism introduction, in theory, the reaction has the potential to establish a new stereocenter with high atom economy and stereoselectivity. Even though catalyst design is an extremely challenging work, over the past decades, there are a broad range of chiral rhodium(II) catalysts have been developed, encompassing rhodium(II) carboxylates, rhodium(II) carboxamides, rhodium(II) phosphonates and rhodium(II) biaryl carboxylates. Furthermore, rhodium carbene precursors such as donor/acceptor-substituted diazo compounds and triazoles derivatives are also critical to asymmetric C–H insertions reactions. Herein, they are briefly summarized in this chapter.

1.2 Chiral ligands in rhodium(II) catalysts

1.2.1 Ligands with central chirality

The dirhodium(II) carboxylates are attractive catalysts, particularly for kinetically very active for decomposition of various carbene precursors due to their electron deficient character. The first application of chiral rhodium(II) carboxylate catalyst was reported by McKervy and co-workers in 1990. They found that proline ligated $\text{Rh}_2(\text{S-BSP})_4$ was shown to be an effective catalyst in the intramolecular C–H insertion of an α -diazo- β -keto sulfone precursor (12% ee) (Figure 1–1).¹¹ Numerous related proline complexes have been synthesized since then. Among them, $\text{Rh}_2(\text{S-DOSP})_4$ discovered by Davies in 1993 is recognized as the exceptional catalyst for reactions of donor/acceptor-substituted carbenoids,¹² and widely utilized in intermolecular enantioselective C–H insertion reactions as well. The conformation of $\text{Rh}_2(\text{S-DOSP})_4$ was considered to prefer a high-symmetry, D_2 -symmetrical complex in which the arylsulfonyl groups were directed in an up-down-up-down fashion pointing out of the O–Rh–O plane on both faces of the catalyst (Figure 1–1).^{12b, 13}

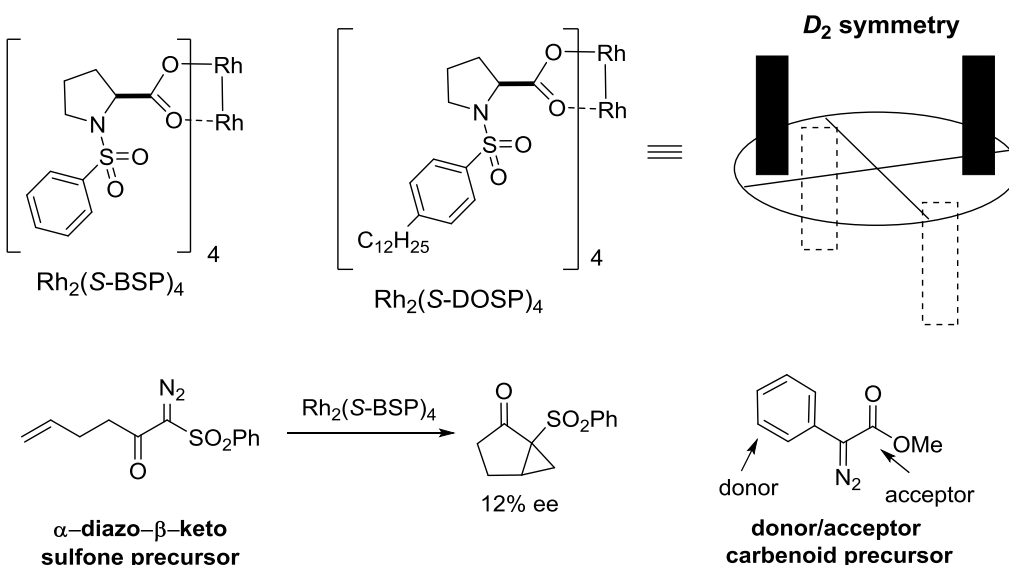


Figure 1–1. Typical proline based chiral dirhodium(II) carboxylates

In the same year, Hashimoto and Ikegami reported the use of phthalimide derivatives of amino acid-based chiral rhodium(II) carboxylates as catalysts (Figure 1–2), proficient in the enantioselective intramolecular C–H insertion reactions of a series of α -diazo- β -keto esters.¹⁴ $\text{Rh}_2(\text{S-PTPA})_4$ shows the phthalimido groups aligned in an up-up-down-down fashion around the dirhodium core, giving these complexes overall C_2 -symmetry. Several related complexes were later prepared, including valine $\{\text{Rh}_2(\text{S-PTV})_4\}$, *tert*-leucinate $\{\text{Rh}_2(\text{S-PTTL})_4\}$, phenylglycine $\{\text{Rh}_2(\text{S-PTPG})_4\}$ derived catalysts, showing improvements in enantioselectivity due to the increased steric hinderance of the alkyl group in the ligand.¹⁵ It is noted that $\text{Rh}_2(\text{S-PTTL})_4$ performed an all-up conformation (C_4 -symmetry) which was determined from its X-ray structure by Fox.¹⁶ In recent years, these complexes are characterized by substitution of the phthalimido hydrogens by fluorine $\{\text{Rh}_2(\text{S-TFPTTL})_4\}$, chlorine $\{\text{Rh}_2(\text{S-TCPTTL})_4\}$ or bromine atoms $\{\text{Rh}_2(\text{S-TBPTTL})_4\}$, resulting in improved reactivity owing to the electron-withdrawing effect and intramolecular halogen bonding.¹⁷

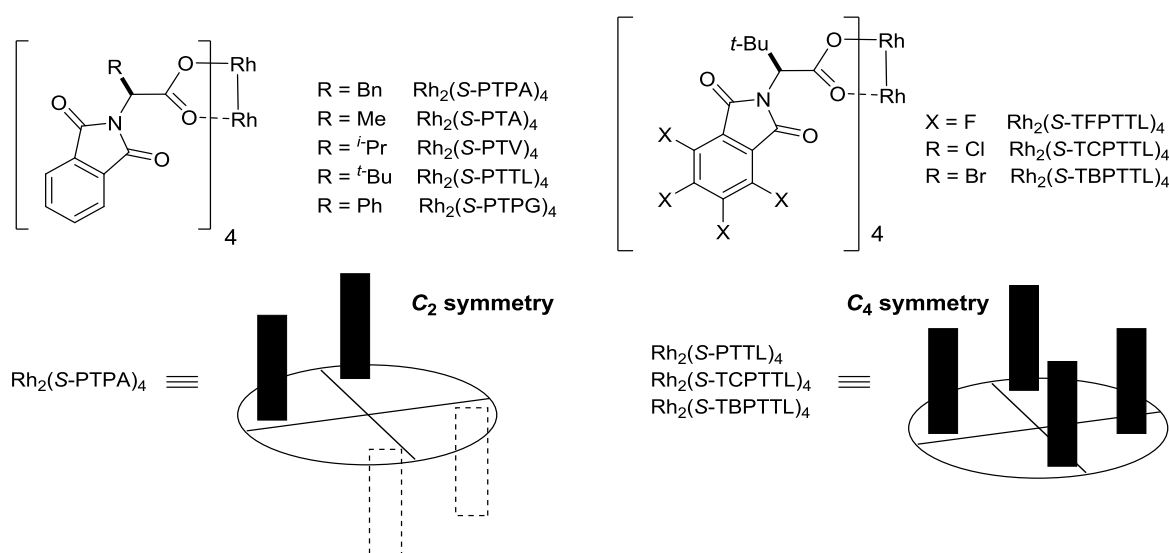


Figure 1–2. Phthalimide derivatives of amino acid-based chiral rhodium(II) carboxylates

From 1990, Doyle and co-workers developed numerous rhodium carboxamidate catalysts including pyrrolidinoes complex, $\text{Rh}_2(5\text{S-MEPY})_4$,¹⁸ oxazolidiones $\text{Rh}_2(4\text{S-MEOX})_4$ ¹⁹ and azetidinones complexes $\text{Rh}_2(4\text{S-MEAZ})_4$ ²⁰ catalysts which were the effective chiral dirhodium(II) carboxamidate catalysts (Figure 1–3). The dirhodium carboxamidates are inherently limited to complexes with over all C_2 -symmetry. This due to the preferred alignment of the carboxamidate ligands in the *cis*(2,2) configuration where two nitrogen and two oxygen atoms are attached to the same Rh atom.²¹ Rhodium carboxamidates are very electron rich due to the relatively high basicity of the carboxamide ligands. This property usually helps to increase the stereoselectivity with these complexes in carbenoid reactions, but to be less active than the dirhodium carboxylates. These catalysts have been employed in enantioselective intramolecular C–H insertions to form substituted γ -lactones and lactams.²²

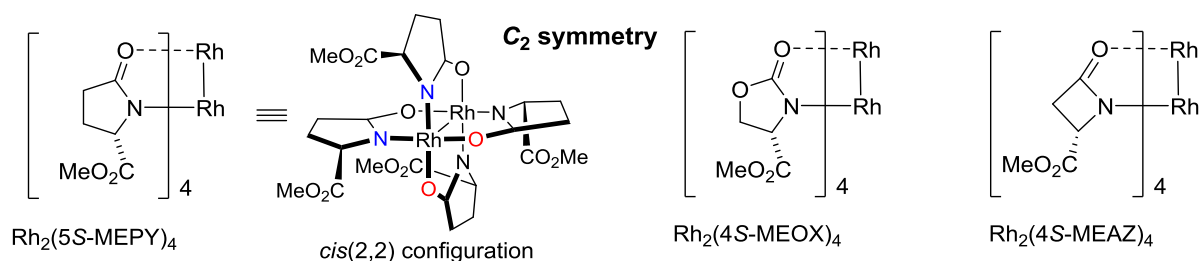


Figure 1–3. Pyrrolidinoes, oxazolidiones and azetidinones based chiral rhodium(II) carboxamidates

These three types of chiral dirhodium carboxamidate and carboxylate catalysts, especially, $\text{Rh}_2(5\text{S-MEPY})_4$, $\text{Rh}_2(\text{S-DOSP})_4$, and $\text{Rh}_2(\text{S-TCPTTL})_4$ typically are the most widely applicable and the choice for stereo- and enantioselective C–H insertion reactions.

1.2.2 Ligands with axial chirality

Besides the amino acid derived rhodium catalysts with central chirality, several chiral rhodium carboxylate catalysts bearing axially chiral biaryl ligands also have been reported, although there are some limitations of wide application to date.

In 1992, chiral rhodium(II) binaphthylphosphate catalysts $\text{Rh}_2(\text{S-BNP})_2(\text{HCO}_3)_2$ and $\text{Rh}_2(\text{R-BNP})_4$ were developed by McKervy and Pirrung, respectively (Figure 1–4).²³ $\text{Rh}_2(\text{R-BNP})_4$ has four atropisomeric binaphthylphosphonate ligands around the dirhodium core. Due to the C_2 -symmetry of the chiral ligands, the overall complex has C_4 -symmetry. These two phosphate catalysts were demonstrated to be sufficient to asymmetric induction in the cycloaddition of diazo compounds. However, the performance of asymmetric induction is not expectable enough.

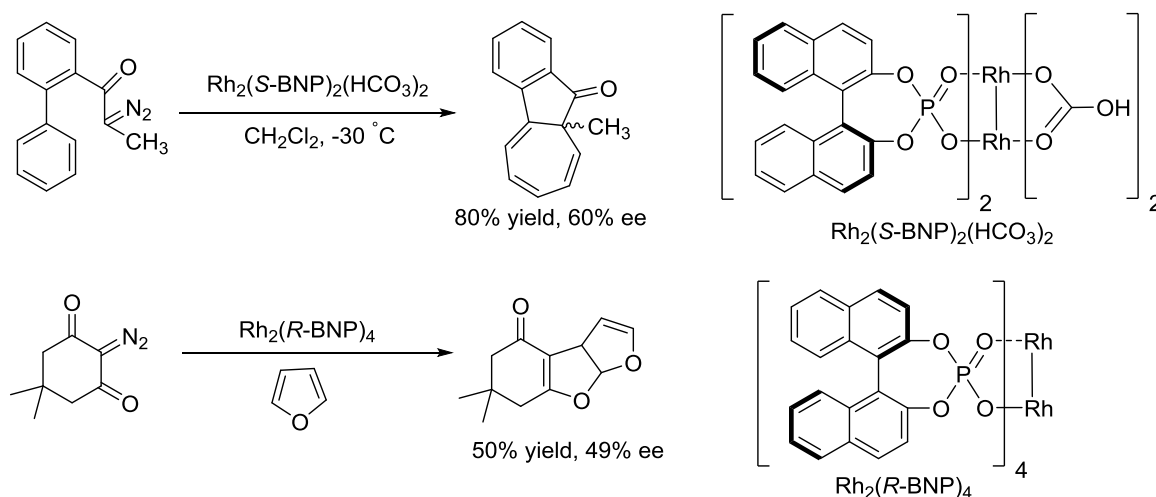


Figure 1–4. Chiral rhodium(II) binaphthylphosphate catalysts

In 1997, Achiwa and co-workers designed and prepared a rhodium catalyst bearing an axially dissymmetric biphenyl carboxylate ligand BDME, which was utilized in asymmetric cyclopropanation of styrene with diazoacetate (Figure 1–5).²⁴ After that, Hashimoto group reported similar new dirhodium carboxylate catalysts cat. **A** and cat. **B** containing an axially chiral biphenyl or binaphthyl skeleton which were shown to provide a reasonable level of asymmetric induction in intramolecular C–H insertion of α -methoxycarbonyl- α -diazoacetamide (up to 52% ee). The X-ray structure showed that cat. **A** has a C_2 symmetric conformation.²⁵ Besides that, there is no other future application with these two rhodium catalysts reported (Figure 1–5).

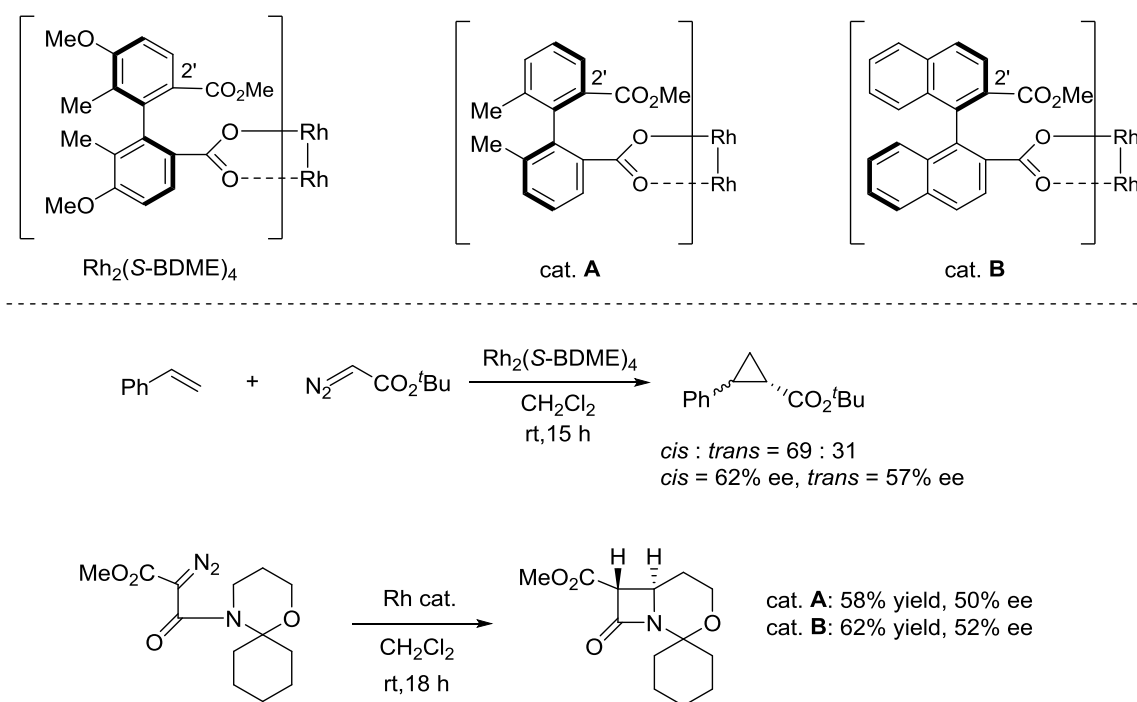


Figure 1–5. Chiral rhodium(II) binaphthyl carboxylate catalysts

The author realized that these three chiral rhodium catalysts bearing axially chiral biaryl ligands are rarely functionalized on their 2'-position (carboxymethyl). With the information from C_2 -symmetric conformation of cat. **A**,²⁵ the introduction of *N*-functionalized group at 2'-position may also direct toward outward respect to axially chiral binaphthyl skeleton (modeled as pink cylinder in Figure 1–6) in its C_2 -symmetric conformation. Therefore, *N*-functionalized group can work not only as a bulky group, but also as a hydrogen bonding donor for substrate recognition (Figure 1–6). As such, they are expected to be suitable for ligand candidates of dirhodium carboxylate catalyst to lead future generations of catalysts having substrate recognition ability through hydrogen bonding.

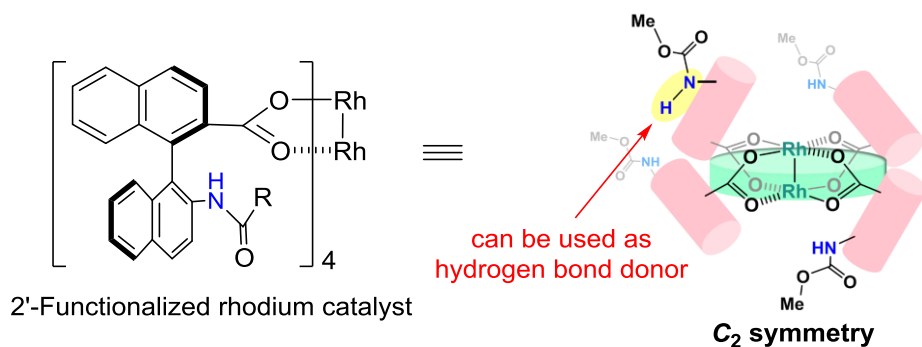


Figure 1–6. Design of 2'-functionalized rhodium catalyst.

1.3 Rhodium carbenoid precursors

Not only the development of chiral rhodium catalyst can highly contribute to carbene C–H insertions, but also substrates design usually play an important role. Diazoacetates are the most preferred substrates for generating reactive rhodium carbene species and it is one of the most fundamental path to achieve C–H insertion reactions. The reactivity and stereoselectivity of C–H insertion reactions are highly dependent on the carbenoid structure which have been classified into three major groups, acceptor, acceptor/acceptor and donor/acceptor carbenoid precursors (Figure 1–7).²⁶ In recent years, due to the the chemistry of the donor/acceptor carbenoids has expanded greatly to a variety of regio- and stereoselective reactions because they display much greater selectivity than the other two carbenoids. Hence, the donor/acceptor diazo compounds, α -aryl- β -diazoacetates, were chosen as the substrate to intramolecular C–H insertion reactions in chapter 3.

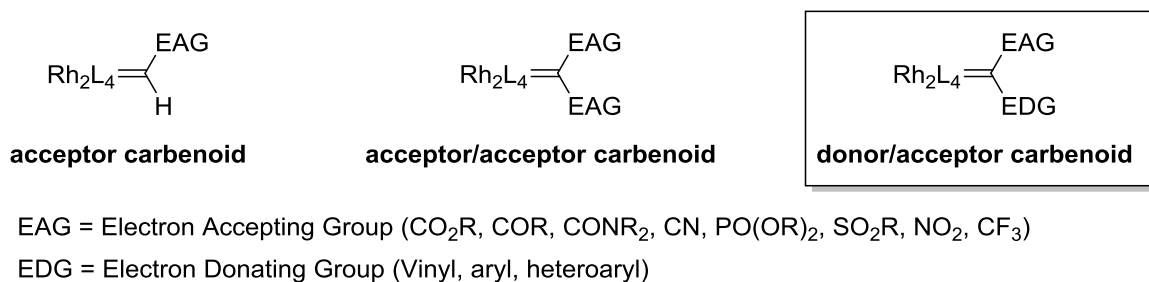
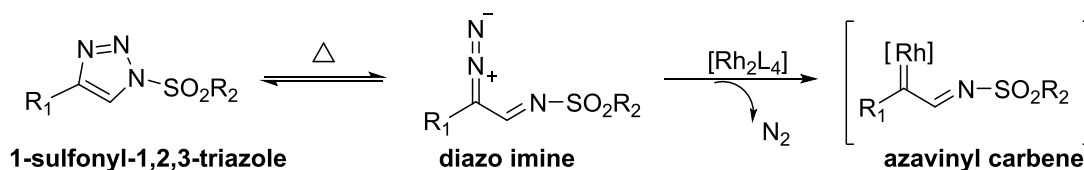


Figure 1–7. Classes of rhodium carbenoids

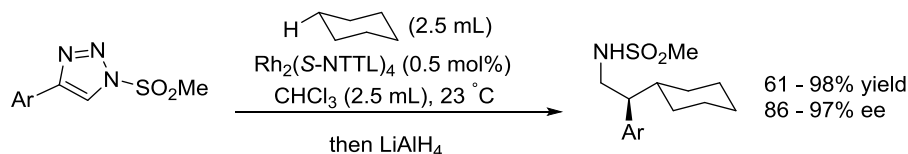
Furthermore, *in-situ* generation of the carbene species has recently been achieved from 1-sulfonyl-1,2,3-triazoles²⁷ which can serve as convenient progenitors of reactive azavinyl carbene, a new type of metal-stabilized donor/acceptor carbenoid.²⁸ The triazole intermediate can be easily prepared by click reaction²⁹ from alkyne and sulfonyl azide. It is thermally and photochemically stable compared to diazocarbonyl compounds. The key reaction sequence, illustrated in Scheme 1–2, is the ring opening of triazoles to generate diazo imines and their subsequent conversion to metal-bound azavinyl carbenes. Consequently, *N*-sulfonyl-1,2,3-triazoles undergo many Rh(II)-catalyzed transformations such as X–H insertion,³⁰ cyclopropanation, [3 + 2] cycloaddition³¹ and arylation reactions³².

Scheme 1–2. Formation of metal-bound azavinyl carbene.

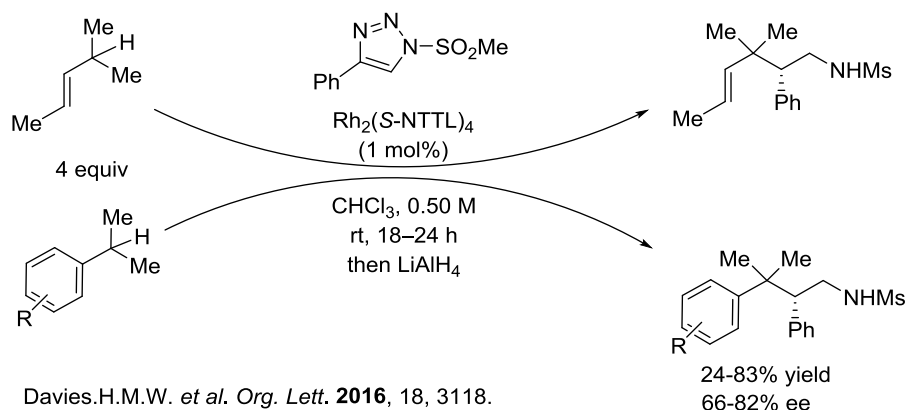


The utility of *N*-sulfonyl-1,2,3-triazoles for selective intermolecular C–H functionalization reactions, to date, has been far less investigated. In 2011, Fokin and co-workers showed that azavinyl carbenes derived from 4-phenyl-*N*-sulfonyl-1,2,3-triazoles undergo highly enantioselective intermolecular C–H functionalization reactions with inactivated alkanes in the presence of $\text{Rh}_2(\text{S-NTTL})_4$ at room temperature, although excess equivalent of alkanes were employed.³³ Most recently, Davies reported an enantioselective intermolecular $\text{C}(\text{sp}^3)\text{--H}$ functionalization in good yields and moderate levels of enantioselectivity (66–82% ee) at the allylic and benzylic positions.³⁴ Similar to Fokin's case, 4-phenyl-*N*-(methanesulfonyl)-1,2,3-triazole and $\text{Rh}_2(\text{S-NTTL})_4$ were used as azavinyl carbene precursor and catalyst, respectively (Scheme 1–3).

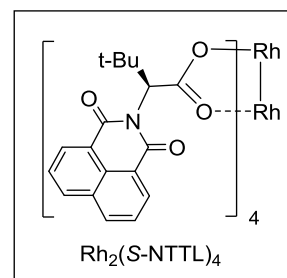
Scheme 1–3. Enantioselective intermolecular C–H functionalization using *N*-sulfonyl-1,2,3-triazoles.



Fokin, V.V. *et al.* *J. Am. Chem. Soc.* **2011**, 133, 10352

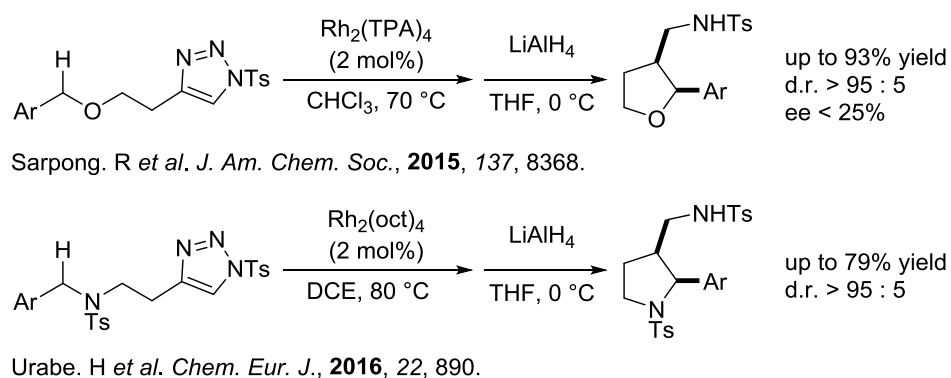


Davies, H.M.W. *et al.* *Org. Lett.* **2016**, 18, 3118.



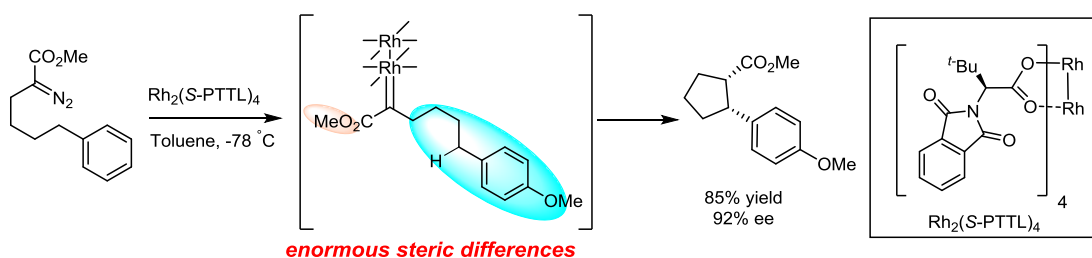
Comparatively, in the area of intramolecular C–H functionalization reactions, very recently, Sarpong and Urabe successively reported a Rh(II)-catalyzed intramolecular cyclization of azavinyl carbene from triazole substrate having alkyl chain substituent (Scheme 1–4). This C–H insertion reaction afforded access to an array of stereodefined *cis*-2,3-disubstituted saturated heterocycles, such as pyrrolidines and tetrahydrofurans.^{35, 36} However, attempts to develop an enantioselective version of this reaction using chiral Rh(II) catalysts were unsuccessful (<25% ee). To the best of my knowledge, there is no precedent for the asymmetric version achieved with satisfactory stereoselectivity for intramolecular azavinyl carbene mediated C–H insertion reactions from triazole precursors.

Scheme 1–4. Synthesis of *cis*-2,3-disubstituted saturated heterocycles by rhodium catalyzed azavinyl carbene C-H insertion.



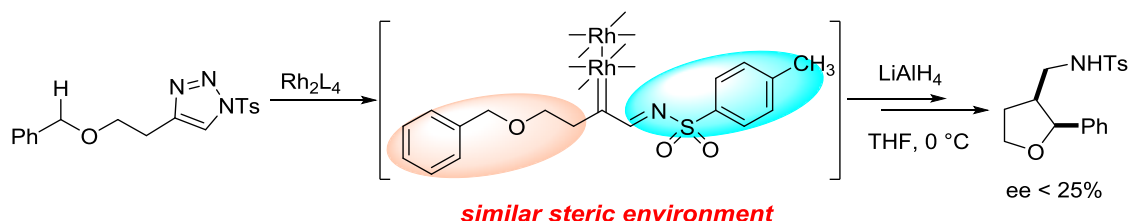
The possible factor leads to this unsuccessful asymmetric induction in an intramolecular C–H insertion was considered as following. Through the overview of reported highly enantioselective intramolecular C–H insertion reactions using diazocarbonyl compounds,³⁷ there is a frequent character of rhodium carbenoid intermediates which have an enormous steric differences of the substituents in the left part (marked in pink) and right part (marked in blue) with respect to carbenoid carbon center (Scheme 1–5).

Scheme 1–5. Enantioselective intramolecular C–H insertions with high enantioselectivity.



In contrast, in the case of using triazole substrate (Scheme 1–6),³⁵ due to the similar steric environments in both ends (marked in pink and blue) of the *N*-sulfonyl azavinyl carbene precursor, discriminating the enantioface of the rhodium carbenoid intermediate by steric control became difficult and finally resulted the low enantioselectivity (Scheme 1–4).

Scheme 1–6. Complications in enantioselective intramolecular C–H functionalization using *N*-sulfonyl-1,2,3-triazoles



1.4 Hydrogen bonding strategy for asymmetric induction

To overcome this complication, the author started the point of idea by introducing an acidic NH group which can serve as a molecular recognition element for substrate. The hydrogen bonding between the acidic NH of the ligand and the substrate can play a key role to realize obvious discrimination of the enantioface of the carbenoid intermediate. This could be a strategy for discriminating the enantioface, which cannot be distinguished well only by steric environment of chiral ligands (Figure 1–8). With this strategy, the author aims to develop a series of rhodium catalysts containing various NH group for achieving a breakthrough of enantioselective intramolecular C–H insertion reactions with triazole substrates.

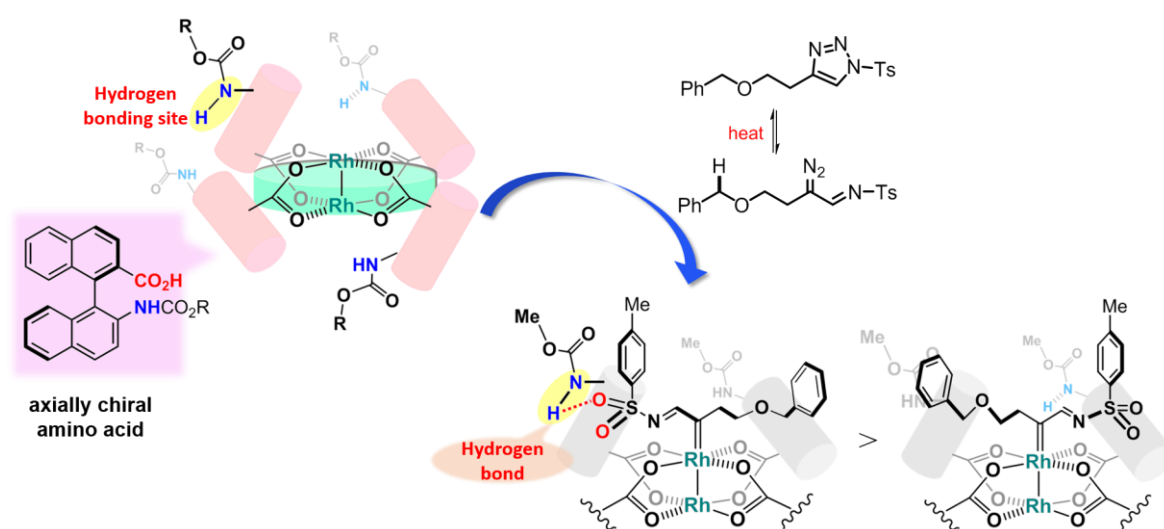
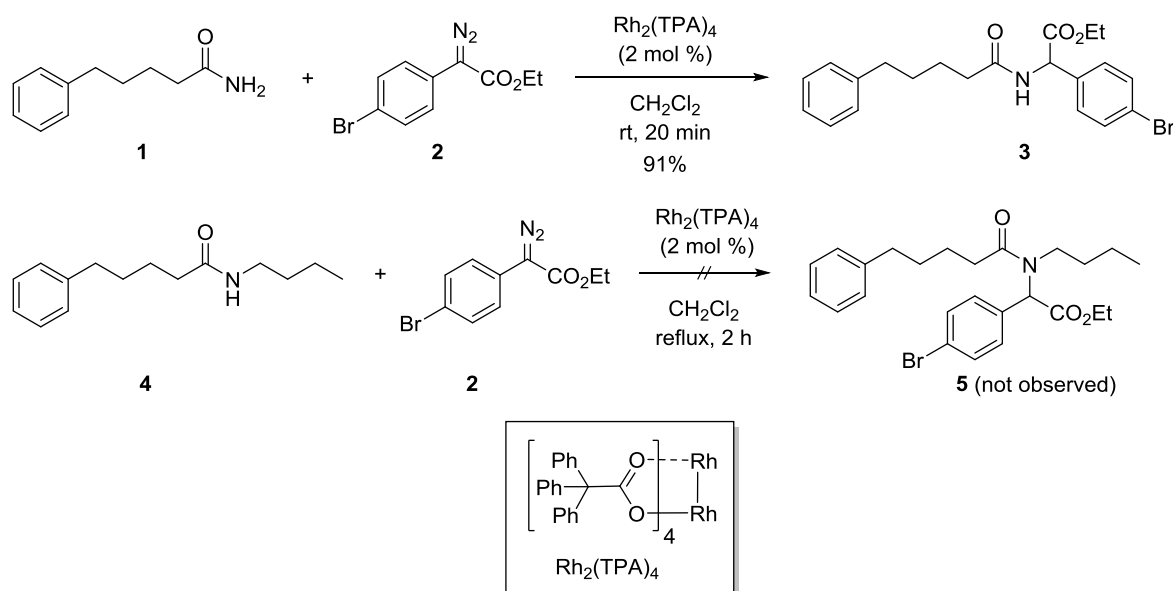


Figure 1–8. Strategy of asymmetric induction mediated by hydrogen bond via *N*-functionalized rhodium catalyst.

However, it is reported that rhodium carbenoid N–H insertion reactions can occur at primary amides, *N*-alkylanilines, and primary ureas with α -diazo- β -ketoesters.³⁸ Hence, there is a risk that NH group of ligand, which was predicted to be used as a hydrogen bond donor, might be trapped by N–H insertion. If this reaction occurs, discrimination of the enantioface of the carbenoid intermediate by hydrogen bonding interaction seems impossible. In order to confirm this, the model experiment was designed and employed. As shown in Scheme 1–7, rapid N–H insertion occurred in the case of primary amide substrate **1** in the presence of 2 mol% $\text{Rh}_2(\text{TPA})_4$. On the other hand, secondary amide **4** is safe to this N–H insertion reaction. As such, *N*-functionalized chain (secondary amide) of axially chiral ligand should be tolerated during C–H insertion.

Scheme 1–7. Reactivity of amide NH group.



With this confirmation to the sluggishness of secondary amide NH to N–H insertion reaction, the rhodium catalysts bearing axially chiral amino acid derivatives were synthesized and described in next chapter in detail.

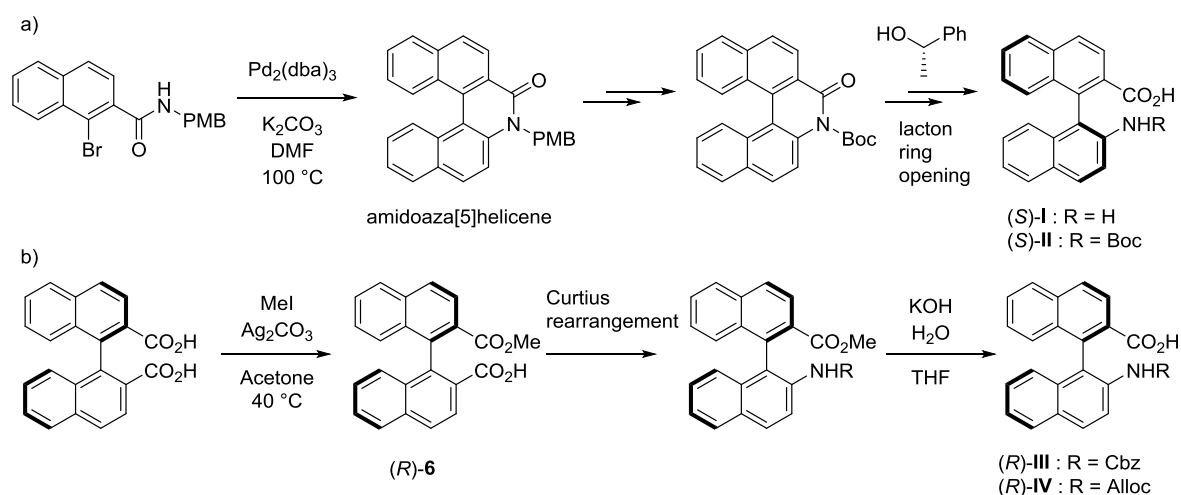
Chapter 2

Synthesis of functionalized dirhodium(II) carboxylate catalysts bearing axially chiral amino acid derivatives

1.1 Synthesis of *N*-functionalized binaphthyl amino acids derivatives

The axially chiral amino acids possessing amino and carboxylic acid groups at the C-2 and C-2' positions and its derivatives (*S*)-**I** and (*S*)-**II**, were reported by our group via an additive-ligand-free Pd catalyzed domino coupling to racemic amidoaza[5]helicenes, followed by lactam ring-opening with an optically active alcohol and subsequent separation of diastereomeric mixture (Scheme 2–1a).³⁹ After that, an improved synthetic strategy toward achieving access to *N*-Cbz and *N*-Alloc axially chiral amino acids, (*R*)-**III** and (*R*)-**IV** were developed via the selective monoesterification of 1,1'-biaryl-2,2'-dicarboxylic acids to (*R*)-**6**, following Curtius rearrangement and ester hydrolysis (Scheme 2–1b).⁴⁰

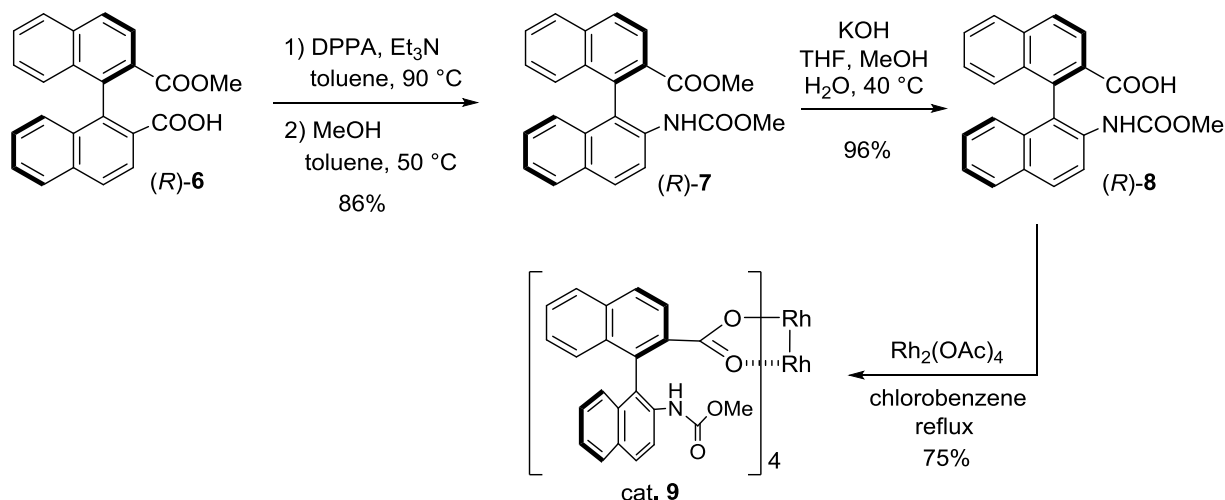
Scheme 2–1. Reported synthetic route of carbamate substituted binaphthyl derivatives



In this study, the efficient route shown in Scheme 2–1b was employed to synthesize various axially chiral amino acid derivatives for dirhodium(II) carboxylate catalysts as depicted in Scheme 2–2.

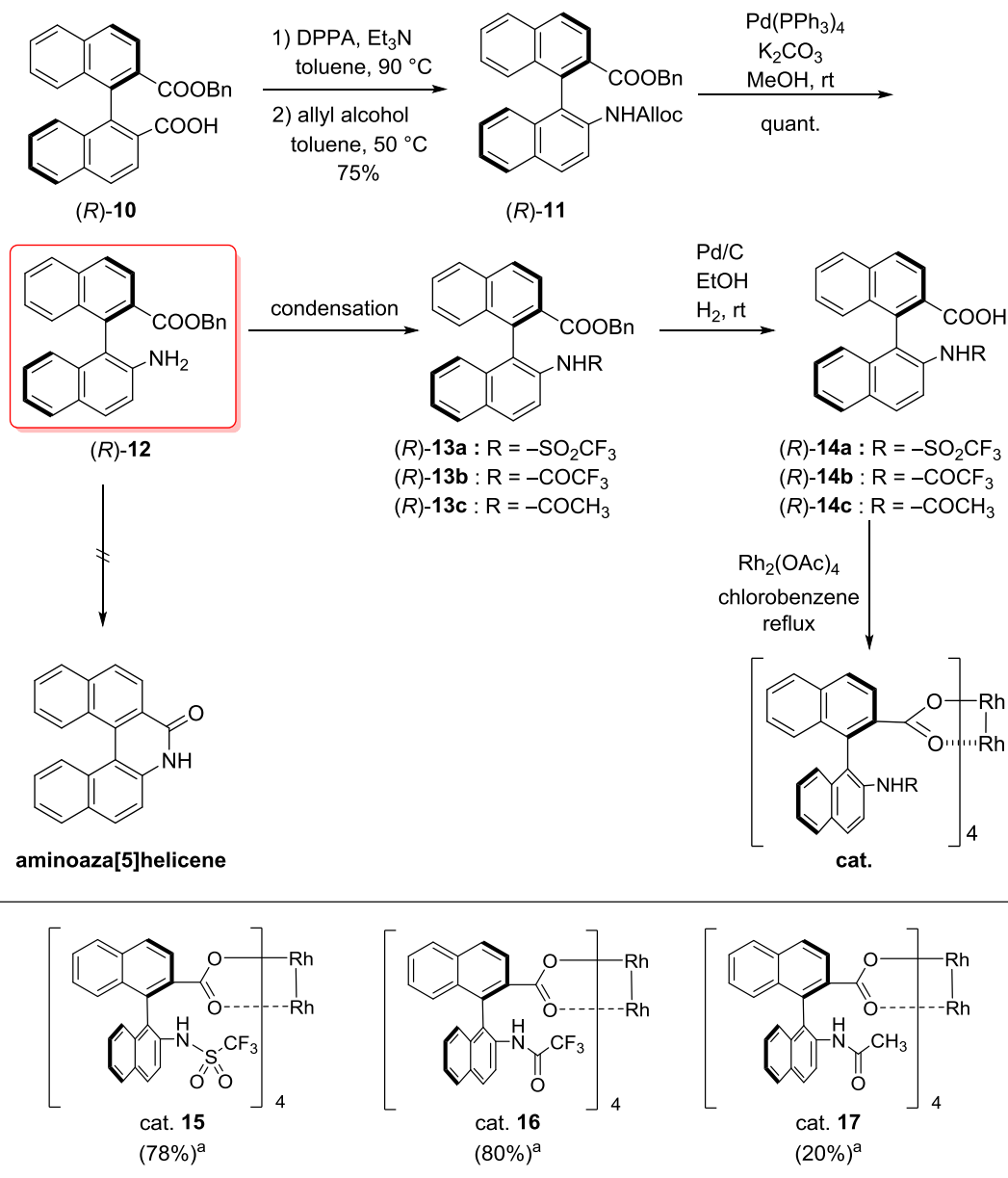
Carboxylic acid (*R*)-**8** possessing *N*-methoxycarbonyl group was prepared from monomethyl ester (*R*)-**6** via a Curtius rearrangement and subsequent selective hydrolysis of the ester group. In the presence of five equivalents of (*R*)-**8**, the ligand exchange of Rh₂(OAc)₄ readily proceeds to give catalyst cat. **9** in 75% yield after recrystallization from propionitrile (Scheme 2–2).

Scheme 2–2. Preparation of dirhodium(II) carboxylates **9**.



For tuning the acidity of NH group of the catalyst, alternative synthetic route, which makes installation of a variety of *N*-functional group feasible, was developed via key intermediate, naphthyl amine (*R*)-**12** (Scheme 2–3). *N*-Alloc monobenzyl ester (*R*)-**11** was prepared from monobenzyl ester (*R*)-**10** via a Curtius rearrangement, and subsequent deprotection of alloc group to give naphthyl amine (*R*)-**12**. Then, *N*-functionalization of (*R*)-**12**, and benzyl group deprotection led to *N*-functionalized carboxylic acids (*R*)-**14a–14c**, having triflic amide, trifluoroacetamide, and acetamide groups, respectively. The ligand exchange of each carboxylic acid afforded rhodium(II) catalysts **15–17**. It is noted that, naphthyl amine (*R*)-**12** is relatively unstable at ambiances conditions, and tend to cyclize to amidoaza[5]helicene. To overcome this problem, the deprotection of alloc group was carried out under mild conditions employing Pd(PPh₃)₄ in MeOH. This method can afford key intermediate (*R*)-**12** without any cyclized byproduct and it is found to be stable for a few days at ambiances conditions.

Scheme 2–3. Transformation to novel *N*-functionalized axially chiral rhodium catalysts.



^a Isolated yield was obtained from (R) -12 over 3 steps.

1.2 X-ray structure of catalyst cat. 9

The single crystals of cat. 9 suitable for X-ray analysis were obtained from propionitrile as a purple colored prisms. The result revealed a C_2 -symmetry-like conformation (Figure 2–1). The carbamate substituted naphthyl rings of each bridging ligand are oriented out from the Rh carboxylate center to the "up-up-down-down" direction as shown in Figures 2–1b. The side view also suggests that a pair of the carbamate substituted naphthyl rings from the adjacent bridging ligands in a "down-down" (quadrant IV) and an "up-up" (quadrant II) orientation. These naphthyl

moieties would work as a shield to control the direction of the intramolecular C–H insertion of the rhodium carbenoid intermediate. The significant structural feature of this catalyst is that the hydrogen atom of NH of carbamate moiety oriented to the rhodium center due to hydrogen bonding interactions with oxygen on O–Rh–O moiety (a : 2.34 Å, b : 2.36 Å) (Figure 2–1c). This hydrogen bonding may help to rigidify the C_2 -symmetry-like conformation and its acidic proton is also possible to act as a hydrogen bond donor with substrate to control the enantioface of carbenoid intermediate.

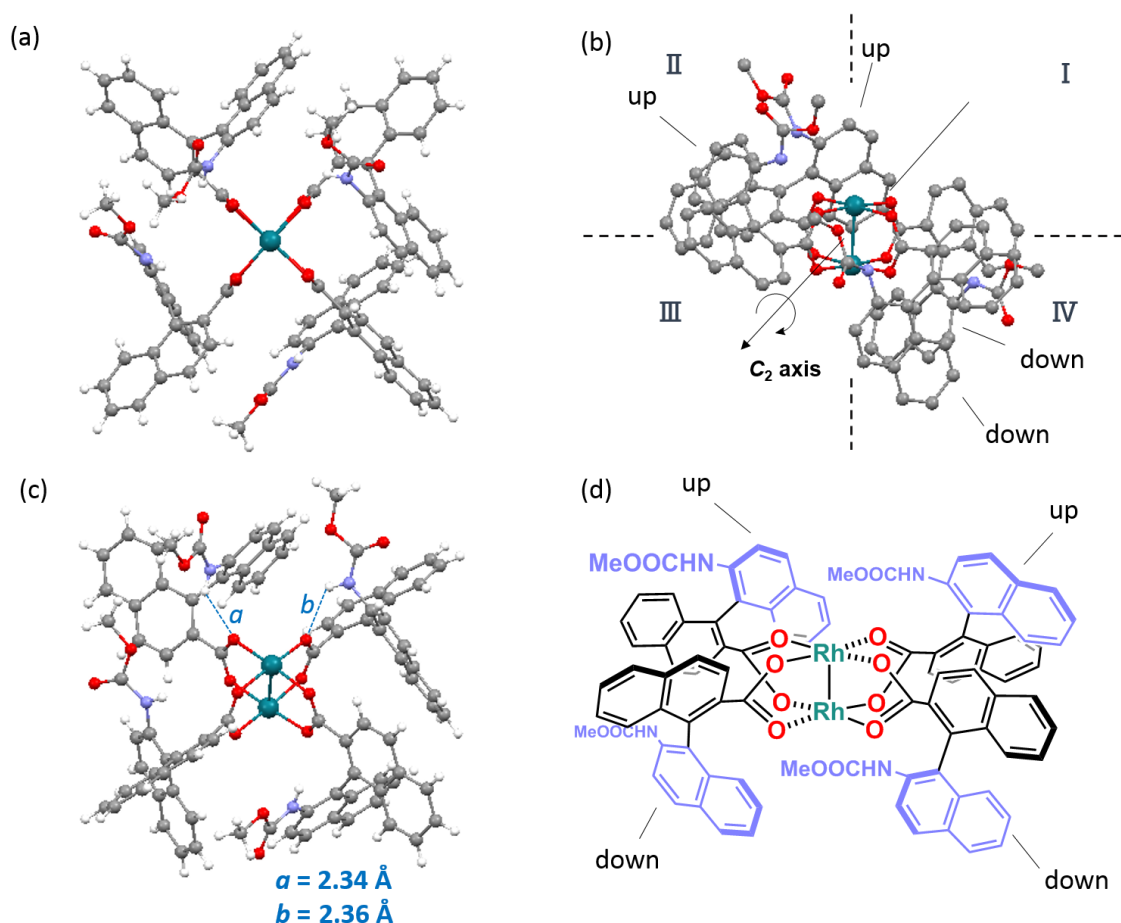


Figure 2–1. Crystal structure of bis(propionitrile) adduct of cat. **9** (50% probability), propionitrile molecules are omitted for clarity. (a) Top view. (b) side view, hydrogen atoms are omitted for clarity. (c) Front view, hydrogen–bonding distance distances in Å.

Even though the alternative D_2 -symmetry-like conformation in an "up-down-up-down" arrangement cannot be ruled out, this conformation seems unlikely (Figure 2–2). It is considered as a thermodynamically disfavor conformation because the two *ortho*-naphthyl rings (marked in blue) directed toward end of the molecule might lead steric repulsion with ligands (L), such as

solvent molecular, coordinating at axial position.

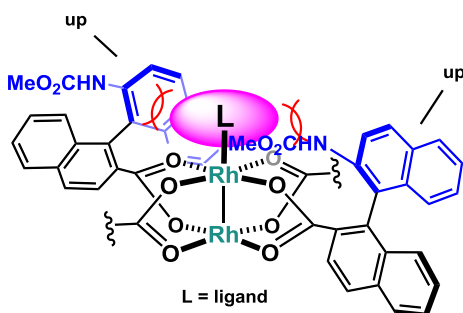


Figure 2–2. Proposed reason to prevent D_2 -symmetry-like conformation.

In summary, the author has synthesized optically active binaphthyl amino acids upon which was introduced for preparation of novel dirhodium(II) carboxylate catalysts. C_2 -symmetric chiral environment of cat. **9** was disclosed by X-ray analysis. NH groups in carbamate side chain is expected to work as a hydrogen bonding recognition site for distinguish between two similarly steric environments, that leads to sharp enantioface control of rhodium carbenoid intermediate. In the next chapter, the ability of asymmetric induction by this series of catalysts was investigated.

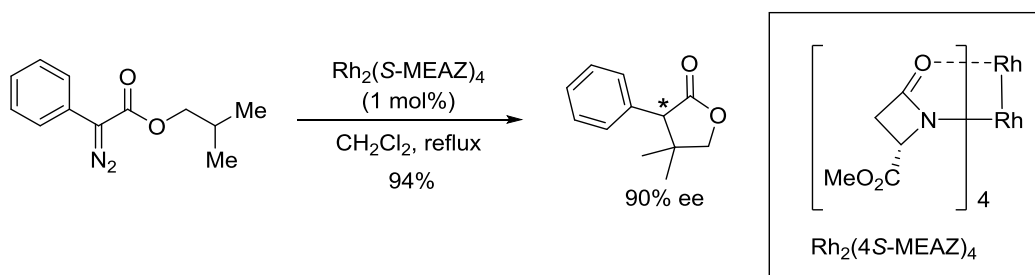
Chapter 3

Rhodium catalyzed stereoselective intramolecular C(sp³)-H bond activation of aryldiazoacetate: Preparation of α -aryl- β -substituted γ -lactones

1.1 Introduction and strategy to synthesis α -aryl- β -substituted γ -lactones via rhodium catalyzed C-H insertion

The synthesis of lactones by catalytic, asymmetric, intramolecular C-H insertion performed with acceptor carbenoid precursors like diazoacetates generally occurs with high enantiocontrol.⁴¹ However, the acceptor/acceptor carbenoid precursors such as diazoacetoacetates and diazomalونات give lower enantioselectivities.⁴² Even though, in recent years, donor/acceptor carbenoids has been widely employed to a variety of regio- and stereoselective reactions due to their greater selectivity than the other two carbenoids,²⁷ there are no examples achieved through both diastereo- and enantiocontrols in lactone synthesis. The single example of enantioselective formation of α,β -disubstituted γ -lactones with specific substrate was shown in Scheme 3-1.⁴³

Scheme 3-1. The single example of enantioselective formation of α,β -disubstituted γ -lactones.



On the other hand, α -aryl- β -substituted γ -lactone **18** is frequently found as the core structure of natural products (Figure 3-1)⁴⁴ and is utilized as an intermediate in the total synthesis of natural products.⁴⁵ We envisioned that one promising way to prepare this disubstituted chiral lactone **18** by asymmetric intramolecular C-H insertion of a donor/acceptor-substituted rhodium carbenoid generated from α -aryl- β -diazoacetate **19** (Figure 3-1).

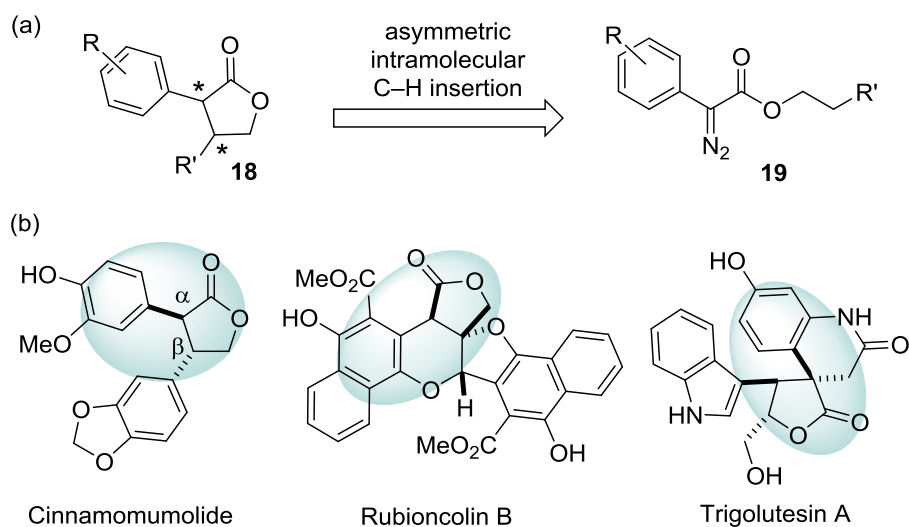


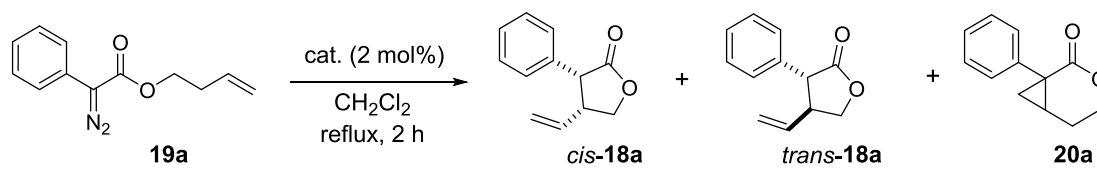
Figure 3–1. (a) Intramolecular C–H insertion to prepare α -aryl- β -substituted γ -lactones. (b) Natural products involving α -aryl- β -substituted γ -lactone.

1.2 Optimization of reaction conditions

Therefore, we picked this intramolecular C–H insertion for the initial evaluation of the catalytic activity and asymmetric induction of cat. **9**. Herein, the condition optimization results of asymmetric intramolecular C–H insertion are described.

First, 3-butenyl α -phenyl- β -diazoacetate **19a** was selected as a substrate due to the high reactivity of the allylic C–H bond in C–H insertion towards five-membered ring formation as well as the versatility of the terminal alkene for further chemical transformations (Table 3–1).

Table 3–1. Asymmetric intramolecular C–H insertion of **18a**.

								
Entry	catalyst	Yield (%) ^a	<i>cis</i> - 18a : <i>trans</i> - 18a ^b	ee (%) <i>cis</i> - 18a	ee (%) <i>trans</i> - 18a	Yield ^a (%) 20a	ee (%) 20a	18a : 20a
1	Rh ₂ (TPA) ₄	60	9.4 : 1	–	–	5	–	11 : 1
2	9	52	6.0 : 1	74 ^c	12	14	8	3.7 : 1
3	Rh ₂ (S-DOSP) ₄	44	2.7 : 1	28 ^c	8	30	40	1.5 : 1
4	Rh ₂ (S-TCPTTL) ₄	39	1 : 1.7	17 ^d	10	25	41	1.5 : 1

^a Isolated yield. ^b Determined by the integration of ¹H NMR. ^c Absolute configuration of major enantiomer is (3*R*,4*R*).

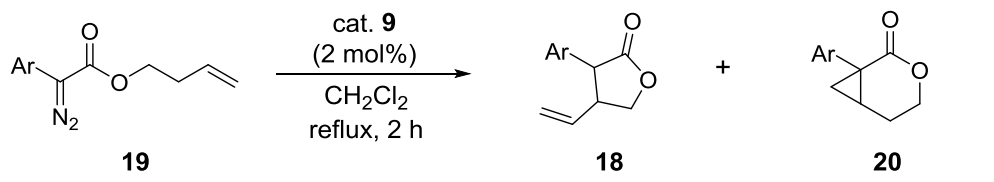
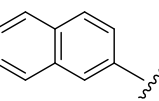
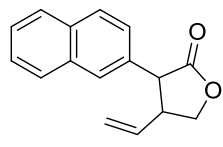
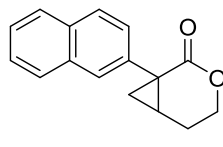
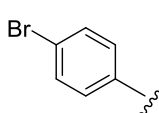
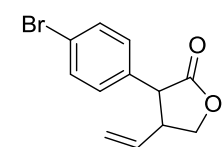
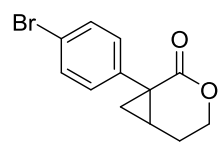
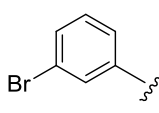
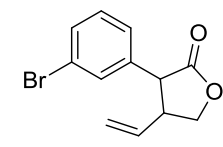
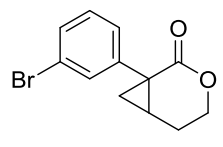
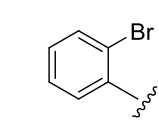
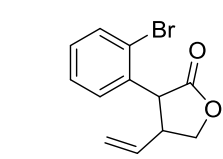
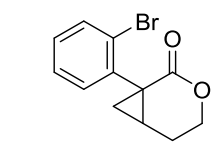
^d Absolute configuration of major enantiomer is (3*S*,4*S*), which is the opposite of the structure shown above.

However, due to presence of the double bond, cyclopropanation may be another possibility to afford fused bicyclic product **20a**. Therefore, the reactivity of **19a** was investigated with achiral dirhodium carboxylate catalyst before testing the catalytic activity and the asymmetric induction of cat. **9**. The author tested Rh₂(TPA)₄ as an achiral catalyst and found that this catalyst promotes the reaction (Table 3–1, Entry 1). Upon treatment of **19a** with 2.0 mol% of Rh₂(TPA)₄ in CH₂Cl₂, intramolecular C–H insertion proceeds smoothly to afford α-phenyl-β-vinyl γ-lactone **18a** in 60% with a high diastereoselectivity (*cis*: *trans* = 9.4 : 1). As expected, cyclopropanation also proceeds to afford **20a** as the minor product in 5% yield (**18a** : **20a** = 11 : 1). Therefore, not only stereoselectivity but also chemoselectivity should be considered in the reaction with a chiral catalyst.

Asymmetric C–H insertion with cat. **9** was carried out (Entry 2). The intramolecular reaction proceeds with 2.0 mol% of cat. **9** to afford **18a** in 52% yield with a *cis* selectivity (*cis* : *trans* = 6.0 : 1). The enantioselectivities of the *cis*- and *trans*-isomers are 74% and 12% ee, respectively. Similarly, cyclopropane **20a** is observed as the minor product in 14% yield and 8% ee, although five-membered ring formation via C–H insertion is still major pathway (**18a** : **20a** = 3.7 : 1).

Under the same reaction conditions, Rh₂(S-DOSP)₄ and Rh₂(S-TCPTTL)₄ were also tested as typical chiral catalysts (Entries 3 and 4). Rh₂(S-DOSP)₄ shows a catalytic activity to give **13a** in 44% yield with a reduced diastereoselectivity (*cis* : *trans* = 2.7 : 1). Furthermore, both the C–H insertion/cyclopropanation ratio (1.5 : 1) and enantioselectivity of the *cis* isomer (28% ee) decrease (Entry 3). Rh₂(S-TCPTTL)₄ is incompatible with substrate **19a** in view of both the *cis/trans* ratio (1 : 1.7) and the ee values of *cis*- and *trans*-**18a** (Entry 4). These results suggest that cat. **9** possesses the appropriate chiral environment for diastereo- and enantioselective intramolecular C–H insertion of α-aryl-β-diazoacetates.

Table 3–2. Asymmetric intramolecular C–H insertion of substrates **19b–19e**.

 19	18	20
Aryldiazoacetate	C–H insertion product	cyclopropanation product
19b Ar = 	 18b 62% <i>cis</i> : <i>trans</i> = 5.8 : 1 <i>cis</i> (72% ee)^a <i>trans</i> (12% ee)	 20b 15% (8% ee)
19c Ar = 	 18c 45% <i>cis</i> : <i>trans</i> = 1.1 : 1 <i>cis</i> (75% ee)^b <i>trans</i> (35% ee)	 20c 15% (8% ee)
19d Ar = 	 18d 59% <i>cis</i> : <i>trans</i> = 1.2 : 1 <i>cis</i> (67% ee)^b <i>trans</i> (43% ee)	 20d 10% (22% ee)
19e Ar = 	 18e 45% <i>cis</i> only (8% ee)	 20e 6% (47% ee)

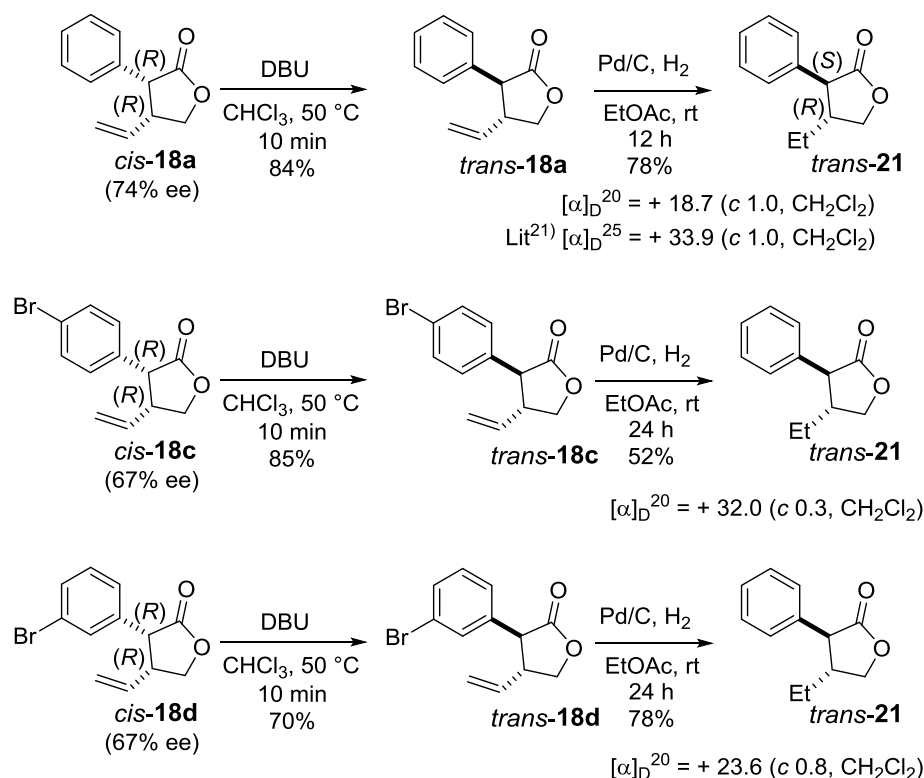
^a The absolute configurations was tentatively assigned to be the same as *cis*-**18a** by analogy. ^b Absolute configuration of major enantiomer is 3*R*,4*R*.

Under the same reaction conditions as Table 3–1, substrate **19b** possessing a β-naphthyl group as an aryl moiety affords **18b** in 62% yield with *cis* selectivity (*cis* : *trans* = 5.8 : 1) in 72% ee for the *cis*-isomer (Table 3–2). Both *para*- and *meta*-bromo substituted aryldiazoacetates **19c**

and **19d** are also readily converted to corresponding γ -lactones **18c** and **18d** in 75% ee and 67% ee for the *cis*-isomers, respectively, although the diastereoselectivities decrease in both cases. It should be noted that Bach and Davies reported *ortho*-substituent in aryldiazoacetate dramatically alters the regioselectivity of C–H insertion to γ -lactone formation.⁴⁶ However, even in the case of diazoacetate **19e** bearing a bromo substituent at *ortho*-position, γ -lactone formation proceeded exclusively to give *cis*-**18e** as a sole diastereomer. For all of the reactions, concomitant formation of bicyclic cyclopropanes **20b–20e** could not be ruled out, although intramolecular C–H insertions are major pathway in every reactions.

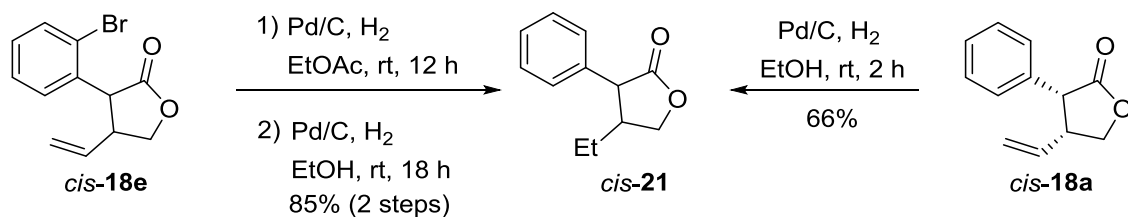
1.3 Determination of the absolute configuration

Scheme 3–2. Determination of the absolute configuration of *cis*-**18a**, **18c**, **18d** through epimerization to the *trans*-isomer.



After transforming to *trans*-**18** through epimerization to the *trans*-isomer with DBU and successive catalytic hydrogenation of the terminal olefin as shown in Scheme 3–2, the absolute configurations of *cis*-**18a**, **18c**, and **18d** are determined to be (3*R*,4*R*) by comparing the optical rotation to the literature data.⁴⁷

Scheme 3–3. Determination of the relative configuration of *cis*-**18e**



Lactone **18e** was converted to *cis*-**21**⁴⁸ under catalytic hydrogenation conditions as shown in Scheme 3–3. The product was found to be identical with the reduced product derived from *cis*-**18a**. Therefore, its γ -lactone structure with *cis* configuration was determined.

1.4 Possible explanation for stereoselectivity

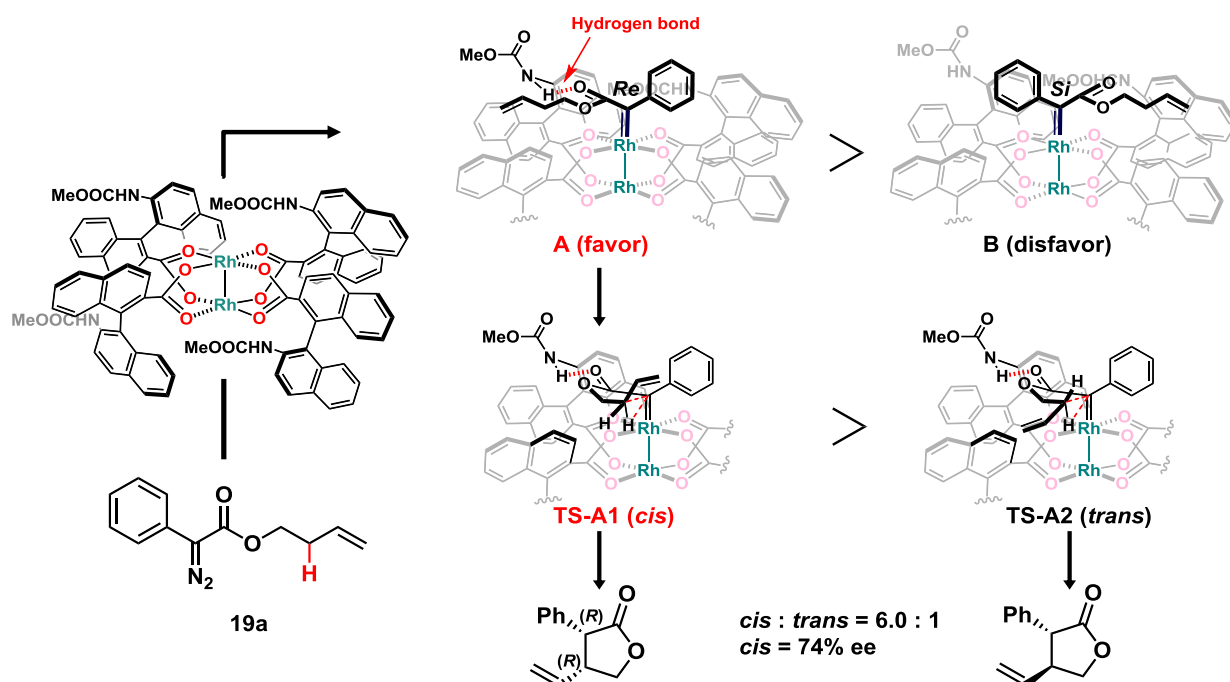


Figure 3-2. A possible explanation for stereoselectivity

The stereoselectivity was considered from the X-ray structure of cat. **9** depicted in Figure 2–2 in chapter 2, and (3*R*,4*R*)-configuration of the major enantiomer of *cis*-products. First, the rhodium carbenoid intermediates **A** and **B** can be generated by decomposition of phenyl diazoacetate **19a**. Take the absolute configuration of *cis*-isomer into account, carbenoid intermediate **A** formed preferentially than intermediate **B** in this enantio-determining step. In intermediate **A**, only *Re*-face of the Rh-carbenoid enantioface was opened because the backside is shielded by the naphthyl moieties. Therefore, C–H insertion proceeded selectively at *Re*-face

of the Rh-carbenoid intermediate. In this diastereo-determining C–H insertion step, transition state to *cis*-isomer (**TS-A1**) is favorable due to presence of the steric repulsion between the vinyl group of the carbenoid and the naphthyl group of the ligand in transition state (**TS-A2**) to *trans*-isomer. Therefore, *cis*-(3*R*,4*R*)-lactone was obtained as a major product.

The key feature of this stereoinduction is the enantiofacial control of rhodium carbenoid intermediate at the enantio-determining step (intermediate **A** vs. **B**). The author speculates that the hydrogen bonding (remarked in red arrow) between the NH group of the ligand and the carbonyl group of the carbenoid enabled this enantiofacial control. Low enantioselectivities observed with Rh₂(*S*-DOSP)₄ and Rh₂(*S*-TCPTTL)₄ (Table 3–1, Entries 3 and 4), both of which do not have any hydrogen bonding donor to the carbenoid, may suggest not only steric control but also hydrogen bonding control is play a role for stereoinduction with cat. **9**.

In summary, the reasonable level of catalytic activity of cat. **9** as well as its diastereo- and enantioselectivities in intramolecular C–H insertion to α -aryl- β -substituted γ -lactones are demonstrated. This stereoselectivity is supposed to be induced by ligand-carbenoid hydrogen bonding interaction. Although further mechanistic studies are required to prove this hypothesis, this hydrogen bonding concept promote the author to perform asymmetric intramolecular C–H insertion with triazole substrates.

Chapter 4

Rhodium catalyzed enantioselective intramolecular C(sp³)-H bond activation with triazoles:

Preparation of α,β -disubstituted tetrahydrofurans

1.1 Difficulty on asymmetric induction with Rh(II) azavinyl carbene equivalents

As described in chapter 1 (Scheme 1–4), *N*-sulfonyl-1,2,3-triazoles exist in equilibrium with its diazoimine tautomer, which serves as the convenient precursor of metal azavinyl carbene complexes. This carbene precursor can be easily prepared from alkynes and azides, which was widely utilized for construction of a variety of *N*-containing heterocycles in recent eight years. Another clear advantage of this chemistry is the ability to access novel carbene intermediates without the need to prepare and isolate diazo compounds.^{28–36}

For the intramolecular C–H insertion, as shown in Figure 4–1, *N*-sulfonyltriazoles **22a** was reported to be utilized for the formation of 2,3-disubstituted tetrahydrofurans and pyrrolidines (Scheme 1–6).^{35, 36}

However, enantioselective version of these intramolecular C–H insertions are known as a recurrent problem in this field, because precedent catalysts could not give sufficient enantioselectivity (Figure 4–1). This problem might come from the difficulty to discriminate the enantioface of the carbenoid by catalysts, due to the similar steric environments of the *N*-sulfonyl azavinyl carbene equivalents as described in Scheme 1–8.

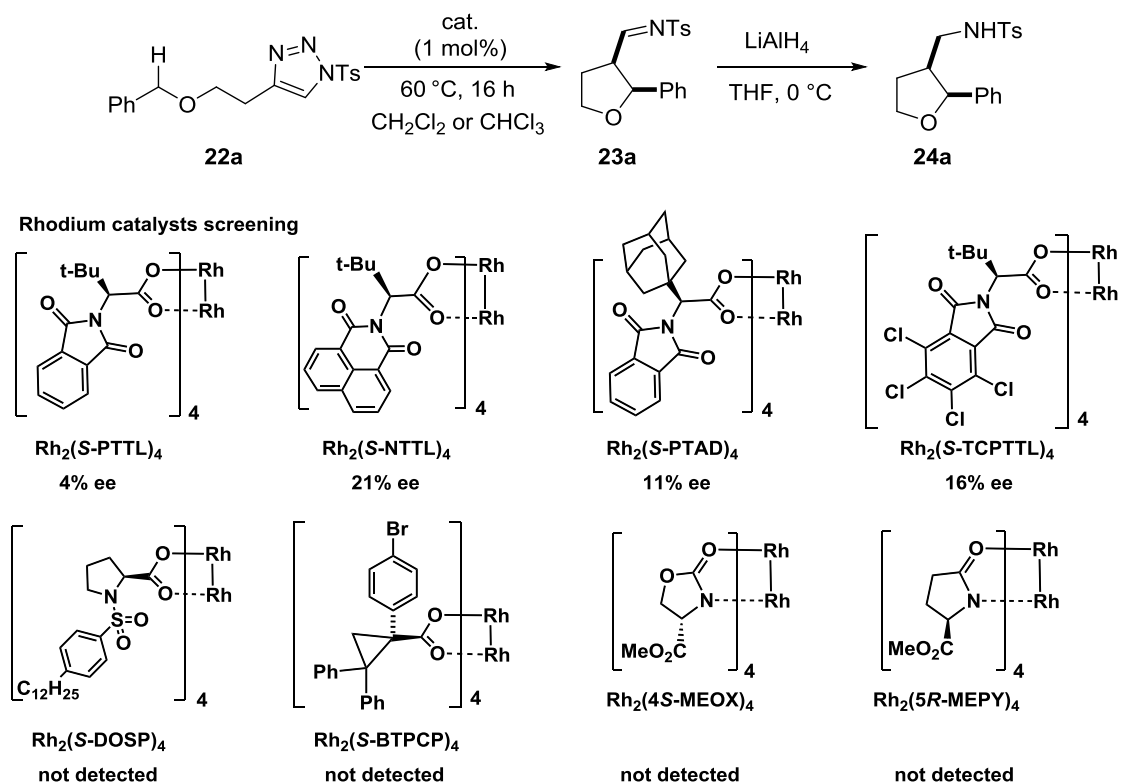


Figure 4-1. Difficulty in enantioselective intramolecular C–H functionalization using *N*-sulfonyl-1,2,3-triazoles³⁵

As described in chapter 2, the author has applied binaphthyl *N*-functionalized amino acid as chiral bridging ligands to prepare chiral Rh(II) carboxylate catalysts. According to X-ray analysis of cat. **9**, the author hypothesized that the hydrogen bonding (remarked in red dash line) between the NH of the ligand and the sulfonyl group of carbenoid can play a key role to realize sharp discrimination of the enantioface of the carbenoid intermediate (Figure 4-2).

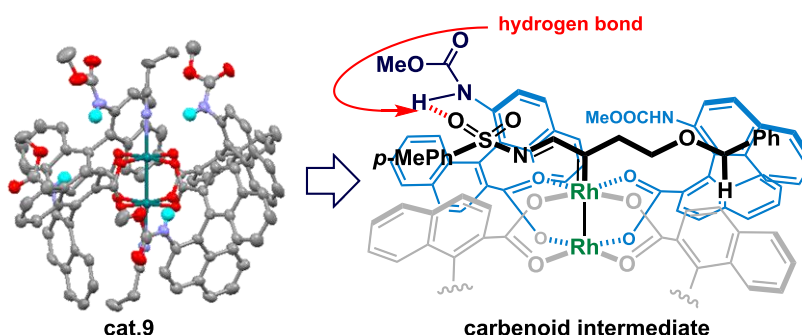


Figure 4-2. Enantioface control by hydrogen bonding interaction

1.2 Survey of the reaction conditions

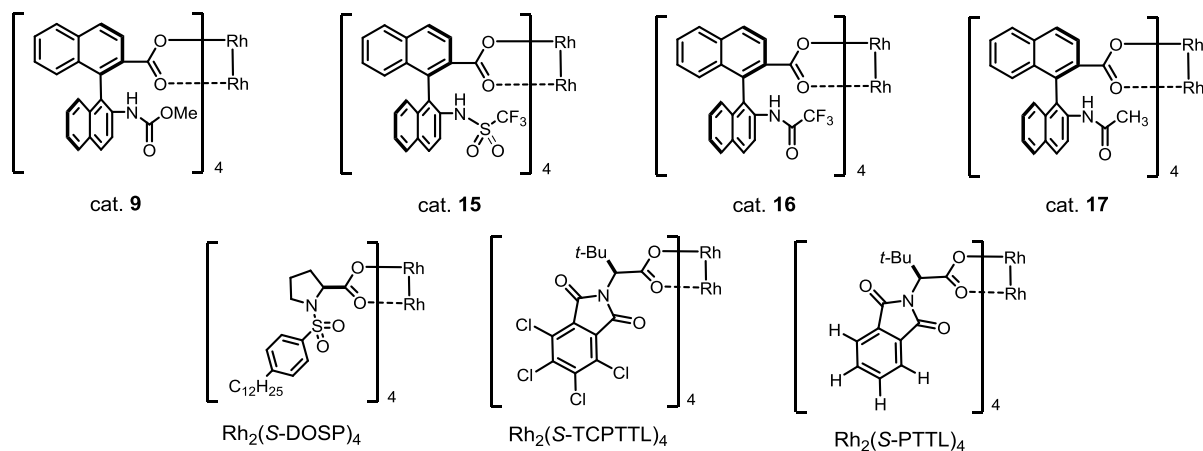
The catalyst screening with substrate **22a** was summarized in Table 4–1. Firstly, precedent catalysts Rh₂(S-DOSP)₄, Rh₂(S-PTTL)₄, and Rh₂(S-TCPTTL)₄ were tested. In the presence of 2 mol% catalyst, the reaction proceeded smoothly at 50 °C for 16 h to form the imine **23a**. This imine was found to be unstable, therefore, stereoselectivity was evaluated with *N*-Ts amine **24a** after NaBH₄ reduction. As reported by Sarpong, obvious enantioselectivities were not observed with Rh₂(S-DOSP)₄ and Rh₂(S-PTTL)₄ (Entries 6 and 7). In the case of Rh₂(S-TCPTTL)₄, no product was obtained and resulted in starting material recovery (Entry 8). The reason was considered that Rh₂(S-TCPTTL)₄ has a halogen bonding which leads a more rigidify conformation compared to Rh₂(S-PTTL)₄. Such rigid conformation can prevent the formation of diazonium complex to inhibit the catalytic cycle. In the end of this chapter, these speculations were discussed again.

On the other hand, under the same conditions, cat. **9** gave 2,3-disubstituted tetrahydrofuran **24a** in 62% yield with a *cis* selectivity (*cis* : *trans* = 1.8 : 1). As expected, obvious enantioselectivity was observed especially in *cis*-isomer (78% ee) (Entry 1). Elongation of the reaction period to 24 h afforded the product in almost quantitative yield (Entry 2). Cat. **15**, **16**, and **17** were also tested (Entries 3–5). However, surprisingly, these catalysts did not promote the reaction, although these catalysts were expected to be further active and selective catalysts due to stronger hydrogen bonding via acidic NH groups. The possible reasons for this unexpected result will be discussed in the end of this chapter.

Table 4–1. Screening of rhodium carboxylate catalyst

Entry	catalyst	Time (h)	Yield ^a (%)	dr <i>cis</i> : <i>trans</i>	ee% ^b <i>cis</i> / <i>trans</i>
1	9	16	62	1.8 : 1	78 / 45
2	9	24	91	1.7 : 1	76 / 43
3	15	16	trace	2.6 : 1	nd
4	16	16	trace	6.0 : 1	nd
5	17	16	trace	nd	nd
6	Rh ₂ (S-DOSP) ₄	16	70	2.1 : 1	9 / 5
7	Rh ₂ (S-PTTL) ₄	16	46	>20 : 1	4 / nd
8	Rh ₂ (S-TCPTTL) ₄	16	trace	nd	nd

^a Determined by NMR analysis of the crude mixture using 1,3,5-trimethoxybenzene as an internal standard. ^b nd = not detected.



Next, temperature effect was examined in the presence of cat. **9** (Table 4–2). It is known that temperature is an important factor not only for hydrogen bonding interaction but also for generation of Rh(II) azavinyl carbene intermediate from *N*-sulfonyl-1,2,3-triazoles. Indeed, the reactivity was found to be sensitive to the reaction temperature. The yield was increased to 91% at 60 °C, however, the enantioselectivity was decreased to 65% ee in *cis*-isomer (Entry 1). On the other hand, only 21% of product was obtained at 40 °C (Entry 3). Therefore, the following solvent screening was carried out at 50 °C.

Table 4–2. Temperature effect

Entry	T (°C)	Yield ^a (%)	dr <i>cis</i> : <i>trans</i>	ee% <i>cis</i> / <i>trans</i>
1	60	91	1.5 : 1	65 / 39
2	50	62	1.8 : 1	78 / 45
3	40	21	1.9 : 1	77 / 45

^a Determined by NMR analysis of the crude mixture using 1,3,5-trimethoxybenzene as an internal standard.

The results of solvent screening were shown in Table 4–3. The reaction proceeded in a variety of nonpolar solvents to give **24a** in moderate yields (42 – 91%). Although the best yield (91%) was obtained in toluene, the ee of *cis*-isomer was decreased to 73% ee (Entry 4). On the other hand, CHCl₃ gave best enantioselectivity (78% ee), although the yield was moderate. According to compressive consideration in these chemical yields and stereoselectivities, CHCl₃ was chosen as the optimized solvent for further study.

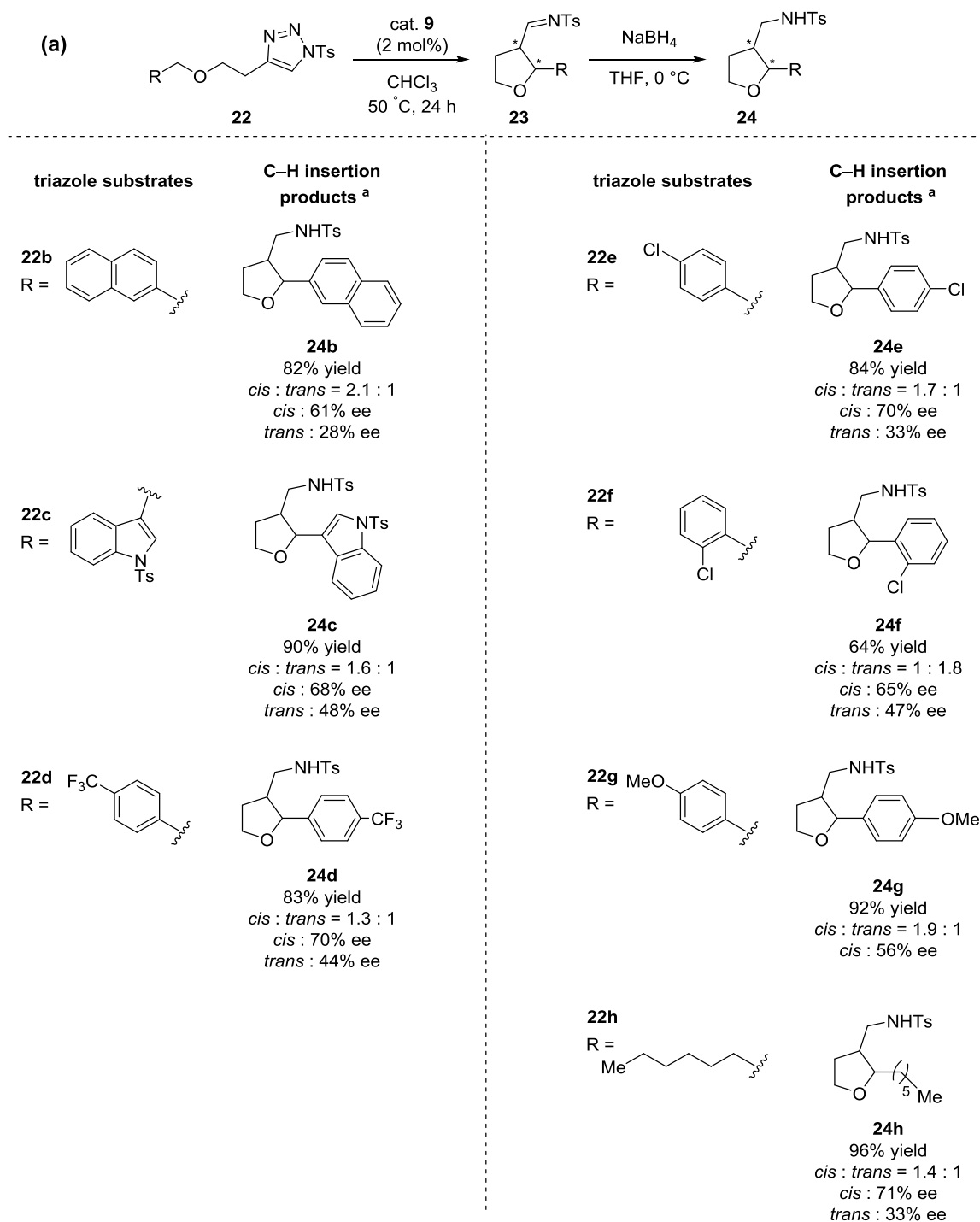
Table 4–3. Solvent effect

Reaction scheme: **22a** $\xrightarrow[\text{Solvent, } 50\text{ }^{\circ}\text{C, 16 h}]{\text{cat. } \mathbf{9} \text{ (2 mol\%)}}$ **23a** $\xrightarrow[\text{THF, } 0\text{ }^{\circ}\text{C}]{\text{NaBH}_4}$ **24a**

Entry	Solvent	Yield ^a (%)	dr <i>cis</i> : <i>trans</i>	ee% <i>cis</i> / <i>trans</i>
1	CHCl ₃	62	1.8 : 1	78 / 45
2	CH ₂ Cl ₂	53	1.9 : 1	78 / 44
3	1,2-DCE	52	1.8 : 1	71 / 38
4	Toluene	91	1.4 : 1	73 / 44
5	Benzene	80	1.5 : 1	69 / 44
6	CF ₃ C ₆ H ₅	42	1.5 : 1	70 / 45

^a Determined by NMR analysis of the crude mixture using 1,3,5-trimethoxybenzene as an internal standard.

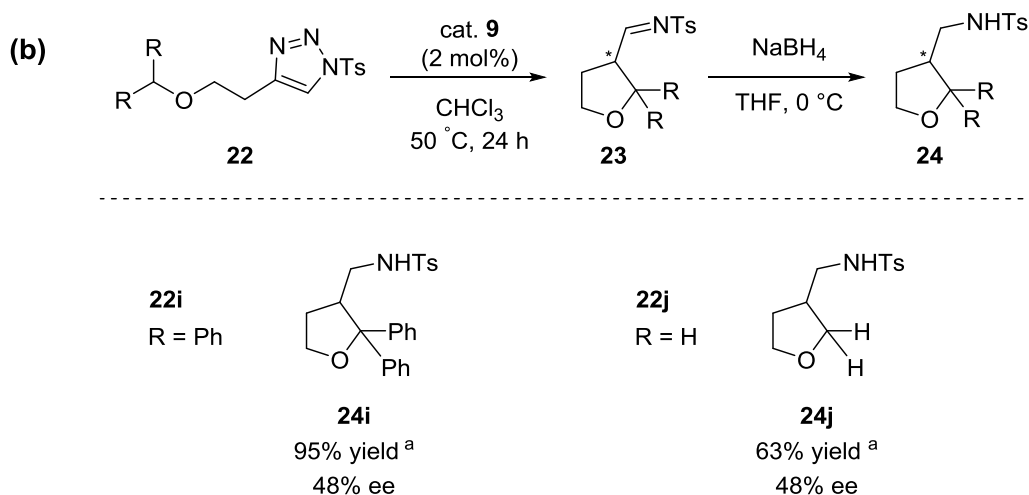
Table 4–4a. Scope of substrates



With the optimized condition (CHCl_3 at $50\text{ }^\circ\text{C}$) in hand, substrate scope was examined as shown in Table 4–4a. A variety of aryl substituted substrates possessing naphthyl (**22b**), indole (**22c**), CF_3 - and Cl-substituted electron deficient phenyl (**22c–22f**), and *p*-methoxyphenyl (**22b**) moiety were found to be compatible to the reaction to give the corresponding products in excellent chemical yield (up to 92%) with good diastereo- and enantioselectivities (*cis/trans* = up to 2.1 :

1, up to 71% ee in *cis* isomer). Furthermore, alkyl substituted substrates (**22h**) was also employed as a substrate to give **24h** in 96% with 71% ee of *cis*-isomer.

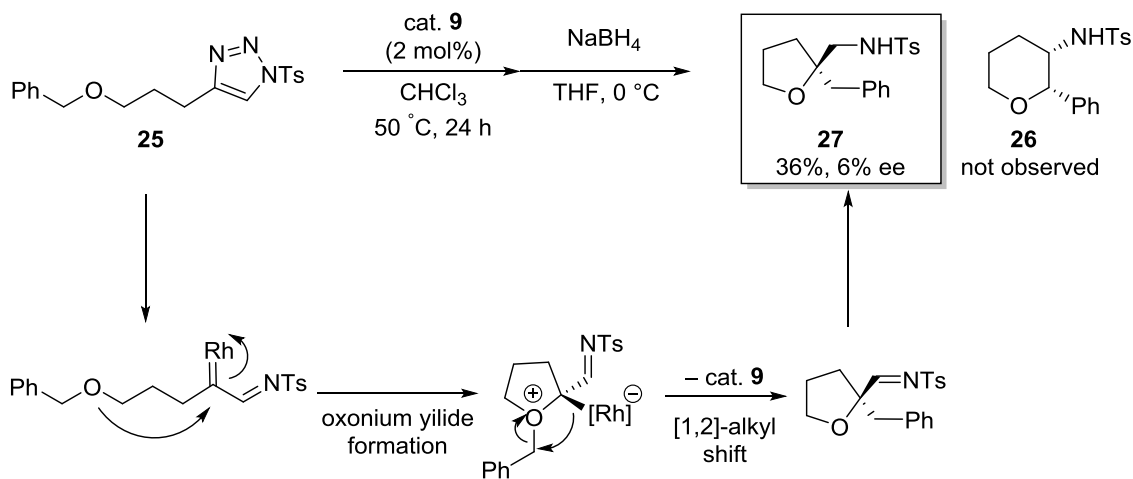
Table 4–4b. Scope of substrates



^a Isolated yields

The substrates having equivalent substituents at ether moiety, **22i** ($\text{R} = \text{Ph}$) and **22j** ($\text{R} = \text{H}$) were also examined (Table 4–4b). In both cases, moderate enantioselectivities were observed.

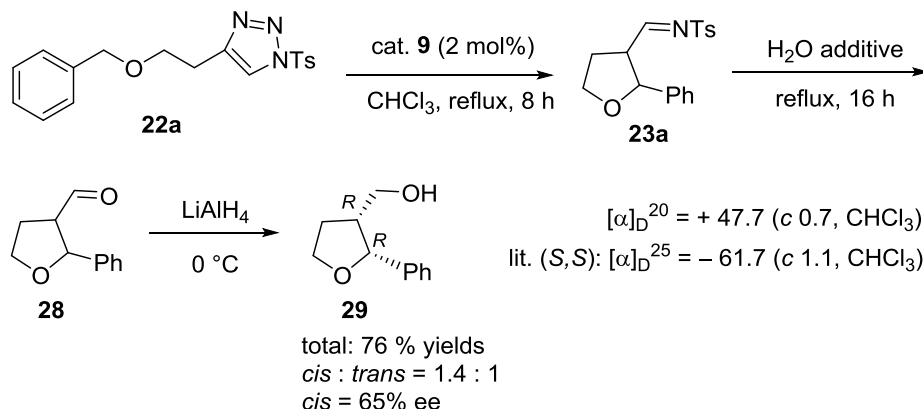
Scheme 4–1. Rh(II)-catalyzed oxonium ylide formation/[1,2]-alkyl shift



Six-membered ring formation was also tested by the use of homologated substrate **25**. However, expected tetrahydropyran **26** was not observed at all. Instead, tetrahydrofuran **27** containing quaternary asymmetric center was obtained in 36% yield and 6% ee. This reaction presumably proceeded through Rh(II)-catalyzed oxonium ylide formation/[1,2]-alkyl shift sequence (Scheme

4-1).³⁵

Scheme 4-2. Determination of the absolute configuration of *cis*-**24a**.



The absolute configurations of the major enantiomer of imine **23a** was determined to be (3*R*,4*R*) by transformation to literature known alcohol **29**, and comparison of their optical rotations.⁴⁹ Alcohol **29** was obtained through hydrolysis of imine **23a** and successive reduction of aldehyde **28** as shown in Scheme 4-2.

1.3 Verification of hydrogen bonding for stereinduction

In order to evaluate whether the hydrogen bonding between NH group of the ligand and sulfonyl group of the substrate is responsible for stereinduction (Figure 4-2), effects of hydrogen bonding acceptor solvents were investigated. It was found that the enantioselectivity of *cis*-isomer was dropped to 66% ee in Et₂O from 78% ee in CHCl₃ (Entry 1 vs 2). Decrease of enantioselectivity was also observed in CH₃CN, although the yield of **24a** was quite low (Entry 4). These results suggest that hydrogen bonding plays a role for stereinduction because hydrogen bonding acceptor solvents (Et₂O and CH₃CN) could competitively bond with the NH of ligand. However, further evaluation by solvent effects was suffered from low conversion as shown in THF (Entry 3) due to coordination character of Lewis basic solvents to rhodium center.

Table 4-5. Influence of the polar solvent on the enantioselective C-H insertion

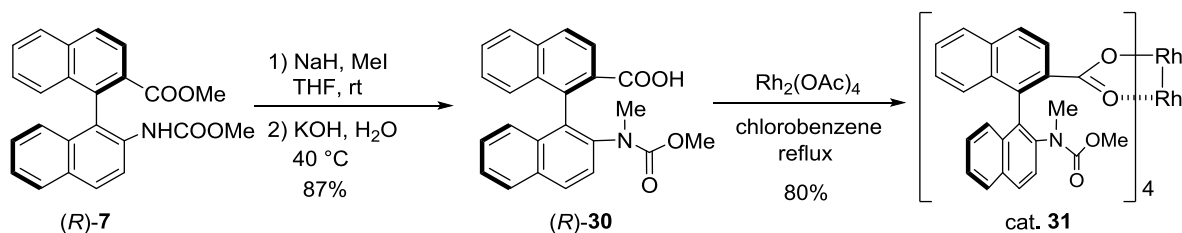
Entry	Solvent	Yield ^a (%)	dr <i>cis</i> : <i>trans</i>	ee% <i>cis</i> / <i>trans</i>
1	CHCl ₃	62	1.8 : 1	78 / 45
2	Et ₂ O	72	1.5 : 1	66 / 42

3	THF	<5	-	-
4	CH ₃ CN	5	1.9 : 1	64 / 31

^a Determined by NMR analysis of the crude mixture using 1,3,5-trimethoxybenzene as an internal standard.

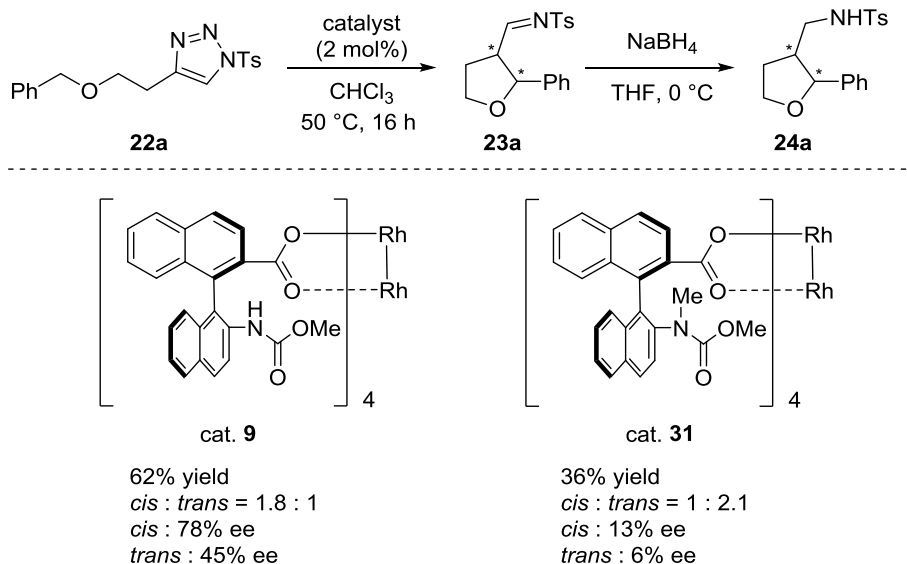
Therefore, the hydrogen bonding was further evaluated with *N*-methyl catalyst **31**, which cannot form hydrogen bonding with substrate. Cat. **31** was prepared from (*R*)-**7** via *N*-methylation with CH₃I as shown in Scheme 4-3.

Scheme 4-3. Preparation of *N*-methylated rhodium catalyst cat.**31**



As shown in Scheme 4-4, drastic decrease of enantioselectivities (13% ee and 6% ee for *cis*- and *trans*-isomers) compare to those with NH cat. **9** (78% ee and 48% ee) was observed. This result illuminated importance of acidic NH group of cat. **9**, and suggested hydrogen bonding plays a role for stereoselection.

Scheme 4-4. Influence of the NH group in ligand on the enantioselective C–H insertion



1.4. Possible explanation for stereoselectivity

Take the role of hydrogen bonding and (2*R*, 3*R*)-configuration of the major enantiomer of *cis*-products, the stereoselectivity can be explained as follows. First, the rhodium carbenoid

intermediates **A** and **B** are generated by decomposition of diazoimine **32**, the tautomer of triazole substrate **22a**. In this enanto-determining step, carbenoid intermediate **A** formed preferentially than intermediate **B** due to the formation of hydrogen bonding. Successive diastereo-determining C–H insertion proceeded selectively at *Re*-face to give *cis*-(2*R*, 3*R*)-**24a** as a major isomer.

As already discussed in previous chapter 3, the key for stereoinduction is the enantiofacial discrimination of rhodium carbenoid intermediate in the enantio-determining step (intermediate **A** vs. **B**). Low enantioselectivities observed with Rh₂(S-DOSP)₄ and Rh₂(S-TCPTTL)₄ without hydrogen bonding donor (Table 4–1, Entries 6 and 7) suggested that hydrogen bonding interaction plays a key role for enantiofacial control in this step.

Obviously, improvement of diastereoselectivity is required for this reaction (*cis/trans* ratio: up to 1.9 : 1). The difference of enantioselectivities of *cis*- and *trans*-isomers (**24a**, *cis*: 78% ee, *trans*: 45% ee, as shown in Table 4–1, Entry 1) suggests that *cis/trans* ratio of the products from intermediates **A** and **B** are different. In other words, intermediate **B** afford the *ent-cis*-isomer as the minor product, which led to lower enantioselectivity of the *trans*-isomer. Therefore, the enantiofacial control of carbenoid intermediates should affect not only for enantioselectivity but also for diastereoselectivity.

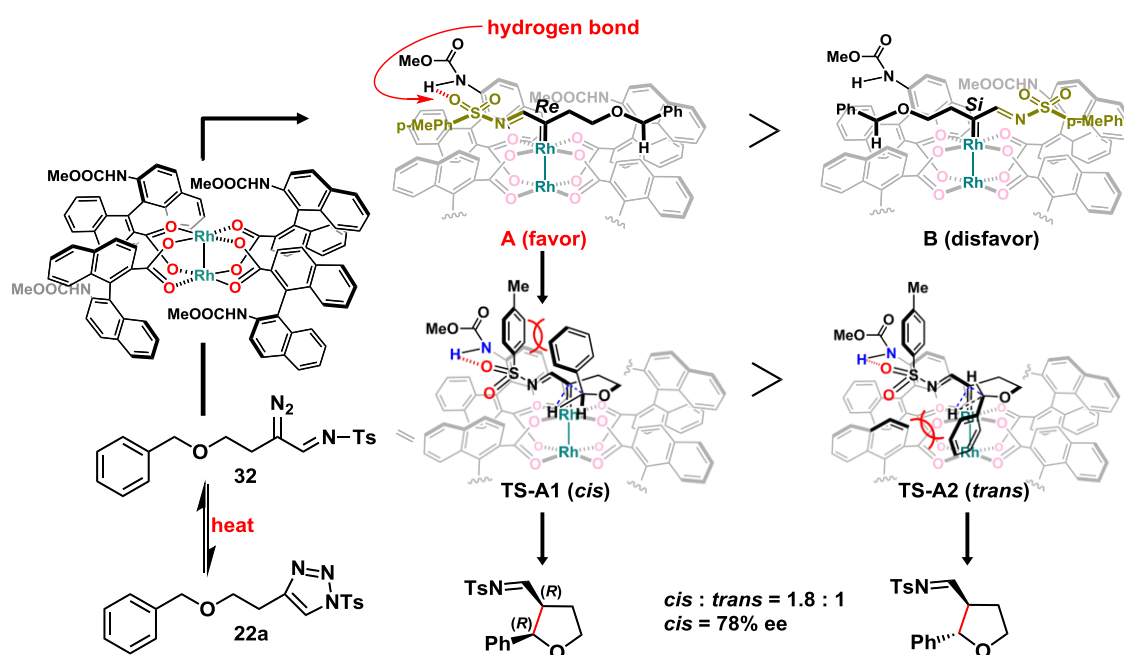


Figure 4–3. Possible explanation for stereoselectivity.

The author expected stronger hydrogen bonding formed by these acidic NH groups is effective to achieve more precise enantiofacial control. Based on the consideration, the author tested catalysts **15**, **16** and **17** possessing more acidic NH group than that of cat. **9**. However, surprisingly,

these catalysts did not show catalytic activities (Table 4–1, Entries 3–5). Following reasons were considered for these unexpected results. The increased acidity of NH strengthened intramolecular hydrogen bonds between NH group and oxygen of O–Rh–O moiety ($\text{--N--H}\cdots\text{O--Rh--O}\cdots\text{H--N--}$) as shown in Figures 2–1c and 4–4a. These hydrogen bonds result rigidify of conformation of the catalyst, that to prevent coordination of diazoimine **32** at the axial position due to steric reason. No catalytic activity of $\text{Rh}_2(\text{S-TCPTTL})_4$ might be explained by similar reason (Table 4–1, Entry 8), because its conformation was further rigid than that of $\text{Rh}_2(\text{S-PTTL})_4$ due to formation of intramolecular halogen bonds. Another reason can also be considered. Diazoimine **32** approach to the axial position could not be accelerated well via intermolecular hydrogen bonding due to great contribution of NH group towards intramolecular hydrogen bonding (Figure 4–4c). These considerations may be clue for improved design of rhodium carboxylate catalyst.

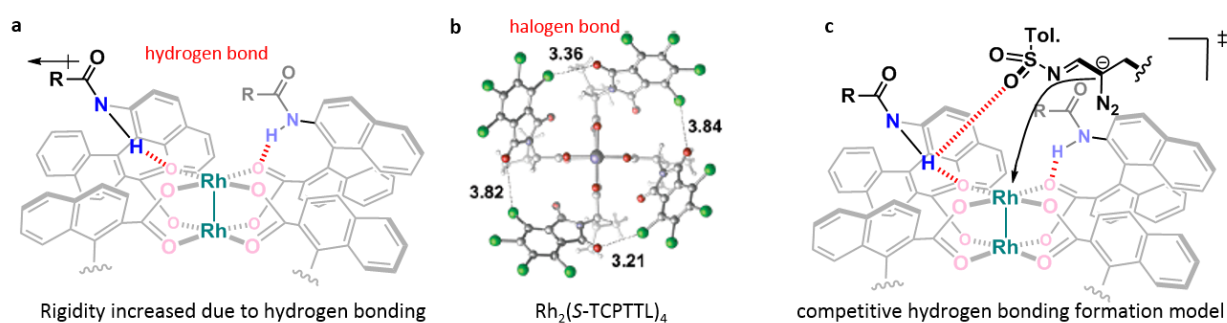


Figure 4–4. Possible reasons for lower reactivity of catalysts **15–17**.

In summary, asymmetric intramolecular C–H insertion of *N*-sulfonyltriazoles was achieved by virtue of hydrogen bonding with the acidic NH group of a supramolecular Rh(II) complex. The key feature of the strategy is to distinguish the enantiofaces of rhodium carbenoid intermediate, which cannot be discriminated well only by steric environment of coordinating ligands, via hydrogen bonding.

Conclusion and perspective

Novel Rh(II) carboxylate catalysts bearing *N*-functionalized binaphthyl amino moieties have been synthesized, and their chiral environment was revealed by X-ray analysis of cat. **9**. With these prepared rhodium catalyst, asymmetric intramolecular C–H insertion of α -aryl- β -diazoacetates and *N*-sulfonyltriazoles were achieved through hydrogen bonding interaction between ligand and carbenoid intermediate.

The author expects the hydrogen bond concept verified in my study will be applied to other asymmetric transformations including intermolecular C–H insertions.

Experimental Section

1. General information

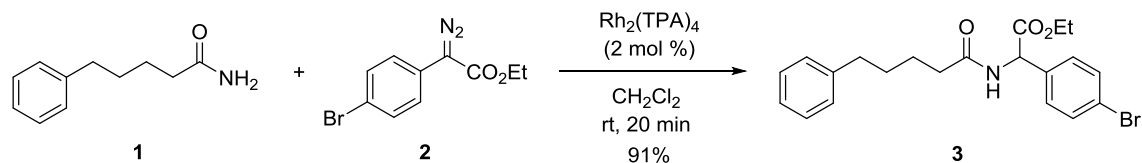
Melting points were measured using a Yanagimoto micro point apparatus. NMR spectra were obtained with a JEOL ECX-400 PKT spectrometer or JEOL ECA-600 spectrometer, chemical shift being given in ppm units (^1H NMR in CDCl_3 : tetramethylsilane as internal standards, indicating 0, ^{13}C NMR in CDCl_3 : CDCl_3 as internal standards, indicating 77.0) and spin-spin coupling constants being given in Hz units. IR spectra were recorded with a JASCO FT-IR 4200 spectrometer. The mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded with a JEOL MStation JMS-700 spectrometer (for FAB) or Bruker Daltonics impact HD-KC (for ESI). Specific rotation was measured with JASCO P-2200 polarimeter.

Silica gel column chromatography was carried out by using Silica gel 60 N (spherical, neutral, 63 ~ 210 μm , Kanto Chemical Co., Inc.). TLC analysis and preparative TLC (PTLC) were performed on commercial glass plates bearing a 0.25 mm layer and 0.5 mm layer of Merck Kiesel-gel 60 F₂₅₄, respectively. Analytical HPLC was run with a JASCO PU-2089 Plus instrument, equipped with a Daicel CHIRALPAK AD-H, CHIRALCEL OD-H, CHIRALPAK IA (4.6 mm $\times$ 250 mm), or CHIRALPAK ID (4.6 mm $\times$ 250 mm) and a JASCO UV-2075 Plus UV/Vis detector (detection: 254 nm). Preparative HPLC was run with a JASCO PU-2086 Plus instrument, equipped with a COSMOSIL 5SL-II (20 mm $\times$ 250 mm) and a JASCO UV-2075 Plus UV/Vis detector (detection: 254 nm).

All chemical reagents were commercially purchased and used without further purification.

2. Chapter 1

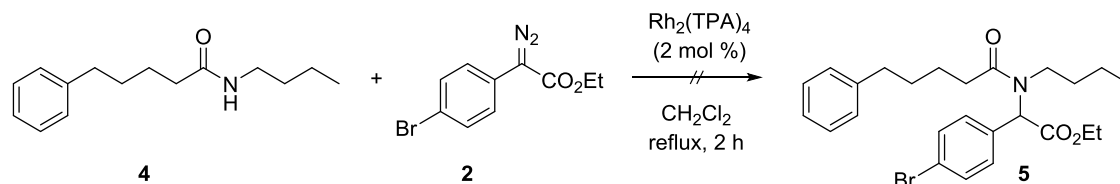
Scheme S1. N–H insertion to amide



Methyl 2-(4-bromophenyl)-2-(5-phenylpentanamido)acetate (**3**)

To a mixture of $\text{Rh}_2(\text{TPA})_4$ (3.0 mg, 2.0 μmol , 2.0 mol%) and primary amide **1** (21 mg, 0.12 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 mL), CH_2Cl_2 solution (0.5 mL) of diazo substrate **2** (27 mg, 0.1 mmol, 1.0 equiv) was added dropwise over 15 min under an Ar atmosphere at room temperature. The mixture was further stirred for 5 min until the color changed from yellow to green totally, and then the solvent was evaporated *in vacuo* to give a residue. The residue was purified by prep. TLC (SiO_2 , hexane : AcOEt = 2 : 1) to afford a product **3**, Yield: 38 mg (91%).

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 1.20 (t, J = 7.1 Hz, 3 H), 1.57–1.71 (m, 4 H), 2.21–2.27 (m, 2 H), 2.60 (t, J = 7.1 Hz, 2 H), 4.09–4.26 (m, 2 H), 5.50 (d, J = 6.9 Hz, 1 H), 6.48 (d, J = 6.9 Hz, 1 H), 7.12–7.15 (m, 2 H), 7.16–7.19 (m, 1 H), 7.20–7.23 (m, 2 H), 7.24–7.28 (m, 2 H), 7.44–7.47 (m, 2 H). HRMS (ESI) m/z calcd for $\text{C}_{21}\text{H}_{15}\text{BrNO}_3$ ($\text{M}+\text{H}$) $^+$ 418.1018, found. 418.1027.

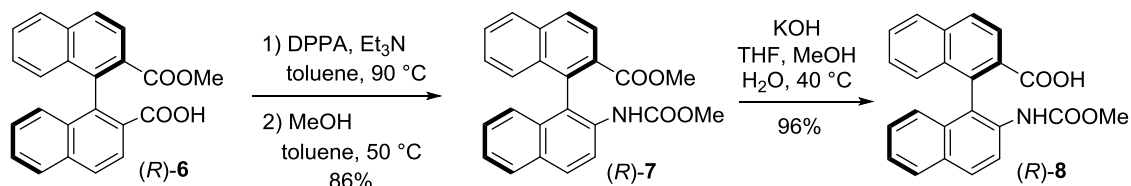


To a refluxing mixture of $\text{Rh}_2(\text{TPA})_4$ (3.0 mg, 2.0 μmol , 2.0 mol%) and secondary amide **4** (28 mg, 0.12 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 mL), CH_2Cl_2 solution (0.5 mL) of diazo substrate **2** (27 mg, 0.1 mmol, 1.0 equiv) was added dropwise over 1.5h under an Ar atmosphere by syringe pump. The mixture was further stirred for 0.5 h, and then the solvent was evaporated *in vacuo* to give a residue. However, the product **5** was not observed by NMR analysis and further separation.

3. Chapter 2

Preparation of rhodium catalyst.

Scheme S2–1. Preparation of *N*-modified axially chiral amino acids



(*R*)-Methyl 2'-((methoxycarbonyl)amino)-[1,1'-binaphthalene]-2-carboxylate ((*R*)-7)

To a solution of (*R*)-2'-((methoxycarbonyl)amino)-[1,1'-binaphthalene]-2-carboxylate ((*R*)-6) (100 mg, 0.28 mmol, 1.0 equiv) in toluene (20 mL) were added DPPA (90 μ L, 0.42 mmol, 1.5 equiv) and Et₃N (0.12 mL, 0.84 mmol, 3.0 equiv) at 0 °C under Ar atmosphere. After being stirred for 2 h at 90 °C, the reaction was cooled to rt and added MeOH (0.11 mL, 2.8 mmol, 10 equiv). The mixture was stirred for 5 h at 50 °C. The reaction was quenched with 2 *N* aq. HCl, and extracted with AcOEt. The organic layer was washed with 2 *N* aq. NaOH, brine and dried over Na₂SO₄, filtered and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography (SiO₂, hexane : AcOEt = 5 : 1) to afford (*R*)-7, Yield: 89 mg (86%).

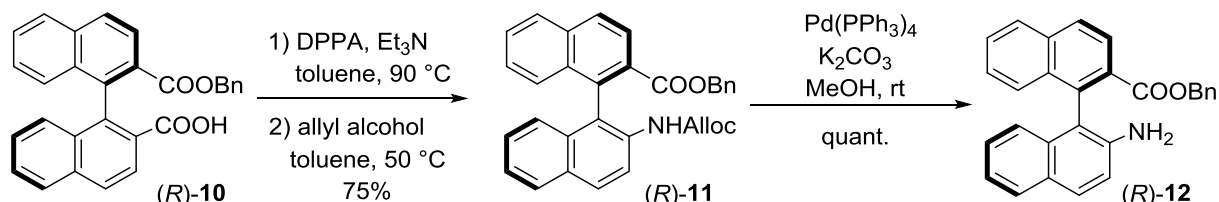
Colorless oil. ¹H NMR (600 MHz, CDCl₃) δ 3.49 (s, 3 H), 3.60 (s, 3 H), 6.25 (br s., 1 H), 6.80 (d, *J* = 8.3 Hz, 1 H), 7.17 (ddd, *J* = 1.2, 7.0, 8.4 Hz, 1 H), 7.22 (d, *J* = 8.7 Hz, 1 H), 7.29–7.38 (m, 2 H), 7.58 (ddd, *J* = 0.9, 7.0, 8.1 Hz, 1 H), 7.88 (d, *J* = 8.2 Hz, 1 H), 7.99 (dd, *J* = 3.2, 8.7 Hz, 1 H), 8.05–8.13 (m, 2 H), 8.35 (br s, 1 H); ¹³C NMR (150 MHz, CDCl₃) δ 52.1, 52.2, 119.9, 124.6, 125.0, 125.9, 126.5, 126.9, 127.6, 127.9, 128.1, 128.2, 128.8, 129.1, 129.8, 129.9, 130.3, 132.4, 132.9, 133.8, 134.9, 135.2, 154.1, 167.5; IR (Neat) 2923, 2852, 1727, 1599, 1503, 1461, 1430, 1280, 1241, 1219 cm⁻¹; HRMS (ESI) *m/z* calcd for C₂₄H₁₉NO₄ (M+H)⁺ 408.1206, found. 408.1218.

(*R*)-2'-((Methoxycarbonyl)amino)-[1,1'-binaphthalene]-2-carboxylic acid ((*R*)-8)

To a solution of (*R*)-7 (92mg, 0.24 mmol, 1.0 equiv) in THF/MeOH/H₂O (1:1:1) (3.0 mL) was added KOH (40mg, 0.71 mmol, 3.0 equiv). After being stirred for 40 min at 40 °C, the reaction was quenched with sat. aq. NH₄Cl, and extracted with AcOEt. The organic layer was washed with brine and dried over Na₂SO₄, filtered and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography (SiO₂, hexane : AcOEt = 1 : 1) to afford (*R*)-8. Yield: 72 mg (96%).

Colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 3.51 (s, 3 H), 6.37 (br s, 1 H), 6.78 (d, *J* = 8.7 Hz, 1 H), 7.12–7.18 (m, 2 H), 7.26–7.30 (m, 1 H), 7.34 (t, *J* = 7.6 Hz, 1 H), 7.6 (t, *J* = 7.3 Hz, 1 H), 7.86 (d, *J* = 7.8 Hz, 1 H), 7.96 (d, *J* = 7.8 Hz, 2 H), 8.03–8.11 (m, 2 H), 8.24 (br s, 1 H); ¹³C NMR (150 MHz, CDCl₃) δ 52.2, 120.2, 124.7, 125.1, 126.2, 126.5, 127.1, 127.5, 127.9, 128.1, 128.4, 128.8, 128.9, 129.1(2C), 130.6, 132.4, 132.8, 133.5, 135.5, 135.8, 154.5, 171.2; IR (Neat) 3061, 1699,

1599, 1504, 1463, 1429, 1223, 909, 769, 732 cm⁻¹; HRMS (ESI) m/z calcd for C₂₃H₁₇NO₄ (M+H)⁺ 394.1050, found. 394.1059.



(R)-Benzyl 2'-(((allyloxy)carbonyl)amino)-[1,1'-binaphthalene]-2-carboxylate ((R)-11)

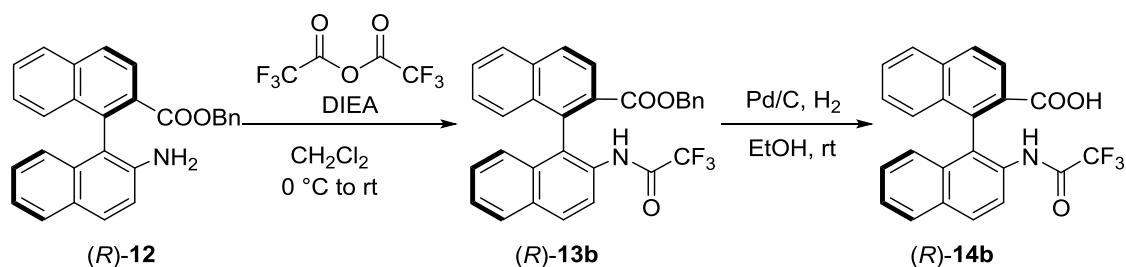
To a solution of (R)-2'-((benzyloxy)carbonyl)-[1,1'-binaphthalene]-2-carboxylic acid ((R)-10) (121 mg, 0.28 mmol, 1.0 equiv) in toluene (20 mL) were added DPPA (90 μ L, 0.42 mmol, 1.5 equiv) and Et₃N (0.12 mL, 0.84 mmol, 3.0 equiv) at 0 °C under Ar atmosphere. After being stirred for 2 h at 90 °C, the reaction was cooled to rt and added allyl alcohol (163 mg, 2.8 mmol, 10 equiv). The mixture was stirred for 5 h at 50 °C. The reaction was quenched with 2 N aq. HCl, and extracted with AcOEt. The organic layer was washed with 2 N aq. NaOH, brine and dried over Na₂SO₄, filtered and concentrated in *vacuo* to give a residue. The residue was purified by column chromatography (SiO₂, hexane : AcOEt = 5 : 1) to afford (R)-11, Yield: 103 mg (75%). Colorless oil, ¹H NMR (600MHz, CDCl₃): δ 4.46–4.52 (m, 2 H), 4.89–4.93 (m, 2 H), 5.12–5.17 (m, 2 H), 5.76–5.83 (m, 1 H), 6.25 (br. s., 1 H), 6.82 (d, J =8.2 Hz, 1 H), 6.86–6.88 (m, 2 H), 7.14–7.19 (m, 3 H), 7.21–7.25 (m, 2 H), 7.30–7.32 (m, 1 H), 7.35 (t, J =7.9 Hz, 1 H), 7.56–7.59 (m, 1 H), 7.85 (d, J =8.2 Hz, 1 H), 7.91 (d, J =8.9 Hz, 1 H), 7.98 (d, J =8.2 Hz, 1 H), 8.08 (d, J =8.9 Hz, 1 H), 8.14 (d, J =8.2 Hz, 1 H), 8.27 (br. s., 1 H); ¹³C NMR (150 MHz, CDCl₃) δ 65.8, 67.1, 118.1, 119.9, 123.4, 124.6, 125.1, 126.0, 126.5, 127.0, 127.6, 128.0 (2C), 128.1, 128.2, 128.3 (2C), 128.9, 129.2, 130.1, 130.3, 132.3, 132.4, 132.9, 133.8, 134.7, 135.0, 135.3, 153.3, 167.2. IR (Neat) 3419, 2921, 1730, 1502, 1458, 1277, 1212, 1128, 970, 766 cm⁻¹; HRMS (ESI) m/z calcd for C₃₂H₂₆NO₄ (M+H)⁺, 488.1862 found 488.1870.

(R)-Benzyl 2'-amino-[1,1'-binaphthalene]-2-carboxylate ((R)-12)

To a solution of (R)-11 (98 mg, 0.2 mmol, 1.0 equiv) in MeOH (4 mL) were added Pd(PPh₃)₄ (12 mg, 0.01 mmol, 5 mol%) and K₂CO₃ (83 mg, 0.6 mmol, 3.0 equiv) at room temperature under Ar atmosphere. After being stirred for 1 h, the mixture was diluted with AcOEt (15 mL) and quenched with aq. NH₄Cl. After extract with EtOAc, the organic layer was washed with brine and dried over Na₂SO₄, filtered and concentrated in *vacuo* to give a residue as a single product. The residue was purified by column chromatography (SiO₂, hexane : AcOEt = 3 : 1) to afford (R)-9, Yield: 81 mg (quant.).

Colorless oil, ¹H NMR (400MHz, CDCl₃) δ 4.97–5.03 (m, 2 H), 6.90–6.93 (m, 3 H), 7.04 (d, J =8.7 Hz, 1 H), 7.15–7.28 (m, 5 H), 7.33–7.39 (m, 1H), 7.46 (d, J =8.2 Hz, 1 H), 7.59 (td, J =7.4,

1.1 Hz, 1 H), 7.78 (d, $J=8.7$ Hz, 1 H), 7.82 (d, $J=7.8$ Hz, 1 H), 8.00 (d, $J=8.2$ Hz, 1 H), 8.07 (d, $J=8.7$ Hz, 1 H), 8.19 (d, $J=8.2$ Hz, 1 H); ^{13}C NMR (100MHz, CDCl_3) δ 66.8, 115.8, 117.9, 122.0, 123.8, 126.2, 126.3, 127.1(2C), 127.7(2C), 127.8, 127.9 (2C), 128.0, 128.1, 128.4, 129.0, 130.1, 132.3, 133.9, 135.2, 135.3, 136.1, 141.5, 167.6. IR (Neat) 3472, 3379, 3059, 1725, 1622, 1380, 1277, 1123, 970, 816, 750, 698 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{28}\text{H}_{21}\text{NNaO}_2$ ($\text{M}+\text{Na}$) $^+$, 426.1470 found 426.1465.



(R)-benzyl 2'-(2,2,2-trifluoroacetamido)-[1,1'-binaphthalene]-2-carboxylate ((R)-13b)

To a solution of **(R)-12** (81 mg, 0.2 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) stirred at 0°C , 2,2,2-trifluoroacetic anhydride (42 μL , 0.3 mmol, 1.5 equiv) and DIEA (42 μL , 0.3 mmol, 1.5 equiv) were added. After being stirred at rt for 0.5h, the reaction was quenched with sat. aq. NH_4Cl , and extracted with AcOEt . The organic layer was washed with brine and dried over Na_2SO_4 , filtered and concentrated in *vacuo* to give a residue as a single product. The residue was purified by column chromatography (SiO_2 , hexane : AcOEt = 2 : 1) to afford **(R)-13b**. Yield: 95 mg (95%). Colorless oil, ^1H NMR (600 MHz, CDCl_3) δ 4.95 (s, 2 H), 6.91–6.94 (m, 3 H), 7.13 (d, $J = 8.3$ Hz, 1 H), 7.18–7.21 (m, 2 H), 7.22–7.27 (m, 2 H), 7.31–7.34 (m, 1 H), 7.44–7.47 (m, 1 H), 7.57–7.60 (m, 1 H), 7.71 (br s., 1 H), 7.91 (d, $J = 8.3$ Hz, 1 H), 7.98 (t, $J = 8.9$ Hz, 2 H), 8.11 (s, 2 H), 8.18 (d, $J = 8.9$ Hz, 1 H). ^{13}C NMR (150 MHz, CDCl_3) δ 67.4, 115.4 (q, $J = 287$ Hz), 120.6, 125.5, 125.6, 125.9, 126.5, 127.0, 127.9, 128.1, 128.2 (2C), 128.3, 128.4 (2C), 129.3, 129.7, 130.0, 131.1, 131.6, 132.1, 132.7, 133.1, 134.7, 135.0, 154.8 (q, $J = 66$ Hz), 167.4. IR (Neat) 3060, 1722, 1509, 1277, 1161, 815, 764 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{30}\text{H}_{20}\text{F}_3\text{NNaO}_3$ ($\text{M}+\text{Na}$) $^+$, 522.1293 found 522.1303.

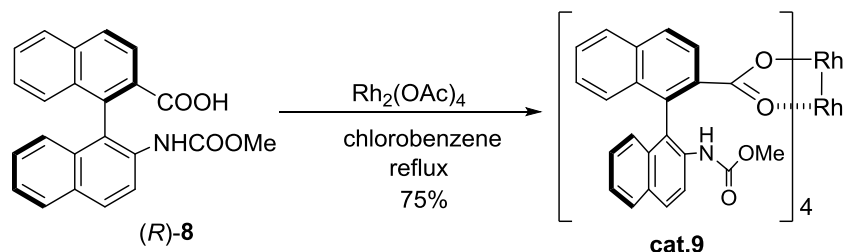
(R)-2'-(2,2,2-trifluoroacetamido)-[1,1'-binaphthalene]-2-carboxylic acid ((R)-14b)

To a solution of **(R)-13b** (50 mg, 0.1 mmol, 1.0 equiv) in EtOH (2 mL), Pd/C (5 mg, 10% wt.) was added and stirred under H_2 (1 atm) atmosphere, After being stirred at room temperature for 4h, the reaction was filtered and concentrated in *vacuo* to give a residue as a single product **(R)-14b** without any further purification. Yield: 41 mg (100%).

Colorless oil, ^1H NMR (600 MHz, CDCl_3) δ 6.83 (d, $J = 8.3$ Hz, 1 H), 7.09 (d, $J = 8.9$ Hz, 1 H), 7.15 (t, $J = 7.6$ Hz, 1 H), 7.29–7.32 (m, 1 H), 7.40 (t, $J = 7.6$ Hz, 1 H), 7.59 (t, $J = 7.6$ Hz, 1 H), 7.78 (br. s., 1 H), 7.87 (d, $J = 8.3$ Hz, 1 H), 7.95–8.05 (m, 4 H), 8.11 (d, $J = 8.9$ Hz, 1 H), 9.75

(br. s., 1 H). ^{13}C NMR (150 MHz, CDCl_3) δ 115.4 (q, $J = 288$ Hz), 121.1, 125.5, 125.7, 126.0, 126.7, 127.0, 127.5, 127.9, 128.1, 128.3, 128.7, 128.8, 129.3, 129.6, 130.9, 131.8, 132.1, 132.7, 134.2, 135.3, 155.1 (q, $J = 38$ Hz), 172.2. IR (Neat) 3401, 3063, 2885, 1722, 1510, 1253, 1165, 909, 814, 734 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{23}\text{H}_{14}\text{F}_3\text{NNaO}_3$ ($\text{M}+\text{Na}$) $^+$, 432.0823 found 432.0830.

Scheme S2–2. General procedure of ligand exchange: Transformation of (*R*)-**8** to cat. **9**.

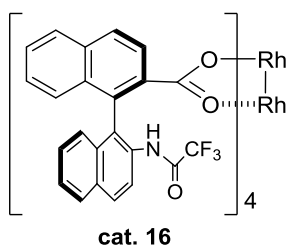


Cat. **9**

A solution of (*R*)-**8** (46 mg, 0.12 mmol) and $\text{Rh}_2(\text{OAc})_4$ (9 mg, 22 μmol) in chlorobenzene (10 mL) was slowly removed under reflux conditions for 4 h. The green residue was diluted with AcOEt (20 mL), washed with sat. aq. NaHCO_3 , brine, and dried over Na_2SO_4 . Then it filtered and concentrated in *vacuo* to give a residue. The residue was purified by column chromatography (SiO_2 , hexane : AcOEt = 10 : 1 to 5 : 1 to 2 : 1 to 3 : 2) to afford cat. **9**. Purified cat. **9** was recrystallized from EtCN to give purple prisms (28 mg, 75%). X-ray analysis revealed the crystals of cat. **9** includes six equivalents of EtCN toward cat. **9**.

Purple prisms. M.p. > 300 $^\circ\text{C}$. $[\alpha]_{\text{D}}^{20} = +98.2$ (c 1.0, CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ 1.40 (t, $J = 7.8$ Hz, 12 H), 2.48 (q, $J = 7.8$ Hz, 9 H), 3.00 (br s, 12 H), 6.09 (s, 4 H), 6.37 (d, $J = 8.7$ Hz, 4 H), 6.83 (d, $J = 8.7$ Hz, 4 H), 6.85–6.91 (m, 4 H), 7.10 (ddd, $J = 1.4, 7.0, 8.6$ Hz, 4 H), 7.15 (t, $J = 7.3$ Hz, 4 H), 7.23 (d, $J = 8.7$ Hz, 4 H), 7.35–7.45 (m, 4 H), 7.73–7.78 (m, 8 H), 7.84 (d, $J = 8.2$ Hz, 4 H), 7.92 (d, $J = 8.7$ Hz, 4 H), 8.13 (br s, 4 H); ^{13}C NMR (600 MHz, CDCl_3) δ 51.7, 120.8, 124.5, 125.5, 126.0, 126.6, 126.9, 127.0, 127.5, 127.6, 127.8 (2C), 127.9, 128.2, 130.1, 130.3 (2C), 132.1, 133.0, 133.1, 134.7, 154.3, 184.4; MS (FAB) m/z 1686 (M) $^+$, 1709 ($\text{M}+\text{Na}$) $^+$. HRMS (FAB) m/z calcd for $\text{C}_{92}\text{H}_{64}\text{N}_4\text{O}_{16}\text{Rh}_2$ (M) $^+$ 1686.2427, found 1686.2412.

Crystallographic data for cat. **9**•6 EtCN: $\text{C}_{110}\text{H}_{94}\text{N}_{10}\text{O}_{16}\text{Rh}_2$, $M = 2017.77$, $0.03 \times 0.01 \times 0.01$ mm^3 , triclinic, P1 (#1), $a = 10.4116(4)$, $b = 15.2831(3)$, $c = 16.3622(5)$ $\text{\AA}$, $\alpha = 71.61^\circ$, $\beta = 89.08^\circ$, $\gamma = 85.19^\circ$, $V = 2461.74(13)$ $\text{\AA}^3$, $Z = 1$, $\rho_{\text{calcd}} = 1.361$ gcm^{-3} , $2\theta_{\text{max}} = 26.00^\circ$, $T = 103(2)$ K, 27189 reflections measured, 18783 unique, The final $R1$ and wR were 0.0726 and 0.1146 (all data). The residual electron densities (peak and hole) were 0.480 and -0.676 $\text{e.\AA}^{-3}$. These data has been deposited with the Cambridge Crystallographic Data Center as CCDC 1510840.



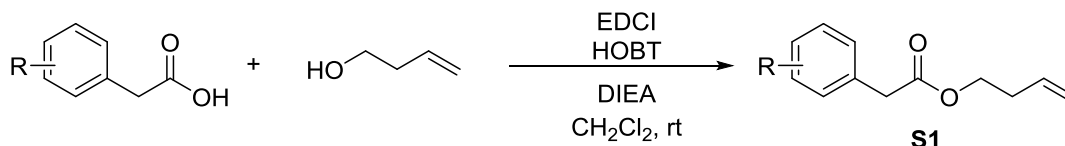
Cat. 16

Yield: 80%. Green powder. M.p. >300 °C. ^1H NMR (400MHz, CDCl_3) δ 8.15 (d, $J=8.7$ Hz, 4 H), 8.08 (d, $J=8.7$ Hz, 4 H), 7.86–7.91 (m, 8 H), 7.74 (d, $J=8.7$ Hz, 4 H), 7.53 (s, 4 H), 7.45 - 7.48 (m, 4 H), 7.14–7.22 (m, 8 H), 6.99 (d, $J=8.7$ Hz, 4 H), 6.80 (d, $J=8.7$ Hz, 4 H), 6.67 (t, $J=7.8$ Hz, 4 H), 6.51 ppm (d, $J=8.7$ Hz, 4 H). ^{13}C NMR (150MHz, CDCl_3) δ 115.3 (q, $J = 287$ Hz), 120.9, 125.7, 125.8, 125.9, 126.3, 126.4, 127.3, 127.6, 127.7, 127.9, 128.5, 128.7 (2C), 130.4, 130.5, 130.9, 131.3, 131.6, 132.6, 134.4, 154.9 (q, $J = 38$ Hz), 184.7. IR (Neat) 3549, 3398, 3062, 1730, 1595, 1532, 1510, 1395, 1266, 1162, 815, 764 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{92}\text{H}_{54}\text{F}_{12}\text{N}_4\text{O}_{13}\text{Rh}_2 (\text{M}+\text{H}_3\text{O})^+$ 1857.1684, found 1857.2045.

3. Chapter 3

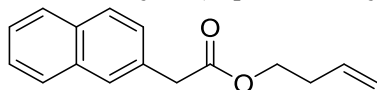
General procedure for preparation of 3-butenyl α -arylacetates

Scheme S3–1. Preparation of 3-butenyl α -arylacetates.



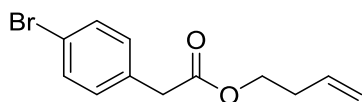
A round bottom flask which was charged with aryl acetic acid (5 mmol, 1.0 equiv) in dry dichloromethane (40 mL) was added EDCI (1.05g, 5.5 mmol, 1.1 equiv) and HOBT (743mg, 5.5 mmol, 1.1 equiv) at rt. After being stirred for 30 min at rt, DIEPA (2.6 mL, 15 mmol, 3.0 equiv) and 3-buten-1-ol (432 mg, 6.0 mmol, 1.2 equiv) was added to the mixture. The reaction was stirred for 12 h. The reaction was quenched by 1N aq. HCl and extracted by AcOEt. The extract was washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to give a residue. The residue was purified by column chromatography (SiO₂, hexane : AcOEt = 9 : 1) to give α -arylacetate **S1**.

But-3-en-1-yl 2-(naphthalen-2-yl)acetate (**S1b**)



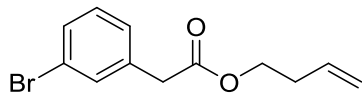
Yield: 1.06 g (88%). Colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 2.34–2.40 (m, 2 H), 3.78 (s, 2 H), 4.16 (t, *J* = 6.6 Hz, 2 H), 5.02–5.10 (m, 2 H), 5.70–5.80 (m, 1 H), 7.40–7.49 (m, 3 H), 7.72 (s, 1 H), 7.78–7.83 (m, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 33.0, 41.5, 63.8, 117.2, 125.7, 126.1, 127.3, 127.6, 127.9, 128.1, 131.5, 132.4, 133.3, 133.8, 171.4; IR (Neat) 3057, 2958, 1735, 1639, 1600, 1384, 1259, 1158, 1021, 991, 918 cm⁻¹; HRMS (FAB) *m/z* calcd for C₁₆H₁₇O₂ (M+H)⁺ 241.1229, found 241.1226.

But-3-en-1-yl 2-(4-bromophenyl)acetate (**S1c**)⁵¹



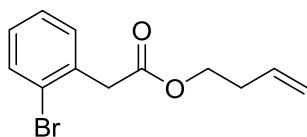
Yield: 1.21 g (90%). Colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 2.34–2.39 (m, 2H), 3.56 (s, 2H), 4.14 (t, *J* = 6.6 Hz, 2H), 5.03–5.10 (m, 2H), 5.74 (ddt, *J* = 6.6, 10.3, 17.2 Hz, 1H), 7.13–7.16 (m, 2H), 7.42–7.45 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 32.9, 40.6, 63.9, 117.3, 121.0, 130.9, 131.5, 132.9, 133.7, 170.9; IR (Neat) 2958, 1737, 1642, 1587, 1489, 1250, 1159, 1012, 922, 810 cm⁻¹; HRMS (FAB) *m/z* calcd for C₁₂H₁₄BrO₂ (M+H)⁺ 269.0177, found 269.0177.

But-3-en-1-yl 2-(3-bromophenyl)acetate (**S1d**)



Yield: 1.16 g (86%). Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 2.34–2.40 (m, 2 H), 3.57 (s, 2 H), 4.15 (t, J = 6.9 Hz, 2 H), 5.04–5.10 (m, 2 H), 5.69–5.79 (m, 1 H), 7.16–7.22 (m, 2 H), 7.38–7.40 (m, 1 H), 7.43–7.45 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 32.92, 40.77, 63.93, 117.34, 122.38, 127.91, 129.94, 130.13, 132.26, 133.68, 136.06, 170.75 ; IR (Neat) 3077, 2958, 1737, 1642, 1570, 1474, 1429, 1249, 1156, 993, 920 cm^{-1} ; HRMS (FAB) m/z calcd for $\text{C}_{12}\text{H}_{14}\text{BrO}_2$ ($\text{M}+\text{H}$) $^+$ 269.0177, found 269.0178.

But-3-en-1-yl 2-(2-bromophenyl)acetate (**S1e**)

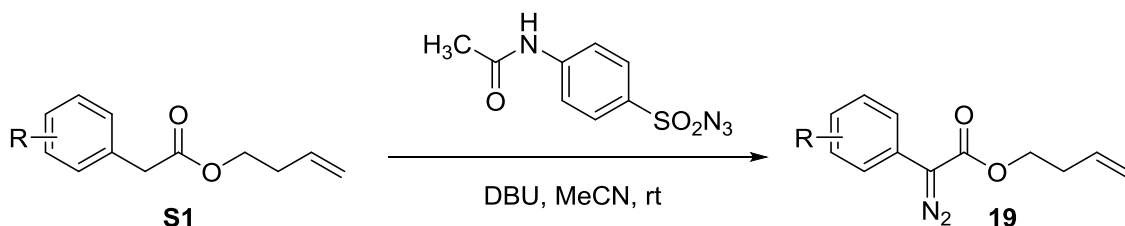


Yield: 1.14 g (85%). Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 2.35–2.40 (m, 2 H), 3.78 (s, 2 H), 4.17 (t, J = 6.6 Hz, 2 H), 5.03–5.10 (m, 2 H), 5.70–5.80 (m, 1 H), 7.11–7.15 (m, 1 H), 7.26–7.29 (m, 2 H), 7.56 (d, J = 7.8 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 32.9, 41.6, 64.0, 117.2, 125.0, 127.4, 128.8, 131.4, 132.7, 133.8, 134.2, 170.4 ; IR (Neat) 3075, 2957, 1739, 1642, 1472, 1440, 1336, 1217, 1163, 1027, 920 cm^{-1} ; HRMS (FAB) m/z calcd for $\text{C}_{12}\text{H}_{14}\text{BrO}_2$ ($\text{M}+\text{H}$) $^+$ 269.0177, found 269.0177.

But-3-en-1-yl 2-phenylacetate (**S1a**)⁵⁰ and but-3-en-1-yl 2-(4-bromophenyl)acetate (**S1c**)⁵¹ for preparing diazoarylacetaes **18a** and **18c** were reported in references 50 and 51, respectively.

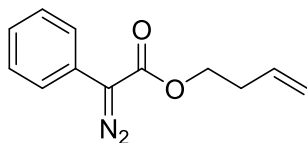
General procedure for preparation of 3-butenyl α -aryl- α -diazoacetate

Scheme S3–2. Preparation of aryldiazoacetate.



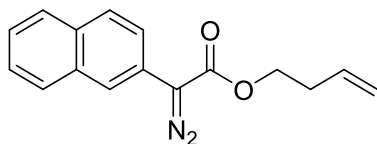
To a solution of phenylacetate **S1** (4 mmol, 1 equiv) in MeCN (5 mL) was added 4-acetamidobenzenesulfonyl azide (1.2 g, 4.8 mmol, 1.2 equiv) and DBU (716 μL , 4.8 mmol, 1.2 equiv) under Ar atmosphere at rt. The mixture was stirred for 12 h. Then solvent were removed in vacuo and the resulting orange residue was purified by column chromatography (SiO_2 , hexane : EtOAc = 9 : 1) to give aryldiazoacetate **19**.

But-3-en-1-yl 2-diazo-2-phenylacetate (**19a**)



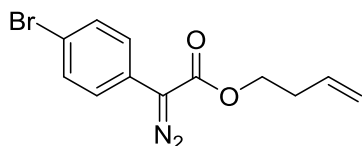
Yield: 787 mg (91%). Orange oil. ^1H NMR (400 MHz, CDCl_3) δ 2.42–2.47 (m, 2 H), 4.31 (t, J = 6.6 Hz, 2 H), 5.08–5.16 (m, 2 H), 5.75–5.85 (m, 1 H), 7.14–7.18 (m, 1 H), 7.34–7.38 (m, 2 H), 7.45–7.48 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 33.3, 63.9, 117.5, 123.9, 125.5, 125.8, 128.9, 133.8, 165.1; IR (Neat) 3076, 2960, 2088, 1706, 1498, 1387, 1344, 1248, 1159, 919, 756 cm^{-1} ; HRMS (FAB) m/z calcd for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_2$ (M) $^+$ 216.0899, found 216.0900.

But-3-en-1-yl 2-diazo-2-(naphthalen-2-yl)acetate (**19b**)



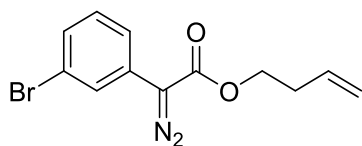
Yield: 1.01 g (95%). Orange oil. ^1H NMR (400 MHz, CDCl_3) δ 2.46–2.51 (m, 2 H), 4.36 (t, J = 6.6 Hz, 2 H), 5.11–5.20 (m, 2 H), 5.79–5.89 (m, 1 H), 7.41–7.49 (m, 2 H), 7.52 (dd, J = 1.8, 8.7 Hz, 1 H), 7.79 (d, J = 8.7 Hz, 2 H), 7.84 (d, J = 8.7 Hz, 1 H), 8.00–8.01 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 33.3, 64.0, 117.6, 121.9, 122.5, 122.7, 125.8, 126.6, 127.6, 127.6, 128.6, 131.4, 133.6, 133.8, 165.3; IR (Neat) 3371, 3059, 2958, 2084, 1703, 1360, 1326, 1254, 1153, 1124, 1042, 736 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 289.0947, found 289.0934.

But-3-en-1-yl 2-(4-bromophenyl)-2-diazoacetate (**19c**)



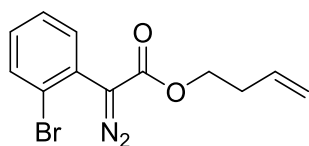
Yield: 1.05 g (89%). Orange oil. ^1H NMR (400 MHz, CDCl_3) δ 2.43–2.49 (m, 2 H), 4.32 (t, J = 6.6 Hz, 2 H), 5.09–5.17 (m, 2 H), 5.75–5.86 (m, 1 H), 7.34–7.37 (m, 2 H), 7.47–7.50 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 33.2, 64.0, 117.6, 119.2, 124.7, 125.3, 132.0, 133.6, 164.7; IR (Neat) 3080, 2958, 2089, 1705, 1491, 1342, 1244, 1160, 1036, 919, 822 cm^{-1} ; HRMS (FAB) m/z calcd for $\text{C}_{12}\text{H}_{11}\text{BrN}_2\text{O}_2$ ($\text{M}+\text{H}$) $^+$ 295.0082, found 295.0074.

But-3-en-1-yl 2-(3-bromophenyl)-2-diazoacetate (**19d**)



Yield: 1.06 g (90%). Orange oil. ^1H NMR (400 MHz, CDCl_3) δ 2.44–2.50 (m, 2 H), 4.33 (t, J = 6.6 Hz, 2 H), 5.10–5.18 (m, 2 H), 5.76–5.86 (m, 1 H), 7.21–7.25 (m, 1 H), 7.28–7.32 (m, 1 H), 7.36–7.39 (m, 1 H), 7.69 (t, J = 1.8 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 33.3, 64.1, 117.7, 122.6, 123.1, 126.5, 128.0, 128., 130.3, 133.7, 164.6; IR (Neat) 3077, 2959, 2090, 1706, 1591, 1479, 1344, 1245, 1161, 1042, 920, 777 cm^{-1} ; HRMS (FAB) m/z calcd for $\text{C}_{12}\text{H}_{11}\text{BrN}_2\text{O}_2$ ($\text{M}+\text{H}$) $^+$ 295.0082, found 295.0076.

But-3-en-1-yl 2-(2-bromophenyl)-2-diazoacetate (**19e**)

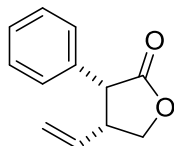


Yield: 956 mg (81%). Orange oil. ^1H NMR (400 MHz, CDCl_3) δ 2.44 (q, J = 6.7 Hz, 2 H), 4.29 (t, J = 6.7 Hz, 2 H), 5.08–5.16 (m, 2 H), 5.74–5.85 (m, 1 H), 7.18–7.22 (m, 1 H), 7.34 (td, J = 1.4, 7.6 Hz, 1 H), 7.51 (dd, J = 1.4, 7.8 Hz, 1 H), 7.61 (dd, J = 1.1, 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 33.3, 64.2, 117.5, 124.4, 125.7, 127.7, 130.0, 132.9, 133.3, 133.8, 165.4; IR (Neat) 3076, 2958, 2097, 1703, 1475, 1286, 1242, 1164, 1066, 1024, 757 cm^{-1} ; HRMS (FAB) m/z calcd for $\text{C}_{12}\text{H}_{11}\text{BrN}_2\text{O}_2$ ($\text{M}+\text{H}$) $^+$ 295.0082, found 295.0090.

Typical procedure of the C-H insertion reaction (Table 3–1, Entry 2)

To a refluxing solution of cat. **9** (10 mg, 6.0 μmol , 2.0 mol%) in CH_2Cl_2 (3.0 mL), CH_2Cl_2 solution (1.5 mL) of **19a** (65 mg, 0.3 mmol) was added dropwise over 1.5 h under an Ar atmosphere via a syringe pump. The mixture was further stirred for 30 min under reflux, and then the solvent was evaporated *in vacuo* to give a residue. The residue was purified by prep. TLC (SiO_2 , hexane : AcOEt = 5 : 1) to afford a mixture of *cis*-**18a** and *trans*-**18a** (30 mg, 52%) and cyclopropanated product **20a** (7.8 mg, 14%). The ratio for *cis*-**18a** : *trans*-**18a** (6.0 : 1) was determined by ^1H NMR integration of the purified mixture of *cis*- and *trans*-**18a**. These isomers were separated by recycled prep. HPLC to determine the enantiomeric excess {column: COSMOSIL 5SL-II (20 mm $\times$ 250 mm), eluent: hexane : EtOAc = 3 : 1, flow rate: 5.0 mL/min, detection: 254 nm}.

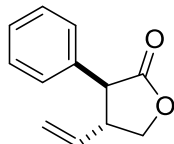
(3*R*, 4*R*)-3-Phenyl-4-vinyldihydrofuran-2(3*H*)-one (*cis*-**18a**)



Colorless oil. $[\alpha]_{\text{D}}^{20}$ = +9.1 (c 0.3, CHCl_3 , 74% ee). ^1H NMR (400 MHz, CDCl_3) δ 3.43–3.49 (m, 1 H), 4.00 (d, J = 8.9 Hz, 1 H), 4.23–4.26 (m, 1 H), 4.48–4.52 (m, 1 H), 5.03 (d, J = 10.3 Hz, 1 H), 5.09 (d, J = 16.5 Hz, 1 H), 5.27–5.36 (m, 1 H), 7.14–7.16 (m, 2 H), 7.27–7.31 (m, 1 H), 7.33–7.37 (m, 2 H); ^{13}C NMR (150 MHz, CDCl_3) δ 45.6, 50.5, 70.4, 118.6, 127.6, 128.7, 129.1, 133.2, 133.3, 176.9. IR (Neat) 3065, 3031, 2985, 2907, 1773, 1497, 1370, 1211, 1149, 1015, 925, 704

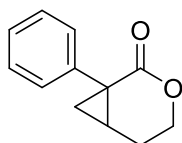
cm⁻¹; HRMS (ESI) *m/z* calcd for C₁₂H₁₂O₂Na (M+Na)⁺ 211.0730, found 211.0727.

trans-3-Phenyl-4-vinyldihydrofuran-2(3H)-one (*trans*-**18a**)⁴



Colorless oil. [α]_D²⁰ = +6.8 {c 0.6, CHCl₃, 57% ee, for (3*S*,4*R*)-**18a**, as shown in the structure, obtained from epimerization of (3*R*,4*R*)-*cis*-**5a**}. ¹H NMR (400 MHz, CDCl₃) δ 3.25–3.34 (m, 1 H), 3.57 (d, *J* = 11.0 Hz, 1 H), 4.06–4.11 (m, 1 H), 4.53 (dd, *J* = 7.6, 8.9 Hz, 1 H), 5.10 (d, *J* = 17.2 Hz, 1 H), 5.17 (d, *J* = 10.3 Hz, 1 H), 5.8 (ddd, *J* = 7.6, 10.1, 17.4 Hz, 1 H), 7.21–7.24 (m, 2 H), 7.29–7.33 (m, 1 H), 7.35–7.40 (m, 2 H); ¹³C NMR (150 MHz, CDCl₃) δ 49.4, 52.0, 69.9, 119.2, 127.8, 128.5, 128.7, 128.8, 134.0, 135.0, 176.4; IR (Neat) 2904, 1774, 1497, 1453, 1373, 1154, 1018, 752, 699 cm⁻¹; HRMS (ESI) *m/z* calcd for C₁₂H₁₂O₂K (M+K)⁺ 227.0469, found 227.04.

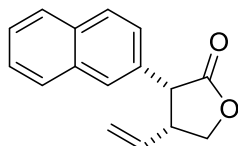
1-Phenyl-3-oxabicyclo[4.1.0]heptan-2-one (**20a**)



Colorless amorphous. M.p. 96–97 °C. ¹H NMR (600 MHz, CDCl₃-*d*) δ 1.52 (dd, *J* = 5.8, 7.9 Hz, 1 H), 1.91 (t, *J* = 5.84 Hz, 1 H), 2.04–2.06 (m, 1 H), 2.42–2.47 (m, 1 H), 4.26 (td, *J* = 3.4, 12.4 Hz, 1 H), 4.36 (dd, *J* = 5.8, 12.0 Hz, 1 H), 7.27–7.29 (m, 1 H), 7.32–7.35 (m, 4 H); ¹³C NMR (150 MHz, CDCl₃) δ 14.9, 21.3, 22.6, 30.3, 65.2, 127.6, 128.4, 129.9, 139.5, 171.9; IR (Neat) 3027, 2920, 1496, 1402, 1256, 1165, 1103, 1019, 942, 762, 703 cm⁻¹; HRMS (ESI) *m/z* calcd for C₁₂H₁₂O₂Na (M+Na)⁺ 211.0730, found 211.0717.

cis-3-(naphthalen-2-yl)-4-vinyldihydrofuran-2(3H)-one (*cis*-**18b**)

{The absolute configuration shown here was tentatively assigned to be the same as (3*R*, 4*R*)-*cis*-**5a** by analogy.}

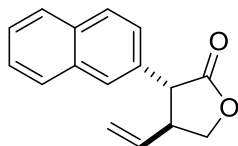


Colorless needles. M.p. 85–86 °C. [α]_D²⁰ = –17.1 (c 1.3, CHCl₃, 72% ee). ¹H NMR (400 MHz, CDCl₃) δ 3.49–3.56 (m, 1H), 4.15 (d, *J* = 8.7 Hz, 1H), 4.29 (dd, *J* = 6.4, 9.2 Hz, 1H), 4.50–4.54 (m, 1H), 4.96–4.99 (m, 1H), 5.06–5.10 (m, 1H), 5.2–5.36 (m, 1H), 7.22 (dd, *J* = 1.8, 8.7 Hz, 1H), 7.46–7.51 (m, 2H), 7.65–7.66 (m, 1H), 7.79–7.83 (m, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 45.7,

50.5, 70.5, 118.8, 126.2, 126.4, 127.1, 127.6, 127.9, 128.0, 128.4, 130.8, 132.6, 133.27, 133.3, 176.9. IR (Neat) 3055, 2908, 1770, 1368, 1210, 1148, 1014, 924, 821, 749 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{16}\text{H}_{14}\text{O}_2\text{Na}$ ($\text{M}+\text{Na}$)⁺ 261.0886, found 261.0890.

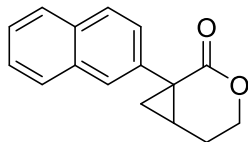
trans-3-(naphthalen-2-yl)-4-vinyldihydrofuran-2(3H)-one (*trans*-**18b**)

{The absolute configuration shown here was tentatively assigned to be the same as (3*R*, 4*S*)-*trans*-**5a** in Table 1 by analogy.}



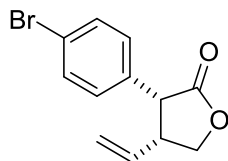
Colorless needles. M.p. 64–66 °C. ^1H NMR (400 MHz, CDCl_3) δ 3.41 (ddt, J = 8.0, 10.4, 11.3 Hz, 1 H), 3.75 (d, J = 11.4, 1 H), 4.14 (dd, J = 9.2, 10.1 Hz, 1 H), 4.58 (dd, J = 8.0, 8.9 Hz, 1 H), 5.07–5.18 (m, 1 H), 5.07–5.12 (m, 1 H), 5.15–5.18 (m, 1 H), 5.78–5.86 (m, 1 H), 7.33 (dd, J = 2.1, 8.5 Hz, 1 H), 7.46–7.51 (m, 2 H), 7.69–7.70 (m, 1 H), 7.81–7.88 (m, 3 H); ^{13}C NMR (150 MHz, CDCl_3) δ 49.5, 52.3, 70.1, 119.3, 125.9, 126.2, 126.4, 127.7, 127.8, 127.9, 128.8, 132.4, 132.8, 133.3, 134.0, 176.4. IR (Neat) 2926, 1770, 1598, 1370, 1152, 1017, 927, 817, 748, 478 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{16}\text{H}_{14}\text{O}_2\text{Na}$ ($\text{M}+\text{Na}$)⁺ 261.0886, found 261.0890.

1-(Naphthalen-2-yl)-3-oxabicyclo[4.1.0]heptan-2-one (**20b**)



Colorless plates. M.p. 162–166 °C. ^1H NMR (400 MHz, CDCl_3) δ 1.63 (dd, J =7.79, 5.95 Hz, 1 H), 1.99 (t, J =5.95 Hz, 1 H), 2.13 - 2.19 (m, 2 H), 2.48 - 2.57 (m, 1 H), 4.31 (td, J =12.37, 3.66 Hz, 1 H), 4.39 - 4.44 (m, 1 H), 7.45 - 7.51 (m, 3 H), 7.75 (d, J =1.83 Hz, 1 H), 7.78 - 7.83 (m, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.9, 21.3, 22.7, 30.5, 65.2, 126.1, 126.2, 127.6, 127.8, 128.1, 128.2, 128.3, 132.7, 133.1, 137.0, 172.0; IR (Neat) 3389, 2918, 2851, 2084, 2363, 2307, 1709, 1391, 1155, 1099, 770 cm^{-1} ; HRMS (TOF) m/z calcd for $\text{C}_{16}\text{H}_{14}\text{O}_2\text{Na}$ ($\text{M}+\text{Na}$)⁺ 261.0886, found 261.0872.

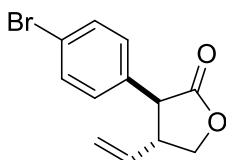
(3*R*, 4*R*)-3-(4-Bromophenyl)-4-vinyldihydrofuran-2(3H)-one (*cis*-**18c**)



Colorless oil. $[\alpha]_{\text{D}}^{20}$ = +9.4 (c 0.4, CHCl_3 , 75% ee). ^1H NMR (400 MHz, CDCl_3) δ 3.43–3.49 (m, 1 H), 3.98 (d, J = 8.2 Hz, 1 H), 4.24 (dd, J = 5.7, 9.4 Hz, 1 H), 4.50 (dd, J = 6.6, 9.4 Hz, 1 H),

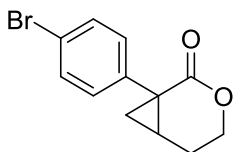
5.05–5.11 (m, 2 H), 5.29–5.38 (m, 1 H), 7.02–7.06 (m, 2 H), 7.47–7.50 (m, 2 H); ^{13}C NMR (150 MHz, CDCl_3) δ 45.5, 49.9, 70.5, 119.1, 121.8, 130.9, 131.8, 132.2, 133.1, 176.2; IR (Neat) 3360, 2922, 2852, 2348, 2314, 1770, 1649, 1596, 1382, 1148 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{11}\text{BrO}_2\text{Na}$ ($\text{M}+\text{Na}$) $^{+}$ 288.9835, found 288.9816.

(3*S*, 4*R*)-3-(4-Bromophenyl)-4-vinyldihydrofuran-2(3*H*)-one (*trans*-**18c**)



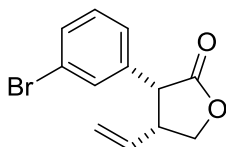
Colorless oil. $[\alpha]_{\text{D}}^{20} = +8.6$ (c 0.6, CHCl_3 , 55% ee). ^1H NMR (400 MHz, CDCl_3) δ 3.21–3.30 (m, 1 H), 3.54 (d, $J = 11.9$ Hz, 1 H), 4.08 (dd, $J = 9.2, 10.1$ Hz, 1 H), 4.53 (dd, $J = 8.0, 8.9$ Hz, 1 H), 5.08–5.21 (m, 2 H), 5.71–5.80 (m, 1 H), 7.10–7.13 (m, 2 H), 7.49–7.53 (m, 2 H); ^{13}C NMR (150 MHz, CDCl_3) δ 49.5, 51.4, 70.0, 119.7, 122.0, 130.3, 132.1, 133.6, 133.9, 175.8; IR (Neat) 3424, 2922, 2852, 2349, 2314, 1773, 1649, 1575, 1384, 1152, 1013, 770 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{11}\text{BrO}_2\text{Na}$ ($\text{M}+\text{Na}$) $^{+}$ 288.9835, found 288.9817.

1-(4-Bromophenyl)-3-oxabicyclo[4.1.0]heptan-2-one (**20c**)



Colorless amorphous. M.p. 117–118 $^{\circ}\text{C}$. ^1H NMR (400 MHz, CDCl_3) δ 1.48 (dd, $J = 8.24, 6.0$ Hz, 1 H), 1.93 (t, $J = 6.0$ Hz, 1 H), 2.02–2.07 (m, 1 H), 2.09–2.15 (m, 1 H), 2.40–2.49 (m, 1 H), 4.26 (td, $J = 3.7, 12.4$ Hz, 1 H), 4.35–4.40 (m, 1 H), 7.20–7.24 (m, 2 H), 7.44–7.47 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.9, 21.1, 22.6, 29.8, 65.2, 121.6, 131.5, 131.7, 138.4, 171.48; IR (Neat) 2921, 2849, 1706, 1487, 1391, 1161, 1101, 1013, 802, 539 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{11}\text{BrO}_2\text{Na}$ ($\text{M}+\text{Na}$) $^{+}$ 288.9835, found 288.9820.

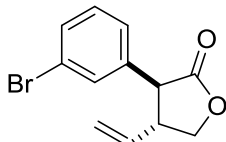
(3*R*, 4*R*)-3-(3-Bromophenyl)-4-vinyldihydrofuran-2(3*H*)-one (*cis*-**18d**)



Colorless oil. $[\alpha]_{\text{D}}^{20} = +21.2$ (c 1.0, CHCl_3 , 67% ee). ^1H NMR (400 MHz, CDCl_3) δ 3.43–3.50 (m, 1 H), 3.98 (d, $J = 8.2$ Hz, 1 H), 4.24–4.28 (m, 1 H), 4.51 (dd, $J = 6.9, 9.6$ Hz, 1 H), 5.07–5.12 (m, 2 H), 5.30–5.39 (m, 1 H), 7.10 (d, $J = 7.8$ Hz, 1 H), 7.23 (t, $J = 7.8$ Hz, 1 H), 7.33 (t, $J = 1.8$ Hz, 1 H), 7.4–7.45 (m, 1 H); ^{13}C NMR (150 MHz, CDCl_3) δ 45.5, 50.0, 70.5, 119.2, 122.7, 127.9, 130.2, 130.9, 132.2, 132.9, 135.5, 176.0; IR (Neat) 3390, 2921, 2849, 2363, 2307, 1770, 1578, 1380,

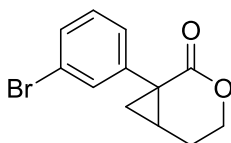
1148, 770 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{11}\text{BrO}_2\text{Na}$ ($\text{M}+\text{Na}$)⁺ 288.9835, found 288.9821.

(3*S*, 4*R*)-3-(3-Bromophenyl)-4-vinyldihydrofuran-2(3*H*)-one (*trans*-**18d**)



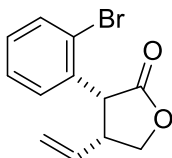
Colorless oil. $[\alpha]_{\text{D}}^{20} = +7.7$ (c 0.7, CHCl_3 , 67% ee). ^1H NMR (400 MHz, CDCl_3) δ 3.25–3.30 (m, 1 H), 3.54 (d, $J = 11.9$ Hz, 1 H), 4.08 (dd, $J = 9.2, 10.1$ Hz, 1 H), 4.54 (dd, $J = 8.0, 8.9$ Hz, 1 H), 5.10–5.22 (m, 2 H), 5.72–5.80 (m, 1 H), 7.15–7.18 (m, 1 H), 7.23–7.27 (m, 1 H), 7.38 (t, $J = 1.8$ Hz, 1 H), 7.44 - 7.47 (m, 1 H); ^{13}C NMR (150 MHz, CDCl_3) δ 49.4, 51.5, 70.0, 119.7, 122.9, 127.3, 130.4, 131.1, 131.6, 133.6, 137.2, 175.6; IR (Neat) 3378, 2917, 2853, 2359, 2307, 1774, 1595, 1380, 1152, 1021, 774 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{11}\text{BrO}_2\text{Na}$ ($\text{M}+\text{Na}$)⁺ 288.9835, found 288.9818.

1-(3-Bromophenyl)-3-oxabicyclo[4.1.0]heptan-2-one (**20d**)



Colorless needles. M.p. 95–96 °C. ^1H NMR (400 MHz, CDCl_3) δ 1.51 (dd, $J = 6.2, 8.0$ Hz, 1 H), 1.93 (t, $J = 6.2$ Hz, 1 H), 2.04–2.15 (m, 2 H), 2.40–2.49 (m, 1 H), 4.26 (td, $J = 3.9, 12.5$ Hz, 1 H), 4.35–4.40 (m, 1 H), 7.21 (t, $J = 7.80$ Hz, 1 H), 7.29 (dt, $J = 1.4, 7.8$ Hz, 1 H), 7.40 - 7.43 (m, 1 H), 7.48 (t, $J = 1.8$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.9, 21.0, 22.6, 30.0, 64.3, 122.1, 128.8, 129.9, 130.7, 132.9, 141.5, 171.4; IR (Neat) 3423, 2969, 2921, 2371, 1717, 1567, 1408, 1256, 1162, 1102, 942, 694 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{11}\text{BrO}_2\text{Na}$ ($\text{M}+\text{Na}$)⁺ 288.9835, found 288.9819.

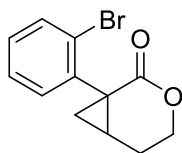
cis-3-(2-Bromophenyl)-4-vinyldihydrofuran-2(3*H*)-one (**18e**)



Colorless oil. ^1H NMR (600 MHz, CDCl_3) δ 3.63–3.67 (m, 1 H), 4.30 (dd, $J = 3.1, 9.3$ Hz, 1 H), 4.51 (d, $J = 8.3$ Hz, 1 H), 4.55 (dd, $J = 6.5, 9.3$ Hz, 1 H), 4.96–4.97 (m, 1 H), 5.01–5.04 (m, 1 H), 5.41 (ddd, $J = 8.9, 10.3, 17.2$ Hz, 1 H), 7.14–7.17 (m, 1 H), 7.22 (dd, $J = 1.7, 7.9$ Hz, 9 H), 7.31–7.32 (m, 1 H), 7.58 (dd, $J = 1.4, 8.3$ Hz, 9 H); ^{13}C NMR (150 MHz, CDCl_3) δ 43.6, 50.1, 70.4, 118.4, 125.5, 127.5, 129.2, 130.8, 132.7, 133.2, 133.4, 175.9; IR (Neat) 3076, 2983, 2906, 1773,

1474, 1370, 1294, 1153, 1025, 923, 750 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{11}\text{BrO}_2\text{Na}$ ($\text{M}+\text{Na}$)⁺ 288.9835, found 288.9818.

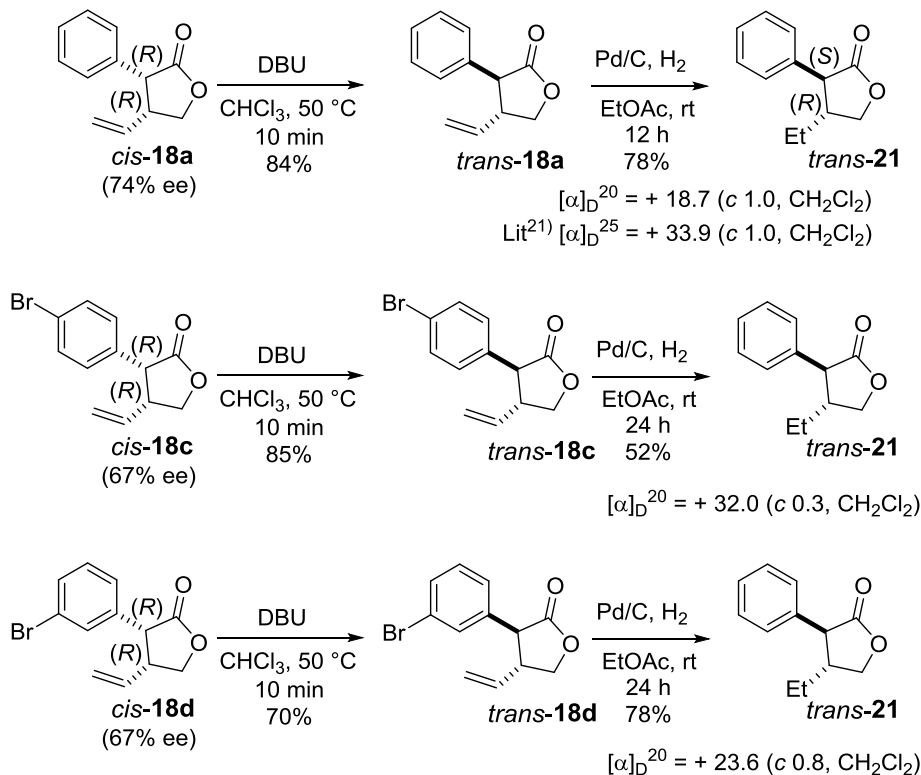
1-(2-Bromophenyl)-3-oxabicyclo[4.1.0]heptan-2-one (**20e**)



Colorless needles. M.p. 130–133 °C. ^1H NMR (400 MHz, CDCl_3) δ 1.59 (br s, 1 H), 1.86–1.89 (m, 1 H), 2.03–2.14 (m, 2 H), 2.67–2.71 (m, 1 H), 4.27 (ddd, $J = 3.7, 11.9, 13.3$ Hz, 1 H), 4.41 (dd, $J = 6.0, 11.9$ Hz, 1 H), 7.15–7.19 (m, 9 H), 7.28–7.36 (m, 2 H), 7.58 (dd, $J = 1.1, 8.0$ Hz, 1 H); ^{13}C NMR (150 MHz, CDCl_3) δ 20.6, 24.1, 30.9, 31.9, 65.2, 127.5, 129.3, 132.3, 132.8, 139.3, 170.5; IR (Neat) 3471, 2927, 1716, 1476, 1269, 1165, 1101, 1019, 947, 758 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{11}\text{BrO}_2\text{Na}$ ($\text{M}+\text{Na}$)⁺ 288.9835, found 288.9822.

Scheme 3–3. Determination of absolute configurations of γ -lactones **18a**, **18c** and **18d**

As shown in Scheme 3–2 in the Chapter 3, relative and absolute configurations of *cis*-**18a**, **18c** and **18d** were determined to be (3*R*,4*R*) by transforming to known compound, *trans*-**21**, and by comparing the optical rotation to the literature data.⁴⁷

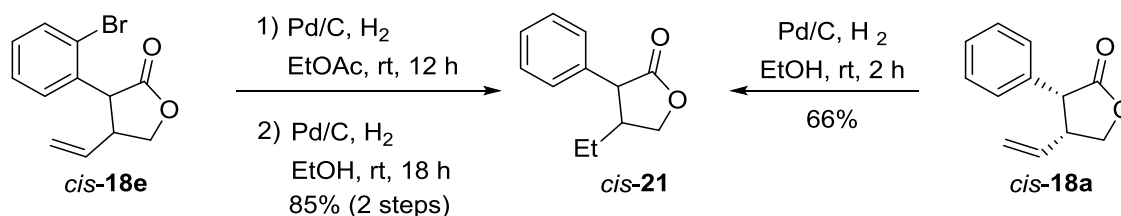


Typical procedure for **Scheme 3–3**:

To a solution of *cis*-**18d** (20 mg, 75 μ mol) in CHCl_3 (1.0 mL) was added DBU (34 μ L, 0.22 mmol, 3.0 equiv) under Ar atmosphere at 50 $^\circ\text{C}$. The mixture was stirred for 10 min. The reaction was quenched with aq. 2 N HCl, and extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give a residue. The residue was purified by preparative TLC (SiO_2 , hexane : AcOEt = 3 : 1) to give *trans*-**18d** (14 mg, 70%).

A solution of *trans*-**18d** (14 mg, 52 μ mol) in AcOEt (1.0 mL) in the presence of 10% Pd-C (2.0 mg) was stirred under H_2 atmosphere for 24 h at rt. The reaction mixture was filtered through a pad of Celite, and the filtrate was evaporated *in vacuo* to give the residue. The residue was purified by prep. TLC (SiO_2 , hexane : AcOEt = 3 : 1) to give *trans*-**21** (7.8 mg, 78%).

Scheme 3–3. Structure determination of γ -lactone **18e**



Procedure for catalytic hydrogenation of *cis*-**18e**:

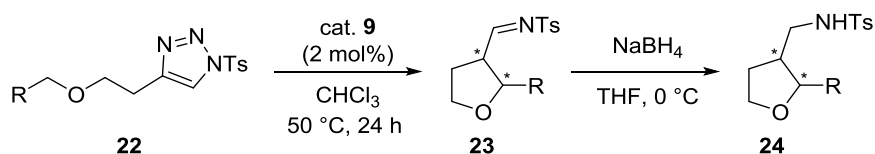
A solution of *cis*-**18e** (13 mg, 50 μ mol) in AcOEt (1.0 mL) in the presence of 10% Pd-C (2.0 mg) was stirred under H_2 atmosphere for 12 h at rt. The reaction mixture was filtered through a pad of Celite, and the filtrate was evaporated *in vacuo* to give the residue (~30% conversion). The residue was dissolved with EtOH (1.0 mL) and applied to hydrogenation conditions again {10% Pd-C (2.0 mg) under H_2 atmosphere, rt, 18 h} to give the residue. The residue was purified by prep. TLC (SiO_2 , hexane : AcOEt = 3 : 1) to give *cis*-**21** (7.9 mg, 85%).

Procedure for catalytic hydrogenation of *cis*-**18a**:

A solution of *cis*-**18a** (3.0 mg, 16 μ mol) in EtOH (1.0 mL) in the presence of 10% Pd-C (2.0 mg) was stirred under H_2 atmosphere for 2 h at rt. The reaction mixture was filtered through a pad of Celite, and the filtrate was evaporated *in vacuo* to give the residue. The residue was purified by prep. TLC (SiO_2 , hexane : AcOEt = 3 : 1) to give *cis*-**21** (2.0 mg, 66%).

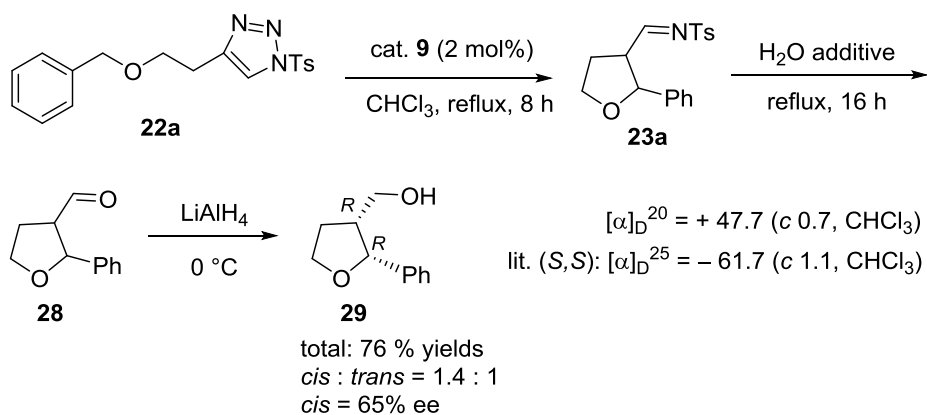
4. Chapter 4

Scheme 4–1. Typical procedure to synthesis of saturated heterocycles by intramolecular Rh(II)-catalyzed azavinyl carbene C–H insertion



A flame-dried 5 mL microwave vial equipped with a magnetic stir-bar was charged with rhodium(II) cat. **9** (5.1 mg, 0.003 mmol, 0.02 equiv), sealed and flushed with Ar. A solution of the *N*-sulfonyltriazole (0.15 mmol, 1.0 equiv) in anhydrous CHCl_3 (1 mL) was added, resulting in a dark pink homogenous solution which was heated to 50 °C in an oil bath and held at this temperature for 24 h. The resulting blue-green homogenous solution was cooled to room temperature and 1,3,5-trimethoxybenzene (8.4 mg, 0.05 mmol, 0.33 equiv) was added as internal standard for NMR yield determination. The reaction mixture was then cooled to 0 °C and NaBH_4 (9 mg, 0.23 mmol, 1.5 equiv) was added slowly, after stirred for 10min, the temperature was raised to RT for additional 20min. After that time, aq. NH_4Cl was added slowly and diluted with ethyl acetate (10 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (2 x 10 mL). The combined organic fractions were washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4 , and concentrated under vacuum to afford the crude saturated heterocycle **24a–24j**, which was analyzed by ^1H NMR and purified by flash chromatography. The ratio for *cis*-**22** : *trans*-**22** was determined by ^1H NMR integration of the purified mixture of *cis*- and *trans*-**22**. These isomers were separated by recycled prep. HPLC to determine the enantiomeric excess {column: COSMOSIL 5SL-II (20 mm x 250 mm), eluent: hexane : EtOAc = 2 : 1, flow rate: 5.0 mL/min, detection: 254 nm}.

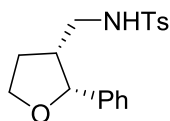
Scheme S4–2. Determination of absolute configurations of 2,3-disubstituted tetrahydrofuran



Procedure for **Scheme S4–2**:

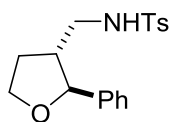
A flame-dried 5 mL microwave vial equipped with a magnetic stir-bar was charged with rhodium(II) cat. **9** (5.1 mg, 3 μ mol, 0.02 equiv), sealed and flushed with Ar. A solution of the *N*-sulfonyltriazole (0.15 mmol, 1.0 equiv) in anhydrous CHCl_3 (1 mL) was added, resulting in a dark pink homogenous solution which was heated to reflux in an oil bath and held at this temperature for 8 h to generate **23a**. Then H_2O (0.2 mL) was added and the mixture was refluxed for continuously 16h. After that, the reaction was extracted with CHCl_3 and washed by with brine and dried over Na_2SO_4 , filtered and concentrated in vacuo to give a residue **28**. The residue **28** was then dissolved in THF (2 mL) and cooled to 0 $^\circ\text{C}$, LiAlH_4 (7 mg, 0.18 mmol, 1.2 equiv) was added very slowly, after stirred for 10 min, the reaction mixture was quenched with h aq. 2 *N* HCl, and extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4 , filtered and concentrated in vacuo to give a residue. The residue was purified by preparative TLC (SiO_2 , hexane : AcOEt = 3 : 1) to give *cis/trans* mixture **29**, Yield: 20 mg (76%).

4-Methyl-*N*-(((2*R*,3*R*)-2-phenyltetrahydrofuran-3-yl)methyl)benzenesulfonamide (*cis*-**24a**)



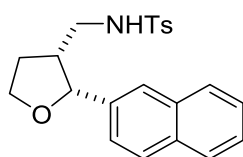
$[\alpha]_{\text{D}}^{20} = +21.5$ (c 1.8, CHCl_3 , 78% ee). ^1H , ^{13}C NMR, IR spectra and HRMS were consistent with the previously reported data.³⁵

trans-4-Methyl-*N*-((2-phenyltetrahydrofuran-3-yl)methyl)benzenesulfonamide (*trans*-**24a**)



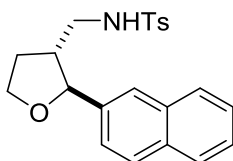
$[\alpha]_{\text{D}}^{20} = +3.8$ (c 0.9, CHCl_3 , 43% ee). ^1H , ^{13}C NMR, IR spectra and HRMS were consistent with the previously reported data.³⁵

cis-4-Methyl-*N*-(((2*R*,3*R*)-2-(naphthalen-2-yl)tetrahydrofuran-3-yl)methyl)benzenesulfonamide (*cis*-**24b**)



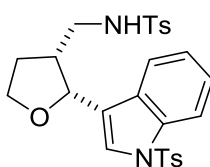
$[\alpha]_{\text{D}}^{20} = -2.4$ (c 1.0, CHCl_3 , 61% ee). ^1H , ^{13}C NMR, IR spectra and HRMS were consistent with the previously reported data.³⁵

trans-4-Methyl-N-(((2R,3R)-2-(naphthalen-2-yl)tetrahydrofuran-3-yl)methyl)benzenesulfonamide (*trans*-**24b**)



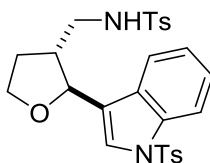
Colorless oil. $[\alpha]_{\text{D}}^{20} = +9.3$ (c 0.9, CHCl_3 , 28% ee). ^1H NMR (CDCl_3 , 400MHz) δ 7.78–7.83 (m, 3 H), 7.65–7.67 (m, 3 H), 7.45–7.51 (m, 2 H), 7.35 (dd, $J=8.2$, 1.8 Hz, 1 H), 7.23 (d, $J=8.2$ Hz, 2 H), 4.62 (d, $J=6.4$ Hz, 1 H), 4.52 (t, $J=6.4$ Hz, 1 H), 4.12–4.18 (m, 1 H), 4.00 (td, $J=8.2$, 6.0 Hz, 1 H), 3.06–3.14 (m, 2 H), 2.39 (s, 3 H), 2.29–2.34 (m, 1 H), 2.17–2.22 (m, 1 H), 1.78–1.84 (m, 5 H); ^{13}C NMR (CDCl_3 , 150MHz) δ 143.6, 138.9, 136.6, 133.2, 133.2, 133.0, 129.8, 128.5, 127.9, 127.7, 127.0, 126.2, 125.9, 124.9, 123.9, 84.0, 67.9, 47.5, 45.0, 30.3, 21.5; IR (Neat) 3276, 2871, 1599, 1448, 1326, 1159, 1091, 817, 663 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{22}\text{H}_{24}\text{NO}_3\text{S}$ ($\text{M}+\text{H}$) $^+$ 382.1477, found 382.1456.

cis-4-Methyl-N-((2-(1-tosyl-1H-indol-3-yl)tetrahydrofuran-3-yl)methyl)benzenesulfonamide (*cis*-**24c**)



$[\alpha]_{\text{D}}^{20} = +81.3$ (c 1.8, CHCl_3 , 68% ee). ^1H , ^{13}C NMR, IR spectra and HRMS were consistent with the previously reported data.³⁵

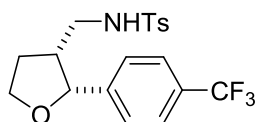
trans-4-Methyl-N-((2-(1-tosyl-1H-indol-3-yl)tetrahydrofuran-3-yl)methyl)benzenesulfonamide (*trans*-**24c**)



White solids. M.p. 152–153 °C. $[\alpha]_{\text{D}}^{20} = +30.5$ (c 0.9, CHCl_3 , 48% ee). ^1H NMR (CDCl_3 , 600MHz) δ 7.95 (d, $J=8.2$ Hz, 1 H), 7.75 (d, $J=8.2$ Hz, 2 H), 7.65 (d, $J=8.2$ Hz, 2 H), 7.51 (d, $J=8.2$ Hz, 1 H), 7.47 (s, 1 H), 7.30 (t, $J=7.6$ Hz, 1 H), 7.18–7.23 (m, 5 H), 4.76 (t, $J=6.5$ Hz, 1 H), 4.71 (d, $J=6.2$ Hz, 1 H), 4.00–4.04 (m, 1 H), 3.90–3.94 (m, 1 H), 2.99–3.08 (m, 2 H), 2.47–2.50 (m, 1 H), 2.40 (s, 3 H), 2.32 (s, 3 H), 2.16–2.22 (m, 1 H), 1.76–1.82 (m, 1 H); ^{13}C NMR (CDCl_3 , 150MHz) δ 145.1, 143.7, 136.5, 135.6, 135.0, 129.9, 129.8, 128.7, 126.9, 126.8, 124.9, 123.5,

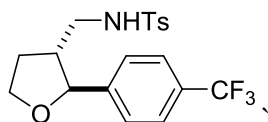
123.3, 122.2, 120.4, 113.7, 77.5, 67.3, 45.2, 44.4, 30.1, 21.5(2C); IR (Neat) 3286, 2872, 1598, 1447, 1369, 1213, 1171, 814, 683 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{27}\text{H}_{28}\text{N}_2\text{NaO}_5\text{S}_2$ ($\text{M}+\text{Na}$)⁺ 547.1337, found 547.1284.

cis-4-Methyl-*N*-((-2-(4-(trifluoromethyl)phenyl)tetrahydrofuran-3-yl)methyl)benzenesulfonamide (*cis*-**24d**)



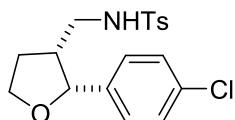
$[\alpha]_{\text{D}}^{20} = +43.4$ (c 0.9, CHCl_3 , 70% ee). ^1H , ^{13}C NMR, IR spectra and HRMS were consistent with the previously reported data.³⁵

trans-4-Methyl-*N*-((-2-(4-(trifluoromethyl)phenyl)tetrahydrofuran-3-yl)methyl)benzenesulfonamide (*trans*-**24d**)



Colorless needles. M.p. 98–99 °C. $[\alpha]_{\text{D}}^{20} = +1.3$ (c 1.0, CHCl_3 , 44% ee). ^1H NMR (CDCl_3 , 600MHz) δ 7.72 (d, $J=8.2$ Hz, 2 H), 7.56 (d, $J=8.2$ Hz, 2 H), 7.38 (d, $J=8.2$ Hz, 2 H), 7.30 (d, $J=8.2$ Hz, 2 H), 4.95 (t, $J=6.2$ Hz, 1 H), 4.61 (d, $J=6.2$ Hz, 1 H), 4.07–4.11 (m, 1H), 3.96–3.99 (m, 1 H), 3.00–3.11 (m, 2 H), 2.43 (s, 3H), 2.19–2.25 (m, 1 H), 2.10–2.15 (m, 1 H), 1.75–1.81 (m, 1 H); ^{13}C NMR (CDCl_3 , 150MHz) δ 146.1, 143.8, 136.5, 129.8, 129.7, 127.0, 126.1, 125.4 (q, $J = 4.8$ Hz), 125.0, 82.8, 67.9, 47.8, 44.8, 30.0, 21.5; IR (Neat) 3277, 2875, 1421, 1327, 1160, 1123, 1067, 815, 663 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{19}\text{H}_{21}\text{F}_3\text{NO}_3\text{S}$ ($\text{M}+\text{H}$)⁺ 400.1194, found 400.1180.

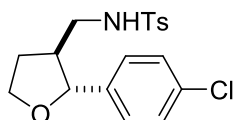
cis-*N*-((-2-(4-chlorophenyl)tetrahydrofuran-3-yl)methyl)-4-methylbenzenesulfonamide (*cis*-**24e**)



Colorless amorphous. M.p. 78–80 °C. $[\alpha]_{\text{D}}^{20} = +24.5$ (c 0.9, CHCl_3 , 70% ee). ^1H NMR (CDCl_3 , 400MHz) δ 7.47–7.49 (m, 2 H), 7.20–7.25 (m, 4 H), 7.11–7.14 (m, 2 H), 4.86 (d, $J=6.0$ Hz, 1 H), 4.28 (t, $J=6.0$ Hz, 1 H), 4.15 (td, $J=8.5, 5.0$ Hz, 1 H), 3.86 (td, $J=8.5, 6.9$ Hz, 1 H), 2.56–2.63 (m, 2 H), 2.47–2.53 (m, 1 H), 2.43 (s, 3 H), 2.16–2.24 (m, 1 H), 1.90–1.98 (m, 1 H); ^{13}C NMR (CDCl_3 , 150MHz) δ 143.5, 137.1, 136.1, 133.2, 129.6, 128.6, 127.1, 126.8, 81.3, 67.2, 43.7, 42.5, 29.7,

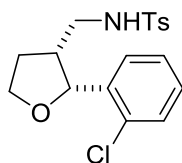
21.5; IR (Neat) 2869, 2356, 1491, 1328, 1158 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{21}\text{ClNO}_3\text{S}$ ($\text{M}+\text{H}$)⁺ 366.0931, found 366.0936.

trans-*N*-((-2-(4-chlorophenyl)tetrahydrofuran-3-yl)methyl)-4-methylbenzenesulfonamide (*trans*-**24e**)



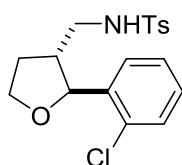
Colorless oil. $[\alpha]_{\text{D}}^{20} = +1.3$ (c 1.0, CHCl_3 , 33% ee). ^1H NMR (CDCl_3 , 400MHz) δ 7.69 (d, $J=8.2$ Hz, 2 H), 7.27–7.31 (m, 4 H), 7.18 (d, $J=8.2$ Hz, 2 H), 4.57 (t, $J=6.4$ Hz, 1 H), 4.47 (d, $J=6.4$ Hz, 1 H), 4.04–4.10 (m, 1 H), 3.92–3.97 (m, 1 H), 2.98–3.09 (m, 2 H), 2.44 (s, 3 H), 2.09–2.21 (m, 2 H), 1.72–1.79 (m, 1 H); ^{13}C NMR (CDCl_3 , 150MHz) δ 143.7, 140.2, 136.6, 133.4, 129.8, 128.7, 127.4, 127.0, 83.1, 67.7, 47.7, 44.8, 30.1, 21.5; IR (Neat) 3279, 2871, 1491, 1327, 1158, 1328, 1159, 816 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{21}\text{ClNO}_3\text{S}$ ($\text{M}+\text{H}$)⁺ 366.0931, found 366.0937.

cis-*N*-((-2-(2-chlorophenyl)tetrahydrofuran-3-yl)methyl)-4-methylbenzenesulfonamide (*cis*-**24f**)



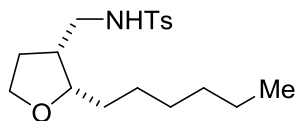
Colorless oil. $[\alpha]_{\text{D}}^{20} = +29.7$ (c 0.9, CHCl_3 , 65% ee). ^1H , ^{13}C NMR, IR spectra and HRMS analyses were consistent with the previously reported data.³⁵

trans-*N*-(2-(2-chlorophenyl)tetrahydrofuran-3-yl)methyl)-4-methylbenzenesulfonamide (*trans*-**24f**)



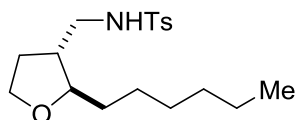
Colorless plates. M.p. 95–96 °C. $[\alpha]_{\text{D}}^{20} = +9.0$ (c 1.8, CHCl_3 , 47% ee). ^1H NMR (CDCl_3 , 400MHz) δ 7.71–7.74 (m, 2 H), 7.38 (dd, $J=7.6$, 1.6 Hz, 1 H), 7.29–7.31 (m, 2 H), 7.18–7.28 (m, 2 H), 4.90 (d, $J=4.6$ Hz, 1 H), 4.83 (t, $J=6.6$ Hz, 1 H), 4.17–4.23 (m, 1 H), 4.00 (d, $J=7.8$ Hz, 1 H), 3.18–3.24 (m, 1 H), 3.03–3.10 (m, 1 H), 2.43 (s, 3H), 2.27–2.32 (m, 1 H), 2.01–2.10 (m, 1 H), 1.88–1.96 (m, 1 H); ^{13}C NMR (CDCl_3 , 150MHz) δ 143.5, 139.8, 136.7, 131.5, 129.8, 129.4, 128.6, 127.2, 127.1, 127.0, 80.5, 68.1, 47.1, 44.8, 28.7, 21.5; IR (Neat) 3371, 2921, 1591, 1415, 1120, 1037 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{20}\text{ClNO}_3\text{SNa}$ ($\text{M}+\text{Na}$)⁺ 388.0750, found 388.0756.

cis-*N*-((2-hexyltetrahydrofuran-3-yl)methyl)-4-methylbenzenesulfonamide (*cis*-**24h**)



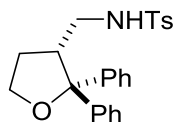
$[\alpha]_D^{20} = -0.8$ (c 1.0, CHCl₃, 71% ee). ¹H, ¹³C NMR, IR spectra and HRMS were consistent with the previously reported data.³⁵

trans-*N*-((2-hexyltetrahydrofuran-3-yl)methyl)-4-methylbenzenesulfonamide (*trans*-**24h**)



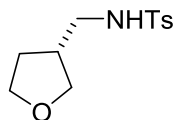
Colorless oil. $[\alpha]_D^{20} = +4.3$ (c 2.0, CHCl₃, 33% ee). ¹H NMR (CDCl₃, 400MHz) δ 7.76 (d, *J*=8.2 Hz, 2 H), 7.32 (d, *J*=7.8 Hz, 2 H), 4.87 (t, *J*=6.4 Hz, 1 H), 3.77–3.81 (m, 1 H), 3.71 (td, *J*=8.1, 6.2 Hz, 1 H), 3.43 (q, *J*=6.0 Hz, 1 H), 2.95–3.02 (m, 1 H), 2.85–2.90 (m, 1 H), 2.44 (s, 3 H), 1.94–2.03 (m, 2 H), 1.58–1.63 (m, 1 H), 1.34–1.43 (m, 3 H), 1.20–1.30 (m, 7 H), 0.87 (t, *J*=6.9 Hz, 3 H); ¹³C NMR (CDCl₃, 150MHz) δ 143.5, 136.7, 129.8, 127.1, 82.2, 66.4, 45.9, 44.2, 34.9, 31.8, 30.2, 29.3, 26.1, 22.6, 21.5, 14.1; IR (Neat) 3272, 2857, 1599, 1455, 1327, 1160, 814, 662 cm⁻¹; HRMS (ESI) *m/z* calcd for C₁₈H₃₀NO₃S (M+H)⁺ 340.1946, found 340.1939.

N-((2,2-diphenyltetrahydrofuran-3-yl)methyl)-4-methylbenzenesulfonamide (**24i**)



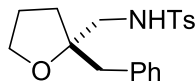
$[\alpha]_D^{20} = -61.2$ (c 0.9, CHCl₃, 48% ee). ¹H, ¹³C NMR, IR spectra and HRMS were consistent with the previously reported data.³⁵

4-Methyl-*N*-((tetrahydrofuran-3-yl)methyl)benzenesulfonamide (**24j**)



$[\alpha]_D^{20} = -6.3$ (c 1.7, CHCl₃, 48% ee). ¹H, ¹³C NMR, IR spectra and HRMS were consistent with the previously reported data.³⁶

N-((2-benzyltetrahydrofuran-2-yl)methyl)-4-methylbenzenesulfonamide (**27**)



Colorless oil. ^1H NMR (CDCl_3 , 400MHz) δ 7.72 (d, $J=8.2$ Hz, 2 H), 7.30 (d, $J=8.7$ Hz, 2 H), 7.19–7.25 (m, 3 H), 7.15 (dd, $J=7.6, 1.6$ Hz, 2 H), 4.67 (t, $J=6.2$ Hz, 1 H), 3.65–3.74 (m, 2 H), 2.84–2.96 (m, 2 H), 2.74–2.81 (m, 2 H), 2.43 (s, 3 H), 1.76–1.86 (m, 3 H), 1.57–1.64 (m, 2 H), 1.21–1.30 ppm (m, 7 H). ^{13}C NMR (CDCl_3 , 150MHz): δ = 143.4, 136.9, 136.6, 130.4, 129.7, 128.1, 127.0, 126.5, 84.0, 68.6, 49.7, 43.3, 32.2, 26.2, 21.5. IR (Neat) 3266, 2924, 2854, 1737, 1493, 1457, 1332, 1261, 1161, 1089, 1033, 810 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{19}\text{H}_{23}\text{NNaO}_3\text{S}$ ($\text{M}+\text{Na}$) $^+$ 368.1294, found 368.1296.

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