ABSTRACT

Title of Document: Selective [3+2] and [3+3]-Cycloaddition Reactions of Nitrones

Xiaochen Wang, Doctor of Philosophy, 2012

Directed By: Professor Michael P. Doyle, Department of Chemistry and Biochemistry

Cationic chiral dirhodium(II,III) carboxamidates, obtained from the oxidation of the corresponding dirhodium(II,II) carboxamidates by nitrosonium salts, are efficient promoters in asymmetric Lewis acid catalyzed reactions. High regiocontrol and stereocontrol have been achieved with the cationic chiral dirhodium(II,III) carboxamidate whose ligand is (*R*)-menthyl (*S*)-2-oxopyrrolidine-5-carboxylate in 1,3-dipolar cycloaddition reactions of nitrones with α,β-unsaturated aldehydes. In addition, higher rates and selectivities have been obtained in hetero-Diels-Alder and carbonyl-ene reactions with the diastereomeric catalyst having the (*S*)-menthyl (*S*)-2-oxopyrrolidine-5-carboxylate ligand. Dramatic solvent influences on reaction rates and selectivities characterize the catalysis of cationic chiral dirhodium(II,III) carboxamidates, and these influences are explained by competitive coordination of solvent to catalyst and by the influenced coordination angle of the aldehyde substrate relative to catalyst by the solvent environment.

Rhodium vinylcarbenes, generated from the reactions between vinyldiazoacetates and dirhodium catalysts, are highly reactive intermediates. Through reacting rhodium vinylcarbenes with nitrones, we have discovered a [3+3]-cycloaddition pathway; and by using chiral dirhodium carboxylates as the catalysts, a highly enantioselective [3+3]-cycloaddition of nitrones with vinyldiazoacetates has been achieved. The products of this [3+3]-cycloaddition are 3,6-dihydro-1,2-oxazines, which are versatile intermediates for the synthesis of α-substituted β-amino acids and related compounds that are not easily accessible by other methods. The broad scope of cyclic and acylic nitrones that are applied demonstrates the power of this methodology. The limitation of this [3+3]-cycloaddition methodology is the requirement of using the β-TBSO-substituted vinyldiazo compounds as the rhodium vinylcarbene precursors.

Although vinyldiazoacetates without the β-TBSO substituent are not reactive for the [3+3]-cycloaddition with nitrones, we have discovered an alternative reaction pathway with an unsubstituted vinyldiazoacetate. The reaction occurs with a dirhodium vinylcarbene-induced [3+2] nitrone cycloaddition, followed by subsequent cascade carbenoid aromatic cycloaddition/N-O cleavage and rearrangement. In this cascade process, both the [3+2]-cycloaddition of nitrones with a rhodium vinylcarbene and the [1,7]-oxygen migration with N-O cleavage are unprecedented in the literature. The complexity of the reaction pathway and the uniqueness of the formed heterocyclic products are of great interest to synthetic chemists.

SELECTIVE [3+2] AND [3+3]-CYCLOADDITION REACTIONS OF NITRONES

By

Xiaochen Wang

Dissertation submitted to the Faculty of the Graduate School of the
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Advisory Committee:
Professor Michael P. Doyle, Chair
Professor Andrei Vedernikov
Professor Herman O. Sintim
Professor Lyle Isaacs
Professor Liangli Yu

Dedication

This dissertation is dedicated to my parents Hong Chen and Huo Wang who through their constant love and support have encouraged me to succeed in the graduate career.

Acknowledgements

Now I am at the finishing line of my 5-year journey to a PhD degree. Looking back at what I have experienced since my flight to the United States landed at the Dulles International Airport on Aug 9, 2007, I would like to say that the journey to a PhD degree is a tough one, especially for a student like me who came from a foreign country. If it weren't for the support from many people, I would never reach the point where I am today. Here, I would like to express my deepest gratitude to all the people who have helped me during my stay in Maryland.

First of all, I would like to thank Professor Michael P. Doyle for mentoring me throughout my graduate career. Mike is such an energetic research advisor that, he replies my emails within seconds after I send him mine, and he gets revision of a manuscript back to me within days after I send him a draft. I have learnt from him not only the knowledge about chemistry, but also the way of being a successful independent researcher. Mike's constant demands for improvement and thoughtful criticisms have helped me to discover more and more potential from myself, and his encouragements for new ideas have really brought me a fruitful graduate career. His passion about science will always inspire me in my future career.

I would also like to thank Professor Qi-Lin Zhou, who was my undergraduate mentor at Nankai University in China. He is the person who showed me the beauty of the real-world research. I benefit a lot from his advice both on my research and on my career.

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For members of the Doyle group, I would like to give my special thank to Dr. Xinfang Xu who partnered with me in the project that led to the publication of my second *JACS* paper. Through the collaboration, my research area was expanded, and this expansion has brought me several high-impact publications. Also, Xinfang's optimistic attitude toward research has encouraged me a lot. I am also grateful to the help from other members of the Doyle group including Dr. Yu Liu, Dr. Jian-hua Xie, Dr. Richard Duffy, Dr. Dmitry Shabashov, Dr. Kan Wang, Dr. Lei Zhou, Dr. Deana Jaber, Dr. Ryan Burgin, Dr. Charles Shanahan, Maxim Ratnikov, Xichen Xu, Phong Truong and Yu Qian.

I would like to acknowledge my roommates Jia Liu and Yu Gu, who came to the United States with me on the same flight and shared an apartment with me since then. I am feeling really lucky to have these tolerant and considerate roommates for the last four and a half years. Now, they are also approaching the finishing line for a PhD degree. I wish them good luck.

Finally, I would like to thank all my family, especially my mother Hong Chen and my father Huo Wang. Their love has guided me through my life.

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List of Abbreviations

Ar	aromatic
Bn	benzyl
^{t}Bu	*tert*-butyl
CAP	caprolactamate
DCM	dichloromethane
DCE	1,2-dichloroethane
DOSP	(*N*-dodecylbenzenesulfonyl)prolinate
dr	diastereomeric ratio
EDA	ethyl diazoacetate
ee	enantiomeric excess
Et	ethyl
Et_3N	triethylamine
EtOAc	ethyl acetate
equiv	equivalent
h	hour
IPPy	pyrrolidine-4-carboxylic acid isopropyl ester
Me	methyl
MEPY	pyrrolidine-4-carboxylic acid methyl ester
MenPy	pyrrolidine-4-carboxylic acid menthyl ester
ML_n	transition metal with ligands
MS	molecular sieves

NMR	nuclear magnetic resonance
NTTL	1,8-napthaloyl-tert-leucinate
NTA	1,8-napthaloylalaninate
OAc	acetate
Oct	octanoate
PTTL	phthaloyl-tert-leucinate
PTA	phthaloylalaninate
PTPA	phthaloylphenylalaninate
Ph	phenyl
^{i}Pr	*iso*-propyl
RT	room temperature
TBS	*tertiary*-butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
TPA	triphenylacetate

Chapter 1

Cationic Chiral Dirhodium Carboxamidates as Lewis Acids

I. Introduction

1.1 Dirhodium(II) Carboxylates and Dirhodium(II) Carboxamidates

Dirhodium(II) compounds have played an important role in the development of catalytic synthetic methodology in organic chemistry. Since the discovery of rhodium acetate [$Rh_2(OAc)_4$] (Figure 1.1) as a catalyst for the decomposition of ethyl diazoacetate in the 1970s,[1] syntheses of dirhodium carboxylates and their catalytic activities in the chemistry involving diazo compounds (Scheme 1.1) have been well studied.[2]

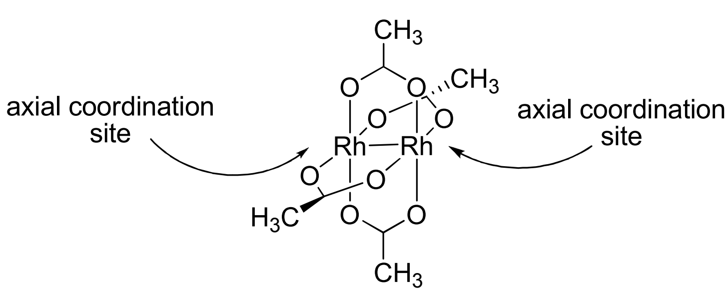
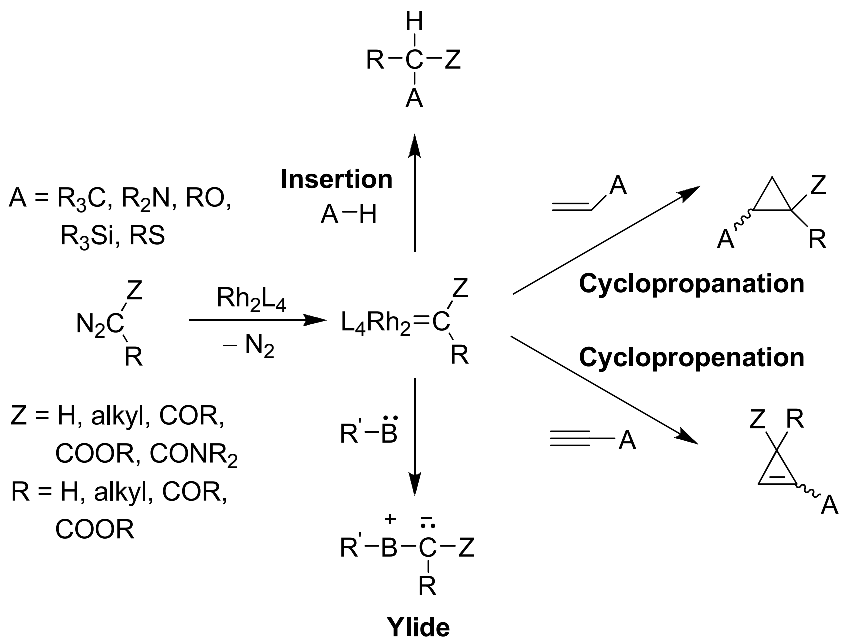
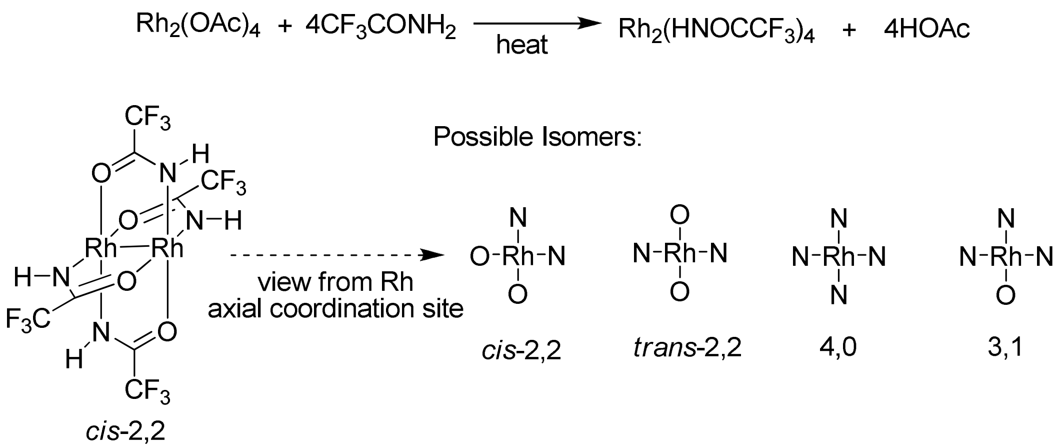


Figure 1.1 Structure of Rhodium Acetate.



Scheme 1.1 Dirhodium(II) Compounds Catalyzed Reactions Involving the Generation of the Rhodium Carbenes from Diazo Compounds.

Different from dirhodium(II) carboxylates, dirhodium(II) carboxamidates are dirhodium compounds that are substituted with amides. The first synthesis of a dirhodium(II) carboxamidate occurred in the 1980s when dirhodium(II) tetra(trifluoroacetamidate) was isolated from a melt of trifluoroacetamide containing $Rh_2(OAc)_4$ (Scheme 1.2).[3] Multiple isomers [(*cis*-2,2), (*trans*-2,2), (4,0) and (3,1)] are possible, but the one in which two nitrogens and two oxygens are bound to each rhodium with the two *cis* nitrogens (the *cis*-2,2 isomer) is the only isomer produced. After that, various dirhodium(II) carboxamidates were prepared and found active in the catalysis with diazo compounds.[2,4]



Scheme 1.2 Synthesis of Dirhodium(II) Tetra(trifluoroacetamidate).

1.2 Chiral Dirhodium(II) Carboxylates and Chiral Dirhodium(II) Carboxamidates

Due to the high demand of the enantioselective variants of the reactons involving dirhodium catalysis, chiral dirhodium(II) carboxylates and chiral dirhodium(II) carboxamidates have been developed.[4] Davies and Hashimoto have made great contributions to the development of chiral dirhodium(II) carboxylates. Davies with *N*-sulfonyl-(*S*)-proline as the bridging ligands[5] and Hashimoto with *N*-phthaloyl-(*S*)-amino acids as the bridging ligands[6] developed a series of chiral dirhodium(II) carboxylates (Figure 1.2) that provide constantly high turnover numbers and enantiocontrol in cyclopropanation, C-H insertion and ylide transformation reactions with diazo compounds.[4,7]

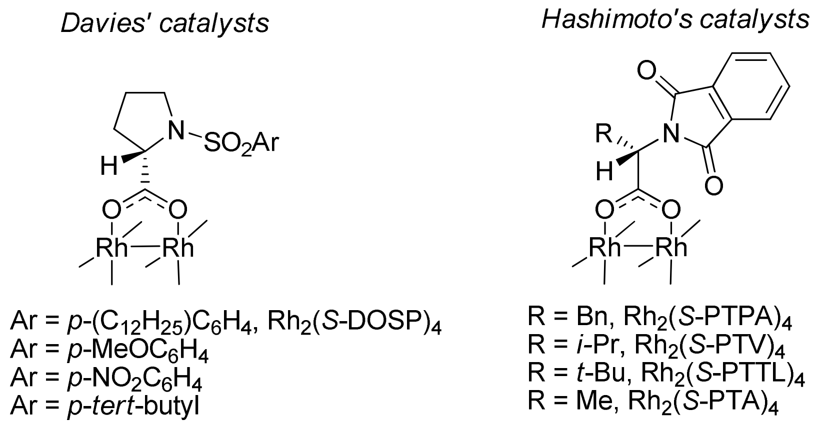


Figure 1.2 Chiral Dirhodium(II) Carboxylates Developed by Davies and Hashimoto.

Our group has developed the syntheses of chiral dirhodium(II) carboxamidates (See examples in Figure 1.3) by the substitution of the acetate ligands in rhodium acetate with chiral lactams.[8] Similar to the formation of dirhodium(II) tetra(trifluoroacetamidate) (Scheme 1.2), the *cis*-2,2 isomer is formed dominantly or exclusively in each preparation. When the other isomers are formed as the minor products, column chromatography will successfully isolate the pure *cis*-2,2 isomer. Therefore, every chiral dirhodium(II) carboxamidate we describe in this dissertation and anywhere else, except specified, is only the *cis*-2,2 isomer.

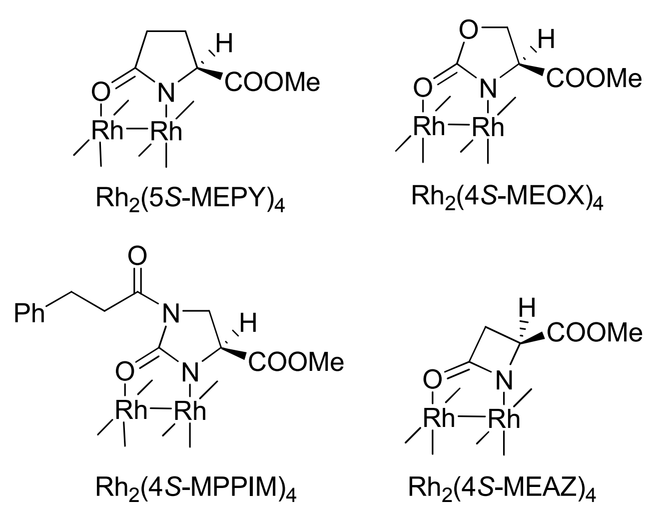
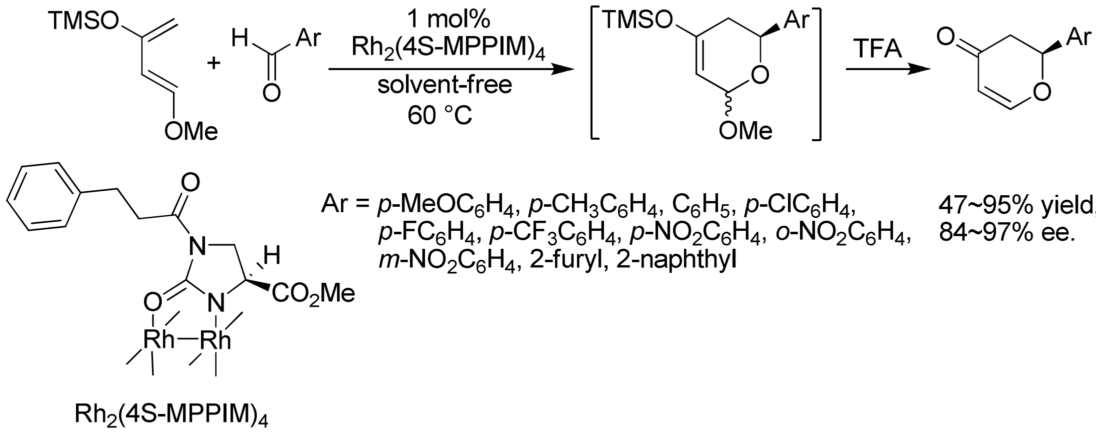


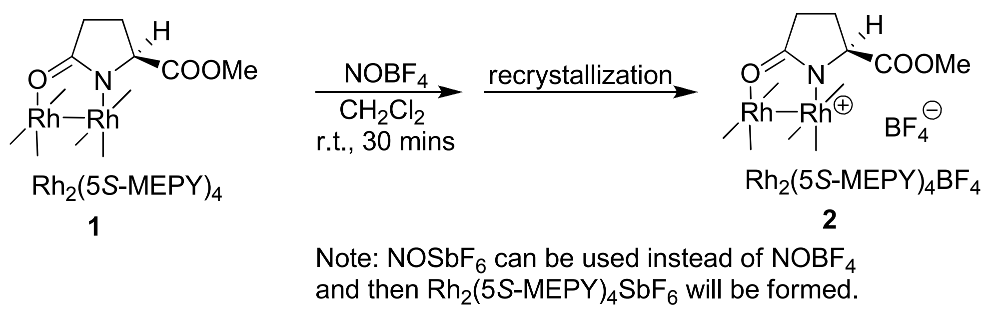
Figure 1.3 Examples of Chiral Dirhodium(II) Carboxamidates.

1.3 Previous Achievements on the Use of Chiral Dirhodium(II) Carboxamidates as the Lewis Acids and the Disovery of Cationic Dirhodium(II,III) Carboxamidates

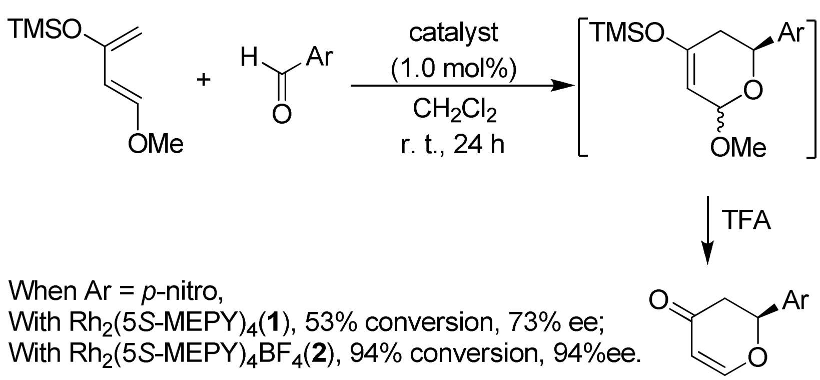
Chiral dirhodium(II) carboxamidates are powerful catalysts for organic transformations. Besides their extensive application in catalytic asymmetric reactions of diazo compounds,[4,7] potential uses in Lewis acid catalysis have been demonstrated in hetero-Diels-Alder reactions, which occur with high turnover numbers and excellent enantioselectivities (Scheme 1.3).[9] However, due to the weak Lewis acidity of dirhodium(II) carboxamidates, their activation of aldehydes by coordination is relatively poor. As a result, a relatively high reaction temperature (60 °C in Scheme 1.3) is necessary to achieve a reasonable reaction rate for the hetero-Diels-Alder reaction.[9] The weak Lewis acidity has also limited their application to other Lewis acid catalyzed reactions. To enhance the Lewis acidity, a convenient oxidation of dirhodium(II) carboxamidates with nitrosonium salts was developed by Dr. Wang in our group to produce cationic dirhodium(II,III) compounds (**1** to **2** in Scheme 1.4).[10] Enhanced Lewis acidity of dirhodium(II,III) compounds has been demonstrated by the increased reaction rates and the improved enantioselectivities in the hetero-Diels-Alder reactions by the comparison with the results from the catalysis of dirhodium(II) carboxamidates (Scheme 1.5).[10] However, the oxidation potential of nitrosonium salts limits the scope of the dirhodium(II,III) compounds. Some dirhodium(II) carboxamidates, like $Rh_2(4S\text{-}MPPIM)_4$ (in Scheme 1.3), were unable to be oxidized by nitrosonium salts.



Scheme 1.3 Rh_2(4*S*-MPPIM)$_4$-Catalyzed Hetero-Diels-Alder Reactions of Aldehydes with trans-1-Methoxy-3-(Trimethysilyloxy)-1,3-Butadiene.

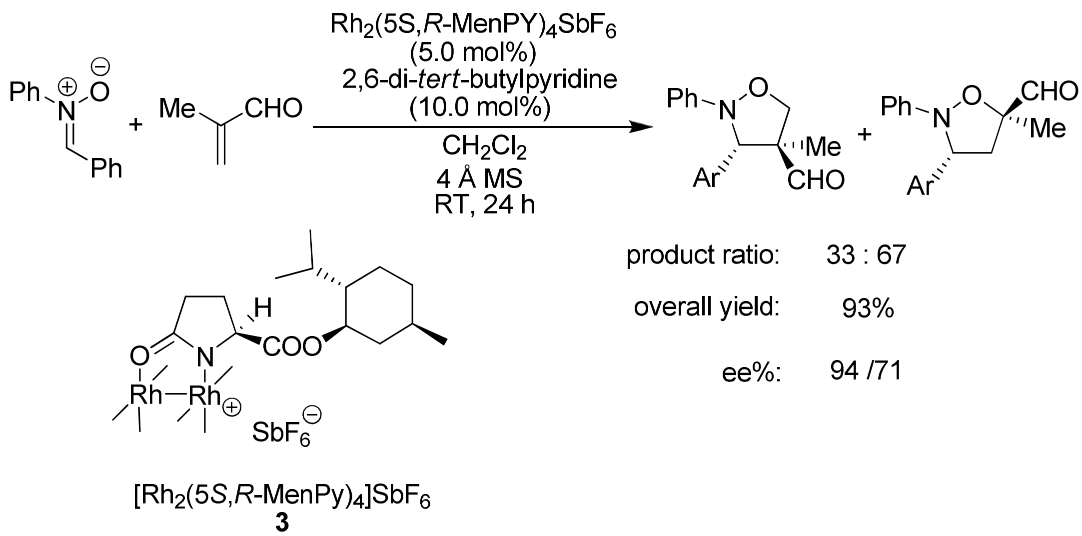


Scheme 1.4 Preparation of Rh_2(5*S*-MEPY)$_4BF_4$ from oxidation of Rh_2(5*S*-MEPY)$_4$ by Nitrosonium Tetrafluoroborate.



Scheme 1.5 Comparison of the Catalytic Efficiency between Rh_2(5*S*-MEPY)$_4$ (**1**) and Rh_2(5*S*-MEPY)$_4BF_4$ (**2**) in the Hetero-Diels-Alder Reaction.

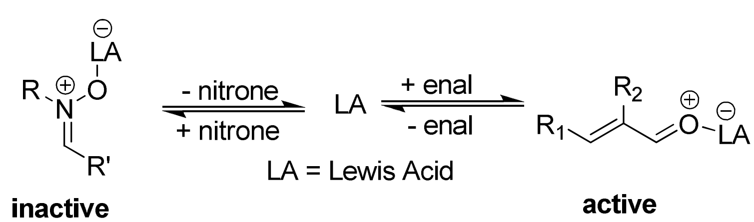
The ability of chiral dirhodium(II,III) carboxamidates to catalyze asymmetric dipolar cycloaddition reactions of α,β-unsaturated aldehydes with nitrones yielding isoxazolidines in high enantioselectivities was an important discovery by previous group members.[10] Isoxazolidines are convenient precusors to β-amino acids, βlactams, and γ-amino alcohols;[11] and the catalytic asymmetric dipolar cycloaddition reactions of nitrones with electron-deficient alkenes has been a challenge in terms of regio- and stereocontrol.[12] The chiral dirhodium(II,III) carboxamidate catalyst $[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ (**3**), which exhibited preferential binding to the aldehyde rather than the nitrone, provided high enantioselectivities and modest regiocontrol in reactions of *N*,α-diphenylnitrone with methacrolein (Scheme 1.6).[10]



Scheme 1.6 $[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ Catalyed Asymmetric Dipolar Cycloaddition Reaction of *N*,α-diphenylnitrone with Methacrolein.

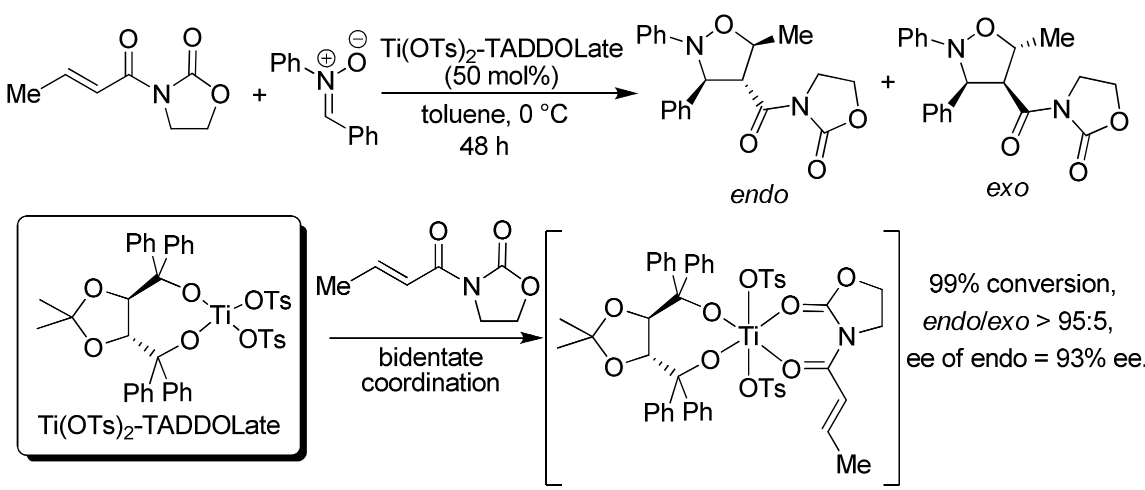
1.4 Limitations on the Asymmetric Nitrone Dipolar Cycloaddition Reactions

The development of catalytic asymmetric methodology of the nitrone dipolar cycloaddition reaction with electron-deficient alkenes has been a challenge.[12] One problem with the Lewis acid activation of α,β-unsaturated carbonyl compounds in the dipolar cycloaddition reactions is the competitive coordination of the dipolar compounds to Lewis acid catalysts, and the coordination slows down or even shuts down the catalytic reaction (Scheme 1.7).[13] To overcome this problem, bidentate dipolarophiles such as those derived from oxazolidinones that provide two-point binding to the chiral Lewis acid were introduced to the cycloaddition process with nitrones because the two-point binding provided by the dipolarophile is stronger than the one point binding of the nitrone to the catalyst.[13] Using this strategy, Jørgensen developed the titanium(IV)-TADDOLate catalyzed dipolar cycloaddition reaction of *N*,α-diphenylnitrone with the dipolarophile functionalized by oxazolidinone which provided high preference for the *endo* product in 93% ee (Scheme 1.8);[14] this was the first example of the catalytic dipolar cycloaddition of nitrones with the α,β-unsaturated carbonyl compounds proceeding with more than 90% ee. After further studies[15] on Lewis acids that provide two-point binding sites, Kanemasa's nickel(II)-bisoxazoline catalyst [$Ni(ClO_4)_2$-(*R*,*R*)-DFBOX] [15d] turned out to be the most efficient one. With 10 mol% of $Ni(ClO_4)_2$-(*R*,*R*)-DFBOX, the reaction between *N*-benzyl-α-phenylnitrone and the oxazolidinone-derived α,β-unsaturated carbonyl compound produced the *endo* cycloaddition product exclusively in 76% yield and 95% ee (Scheme 1.9).[15d]



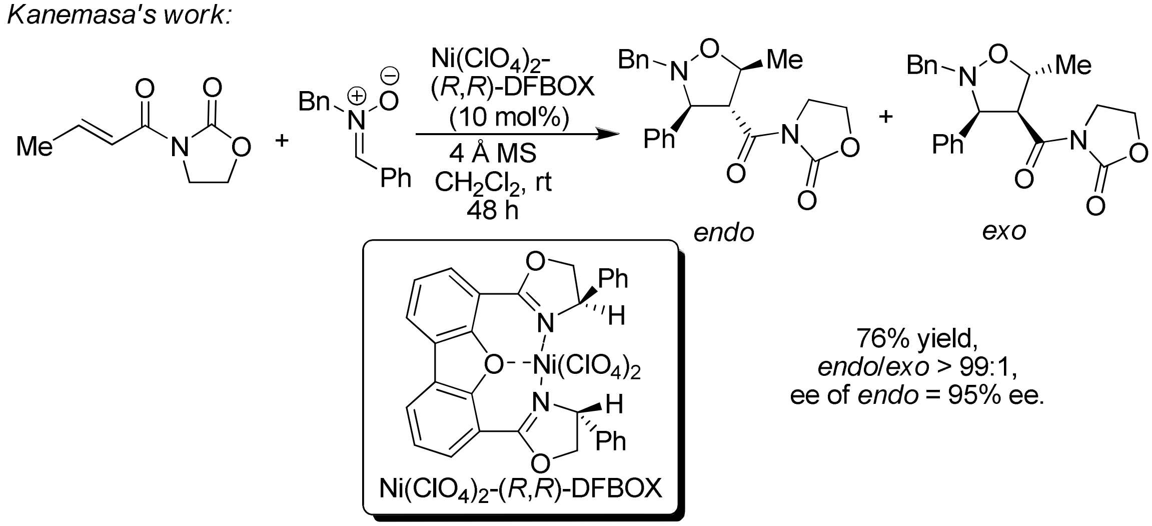
Scheme 1.7 Reaction Inhibition by Competitive Coordination of Nitrones to the Lewis Acids.

Jørgensen's work:



Scheme 1.8 Ti(OTs)$_2$-TADDOLate Catalyzed Dipolar Cycloaddition Reaction of *N*,α-Diphenylnitrone with the Dipolarophile Functionalized by Oxazolidinone.

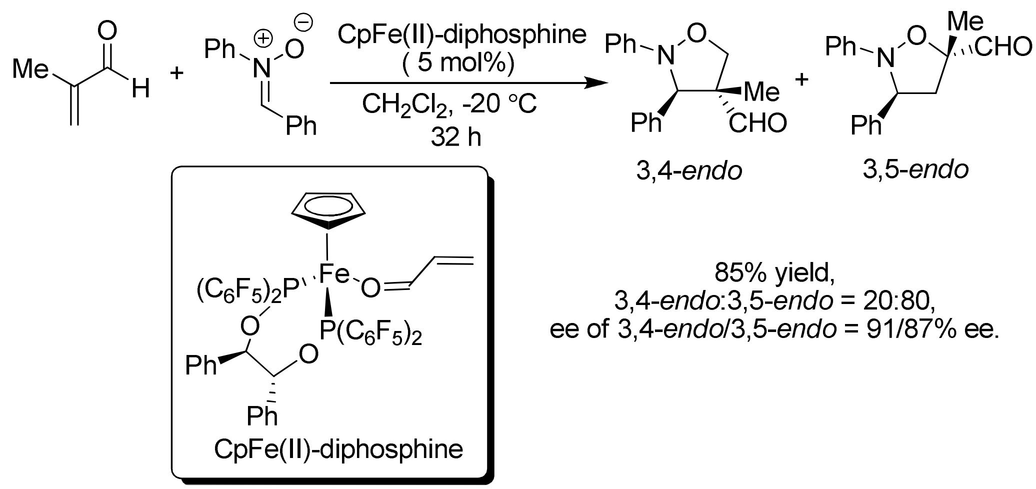
Kanemasa's work:



Scheme 1.9 Ni(ClO$_4$)$_2$-(*R*,*R*)-DFBOX Catalyed Dipolar Cycloaddition Reaction of *N*-Benzyl-α-phenylnitrone with the Dipolarophile Functionalized by Oxazolidinone.

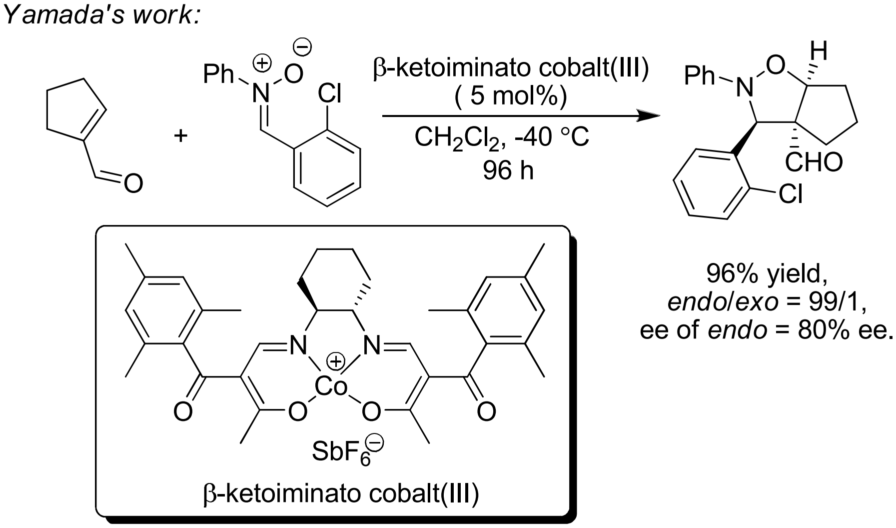
However, the requirement of handling the auxiliary as well as the high catalyst loading of 10~50 mol% makes this methodology less attractive. Although use of monodentate dipolarophiles (e.g., methacrolein in Scheme 1.6) would be ideal, there have been few examples of success. Besides the inhibition of the catalytic reaction by the nitrone coordination to Lewis acids, lack of regiocontrol has also become a barrier for the application of the α,β-unsaturated aldehydes as the dipolarophile. The first breakthrough was made by Kündig, who prepared a CpFe(II)-diphosphine catalyst for the dipolar cycloaddition reaction of *N*,α-diphenylnitrone with methacrolein.[16] With 5 mol% catalyst, the 3,4-*endo* and the 3,5-*endo* isomers were produced in a ratio of 20:80 with complete diastereocontrol, and the enantiomeric excesses were 91% ee and 87% ee (Scheme 1.10). Shortly after Kündig's work was published, Yamada reported the complete regiocontrol with β-ketoiminato cobalt(III) catalyst for the transformation between diarylnitrones and 1-cyclopentene-1-carbaldehyde (Scheme 1.11),[17] but complete regiocontrol relied on the choice of 1-cyclopentene-1-carbaldehyde as the substrate, and high enantiocontrol was only observed for several nitrones having *ortho*-substitution on the α-Ar ring. Later, Carmona developed the Cp*Rh(III)-diphosphine catalyst and used this catalyst to investigate the dipolar cycloaddition reaction previously studied by Kündig (Scheme 1.12).[18] Interestingly, the 3,4-regioisomer was favored with Carmona's catalyst, which was opposite to the results from Kündig. Kanemasa also applied his $Ni(ClO_4)_2$-(*R*,*R*)-DFBOX catalyst to dipolar cycloaddition with methacrolein.[19] Although high enantiomeric excesses were obtained with Kanemasa's catalyst, regioselectivities were very poor (Scheme 1.12). More recently, Maruoka prepared a μ-oxo bis-Ti(IV) oxide catalyst ligated with chiral BINOLs, and found that this catalyst efficiently catalyzed the reaction between *N*-benzyl-α-phenylnitrone and acrolein yielding the 3,4-*endo* product in excellent selectivities (Scheme 1.13).[20] Before the current work with chiral dirhodium catalysis, Maruoka's μ-oxo bis-Ti(IV) oxide catalyst was the most efficient catalyst in the cycloaddition reactions of nitrones with enals, although results were not reported from the reactions with *N*,α-diphenylnitrone to make the direct comparison with Kündig's and Carmona's catalysts.

Kündig's work:

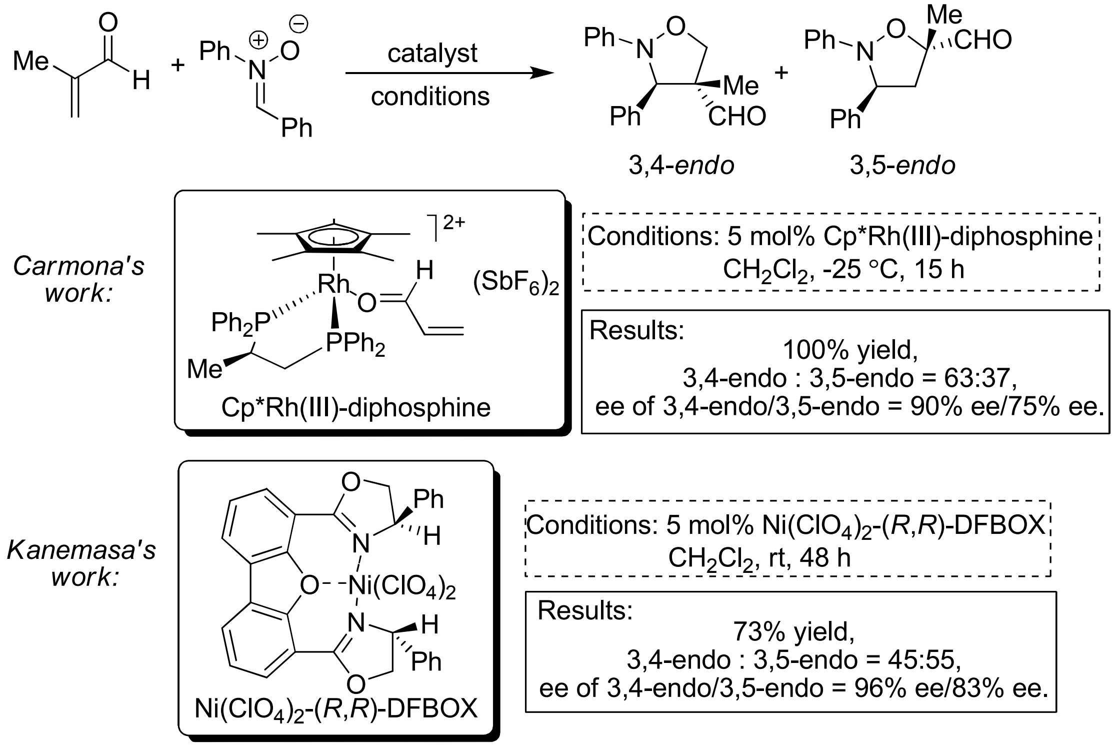


Scheme 1.10 CpFe(II)-diphosphine Catalyzed Cycloaddition Reaction of *N*,α-Diphenylnitrone with Methacrolein.

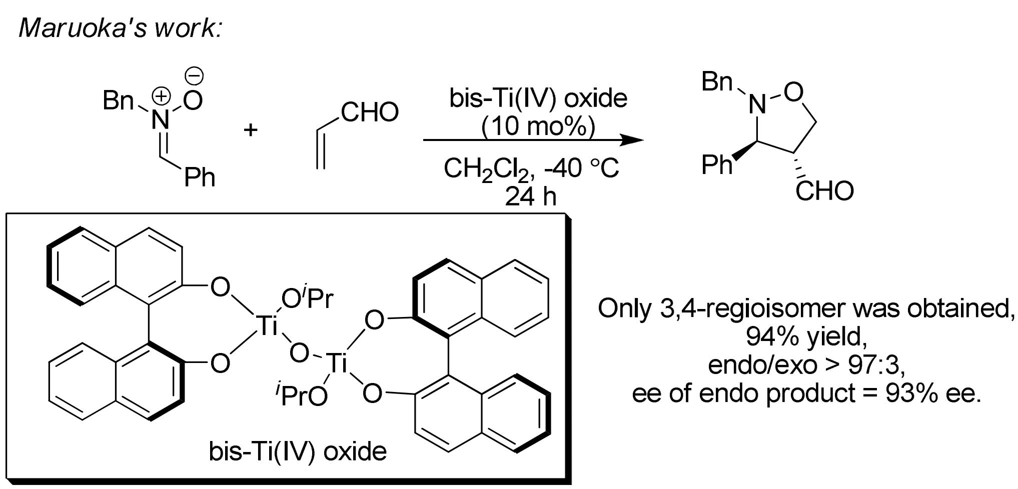
Yamada's work:



Scheme 1.11 β-Ketoiminato Cobalt(III) Catalyzed Dipolar Cycloaddition Reactions of the Nitrone with the Enal.



Scheme 1.12 Carmona's Rh(III) catalyst and Kanemasa's Ni(II) catalyst in the Dipolar Cycloaddition Reaction of *N*,α-Diphenylnitrone with Methacrolein.



Scheme 1.13 Bis-Ti(IV) oxide Catayzed Reaction between *N*-Benzyl-α-phenylnitrone and Acrolein.

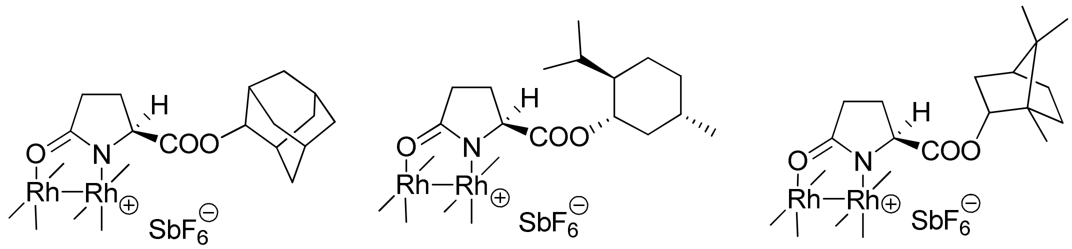
1.5 My Research Goal

With the preliminary success from previous group members on the dipolar cycloaddition reactions of diarylnitrones with methacrolein catalyzed by chiral dirhodium(II,III) carboxamidate catalysts (Scheme 1.6),[10] I and my colleagues sought to design a new chiral dirhodium(II,III) carboxamidate catalyst or find a different set of reaction conditions to achieve enhanced product selectivities and a broad substrate scope in nitrone dipolar cycloaddition reactions with α,β-unsaturated aldehydes. If successful, we would apply the chiral dirhodium(II,III) carboxamidate catalysts to other Lewis acid catalyzed reactions.

II. Results and Discussion

2.1 Initial Attempts with New Chiral Dirhodium(II,III) Carboxamidates

To improve the selectivities of the dipolar cycloaddition reactions of nitrones with α,β-unsaturated aldehydes, we prepared a new set of catalysts which incorporated *S*-pyroglutamic acid esters as the ligands (Figure 1.4). These catalysts are all analogs of $[Rh_2(5S,R\text{-MenPy})_4]SbF_6$, with which the preliminary result was obtained. The ester part of $[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ was changed to 2-adamantyl, (+)-menthyl and (*S*)-bornyl to produce $[Rh_2(5S\text{-AdPy})_4]SbF_6$, $[Rh_2(5S,S\text{-MenPy})_4]SbF_6$ and $[Rh_2(5S,S\text{-BornPy})_4]SbF_6$. However, these catalysts did not show better selectivities than $[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ (results are partially disclosed in Table 1.1 in section 2.2). Then, we decided to look at the possibilities of further optimization on the reaction conditions.



$[Rh_2(5S\text{-AdPy})_4]SbF_6$ $[Rh_2(5S,S\text{-MenPy})_4]SbF_6$ $[Rh_2(5S,S\text{-BornPy})_4]SbF_6$

Figure 1.4 New Chiral Dirhodium(II,III) Carboxamidate Catalyts

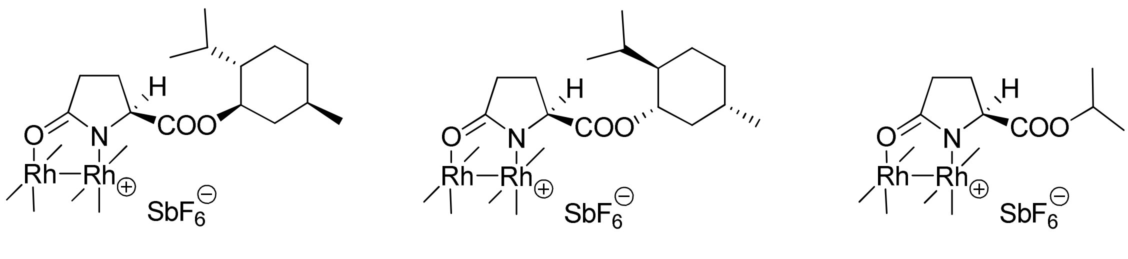
2.2 Observation of Solvent Effect

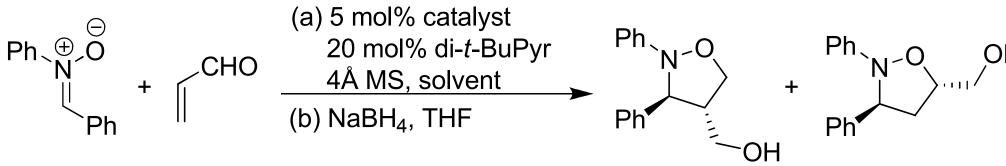
Previous group members surveyed catalysts and the reaction temperature, and they found that $[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ was the best catalyst and room temperature of 23 °C provided the optimum selectivities with fast reaction rate. However, the solvent was never optimized because of three reasons: 1) the earliest chiral dirhodium(II,III) carboxamidate, $Rh_2(5S\text{-MEPY})_4BF_4$, is only soluble in chlorocarbon solvents, so the previous workers did not expect any of the cationic chiral dirhodium(II,III) carboxamidates to be soluble in non-polar solvents; 2) diarylnitrones are very soluble in chlorocarbon solvents but only moderately soluble in non-polar solvents; 3) the other groups who worked on the nitrone dipolar cycloaddition reactions with α,β-unsaturated aldehydes only reported dichloromethane as the reaction solvent presumably indicating the absence of solvent effect in their systems.[16–20] However, we found that $[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ and all the catalysts in Figure 1.4 were all very soluble in non-polar solvents probably due to the low polarity of the bulky hydrocarbon ester in each ligand. Screening of the reaction solvents revealed a substantial solvent effect for the dipolar cycloaddition reactions of nitrones with α,β-unsaturated aldehydes catalyzed by chiral dirhodium(II,III) carboxamidates.

Nitrone cycloaddition reactions were performed by preparing the [Rh_2(5*S*,*R*-MenPy)$_4$]SbF_6 (**3**) catalyst from its dirhodium(II,II) precursor Rh_2(5*S*,*R*-MenPy)$_4$ *in situ* by treatment with nitrosonium hexafluoroantimonate in the presence of 2,6-di-*tert*-butylpyridine and 4 Å molecular sieves in the reaction solvent, then sequentially adding the α,β-unsaturated aldehyde and nitrone. With 5 mol % of **3** in dichloromethane at 0 °C the cycloadducts of acrolein and *N*,α-diphenylnitrone were obtained after 5 h that, following borohydride reduction, were analyzed as a 70:30 ratio of 3,4-(**6**):3,5-(**7**) regioisomers in 73% isolated yield (eq 1). The diastereomeric ratio of 3,4-*endo* (**6**-*endo*) to 3,4-*exo* product was 92:8, and **6**-*endo* was obtained with 78% ee. In an effort to improve selectivity by variation of the solvent, we were surprised to discover an exceptionally large influence of reaction solvent on reactivity and selectivity (Table 1.1). Changing the reaction solvent from dichloromethane to chloroform resulted in a slight increase in regio- and enantiocontrol, but percent conversion over the same reaction time decreased dramatically. The non-aromatic hydrocarbon cyclohexane increased the regio- and enantiocontrol dramatically, and also the reaction rate. Monohalobenzene solvents also exhibited enhanced percent conversion and regioselectivity compared to dichloromethane, and selectivities increased from iodobenezene to chlorobenzene to fluorobenzene. However, toluene was found to be the optimal solvent, producing **6** and **7** with a regioselectivity of 96:4 (**6**:**7**), a diastereomer ratio of 94:6 (**6**-*endo*:**6**-*exo*), and an enantiomeric excess of 94% (**6**-*endo*) in 94% overall yield after only 1 hour of reaction time. Similar rate and selectivity enhancements in toluene occurred with the diastereomeric [Rh_2(5*S*,*S*-

MenPy)$_4$]SbF$_6$ (**4**) and [Rh$_2$(5*S*-IPPy)$_4$]SbF$_6$ (**5**), although enantio- and regiocontrol for the production of **6** were not as good as [Rh$_2$(5*S*,*R*-MenPy)$_4$]SbF$_6$ (**3**) (Table 1.1).

Table 1.1 Influence of Solvent on Regioselectivity and Stereocontrol in Chiral Dirhodium(II,III) Carboxamidate Catalyzed Reactions of *N*,α-Diphenylnitrone with Acrolein.





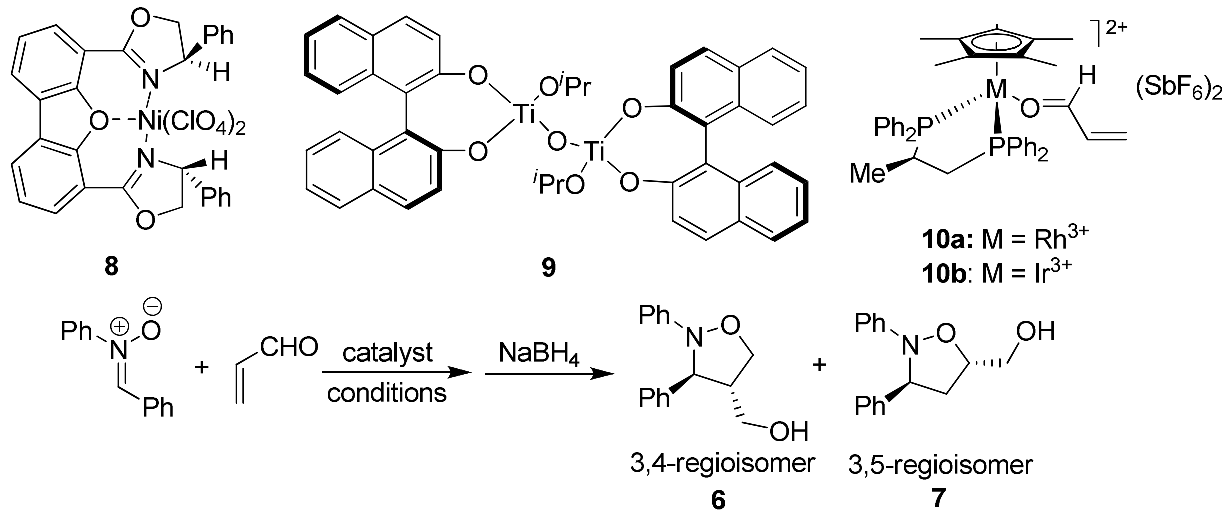
(1)

catalyst /mol%	solvent	*T* (°C)	t (h)	yield (%)[a]	**6**:**7**[b]	dr of **6**[b]	ee of **6**-*endo* (%)[c]
3/5	CH_2Cl_2	0	5	73	70:30	92:8	78
3/5	$CHCl_3$	0	5	40	75:25	91:9	83
3/5	*c*-C_6H_{12}	0	2	93	88:12	93:7	91
3/5	PhI	0	2	73	83:17	94:6	90
3/5	PhCl	0	2	91	83:17	93:7	90
3/5	PhF	0	2	92	91:9	94:6	92
3/5	PhMe	0	1	94	96:4	94:6	94
3/5	PhMe	-20	4	93	96:4	94:6	93
4/5	CH_2Cl_2	0	5	55	74:26	91:9	71
4/5	PhMe	0	1	94	94:6	94:6	90
5/5	CH_2Cl_2	0	5	67	67:33	92:8	27
5/5	PhMe	0	2	92	88:12	93:7	76

[a] Isolated product yield following chromatography. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC analysis (OD-H column).

2.3 Comparison with Other Catalysts

Table 1.2 Optimum Results Reported with Other Chiral Lewis Acid Catalysts.



catalyst /mol%	solvent	T (°C)	t (h)	yield (%)[a]	**6**:**7**[b]	dr of **6**[b]	ee of **6**-*endo* (%)[c]
8[d]/10	CH_2Cl_2	-10	72	75	26:74	95:5	91
9[e]/10	CH_2Cl_2	-40	24	94	>99:1	>97:3	93
10a[f]/5	CH_2Cl_2	-25	16	(100)[g]	>99:1[h]	>99:1[h]	78
10b[f]/5	CH_2Cl_2	-25	16	(100)[g]	>99:1[h]	>99:1[h]	90

[a] Isolated product yield following chromatography. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC analysis (OD-H column). [d] Reference 19. [e] Reference 20; *N*-benzyl-α-phenylnitrone was used instead of *N*,α-diphenylnitrone in this case. [f] Reference 18: a seven-fold molar excess of acrolein was used. [g] Percent conversion based on ^{1}H NMR analysis; isolated product yield not given. [h] Only the **6**-*endo* cycloaddition product was reported.

To demonstrate the superiority of $[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ (**3**) to other catalytic systems, we compared the optimum results (Table 1.2) from the four best-performing catalysts in the literature (**8**,[19] **9**,[20] **10a**,[18] and **10b**[18]) to ours. The Kanemasa catalyst (**8**) provides good enantiocontrol, but cycloaddition occurs with poor regioselectivity.[19] Maruoka's μ-oxo bis-Ti(IV) oxide catalyst (**9**) has only shown its effectiveness with *N*-benzyl-substituted nitrones, but no results have been reported with *N*,α-diphenylnitrone.[20] Extensive studies performed by Carmona and coworkers with cationic Cp*Rh(III)L* (**10a**) and Cp*Ir(III)L* (**10b**) catalysts (L* =

chiral diphosphine ligand) also show high regioselectivity in this dipolar cycloaddition reaction, but enantiocontrol is metal ion dependent with the Ir(III) catalyst exhibiting higher enantiocontrol than that with Rh(III).[18] Solvent effects with these catalysts were not discussed in their work, and dichloromethane was the only solvent reported.

Low reaction temperatures ranging from -10 to -40°C were adopted with cycloaddition reactions catalyzed by **8–10**, and we presume that the best results were obtained at the reported temperatures. However, $[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ (**3**) does not require a temperature lower than 0 °C to achieve the best performance. Moreover, the reaction time has been significantly shortened to 1 h. Therefore, catalysis of nitrone cycloaddition to acrolein by **3** in toluene at 0 °C provides selectivities that are at least as good as the best of the alternatives, but with much faster reaction rates and milder conditions.

2.4 Explanation of the Solvent Effect

Noticing the significant shortening of the reaction time by switching the reaction solvent from dichloromethane to toluene, we decided to plot percent conversion of nitrones as a function of time for the reactions of *N*,α-diphenylnitrone with acrolein catalyzed by $[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ (**3**) in various solvents. The reaction rates decreased from toluene to iodobenzene with chlorobenzene in between, and the rate dropped significantly in dichloromethane (Figure 1.5). Use of strongly-coordinating[21] acetonitrile as the reaction solvent completely shuts down the catalytic reaction.

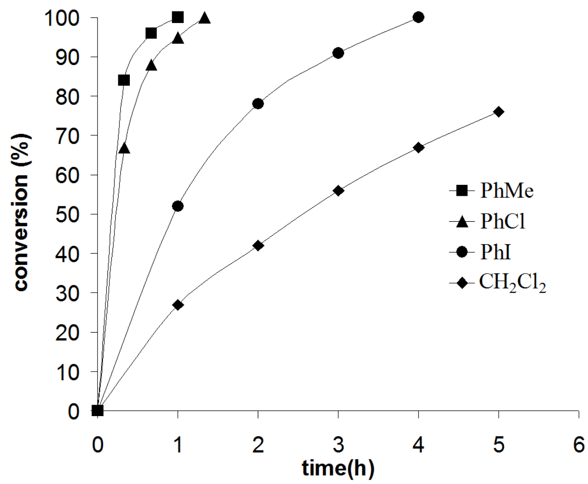
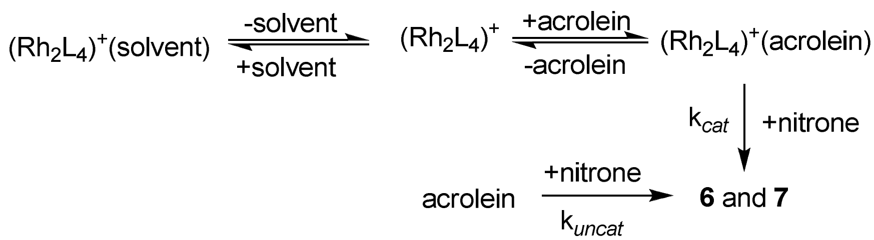


Figure 1.5 Plot of Conversion (%) as a Function of Time for the Standard Reaction of *N*,α-Diphenylnitrone with Acrolein Catalyzed by $[Rh_2(5S,R\text{-}MenPy)_4]SbF_6$ in PhMe, PhCl, PhI, and CH_2Cl_2 at 0 °C.

Solvent effects in 1,3-dipolar cycloaddition reactions have been reviewed,[22] and there is at least one case[23] that solvents of low polarity improve the regiocontrol based on computational studies. However, solvent effects in reactions associated with transition metal catalysis have been attributed to many causes, including solvent coordination to transition metals[24] and stabilization or destabilization of the transition state by solvent medium.[25] The trend depicted in Figure 1.5 strongly suggests that coordination of polar solvents to **3** inhibits the coordination of acrolein thereby slowing down the catalytic reaction. The background reaction was also investigated in both dichloromethane and toluene, and after 24 hours of reaction at room temperature, 78% conversion to cycloaddition products was observed with a 16:84 ratio of 3,4-regioisomer (**6**): 3,5-regioisomer (**7**) and a diastereomeric ratio of 3,4-*endo*:3,4-*exo* of 74:26 showing no dependence on the solvent selection. After obtaining these results, we easily generated one cause of the solvent influence on the reaction rates and selectivities, which is depicted in Scheme 1.14. Competition between solvent and acrolein for the active site of the Lewis acid catalyst inhibits the rate of catalytic conversion of acrolein to its dipolar cycloaddition products and increases the relative importance of the uncatalyzed pathway to these same products. Since the uncatalyzed reaction produces racemic **6** and favors regioisomer **7** over **6**, the influence of solvent on both enantio- and regioselectivity can be appreciated from this competitive coordination.



Scheme 1.14 Influence of Solvent Coordination to Catalyst on Product Formation.

Although Scheme 1.14 explains reactivity and selectivity qualitatively, there is still inconsistency in the case of chloroform as solvent, where a significant decrease in reactivity, but a slight increase in selectivity was observed compared to that of dichloromethane (Table 1.1). In a search for other contributing factors, DFT calculations were performed on the complex of acrolein coordinated to Rh_2(5*S*-IPPy)$_4^+$(**5**), which is the isopropyl analog of **3** and **4**. The solvent influence on the reactivities and selectivities of the nitrone dipolar cycloaddition reactions catalyzed by **5** was also recorded in Table 1.1. The B3LYP functional with the LANL2DZ basis set and the CPCM solvation model was applied in this calculation. In the optimized geometries at the ground state, when a different solvent environment was selected acrolein coordination to Rh adopted different dihedral angles relative to catalyst ligands. In dichloromethane (**A** in Figure 1.6), the dihedral angle involving the atoms O-Rh(catalyst)-O=C(acrolein) was 32.7°, whereas in toluene (**B** in Figure 1.6) the same angle decreased to 6.6°. When the calculation was done in the gas phase, the same angle was even smaller. These results clearly indicate that the dielectric constant of solvent influences the stable conformation of the catalyst-acrolein complex. A solvent of a larger dielectric constant will result in a larger dihedral angle depicted in Figure 1.6. Considering that the enantiocontrol occurs by selective shielding of the top and bottom sides of acrolein by two esters of the chiral pyrrolidinone ligands on each rhodium face (represented as E in Figure 1.6), the greater shielding of one side of acrolein in toluene suggests greater facial differentiation of acrolein.

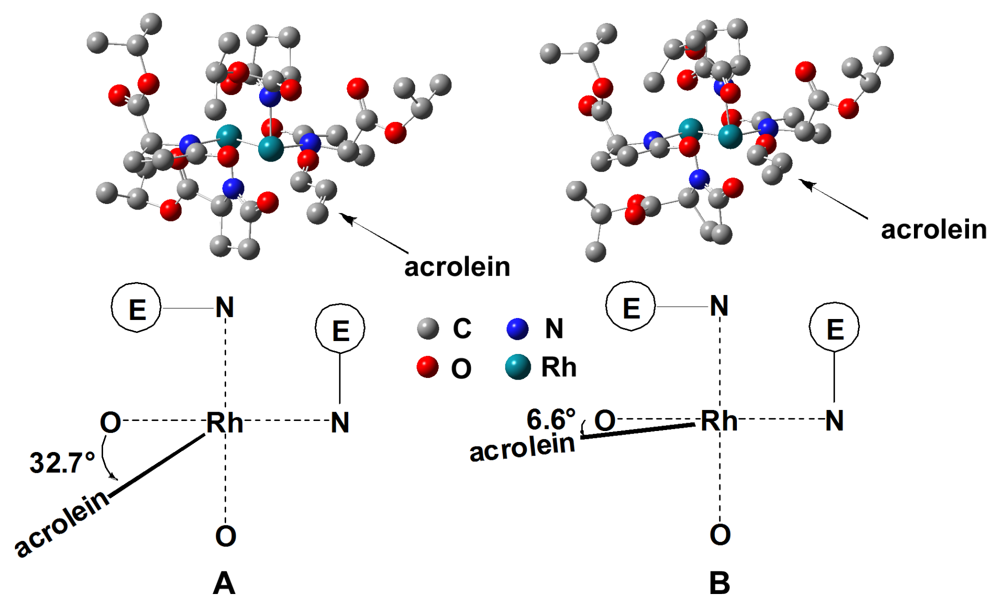
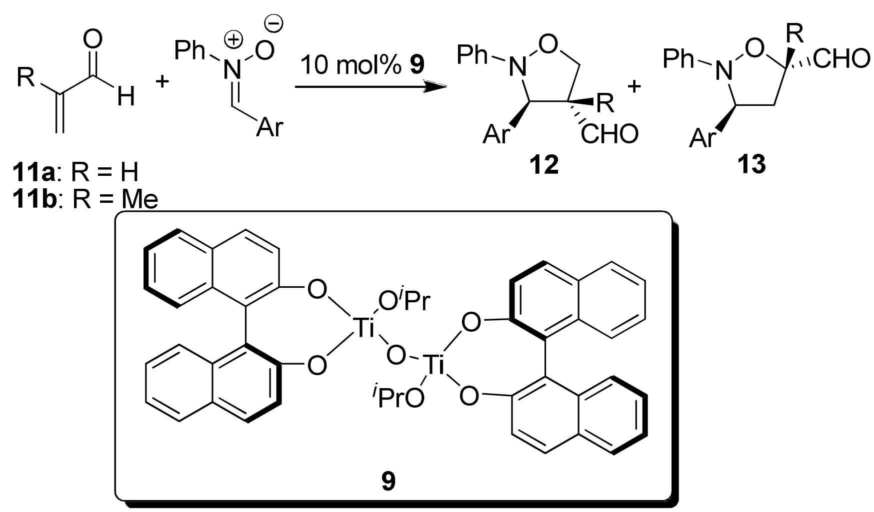


Figure 1.6 Energy Minimized Geometries of Acrolein-$Rh_2(5S\text{-IPPy})_4^+$ Complex in Dichloromethane (**A**) and Toluene (**B**) Obtained from DFT Calculation (B3LYP). (Hydrogens Omitted).

2.5 Test of Solvent Effect on μ-Oxo Bis-Ti(IV) Oxide

Solvent effects on catalysts **8–10** were not reported in literature. To test the possibility of solvent influence, μ-oxo bis-Ti(IV) oxide (**9**) was selected as the test candidate because it had provided the highest selectivities from nitrone cycloadditions with acrolein among **8–10**. The dipolar cycloaddition reactions of *N*,α-diphenylnitrone with acrolein and methacrolein were run with the solvent of toluene and dichloromethane, and the results are summarized in Table 1.3. No apparent solvent effect was found for either aldehyde. In his earlier communication, Maruoka chose *N*-benzyl-α-phenylnitrones as the standard substrate, and reported formation of only the 3,4-*endo* isomer in high yield and enantioselectivity, but he did not report the results with *N*,α-diphenylnitrones.[20] Actually, with acrolein, selectivities with **9** are not as good as those with $[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ (**3**), and with methacrolein, regioselectivity is very low (Table 1.3). Interestingly, high enantiomeric excess was obtained for the 3,5-*endo* product with **9**, which is the reverse of what is observed with $[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ (**3**). Maruoka also pointed out that a sterically encumbered *N*-substituent on the nitrone was essential for high stereocontrol with his μ-oxo bis-Ti(IV) oxide catalyst, and *N*-diphenylmethyl substituted nitrones were used in place of the *N*-benzyl analogues when these cycloaddition reactions were carried out with methacrolein.[20]

Table 1.3 μ-Oxo Bis-Ti(IV) Oxide (**9**) Catalyzed 1,3-Dipolar Cycloaddition Reactions.[a]



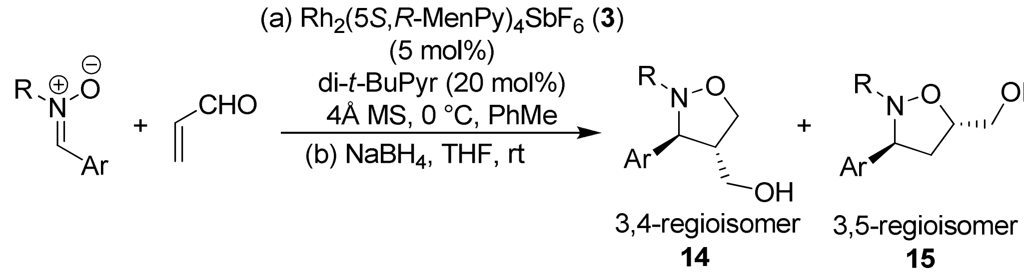
enal	Ar	solvent	t(h)	yield(%)[b]	**12**:**13**[c]	dr[c]	ee% (**12**-*endo/***13**-*endo*)[d]
11a	Ph	CH_2Cl_2	1	95	99:1	86:14	87/-
11a	Ph	PhMe	1	95	99:1	86:14	82/-
11b	Ph	CH_2Cl_2	2	88	56:44	>99:1	81/98
11b	Ph	PhMe	2	89	52:48	>99:1	80/98
11b	4-MeOPh	CH_2Cl_2	2	70	82:18	>99:1	77/95
11b	4-CF_3Ph	CH_2Cl_2	3	92	40:60	>99:1	67/95

[a] The reactions were carried out with 0.5 mmol nitrone, 0.8 mmol enal and 0.05 mmol μ-oxo bis-Ti(IV) oxide; Reactions with **11a** were carried out at -20 °C; Reactions with **11b** were carried out at 0 °C. [b] Isolated product yield. [c] Determined by ^{1}H NMR spectroscopy; complete diastereoselectivity for *endo* product was observed for cycloadditions with **11b**. [d] Determined by ^{1}H NMR after formation of diastereomeric imines with (*R*)-(+)-α-methylbenzylamine or by HPLC (OD-H column) after borohydride reduction.

2.6 Substrate Scope with [Rh_2(5*S*,*R*-MenPy)$_4$]SbF_6

To investigate the generality of the enantioselective dipolar cycloadditions of nitrones with α,β-unsaturated aldehydes catalyzed by [Rh_2(5*S*,*R*-MenPy)$_4$]SbF_6 (**3**), various nitrones were subjected to the optimal conditions, and the results are summarized in Table 1.4. High yields with excellent diastereo- and enantioselectivities were obtained regardless of the nature of substituents. As was previously established by our group with methacrolein,[10] and confirmed by Kündig,[16] electron-withdrawing groups in Ar decrease regioselectivity; but for reactions performed in toluene, even nitrones having electron-withdrawing groups in Ar such as trifluoromethyl (entry 5) provide high regiocontrol for the 3,4-cycloaddition product (**14**).

Table 1.4 Effect of Nitrone Substituents on Regioselectivity and Enantiocontrol in the Cycloaddition Reactions with Acrolein Catalyzed by $[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ (**3**).

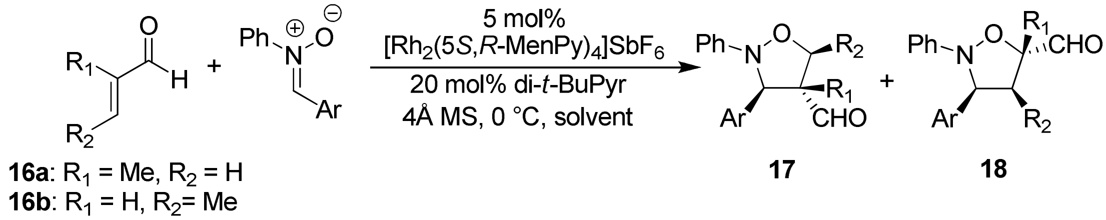


Entry	R	Ar	t (h)	yield (%)[a]	**14**:**15**[b]	dr of **14**[b]	ee of **14**-*endo* (%)[c]
1	Ph	Ph	1	94	96:4	94:6	94
2	Ph	4-MeOPh	1	92	>99:1	95:5	98
3	Ph	4-MePh	1	94	99:1	94:6	96
4	Ph	4-ClPh	3	86	95:5	92:8	96
5	Ph	4-CF_3Ph	3	90	87:13	94:6	96
6	Ph	2-furyl	4	89	>99:1	88:12	90
7	Ph	2-naphthyl	2	90	99:1	94:6	97
8	Bn	Ph	3	91	>99:1	98:2	95 (*S*,*S*)[d]

[a] Isolated product yield. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC analysis (OD-H column). [d] The absolute configuration was determined by comparison with literature.[20]

Dipolar cycloadditions to methacrolein (**16a**) and *trans*-crotonaldehyde (**16b**) catalyzed by $[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ (**3**) are reported in Table 1.5. Solvent-enhanced regiocontrol is evident in these results. With *N*,α-diphenylnitrone, for example, regioselectivity for **17**:**18** changed from 34:66 to 79:21 favoring **17** upon changing the solvent from dichloromethane to toluene. In addition, enantioselectivities for **17**, which were already high from reactions catalyzed by **3** performed in dichloromethane, are further enhanced with reactions performed in toluene. Enantiocontrol in catalytic formation of the 3,4-*endo* cycloadducts obtained from these substrates using **3** is at the highest level reported compared to the previously reported examples.[16–20] The advantages of the cationic catalyst $[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ (**3**) are evident.

Table 1.5 $[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ (**3**)-Catalyzed Asymmetric Nitrone Cycloaddition Reactions with Methacrolein (**16a**) and trans-Crotonaldehyde (**16b**).



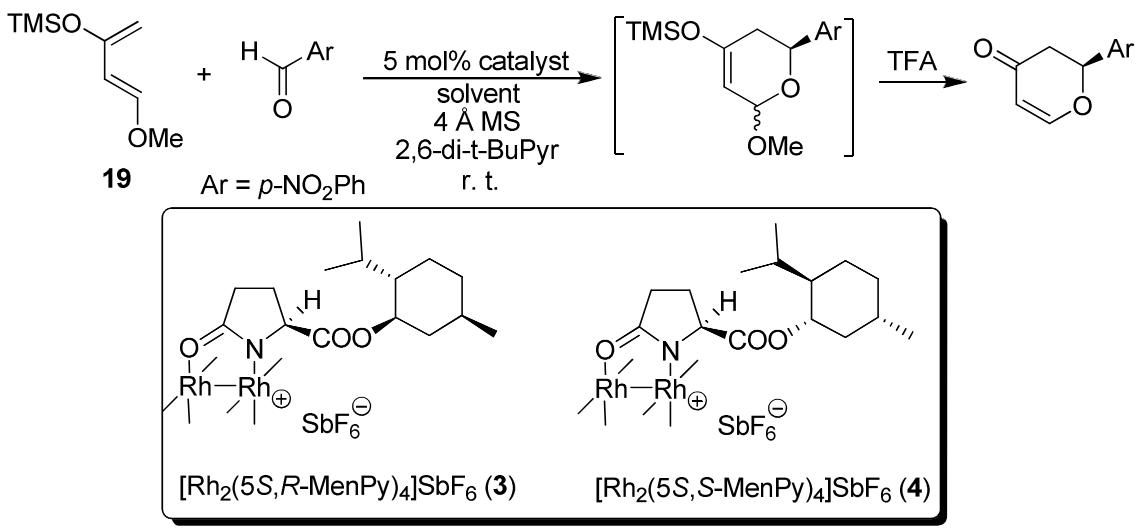
entry	enal	Ar	solvent	time (h)	yield[a] (%)	**17**:**18**[b]	ee% (**17**-*endo*/**18**-*endo*)[c]
1	**16a**	4-MeOPh	CH_2Cl_2	5	40	70:30	96/63
2	**16a**	4-MeOPh	PhMe	5	91	97:3	99/-
3	**16a**	Ph	CH_2Cl_2	5	42	34:66	94/66
4	**16a**	Ph	PhMe	5	95	79:21	98/56
5	**16a**	4-MePh	PhMe	4	96	89:11	97/60
6	**16a**	4-ClPh	PhMe	20	82	53:47	99/72
7	**16a**	4-CF_3Ph	PhMe	20	96	30:70	96/62
8	**16a**	2-furyl	PhMe	20	91	79:21	98/54
9	**16a**	2-naphthyl	PhMe	20	96	70:30	95/52
10	**16b**	Ph	PhMe	24	78[d]	>99:1	95[e]/-

[a] Isolated product yield. [b] Determined by ^{1}H NMR spectroscopy; complete diastereoselectivities for *endo* products were observed for these cycloaddition reactions. [c] Determined by ^{1}H NMR after formation of diastereomeric imines with (*R*)-(+)-α-methylbenzylamine. [d] Borohydride reduction was carried out in this case; Isolated yield of the product after reduction. [e] Determined by HPLC analysis (OD-H column).

2.7 Application of Chiral Dirhodium(II,III) Carboxamidates in Other Lewis Acid-Catalyzed Reactions

The hetero-Diels-Alder reaction[26] and the carbonyl-ene reaction[27] were also investigated for solvent influence under the catalysis of cationic chiral dirhodium carboxamidates. Previously, our group successfully achieved the enantioselective hetero-Diels-Alder reactions between *trans*-1-methoxy-3-(trimethysilyloxy)-1,3-butadiene (the Danishefsky diene) and aldehydes with $Rh_2(S\text{-MEPY})_4SbF_6$ as the catalyst and dichloromethane as the solvent (Scheme 1.3 in section 1.3).[10] However, due to the poor solubility of Rh_2(*S*-MEPY)$_4$$SbF_6$ in aromatic solvents, a solvent survey was not performed. With 5 mol% [Rh_2(5*S*,*R*-MenPy)$_4$]SbF_6 (**3**), reactions of *p*-nitrobenzaldehyde with the Danishefsky diene (**19**) in both solvents at room temperature are relatively slow, they do not exhibit rate enhancement by changing the solvent from dichloromethane to toluene, but enhancement in enantioselectivity is evident (Table 1.6). However, the diastereomeric [Rh_2(5*S*,*S*-MenPy)$_4$]SbF_6 (**4**) noticeably improved reaction rates and exhibited substantial rate enhancement by changing the reaction solvent to toluene. In this latter case there was not a significant solvent-induced change in enantioselectivity.

Table 1.6 Solvent Influence on the Asymmetric Hetero-Diels-Alder Reaction of *p*-Nitrobenzaldehyde with the Danishefsky Diene (**19**) Catalyzed by Rh(II)Rh(III) Catalysts.[a]



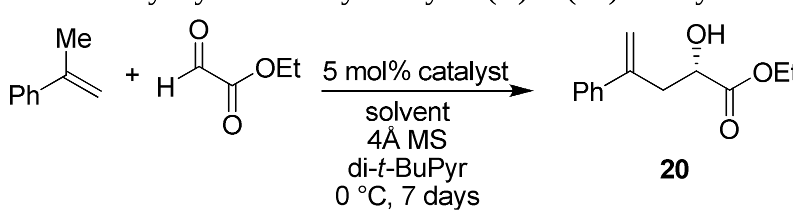
catalyst	solvent	t (h)	yield (%)[b]	ee%[c]
[Rh_2(5*S*,*R*-MenPy)$_4$]SbF_6 (**3**)	CH_2Cl_2	24	68	83
[Rh_2(5*S*,*R*-MenPy)$_4$]SbF_6 (**3**)	PhMe	24	52	91
[Rh_2(5*S*,*S*-MenPy)$_4$]SbF_6 (**4**)	CH_2Cl_2	24	86	91
[Rh_2(5*S*,*S*-MenPy)$_4$]SbF_6 (**4**)	PhMe	2	97	94

[a] The reactions were performed with 0.5 mmol *p*-nitrobenzaldehyde, 0.6 mmol Danishefsky diene, 0.025 mmol catalyst, 0.1 mmol 2,6-di-*t*-BuPyr and 300 mg 4 Å MS in 1.5 mL solvent at room temperature. [b] Yield of the isolated product. [c]

Determined by HPLC (OD-H column); The absolute configuration of the product was determined to be *S* by comparison with literature.[9d]

The carbonyl-ene reaction is a useful transformation, producing synthetically versatile homoallylic alcohols.[27] Efforts toward developing chiral Lewis acids for the enantioselective variants of the reaction have resulted into a few successful examples.[27,28] To test the degree of enantiocontrol with cationic chiral dirhodium carboxamidate catalysts, we decided to investigate the intermolecular carbonyl-ene reaction of ethyl glyoxylate with α-methylstyrene, which also served as the standard reaction for many other Lewis acids.[28] With 5 mol% $[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ (**3**) in dichloromethane at 0 °C the homoallylic alcohol **20** was produced in 60% yield and with 38% ee (Table 1.7). Changing the solvent to toluene resulted into a lower yield but much higher enantiomeric excess. Similar to the results from the hetero-Diels-Alder reaction, use of $[Rh_2(5S,S\text{-MenPy})_4]SbF_6$ (**4**) in toluene improved the yield to 90% and the enantiomeric excess to 94%. The drawback of the current catalytic system is that the reaction requires a long reaction time of 7 days to achieve high conversion. Increasing the reaction temperature shortened the reaction time but at the cost of 5~10% ee decrease of **20**.

Table 1.7 Solvent Influence on the Asymmetric Carbonyl-ene Reaction of Ethyl Glyoxylate with α-Methylstyrene Catalyzed by Rh(II)Rh(III) Catalysts.[a]



20

Catalyst	solvent	yield (%)[b]	ee%[c]
$[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ (**3**)	CH_2Cl_2	60	38
$[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ (**3**)	PhMe	37	70
$[Rh_2(5S,S\text{-MenPy})_4]SbF_6$ (**4**)	CH_2Cl_2	52	63
$[Rh_2(5S,S\text{-MenPy})_4]SbF_6$ (**4**)	PhMe	90	94

[a] The reactions were performed with 2.5 mmol α-methylstyrene, 0.5 mmol ethyl glyoxylate, 0.025 mmol catalyst, 0.1 mmol 2,6-di-*t*-BuPyr and 300 mg 4 Å MS in 1.0 mL solvent at 0 °C. [b] Yield of the isolated product. [c] Determined by HPLC (AD-H column); The absolute configuration of the product was determined to be *S* by comparison with literature.[28d]

III. Conclusion

We have discovered solvent-dependent rate and selectivity improvement with chiral cationic dirhodium(II,III) carboxamidates in nitrone dipolar cycloaddition reactions, hetero-Diels-Alder reactions, and carbonyl-ene reactions. With 1,3-dipolar cycloaddition reactions of nitrones with α,β-unsaturated aldehydes use of Rh_2(5*S*,*R*-MenPy)$_4$$SbF_6$ (**3**) in toluene provided rate enhancements as well as significant improvements in regioselectivities and enantioselectivities over those obtained in dichloromethane. Rate and enantioselectivity enhancements were obtained with [Rh_2(5*S*,*S*-MenPy)$_4$]SbF_6 (**4**) in hetero-Diels-Alder and carbonyl-ene reactions over those obtained in dichloromethane. These enhancements are attributed to diminished or absent association of toluene with the catalyst which lessens the relative importance of the uncatalyzed background reaction. Different coordination angles for aldehyde association with rhodium in the different solvent environments may also contribute to enhanced enantiocontrol in toluene. Further research is underway to uncover the generality of these rate and selectivity improvements in other Lewis acid-catalyzed reactions.

IV. Experimental Section

4.1 Materials

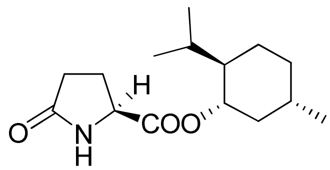
Rh_2(5*S*,*R*-MenPy)$_4$,[10] Rh_2(5*S*-IPPy)$_4$,[4] *trans*-1-methoxy-3-(trimethysilyloxy)-1,3-butadiene[29] and nitrones[30] were prepared according to the literature procedures. Acrolein, *trans*-crotonaldehyde, methacrolein, ethyl glyoxylate and α-methylstyrene were obtained from commercial sources and freshly distilled before use. Solvents were used after distillation. All the other chemicals were obtained from commercial sources and used without further purification.

4.2 General Information

All reactions, unless noted, were carried out under an inert atmosphere of dried nitrogen in flame-dried or oven-dried glassware with magnetic stirring. Analytical thin layer chromatography (TLC) was performed on Dynamic Adsorbents precoated (0.25 mm thickness) silica gel plates with F_{254} indicator. Visualization was accomplished by UV light (254 nm) or with phosphomolybdic acid (PMA) solution in ethanol. Flash chromatography was performed with silica gel (32-63 µm) supplied by Dynamic Adsorbents. ^{1}H NMR spectra were recorded on a Bruker DRX-400 (400 MHz) spectrometer or a Bruker DRX-500 (500 MHz) spectrometer, and chemical shifts were reported in ppm using tetramethylsilane (δ = 0 ppm for ^{1}H) as the internal standard. The peak information was described as: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = composite; coupling constant(s) in Hz. ^{13}C NMR spectra were recorded on a Bruker DRX-500 (125 MHz) spectrometer with complete proton decoupling, and the chemical shifts were reported in ppm using $CDCl_3$ (δ = 77.0 ppm) as the internal standard. IR spectra were recorded on a JASCO FT/IR 4100 spectrometer. Enantioselectivity was determined on an Agilent 1200 Series HPLC using a Daicel Chiralcel OD-H column or an AD-H column. High-resolution mass analyses (HRMS) were performed on JEOL AccuTOF-CS mass spectrometer using CsI as the standard.

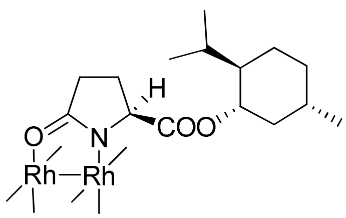
4.3 Experimental Procedures And Compound Characterizations

Synthesis of (*S*)-[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl] 2-Oxopyrrolidine-5-carboxylate, *S*,*S*-MenPy-H. A 100 mL round-bottom flask was charged with L-pyroglutamic acid (1.29 g, 10 mmol), (+)-menthol (1.56 g, 10 mmol) and 4-dimethylaminopyridine (0.24 g, 2 mmol) and purged with nitrogen. Dry CH_2Cl_2 (20 mL) was added, and the mixture was cooled to 0 °C with an ice bath. A solution of *N*,*N′*-dicyclohexylcarbodiimide (2.27 g, 11 mmol) in CH_2Cl_2 (20 mL) was added to the reaction mixture over a period of 30 min, and then the reaction mixture was stirred at room temperature for 20 h. The white solid was removed by filtration. The solution was evaporated to dryness under reduced pressure, and the residue was dissolved in ethyl acetate (100 mL) and washed with 1 M HCl (20 mL), 5% $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The resulting solid was purified by column chromatography (ethyl acetate: hexane = 5:2) to yield a white solid product (2.30 g, 86% yield).



(*S*)-[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl] 2-Oxopyrrolidine-5-carboxylate, *S*,*S*-MenPy-H. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.44 (s, 1H, NH), 4.74 (dt, 1H, *J* = 4.4, 10.9 Hz), 4.23 (dd, 1H, *J* = 5.4, 8.6 Hz), 2.55-2.45 (m, 1H), 2.40-2.32 (comp, 2H), 2.22-2.16 (m, 1H), 2.02-1.96 (m, 1H), 1.85-1.80 (m, 1H), 1.72-1.66 (comp, 2H), 1.55-1.39 (comp, 2H), 1.10-0.85 (comp, 9H), 0.76 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.68, 171.47, 75.73, 55.61, 46.87, 40.66, 34.05, 31.33, 29.28, 26.26, 24.97, 23.21, 21.89, 20.71, 16.08; $[\alpha]^{20}_D$ = +59.3 (*c* 0.96, CH_2Cl_2). HRMS (ESI) calculated for $C_{15}H_{26}NO_3$: *m/z* 268.1907 ($[M + H]^+$), found: *m/z* 268.1912.

Synthesis of Dirhodium(II) Tetrakis{(*S*)-[(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl] 2-Oxopyrrolidine-5-carboxylate}, Rh_2(5*S*,*S*-MenPy)$_4$. The previously reported standard procedure was followed.[4] Dirhodium(II) acetate (330 mg, 0.747 mmol), (*S*)-[(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl] 2-oxopyrrolidine-5-carboxylate (2.1 g, 7.85 mmol) and chlorobenzene (20 mL) were mixed in a 50 mL round-bottom flask fitted with Soxhlet extraction apparatus into which was placed a cellulose thimble containing 2:1 Na_2CO_3/sand. The resulting mixture was heated at vigorous reflux for 20 hours, at which time HPLC analysis (Microsorb-MV 100-5 CN column, 2% MeCN in MeOH, flow 1.0 mL/min) showed the reaction to be complete. After cooling to room temperature, the solvent was removed under reduced pressure, and the resulting blue oil was chromatographed on BAKERBOND-CN silica (40 μm Prep LC packing) eluting with MeOH. The first brown band was the excess ligand, and then 1% MeCN in MeOH was used to wash off the desired catalyst band which had a red color. The solvent of the collected catalyst band was removed under reduced pressure, and the resulting blue solid material was heated at 120 °C under high vacuum for 2 hour. The catalyst was finally obtained as a green powder (696 mg, 73% yield).

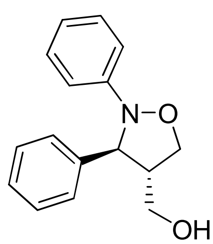


Rh_2(5*S*,*S*-MenPy)$_4$

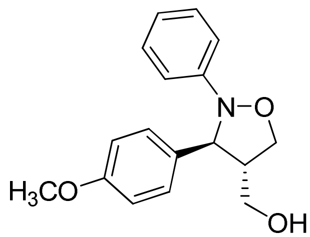
Dirhodium(II) Tetrakis{(*S*)-[(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl] 2-Oxopyrrolidine-5-carboxylate}, Rh_2(5*S*,*S*-MenPy)$_4$. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.67-4.59 (comp, 4H), 4.28-4.24 (comp, 2H), 3.94-3.89 (comp, 2H) , 2.85-0.71 (comp, 88H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 188.58, 187.44, 174.40, 173.89, 74.44, 74.13, 66.41, 47.29, 47.24, 41.56, 40.88, 34.55, 34.26, 31.49, 31.39, 31.32, 26.68, 26.60, 26.22, 23.54, 23.36, 22.18, 20.77, 20.72, 16.29. 16.13 (missing 4 carbons due to overlapping signals); $[\alpha]^{20}_D$ = -113.85 (*c* 0.130, *i*-PrOH). HRMS (ESI) calculated for $C_{60}H_{97}N_4O_{12}Rh_2$: *m/z* 1271.5208 ($[M + H]^+$), found: *m/z* 1271.5207.

General Procedure for the Asymmetric 1,3-Dipolar Cycloaddition Reactions of Nitrones with α,β-Unsaturated Aldehydes Catalyzed by [Rh_2(5*S*,*R*-MenPy)$_4$]SbF_6. A 10 ml Schlenk flask charged with a magnetic stir bar and 4 Å molecular sieves (300 mg) was placed under high vacuum and heated by Bunsen burner to dryness. After cooling to room temperature, Rh_2(5*S*,*R*-MenPy)$_4$ (33.8 mg, 0.026 mmol), 2,6-di-*tert*-butylpyridine (22 μL, 0.10 mmol) and toluene (1.0 mL) were added under the flow of N_2. The resulting green solution was stirred for 10 min before $NOSbF_6$ (6.6 mg, 0.025 mmol) was added. The solution was allowed to stir for additional 30 min, during which time the color gradually turned from green to deep red. Freshly distilled acrolein (54 μL, 0.80 mmol) was added *via* a micro syringe to the flask that was then placed in an ice bath, and the mixture was stirred for 10 min. Nitrone (0.50 mmol) in toluene (1.5 mL) was added dropwise within 1 min (gentle heating aids dissolution of nitrones in toluene; *N*-phenyl-α-(4-chlorophenyl)nitrone and *N*-phenyl-α-(4-trifluoromethylphenyl)nitrone were added as solids because of their relatively poor solubility, followed by the addition of 1.5 mL toluene). The solution was stirred at 0 °C until the completion of the reaction indicated by TLC analysis of the reaction mixture. The entire reaction mixture was then loaded on a short silica column and eluted with CH_2Cl_2 to remove the catalyst and 4 Å molecular sieves. The collected solution was concentrated, and regioselectivity and diastereoselectivity were determined by ^1H NMR analyses by integration of the aldehyde peaks from the regio- and diastereoisomers. The aldehyde product mixture was then dissolved in THF (5.0 mL) and treated with $NaBH_4$ (56.7 mg, 1.50 mmol) at room temperature for 30 min. The mixture was then poured into a saturated solution of NH_4Cl (aq.) (20 mL) and extracted with ethyl acetate (3×15 mL). The combined organic layer was dried with anhydrous Na_2SO_4 and concentrated. The resulting oil was purified by flash chromatography (hexane : ethyl acetate = 2:1) to obtain the final product that was then analyzed for enantiomeric excess by HPLC analysis.

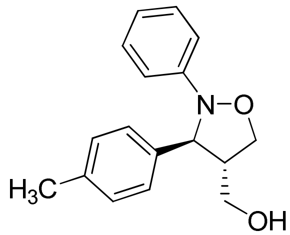
General Procedure for the Asymmetric 1,3-Dipolar Cycloaddition Reactions of Nitrones with α,β-Unsaturated Aldehydes Catalyzed by the μ-Oxo Bis-Ti(IV) Oxide Catalyst.[20] To a stirred mixture of Ag_2O (12 mg, 0.05 mmol) in CH_2Cl_2 (0.5 mL) was added 1.0 M hexane solution of ClTi(O*i*-Pr)$_3$ (100 μL, 0.10 mmol) at room temperature. After stirring for 5 hours at room temperature, a solution of (*S*)-BINOL (28.6 mg, 0.10 mmol) in CH_2Cl_2 (0.7 mL) was added to the mixture, which was then stirred for 2 hours at room temperature to afford the dark orange solution of chiral μ-oxo bis-Ti(IV) oxide. The solution was cooled to -20 °C (or 0 °C for methacrolein). To the catalyst solution was added acrolein (54 μL, 0.80 mmol), followed by the nitrone in CH_2Cl_2 (1.3 mL). The resulting mixture was stirred at -20 °C until the completion of the reaction indicated by TLC analysis of the reaction mixture. The workup was identical to the procedure described for [Rh_2(5*S*,*R*-MenPy)$_4$]SbF_6.



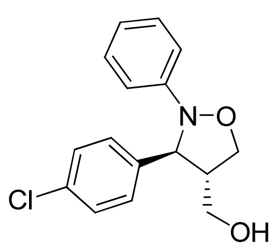
2,3-Diphenylisoxazolidine-4-methanol. Obtained as a colorless oil in 94% overall yield. Regioselectivity and diastereoselectivity were determined by ^{1}H NMR of the aldehyde precursor: 3,4-isomer: 3,5-isomer = 96:4; 3,4-*endo*:3,4-*exo* = 94:6 (3,4-*endo*: δ 9.69, d, 1H, *J* = 2.0 Hz; 3,4-*exo*: δ 9.22, d, 1H, *J* = 2.8 Hz; 3,5-*endo*: δ 9.83, d, 1H, *J* = 1.6 Hz). The 3,4-*endo* product was obtained in 94% ee (OD-H, 95:5 Hexane/*i*-PrOH, 1.0 mL/min, 254 nm, major enantiomer t_r = 21.7 min, minor enantiomer t_r = 34.7 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, 2H, *J* = 7.2 Hz), 7.40-7.36 (comp, 2H), 7.31-7.29 (m, 1H), 7.23-7.18 (comp, 2H), 6.96-6.89 (comp, 3H), 4.36 (d, 1H, J = 5.6 Hz), 4.33 (dd, 1H, J = 7.2, 8.4 Hz), 3.96 (dd, 1H, J = 6.0, 8.4 Hz), 3.82-3.69 (comp, 2H), 2.93-2.84 (m, 1H), 1.49 (t, 1H, J = 4.8 Hz, -OH). This compound has been fully characterized previously.[19]



3-(4-Methoxyphenyl)-2-phenylisoxazolidine-4-methanol. Obtained as a colorless oil in 92% overall yield. Regioselectivity and diastereoselectivity were determined by ^{1}H NMR of the aldehyde precursor: 3,4-isomer: 3,5-isomer > 99:1; 3,4-*endo*:3,4-*exo* = 95:5 (3,4-*endo*: δ 9.68, d, 1H, J = 2.0 Hz; 3,4-*exo*: δ 9.23, d, 1H, J = 3.2 Hz; 3,5-*endo*: δ 9.83, d, 1H, J = 1.6 Hz). The 3,4-*endo* product was obtained in 98% ee (OD-H, 93:7 Hexane/*i*-PrOH, 1.0 mL/min, 254 nm, major enantiomer t_r = 20.7 min, minor enantiomer t_r = 28.8 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, 2H, J = 8.4 Hz), 7.23-7.18 (comp, 2H), 6.96-6.90 (comp, 5H), 4.33 (dd, 1H, J = 7.2, 8.4 Hz), 4.27 (d, 1H, J = 5.6 Hz), 3.96 (dd, 1H, J = 8.4, 6.0 Hz), 3.82 (s, 3H), 3.78-3.68 (comp, 2H), 2.89-2.81 (m, 1H), 1.46 (t, 1H, J = 4.8 Hz, -OH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.99, 151.14, 133.99, 128.70, 127.79, 121.68, 114.91, 114.23, 71.83, 69.30, 62.76, 56.65, 55.28. IR (cm^{-1}): 3415, 2955, 2872, 1611, 1596, 1510, 1489, 1245, 1174, 1030, 832, 752. HRMS (ESI) calculated for $C_{17}H_{20}NO_3$: *m/z* 286.1438 ($[M + H]^+$), found: *m/z* 286.1441.

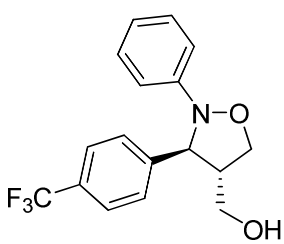


3-(4-Methylphenyl)-2-phenylisoxazolidine-4-methanol. Obtained as a colorless oil in 94% overall yield. Regioselectivity and diastereoselectivity were determined by ^{1}H NMR of the aldehyde precursor: 3,4-isomer: 3,5-isomer = 99:1; 3,4-*endo*:3,4-*exo* = 94:6 (3,4-*endo*: δ 9.68, d, 1H, J = 2.0 Hz; 3,4-*exo*: δ 9.22, d, 1H, J = 3.2 Hz; 3,5-*endo*: δ 9.83, d, 1H, J = 1.6 Hz). The 3,4-*endo* product was obtained in 96% ee (OD-H, 93:7 Hexane/*i*-PrOH, 1.0 mL/min, 254 nm, major enantiomer t_r = 13.6 min, minor enantiomer t_r = 19.7 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, 2H, J = 8.0 Hz), 7.22-7.18 (comp, 4H), 6.95 (d, 2H, J = 8.0 Hz), 6.91 (t, 1H, J = 7.2 Hz), 4.32 (dd, 1H, J = 7.2, 8.4 Hz), 4.29 (d, 1H, J = 6.4 Hz), 3.95 (dd, 1H, J = 6.0, 8.4 Hz), 3.81-3.68 (comp, 2H), 2.89-2.81 (m, 1H), 2.36 (s, 3H), 1.44 (t, 1H, J = 5.2 Hz, -OH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.19, 139.07, 137.19, 129.54, 128.73, 126.54, 121.61, 114.80, 72.02, 69.31, 62.81, 56.76, 21.09. IR (cm^{-1}): 3394, 2942, 2870, 2359, 2338, 1734, 1597, 1488, 1452, 1374, 1263, 1031, 818, 752. HRMS (ESI) calculated for $C_{17}H_{20}NO_2$: *m/z* 270.1489 ($[M + H]^+$), found: *m/z* 270.1494.

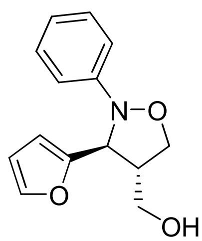


3-(4-Chlorophenyl)-2-phenylisoxazolidine-4-methanol. Obtained as a colorless oil in 86% overall yield. Regioselectivity and diastereoselectivity were determined by ^{1}H

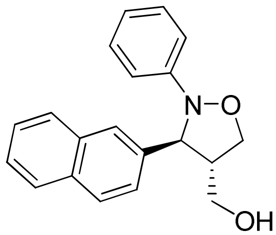
NMR of the aldehyde precursor: 3,4-isomer: 3,5-isomer = 95:5; 3,4-*endo*:3,4-*exo* = 92:8 (3,4-*endo*: δ 9.68, d, 1H, J = 2.0 Hz; 3,4-*exo*: δ 9.23, d, 1H, J = 3.2 Hz; 3,5-*endo*: δ 9.82, d, 1H, J = 1.2 Hz). The 3,4-*endo* product was obtained in 96% ee (OD-H, 93:7 Hexane/*i*-PrOH, 1.0 mL/min, 254 nm, major enantiomer t_r = 14.4 min, minor enantiomer t_r = 25.2 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, 2H, J = 8.4 Hz), 7.33 (d, 2H, J = 8.4 Hz), 7.23-7.18 (comp, 2H), 6.94-6.91 (comp, 3H), 4.36 (d, 1H, J = 5.2 Hz), 4.27 (dd, 1H, J = 8.4, 7.2 Hz), 3.91 (dd, 1H, J = 8.4, 6.0 Hz), 3.72-3.66 (comp, 2H), 2.86-2.75 (m, 1H), 1.70 (t, 1H, J = 4.8 Hz, -OH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.82, 140.71, 133.18, 128.96, 128.84, 127.98, 121.84, 114.69, 71.49, 69.14, 62.65, 56.61. IR (cm^{-1}): 3420, 2937, 2872, 2358, 1712, 1597, 1488, 1247, 1090, 1030, 1013, 845, 754. HRMS (ESI) calculated for $C_{16}H_{17}ClNO_2$: *m/z* 290.0942 ($[M + H]^+$), found: *m/z* 290.0955.



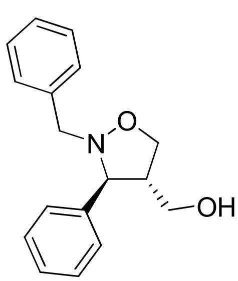
2-Phenyl-3-(4-trifluoromethylphenyl)isoxazolidine-4-methanol. Obtained as a colorless oil in 90% overall yield. Regioselectivity and diastereoselectivity were determined by ^{1}H NMR of the aldehyde precursor: 3,4-isomer: 3,5-isomer = 87:13; 3,4-*endo*:3,4-*exo* = 94:6 (3,4-*endo*: δ 9.67, d, 1H, J = 1.6 Hz; 3,4-*exo*: δ 9.21, d, 1H, J = 3.2 Hz; 3,5-*endo*: δ 9.81, d, 1H, J = 1.6 Hz). The 3,4-*endo* product was obtained in 96% ee (OD-H, 93:7 Hexane/*i*-PrOH, 1.0 mL/min, 254 nm, major enantiomer t_r = 11.8 min, minor enantiomer t_r = 23.8 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68-7.62 (comp, 4H), 7.26-7.21 (comp, 2H), 6.96-6.92 (comp, 3H), 4.52 (d, 1H, J = 5.2 Hz), 4.30 (dd, 1H, *J* = 8.4, 7.6 Hz), 3.94 (dd, 1H, *J* = 8.4, 6.4 Hz), 3.75 (dd, 2H, *J* = 4.8, 6.4 Hz), 2.90-2.81 (m, 1H), 1.55 (t, 1H, *J* = 4.4 Hz, -OH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.77, 146.46, 129.70 (q, *J* = 32.5 Hz), 128.94, 126.93, 125.78 (q, *J* = 4.0 Hz), 124.12 (q, *J* = 269.6 Hz), 121.91, 114.58, 71.61, 69.11, 62.75, 56.67. IR (cm^{-1}): 3422, 2945, 2869, 2338, 1597, 1489, 1323, 1163, 1112, 1066, 1017, 853, 754. HRMS (ESI) calculated for $C_{17}H_{17}F_3NO_2$: *m/z* 324.1206 ([M + H]$^+$), found: *m/z* 324.1206.



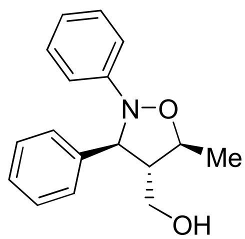
2-Phenyl-3-(2-furyl)isoxazolidine-4-methanol. Obtained as a colorless oil in 89% overall yield. Regioselectivity and diastereoselectivity were determined by ^{1}H NMR of the aldehyde precursor: 3,4-isomer: 3,5-isomer > 99:1; 3,4-*endo*:3,4-*exo* = 88:12 (3,4-*endo*: δ 9.66, d, 1H, *J* = 1.6 Hz; 3,4-*exo*: δ 9.43, d, 1H, *J* = 2.8 Hz; 3,5-*endo*: δ 9.82, d, 1H, *J* = 1.6 Hz). The 3,4-*endo* product was obtained in 90% ee (OD-H, 93:7 Hexane/*i*-PrOH, 1.0 mL/min, 254 nm, major enantiomer t_r = 16.4 min, minor enantiomer t_r = 24.6 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.42 (m, 1H), 7.28-7.23 (comp, 2H), 7.05 (d, 2H, *J* = 7.6 Hz), 6.99-6.94 (m, 1H), 6.37-6.35 (comp, 2H), 4.51 (d, 1H, *J* = 5.2 Hz), 4.34 (dd, 1H, *J* = 7.2, 8.4 Hz), 3.95 (dd, 1H, *J* = 6.0, 8.4 Hz), 3.79-3.67 (comp, 2H), 3.19-3.11 (m, 1H), 1.53 (t, 1H, *J* = 4.8 Hz, -OH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.63, 150.76, 142.47, 128.84, 122.12, 114.98, 110.45, 107.07, 69.32, 66.30, 62.70, 52.42. IR (cm^{-1}): 3426, 2945, 2877, 2348, 1735, 1597, 1487, 1242, 1043, 748. HRMS (ESI) calculated for $C_{14}H_{16}NO_3$: *m/z* 246.1125 ([M + H]$^+$), found: *m/z* 246.1134.



2-Phenyl-3-(2-naphthyl)isoxazolidine-4-methanol. Obtained as a colorless oil in 90% overall yield. Regioselectivity and diastereoselectivity were determined by ^{1}H NMR of the aldehyde precursor: 3,4-isomer: 3,5-isomer = 99:1; 3,4-*endo*:3,4-*exo* = 94:6 (3,4-*endo*: δ 9.75, d, 1H, *J* = 2.0 Hz; 3,4-*exo*: δ 9.22, d, 1H, *J* = 3.2 Hz; 3,5-*endo*: δ 9.87, d, 1H, *J* = 1.6 Hz). The 3,4-*endo* product was obtained in 97% ee (OD-H, 90:10 Hexane/*i*-PrOH, 1.0 mL/min, 240 nm, major enantiomer t_r = 24.0 min, minor enantiomer t_r = 22.3 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.90-7.82 (comp, 3H), 7.66 (dd, 1H, *J* = 1.6, 8.4 Hz), 7.51-7.46 (comp, 2H), 7.22-7.18 (comp, 2H), 6.98 (d, 2H, *J* = 7.6 Hz), 6.93-6.90 (m, 1H), 4.51 (d, 1H, *J* = 5.2 Hz), 4.36 (dd, 1H, *J* = 7.2, 8.4 Hz), 4.00 (dd, 1H, *J* = 6.4, 8.4 Hz), 3.85-3.72 (comp, 2H), 2.97-2.90 (m, 1H), 1.57 (t, 1H, *J* = 4.8 Hz, -OH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.19, 139.53, 133.45, 132.92, 128.90, 128.81, 127.90, 127.72, 126.30, 125.95, 125.30, 124.65, 121.71, 114.79, 72.38, 69.32, 62.79, 56.67. HRMS (ESI) calculated for $C_{20}H_{20}NO_2$: *m/z* 306.1489 ($[M + H]^+$), found: *m/z* 306.1502.

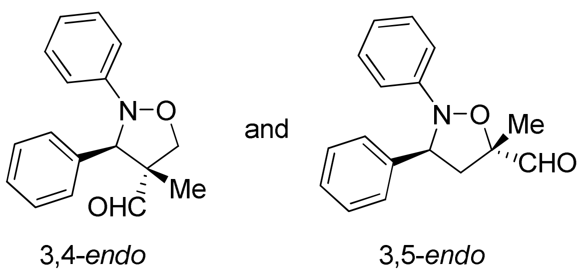


2-Benzyl-3-phenylisoxazolidine-4-methanol. Obtained as a colorless oil in 91% overall yield. Regioselectivity and diastereoselectivity were determined by ^{1}H NMR of the aldehyde precursor: 3,5-isomer was not detected at all. 3,4-*endo*:3,4-*exo* = 98:2 (3,4-*endo*: δ 9.78, d, 1H, J = 2.0 Hz; 3,4-*exo*: δ 9.29, d, 1H, J = 3.2 Hz). The 3,4-*endo* product was obtained in 95% ee (OD-H, 96:4 Hexane/*i*-PrOH, 1.0 mL/min, 230 nm, major enantiomer t_r = 23.1 min, minor enantiomer t_r = 21.0 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, 2H, J = 7.2 Hz), 7.38-7.20 (comp, 8H), 4.17 (dd, 1H, J = 8.4, 8.4 Hz), 3.93 (d, 1H, J = 14.4 Hz), 3,88 (dd, 1H, J = 4.4, 8.4 Hz), 3.75-3.64 (comp, 3H), 3,46 (d, 2H, J = 7.6 Hz), 2.80-2.70 (m, 1H), 1.60 (br, 1H, -OH). This compound has been fully characterized before.[9d]



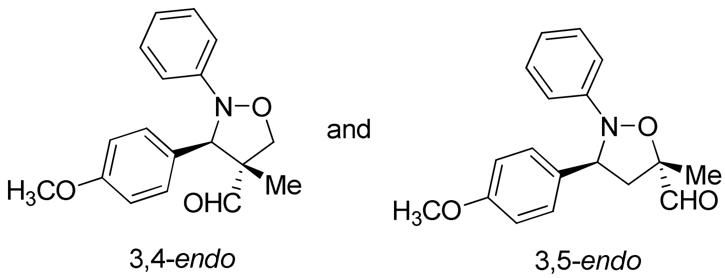
5-Methyl-2,3-diphenylisoxazolidine-4-methanol. Obtained as a colorless oil in 78% overall yield. Regioselectivity and diastereoselectivity were determined by ^{1}H NMR of the aldehyde precursor: 3,5-isomer was not detected at all. 3,4-*endo*:3,4-*exo* = 99:1 (3,4-*endo*: δ 9.70, d, 1H, J = 2.4 Hz; 3,4-*exo*: δ 9.18, d, 1H, J = 3.2 Hz). The 3,4-*endo* product was obtained in 95% ee (OD-H, 93:7 Hexane/*i*-PrOH, 1.0 mL/min, 254 nm, major enantiomer t_r = 11.3 min, minor enantiomer t_r = 17.6 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, 2H, J = 7.2 Hz), 7.40-7.36 (comp, 2H), 7.31-7.19 (comp, 3H), 6.96 (d, 2H, J = 8.0 Hz), 6.92-6.86 (m, 1H), 4.52 (d, 1H, J = 6.8 Hz), 4.17 (dq, 1H, J = 6.0, 8.4 Hz), 3.83-3.70 (comp, 2H), 2.45-2.38 (m, 1H), 1.47 (d, 3H, J = 6.0 Hz), 1.34 (t, 1H, J = 5.2 Hz, -OH). This compound has been fully characterized before.[19]

Procedure for Determination of Enantiomeric Excess for the Asymmetric 1,3-Dipolar Cycloaddition Reactions of Nitrones with Methacrolein Catalyzed by $[Rh_2(5\boldsymbol{S},\boldsymbol{R}\text{-MenPy})_4]SbF_6$. After determination of regioselectivity and diastereoselectivity as described earlier, a product mixture prior to reduction was purified by flash chromatography on silica gel (using CH_2Cl_2 as the eluent) to afford an inseparable mixture of the cycloadducts which still had the aldehyde functionality. The enantiomeric excess was determined according to the literature[5] by ^{1}H NMR spectroscopy after *in situ* formation of diastereomeric imines with (*R*)-(+)-α-methylbenzylamine (Acros, > 99%): 20 mg (1.0 eq) of product and 2.0 eq of (*R*)-(+)-α-methylbenzylamine were mixed in 0.6 ml C_6D_6; after one night at room temperature all of the aldehydes were converted to imines.

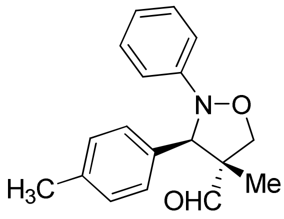


4-Methyl-2,3-diphenylisoxazolidine-4-carbaldehyde and 5-Methyl-2,3-diphenylisoxazoli-dine-5-carbaldehyde. Regioselectivity and diastereoselectivity were determined by ^{1}H NMR spectral analyses (C_6D_6, 400 MHz): 3,4-*exo* was not detected at all. 3,4-*endo*:3,5-*endo* = 79:21 (3,4-*endo*: δ 9.08, s, 1H; 3,5-*endo*: δ 9.47, s, 1H). Enantiomeric excesses of products were determined by ^{1}H NMR spectral analyses after *in situ* formation of diastereomeric imines with (*R*)-(+)-α-methylbenzylamine (Acros, > 99%). The diastereomeric excesses of imines were determined by integration of the O-N-C(3)**H**(Ph) signals: ^{1}H NMR (C_6D_6, 400 MHz)

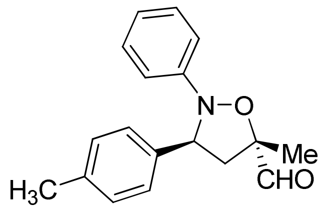
3,4-*endo*: O-N-C(3)**H1**(Ph), s, 4.96 ppm; O-N-C(3)**H2**(Ph), s, 4.92 ppm; d. r. = 99:1. 3,5-*endo*: O-N-C(3)**H1**(Ph), t, 5.05 ppm; O-N-C(3)**H2**(Ph), t, 4.73 ppm; d. r. = 78:22. Therefore, 98% ee for 3,4-*endo* and 56% ee for 3,5-*endo* were obtained after the cycloaddition reaction. These compounds have been fully characterized previously.[10]



3-(4-Methoxyphenyl)-4-methyl-2-phenylisoxazolidine-4-carbaldehyde and 3-(4-Methoxyphenyl)-5-methyl-2-phenylisoxazolidine-5-carbaldehyde. Regioselectivity and diastereoselectivity were determined by ^{1}H NMR spectral analyses (C_6D_6, 400 MHz): 3,4-*exo* was not detected at all. 3,4-*endo*:3,5-*endo* = 97:3 (3,4-*endo*: δ 9.14, s, 1H; 3,5-*endo*: δ 9.51, s, 1H). Enantiomeric excesses of products were determined by ^{1}H NMR spectral analyses after *in situ* formation of diastereomeric imines with (*R*)-(+)-α-methylbenzylamine (Acros, > 99%). The diastereomeric excesses of imines were determined by integration of the O-N-C(3)**H**(4-MeOPh) signals: ^{1}H NMR (C_6D_6, 400 MHz) 3,4-*endo*: O-N-C(3)**H1**(4-MeOPh), s, 4.93 ppm; O-N-C(3)**H2**(4-MeOPh), s, 4.88 ppm; d. r. = 99.5:0.5. Therefore, 99% ee for 3,4-*endo* product was obtained . These compounds have been fully characterized previously.[10]

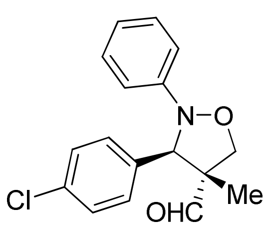


and

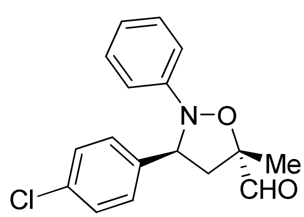


3,4-*endo* 3,5-*endo*

4-Methyl-2-phenyl-3-*p*-tolylisoxazolidine-4-carbaldehyde and 5-Methyl-2-phenyl-3-*p*-tolylisoxazolidine-5-carbaldehyde. Regioselectivity and diastereoselectivity were determined by ^{1}H NMR spectral analyses (C_6D_6, 400 MHz): 3,4-*exo* was not detected at all. 3,4-*endo*:3,5-*endo* = 89:11 (3,4-*endo*: δ 9.19, s, 1H; 3,5-*endo*: δ 9.56, s, 1H). Enantiomeric excesses of products were determined by ^{1}H NMR spectral analyses after *in situ* formation of diastereomeric imines with (*R*)-(+)-α-methylbenzylamine (Acros, > 99%). The diastereomeric excesses of imines were determined by integration of the O-N-C(3)**H**(4-MePh) signals: ^{1}H NMR (C_6D_6, 400 MHz) 3,4-*endo*: O-N-C(3)**H1**(4-MePh), s, 5.00 ppm; O-N-C(3)**H2**(4-MePh), s, 4.98 ppm; d. r. = 98.5:1.5. 3,5-*endo*: O-N-C(3)**H1**(4-MePh), t, 5.12 ppm; O-N-C(3)**H2**(4-MePh), t, 4.80 ppm; d. r. = 80:20. Therefore, 97% ee for 3,4-*endo* and 60% ee for 3,5-*endo* were obtained after the cycloaddition reaction. These compounds have been fully characterized previously.[16]

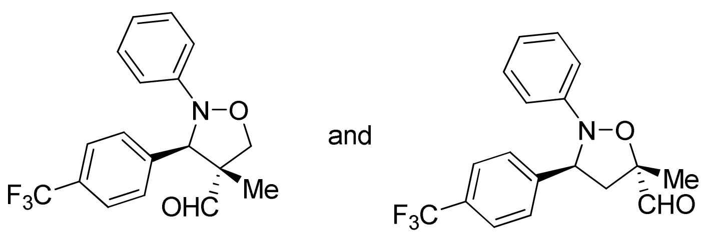


and



3,4-*endo* 3,5-*endo*

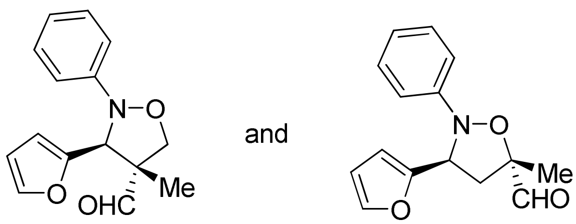
3-(4-Chlorophenyl)-4-methyl-2-phenylisoxazolidine-4-carbaldehyde and 3-(4-Chlorophenyl)-5-methyl-2-phenylisoxazolidine-5-carbaldehyde. Regioselectivity and diastereoselectivity were determined by ^{1}H NMR spectral analyses ($CDCl_3$, 400 MHz): 3,4-*exo* was not detected at all. 3,4-*endo*:3,5-*endo* = 53:47 (3,4-*endo*: δ 4.87, s, 1H; 3,5-*endo*: δ 4.74, t, 1H, *J* = 7.6 Hz). Enantiomeric excesses of products were determined by ^{1}H NMR spectral analyses after *in situ* formation of diastereomeric imines with (*R*)-(+)-α-methylbenzylamine (Acros, > 99%). The diastereomeric excesses of imines were determined by integration of the O-N-C(3)**H**(4-ClPh) signals: ^{1}H NMR (CD_3CN, 600 MHz) 3,4-*endo*: O-N-C(3)**H1**(4-ClPh), s, 5.07 ppm; O-N-C(3)**H2**(4-ClPh), s, 5.06 ppm; d. r. > 99.5:0.5. 3,5-*endo*: O-N-C(3)**H1**(4-ClPh), t, 5.00 ppm; O-N-C(3)**H2**(4-ClPh), t, 4.76 ppm; d. r. = 86:14. Therefore, 99% ee for 3,4-*endo* and 72% ee for 3,5-*endo* were obtained after the cycloaddition reaction. These compounds have been fully characterized previously.[16]



3,4-*endo* 3,5-*endo*

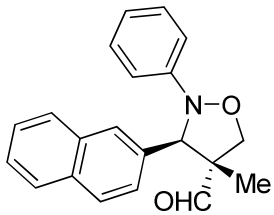
4-Methyl-2-phenyl-3-[4-(trifluoromethyl)phenyl]isoxazolidine-4-carbaldehyde and 5-Methyl-2-phenyl-3-[4-(trifluoromethyl)phenyl]isoxazolidine-5-carbaldehyde. Regioselectivity and diastereoselectivity were determined by ^{1}H NMR spectral analyses (C_6D_6, 400 MHz): 3,4-*exo* was not detected at all. 3,4-*endo*:3,5-*endo* = 30:70 (3,4-*endo*: δ 9.05, s, 1H; 3,5-*endo*: δ 9.48, s, 1H). Enantiomeric excesses of products were determined by ^{1}H NMR spectral analyses after *in situ* formation of diastereomeric imines with (*R*)-(+)-α-methylbenzylamine (Acros, > 99%). The diastereomeric excesses of imines were determined by integration of the O-N-

C(3)**H**(4-CF_3Ph) signals: ^{1}H NMR (C_6D_6, 400 MHz) 3,4-*endo*: O-N-C(3)**H1**(4-CF_3Ph), s, 5.09 ppm; O-N-C(3)**H2**(4-CF_3Ph), s, 4.98 ppm; d. r. = 98:2. 3,5-*endo*: O-N-C(3)**H1**(4-CF_3Ph), t, 5.03 ppm; O-N-C(3)**H2**(4-CF_3Ph), t, 4.71 ppm; d. r. = 81:19. Therefore, 96% ee for 3,4-*endo* and 62% ee for 3,5-*endo* were obtained after the cycloaddition reaction. These compounds have been fully characterized previously.[16]

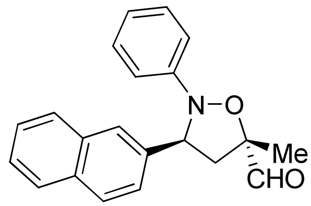


3,4-*endo* 3,5-*endo*

3-(Furan-2-yl)-4-methyl-2-phenylisoxazolidine-4-carbaldehyde and 3-(Furan-2-yl)-5-methyl-2-phenylisoxazolidine-5-carbaldehyde. Regioselectivity and diastereoselectivity were determined by ^{1}H NMR spectral analyses (C_6D_6, 400 MHz): 3,4-*exo* was not detected at all. 3,4-*endo*:3,5-*endo* = 79:21 (3,4-*endo*: δ 9.08, s, 1H; 3,5-*endo*: δ 9.48, s, 1H). Enantiomeric excesses of products were determined by ^{1}H NMR spectra analyses after *in situ* formation of diastereomeric imines with (*R*)-(+)-α-methylbenzylamine (Acros, > 99%). The diastereomeric excesses of imines were determined by integration of the O-N-C(3)**H**(furan-2-yl) signals: ^{1}H NMR (C_6D_6, 500 MHz) 3,4-*endo*: O-N-C(3)**H1**(furan-2-yl), s, 5.30 ppm; O-N-C(3)**H2**(furan-2-yl), s, 5.26 ppm; d. r. = 99:1. 3,5-*endo*: O-N-C(3)**H1**(furan-2-yl), t, 5.21 ppm; O-N-C(3)**H2**(furan-2-yl), t, 4.90 ppm; d. r. = 77:23. Therefore, 98% ee for 3,4-*endo* and 54% ee for 3,5-*endo* were obtained after the cycloaddition reaction. These compounds have been fully characterized previously.[16]



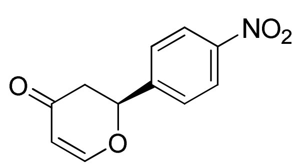
and



3,4-*endo* 3,5-*endo*

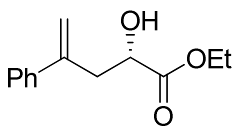
4-Methyl-3-(naphthalen-2-yl)-2-phenylisoxazolidine-4-carbaldehyde and 5-Methyl-3-(naphthalen-2-yl)-2-phenylisoxazolidine-5-carbaldehyde. Regioselectivity and diastereoselectivity were determined by ^{1}H NMR spectral analyses (C_6D_6, 400 MHz): 3,4-*exo* was not detected at all. 3,4-*endo*:3,5-*endo* = 70:30 (3,4-*endo*: δ 9.21, s, 1H; 3,5-*endo*: δ 9.58, s, 1H). Enantiomeric excesses of products were determined by ^{1}H NMR spectral analyses after *in situ* formation of diastereomeric imines with (*R*)-(+)-α-methylbenzylamine (Acros, > 99%). The diastereomeric excesses of imines were determined by integration of the O-N-C(3)**H**(naphthalen-2-yl) signals: ^{1}H NMR (C_6D_6, 400 MHz) 3,4-*endo*: O-N-C(3)**H1**(naphthalen-2-yl), s, 5.26 ppm; O-N-C(3)**H2**(naphthalen-2-yl), s, 5.19 ppm; d. r. = 97.5:2.5. 3,5-*endo*: O-N-C(3)**H1**(naphthalen-2-yl), t, 5.30 ppm; O-N-C(3)**H2**(naphthalen-2-yl), t, 4.99 ppm; d. r. = 76:24. Therefore, 95% ee for 3,4-*endo* and 52% ee for 3,5-*endo* were obtained after the cycloaddition reaction. These compounds have been fully characterized previously.[16]

Procedure for the Asymmetric Hetero-Diels-Alder Reaction of *p*-Nitrobenzaldehyde with the Danishefsky Diene Catalyzed by Rh_2(5*S*,*S*-MenPy)$_4$$SbF_6$. A 10 ml Schlenk flask charged with a magnetic stir bar and 4 Å molecular sieves (300 mg) was placed under high vacuum and heated by Bunsen burner to dryness. After cooling to room temperature, Rh_2(5*S*,*S*-MenPy)$_4$ (33.8 mg, 0.026 mmol), 2,6-di-*tert*-butylpyridine (22 μL, 0.10 mmol) and toluene (1.0 mL) were added under a flow of N_2. The resulting green solution was stirred for 10 min before $NOSbF_6$ (6.6 mg, 0.025 mmol) was added. The solution was allowed to stir for an additional 30 min, during which time the color gradually turned from green to deep red. *p*-Nitrobenzaldehyde (76 mg, 0.5 mmol) was added into the mixture, followed by the addition of 0.5 mL toluene. Then, the Danishefsky diene (120 μL, 0.62 mmol) was added *via* a micro syringe to the flask. The solution was stirred at room temperature until completion of the reaction (TLC). Three drops of TFA were added, and the reaction solution was stirred for an additional 30 min., then 5 mL CH_2Cl_2 was added to dilute the solution. The mixture was washed with saturated $NaHCO_3$ and brine solution, then the organic layer was concentrated and chromatographed on silica gel with hexane:ethyl acetate (2:1) to isolate the product (104 mg, 95% yield).



(*S*)-2-(4-Nitrophenyl)-2*H*-pyran-4(3*H*)-one. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, 2H, *J* = 8.8 Hz), 7.59 (d, 2H, *J* = 8.8 Hz), 7.51 (d, 1H, *J* = 6.0 Hz), 5.58 (dd, 1H, *J* = 6.0, 0.9 Hz), 5.55 (dd, 1H, *J* = 3.7, 14.0 Hz), 2.86 (dd, 1H, *J* = 14.0, 16.8 Hz), 2.73 (ddd, 1H, *J* = 0.9, 3.7, 16.8 Hz). This compound has been fully characterized previously.[9d] The enantiomeric excess was determined to be 94% ee (OD-H, 80:20 Hexane/*i*-PrOH, 1.0 mL/min, 254 nm, major enantiomer t_r = 22.6 min, minor enantiomer t_r = 32.0 min).

Procedure for the Asymmetric Carbonyl-ene Reaction of Ethyl Glyoxylate with α-Methylstyrene Catalyzed by $Rh_2(5S,S\text{-MenPy})_4SbF_6$. After $Rh_2(5S,S\text{-MenPy})_4SbF_6$ (0.025 mmol) was generated *in situ* in toluene (1.0 mL) in a Schlenk flask (procedure same as that for the hetero-Diels-Alder reaction), α-methylstyrene (325 μL, 2.5 mmol) was added to the catalyst solution and stirred for 10 min, followed by the addition of ethyl glyoxylate (0.5 mmol). The resulting solution was stirred at 0 °C in an ice bath for 7 days (the temperature of the ice bath was maintained by constantly decanting water and adding ice). The reaction mixture was concentrated and directly loaded onto a silica column (hexane:ethyl acetate = 3:1) to isolate the product (99 mg, 90% yield).



(*S*)-Ethyl 2-Hydroxy-4-phenylpent-4-enoate. ^1H NMR (400 MHz, $CDCl_3$): δ 7.44-7.39 (comp, 2H), 7.36-7.30 (comp, 2H), 7.30-7.25 (m, 1H), 5.39 (s, 1H), 5.21 (s, 1H), 4.30-4.23 (m, 1H), 4.15-4.00 (comp, 2H), 3.05 (dd, 1H, *J* = 4.4, 14.4 Hz), 2.84 (dd, 1H, *J* = 7.6, 14.4 Hz), 2.75 (d, 1H, *J* = 6.3 Hz), 1.23 (t, 3H, *J* = 7.1 Hz). This compound has been fully characterized previously.[28d] The enantiomeric excess was determined to be 94% ee (AD-H, 98.5:1.5 Hexane/*i*-PrOH, 1.0 mL/min, 254 nm, major enantiomer t_r = 25.5 min, minor enantiomer t_r = 29.0 min).

NMR graphs and HPLC chromatograms can be obtained from the supporting information of the paper published in the *Journal of the American Chemical Society*: Wang, X.; Weigl, C.; Doyle, M. P. *J. Am. Chem. Soc.* **2011**, *133*, 9572.

4.4 Data Table for Figure 1.5

Conversion (%) as a function of time for the standard reaction of *N*,α-diphenylnitrone with acrolein catalyzed by $[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ in PhMe, PhCl, PhI, and CH_2Cl_2 at 0 °C (plotted in Figure 1.5).[a]

reaction time	conversion(%)[b] in PhMe	conversion(%)[b] in PhCl	conversion(%)[b] in PhI	conversion(%)[b] in CH_2Cl_2
after 20 min	84	67	n. d.	n. d.
40 min	96	88	n. d.	n. d.
1 h	100	95	52	27
1 h 20 min		100	n. d.	n. d.
2 h			78	42
3 h			91	56
4 h			100	67
5 h				76

[a] The general procedure was carried out. [b] Determined by ^{1}H NMR; conversion (%) based on nitrone; n. d. = not determined.

4.5 DFT Calculation Details

DFT Calculations of the Ground-state Acrolein-$Rh_2(5S\text{-IPPy})_4^+$ Complex in the Solvent of Toluene and Dichloromethane. Calculations were performed with Gaussian 03 software.[31] The B3LYP functional with the LANL2DZ basis set and the CPCM solvation model was applied in these calculations. The vibrational frequencies calculated for the energy minimized geometries are all positive.

The Ground-State Conformation of Acrolein-$Rh_2(5S\text{-IPPy})_4^+$ in Dichloromethane:

E_{0K} = -2779.878836, H_{298K} = -2779.818320, G_{298K} = -2779.979118 (Hartree/Particle)

Center Atomic Atomic Coordinates (Angstroms)

Number	Number	Type	X	Y	Z
1	45	0	-1.356057	-0.619541	-0.511208
2	45	0	0.866538	-0.526415	0.590871
3	7	0	-1.828408	-2.030491	0.819371
4	7	0	-1.895902	0.879558	0.713177
5	7	0	1.381101	-2.113976	-0.548887
6	7	0	1.409834	0.783425	-0.833981
7	8	0	-0.654692	0.711130	-1.920336
8	8	0	-0.636854	-2.139844	-1.725142
9	8	0	0.171016	1.017547	1.790645
10	8	0	0.140723	-1.841554	2.049097
11	6	0	-1.037122	-2.362190	1.848421
12	6	0	-1.064300	1.401100	1.625473
13	6	0	0.583803	1.127089	-1.822159
14	6	0	0.549341	-2.625945	-1.456458
15	6	0	2.734725	1.433778	-0.980717
16	1	0	3.529167	0.711883	-0.797919
17	6	0	2.628979	-2.902938	-0.447764
18	1	0	2.886613	-3.080255	0.597678
19	6	0	-3.221524	1.548873	0.750682
20	1	0	-4.014234	0.803361	0.697569
21	6	0	-2.997252	-2.940882	0.751436
22	1	0	-2.764814	-3.763176	0.054524
23	8	0	2.812860	-0.485470	1.595468
24	6	0	2.936375	-0.186802	2.822636
25	1	0	2.046446	0.089256	3.402687
26	6	0	4.226082	-0.192325	3.494996
27	1	0	5.099008	-0.459565	2.904629
28	6	0	4.316136	0.127355	4.812609
29	1	0	3.437388	0.394372	5.397645

30	1	0	5.270978	0.128401	5.330780
31	6	0	1.113752	-3.859128	-2.135841
32	1	0	0.355933	-4.642688	-2.218908
33	1	0	1.442933	-3.601978	-3.150032
34	6	0	2.294559	-4.239989	-1.205187
35	1	0	3.156548	-4.635814	-1.747546
36	1	0	1.979002	-4.990397	-0.474228
37	6	0	1.235961	2.046356	-2.835552
38	1	0	1.016723	1.721279	-3.856437
39	1	0	0.845794	3.062617	-2.709544
40	6	0	2.737851	1.941760	-2.462880
41	1	0	3.233306	1.187574	-3.080442
42	1	0	3.269323	2.889467	-2.578518
43	6	0	2.945061	2.585144	0.014699
44	8	0	3.964820	2.687976	0.725915
45	8	0	1.928504	3.491990	-0.029416
46	6	0	1.937510	4.758198	0.803635
47	1	0	0.959498	5.170962	0.537517
48	6	0	3.814930	-2.200567	-1.121044
49	8	0	3.723797	-1.419949	-2.088279
50	8	0	4.982539	-2.612088	-0.547692
51	6	0	6.341433	-2.221968	-1.097646
52	1	0	6.991813	-2.746295	-0.391063
53	6	0	-1.715771	2.485211	2.460421
54	1	0	-1.319348	3.461583	2.158953
55	1	0	-1.498043	2.345312	3.522995
56	6	0	-3.217358	2.327999	2.110974
57	1	0	-3.736249	3.287119	2.041414
58	1	0	-3.724828	1.720737	2.866713
59	6	0	-3.441290	2.493608	-0.441382
60	6	0	-4.206993	-2.231204	0.157427

61	8	0	-4.476544	2.474555	-1.136118
62	8	0	-4.107956	-1.204303	-0.552876
63	8	0	-2.413204	3.374862	-0.591231
64	8	0	-5.357903	-2.878084	0.446879
65	6	0	-6.707541	-2.444282	-0.112032
66	1	0	-7.348268	-3.212257	0.330570
67	6	0	-3.122168	-3.500963	2.200226
68	1	0	-3.775128	-2.857246	2.797956
69	1	0	-3.531608	-4.512440	2.209509
70	6	0	-1.660523	-3.433813	2.725784
71	1	0	-1.586237	-3.170320	3.784628
72	1	0	-1.123507	-4.380122	2.579498
73	6	0	-2.492042	3.836558	-3.065149
74	1	0	-1.769768	3.019483	-3.167720
75	1	0	-3.492203	3.455552	-3.288008
76	1	0	-2.240934	4.612632	-3.799318
77	6	0	-3.508500	5.488298	-1.360306
78	1	0	-3.377895	6.343154	-2.035770
79	1	0	-4.509816	5.075495	-1.514197
80	1	0	-3.423929	5.854105	-0.330368
81	6	0	-2.421475	4.449858	-1.661339
82	1	0	-1.432496	4.889416	-1.498684
83	6	0	3.047758	5.699759	0.322486
84	1	0	2.926717	6.672435	0.815589
85	1	0	4.039289	5.308077	0.567667
86	1	0	2.980996	5.857781	-0.760209
87	6	0	1.972591	4.436372	2.302643
88	1	0	1.224952	3.675325	2.551949
89	1	0	2.958281	4.081461	2.614794
90	1	0	1.733770	5.348956	2.863274
91	6	0	6.568010	-0.709947	-0.985312

92	1	0	5.960319	-0.157192	-1.706940
93	1	0	6.339000	-0.355268	0.026305
94	1	0	7.625740	-0.498501	-1.186412
95	6	0	6.534564	-2.797389	-2.505629
96	1	0	7.581243	-2.657271	-2.802937
97	1	0	6.319706	-3.872251	-2.519395
98	1	0	5.896392	-2.293647	-3.237273
99	6	0	-7.093924	-1.064246	0.430051
100	1	0	-6.992529	-1.031908	1.521039
101	1	0	-6.485064	-0.271502	-0.013474
102	1	0	-8.145658	-0.873647	0.182663
103	6	0	-6.719488	-2.568261	-1.639176
104	1	0	-6.370110	-3.558842	-1.952483
105	1	0	-7.751620	-2.446939	-1.990479
106	1	0	-6.100347	-1.800869	-2.112262

The Ground-State Conformation of Acrolein-Rh_2(5*S*-IPPy)$_4^+$ in Toluene:

E_{0K} = -2779.811496, H_{298K} = -2779.751382, G_{298K} = -2779.911345 (Hartree/Particle)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	45	0	-1.269326	-0.575397	-0.779344
2	45	0	0.837200	-0.600866	0.538418
3	7	0	-1.910564	-2.083640	0.384261
4	7	0	-1.925487	0.818845	0.502053
5	7	0	1.453365	-2.093385	-0.677069
6	7	0	1.519867	0.823300	-0.715040
7	8	0	-0.434859	0.850484	-1.988124

8	8	0	-0.454203	-1.999653	-2.022989
9	8	0	0.040072	0.873111	1.764733
10	8	0	-0.035807	-2.027725	1.777819
11	6	0	-1.189260	-2.518150	1.429157
12	6	0	-1.177834	1.270696	1.517445
13	6	0	0.793653	1.236654	-1.755476
14	6	0	0.707592	-2.506393	-1.703890
15	6	0	2.854286	1.491240	-0.697029
16	1	0	3.620507	0.758886	-0.443679
17	6	0	2.684427	-2.901232	-0.535248
18	1	0	2.838347	-3.182757	0.508129
19	6	0	-3.273530	1.446490	0.495890
20	1	0	-4.035221	0.670473	0.426395
21	6	0	-3.127938	-2.904010	0.182011
22	1	0	-3.213867	-3.199092	-0.866729
23	8	0	2.643286	-0.740513	1.711902
24	6	0	2.792554	-0.117930	2.806962
25	1	0	2.010685	0.568380	3.149173
26	6	0	3.966148	-0.320813	3.645522
27	1	0	4.719831	-1.017725	3.286096
28	6	0	4.091279	0.333547	4.827144
29	1	0	3.331822	1.032583	5.174359
30	1	0	4.955196	0.189860	5.470405
31	6	0	1.343793	-3.661422	-2.454724
32	1	0	0.601216	-4.421312	-2.712319
33	1	0	1.777410	-3.288579	-3.391044
34	6	0	2.422282	-4.151341	-1.452707
35	1	0	3.335194	-4.504693	-1.938319
36	1	0	2.031955	-4.969097	-0.838003
37	6	0	1.551509	2.196195	-2.651982
38	1	0	1.413124	1.931745	-3.704084

39	1	0	1.176707	3.215118	-2.500316
40	6	0	3.010127	2.030925	-2.148450
41	1	0	3.528739	1.268207	-2.736494
42	1	0	3.574812	2.963819	-2.188726
43	6	0	2.882910	2.568977	0.407933
44	8	0	3.247651	2.334046	1.576704
45	8	0	2.466123	3.786692	-0.044026
46	6	0	2.447121	5.014672	0.842526
47	1	0	2.108973	5.767090	0.122591
48	6	0	3.935679	-2.149924	-1.008358
49	8	0	3.939613	-1.204817	-1.818241
50	8	0	5.044188	-2.719374	-0.451326
51	6	0	6.447864	-2.294876	-0.824910
52	1	0	7.028387	-2.969142	-0.187245
53	6	0	-1.899115	2.300775	2.363050
54	1	0	-1.462521	3.288259	2.174106
55	1	0	-1.781140	2.079061	3.427992
56	6	0	-3.364192	2.198017	1.866322
57	1	0	-3.837144	3.177481	1.764888
58	1	0	-3.961920	1.594035	2.555078
59	6	0	-3.470337	2.354620	-0.726655
60	6	0	-4.404295	-2.143536	0.570503
61	8	0	-4.356284	2.151103	-1.575059
62	8	0	-4.486696	-1.362057	1.537951
63	8	0	-2.586702	3.396587	-0.738952
64	8	0	-5.419292	-2.488471	-0.267067
65	6	0	-6.839788	-1.983252	-0.089249
66	1	0	-7.315123	-2.454659	-0.954923
67	6	0	-2.591588	4.417532	-1.859595
68	1	0	-1.722372	5.019809	-1.573532
69	6	0	-2.917320	-4.146640	1.122617

70	1	0	-3.850402	-4.471740	1.589773
71	1	0	-2.530397	-4.981528	0.529590
72	6	0	-1.860257	-3.671007	2.153041
73	1	0	-2.318897	-3.296284	3.076246
74	1	0	-1.134021	-4.440645	2.428017
75	6	0	1.407266	4.857306	1.957947
76	1	0	0.429286	4.597178	1.536329
77	1	0	1.706666	4.088324	2.675108
78	1	0	1.306031	5.812335	2.488948
79	6	0	3.861312	5.360984	1.325193
80	1	0	4.560843	5.401106	0.482038
81	1	0	3.843468	6.353245	1.793621
82	1	0	4.225477	4.636299	2.058022
83	6	0	6.709421	-0.839896	-0.415857
84	1	0	6.177602	-0.140244	-1.066472
85	1	0	6.407421	-0.667131	0.623993
86	1	0	7.785027	-0.636671	-0.492906
87	6	0	6.728300	-2.603399	-2.300838
88	1	0	7.794182	-2.440441	-2.504511
89	1	0	6.500581	-3.651144	-2.529329
90	1	0	6.147383	-1.955497	-2.963492
91	6	0	-6.906229	-0.457428	-0.223854
92	1	0	-6.521165	0.040448	0.670647
93	1	0	-6.347548	-0.106756	-1.098978
94	1	0	-7.955179	-0.163016	-0.356417
95	6	0	-7.437699	-2.538808	1.208628
96	1	0	-8.506937	-2.294711	1.241432
97	1	0	-7.341063	-3.630089	1.248306
98	1	0	-6.958025	-2.100613	2.089032
99	6	0	-2.341876	3.750888	-3.218953
100	1	0	-1.516617	3.033218	-3.155052

101	1	0	-3.231181	3.225378	-3.575824
102	1	0	-2.076535	4.526230	-3.949657
103	6	0	-3.864080	5.271024	-1.792795
104	1	0	-3.780440	6.094835	-2.513132
105	1	0	-4.749681	4.681556	-2.046568
106	1	0	-3.993905	5.706382	-0.794874

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Chapter 2

Asymmeric [3+3]-Cycloaddition Reactions of Nitrones with Electrophilic Vinylcarbene Intermediates

I. Introduction

<u>1.1 General Introduction</u>

Nitrones (Figure 2.1), an important class of dipolar compounds, have been widely used in the preparation of isoxazolidines through [3+2]-dipolar cycloaddition reactions with alkenes (Scheme 2.1).[1] In Chapter 1, I have introduced a highly selective [3+2]-cycloaddition reaction of nitrones with α,β-unsaturated aldehydes by use of the cationic chiral dirhodium carboxamidates.[2] I and my colleagues envisioned that, when a rhodium carbene (**1**), which is generated from a vinyldiazoacetate and a dirhodium catalyst (Rh_2L_4), is treated with a nitrone, a stepwise [3+3]-cycloaddition or a concerted [3+2]-cycloaddition could occur (Scheme 2.2). With the work described in this chapter, the [3+3]-cycloaddition pathway between nitrones and rhodium vinylcarbenes (drawn with dashed arrows in Scheme 2.2) has been confirmed. Herein I will discuss the background of this [3+3]-cycloaddition and its scope and limitations.

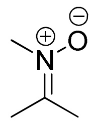
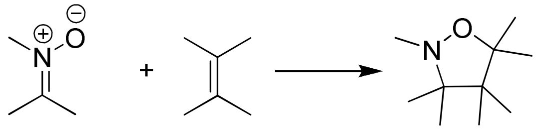
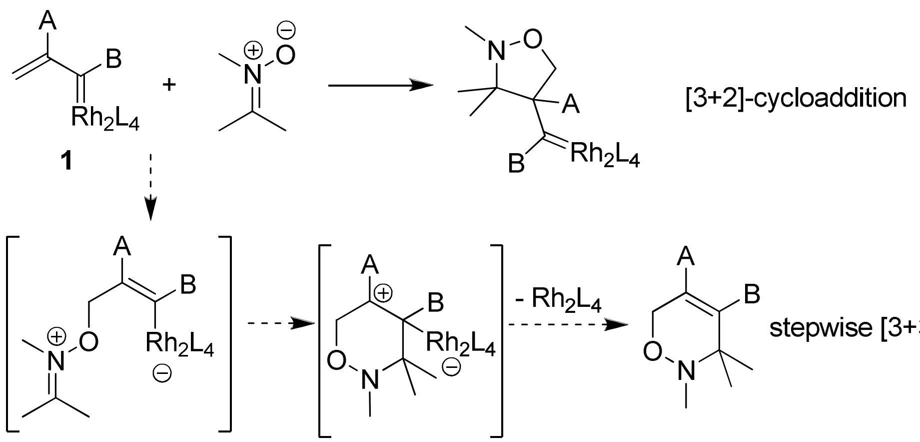


Figure 2.1 General Structural Representation for Nitrones.



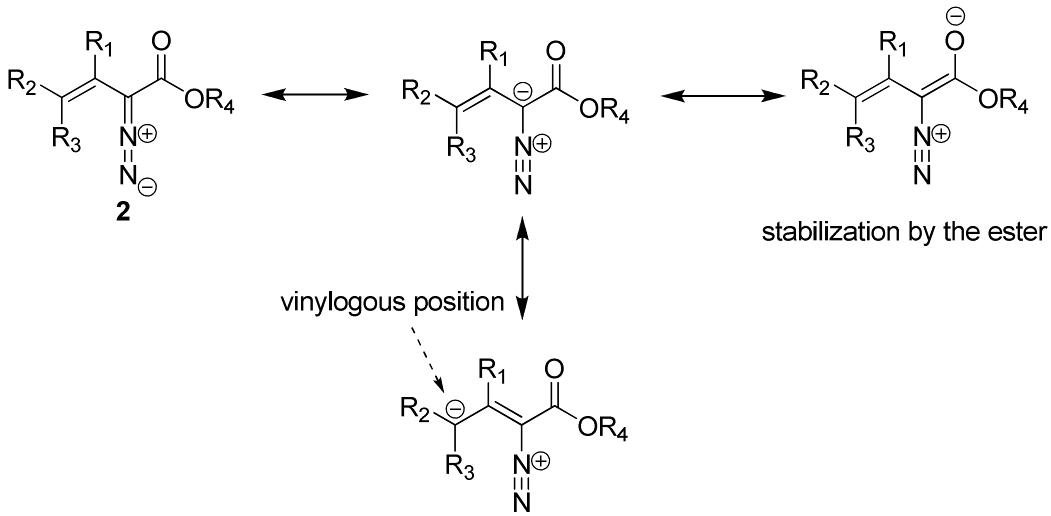
Scheme 2.1 General Representation of [3+2]-Cycloaddition Reactions of Nitrones with Alkenes.



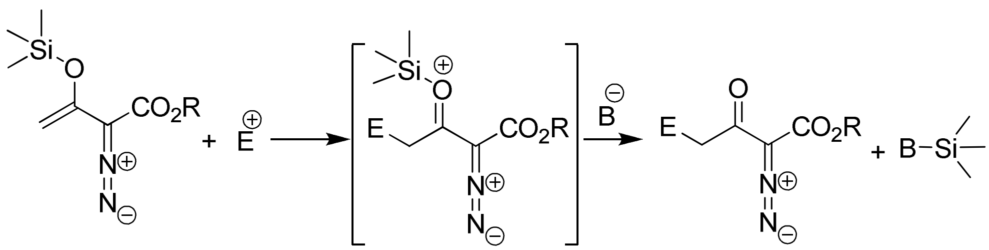
Scheme 2.2 [3+2] or [3+3]-Cycloaddition of Nitrones with Rhodium Vinylcarbenes.

<u>1.2 Vinyldiazoacetates</u>

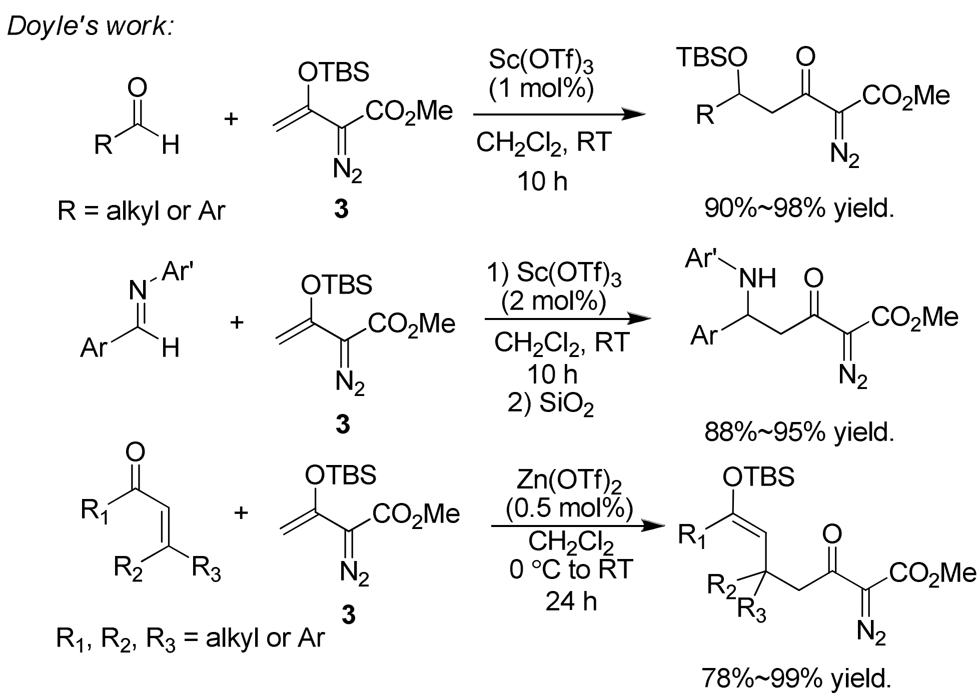
A vinyldiazoacetate (**2**) is an α-diazoacetate bonded through the diazo carbon to a vinyl group.[3] In this highly conjugated structure (Scheme 2.3) electron distribution can be viewed as giving excess electron density to the γ-vinyl carbon that is referred to as the vinylogous position. When the β-substituent (R_1 in Scheme 2.3) is a siloxy group, the vinylogous site of a vinyldiazoacetate is nucleophilic (Scheme 2.4). Based on this knowledge, the Doyle group has developed the Mukaiyama-aldol reaction,[4] the Mannich reaction[4] and the Mukaiyama-Michael reaction[5] of the β-siloxy-substituted vinyldiazoacetates (e.g., **3**) with electrophiles (Scheme 2.5), all of which occurred in high yields.



Scheme 2.3 Resonance Forms of Vinyldiazoacetates.

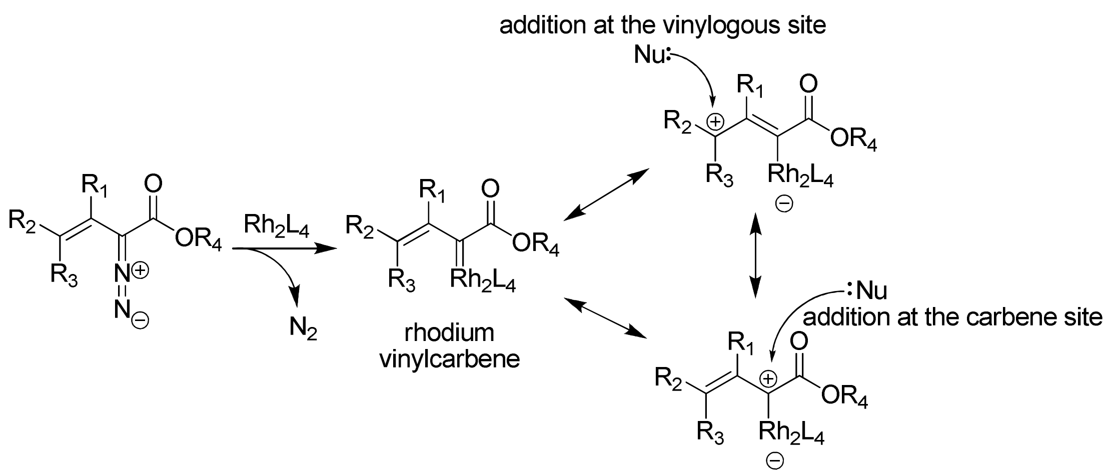


Scheme 2.4 General Scheme for the Nucleophilic Addition of a β-Siloxy-Substituted Vinyldiazoacetate to an Electrophile.



Scheme 2.5 Examples of the Nucleophilic Addition of a β-Siloxy-Substituted Vinyldiazoacetate to Electrophiles.

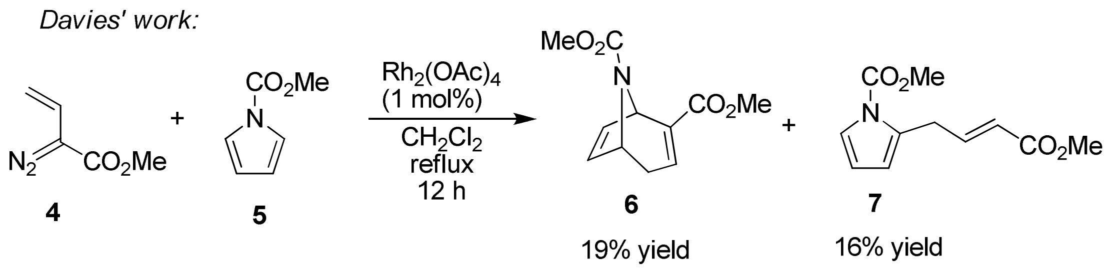
When a dirhodium carboxylate or a dirhodium carboxamidate (discussed in the introduction section of Chapter 1) is added to a vinyldiazoacetate, a rhodium vinylcarbene is formed through the evolution of nitrogen gas from the vinyldiazoacetate (Scheme 2.6).[3] The introduction of the electron-deficient carbon center in a rhodium vinylcarbene makes both the vinylogous site and the carbene site electrophilic (Scheme 2.6),[4] which is the reverse of the polarization in the original vinyldiazoacetate (Scheme 2.3). Reactions at the carbene site have been well documented,[6] but the reactivities of the vinylogous site have attracted much less attention.[7]



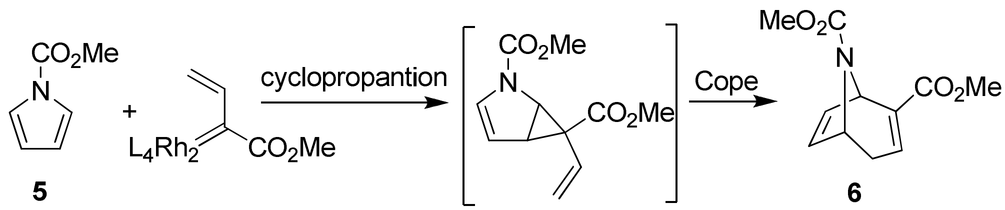
Scheme 2.6 Formation and Resonance Forms of Rhodium Vinylcarbenes.

The possibility of a nucleophilic attack at the vinylogous site of a rhodium vinylcarbene was first confirmed by Davies[7a] when he observed alkylation at the vinylogous site (product **7**) in reactions of methyl 2-diazo-3-butenoate (**4**) with *N*-(methoxycarbonyl)pyrole (**5**) catalyzed by $Rh_2(OAc)_4$ (Scheme 2.7). Davies' purpose of setting up this reaction was to prepare a nitrogen-bridged cycloheptadiene **6** *via* a tandem cyclopropanation/Cope rearrangement cascade process (Scheme 2.8).

However, in refluxing dichloromethane with 1 mol% of $Rh_2(OAc)_4$, reaction of **4** with **5** only provide **6** in 19% yield together with a 16% yield of **7** (Scheme 2.7).[7a]

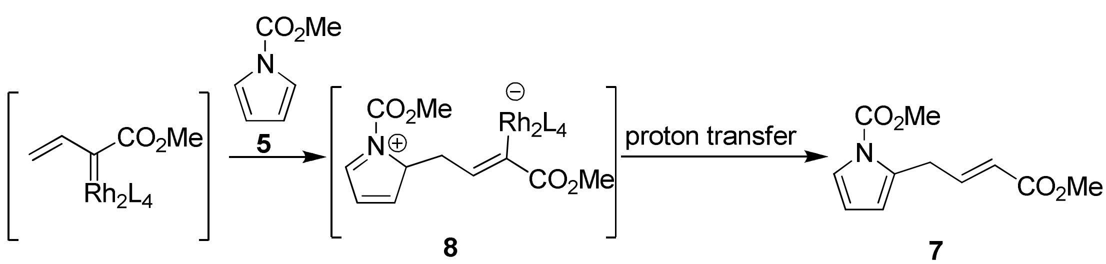


Scheme 2.7 Observation of the Vinylogous Addition.



Scheme 2.8 Cascade Process for the Formation of **6**.

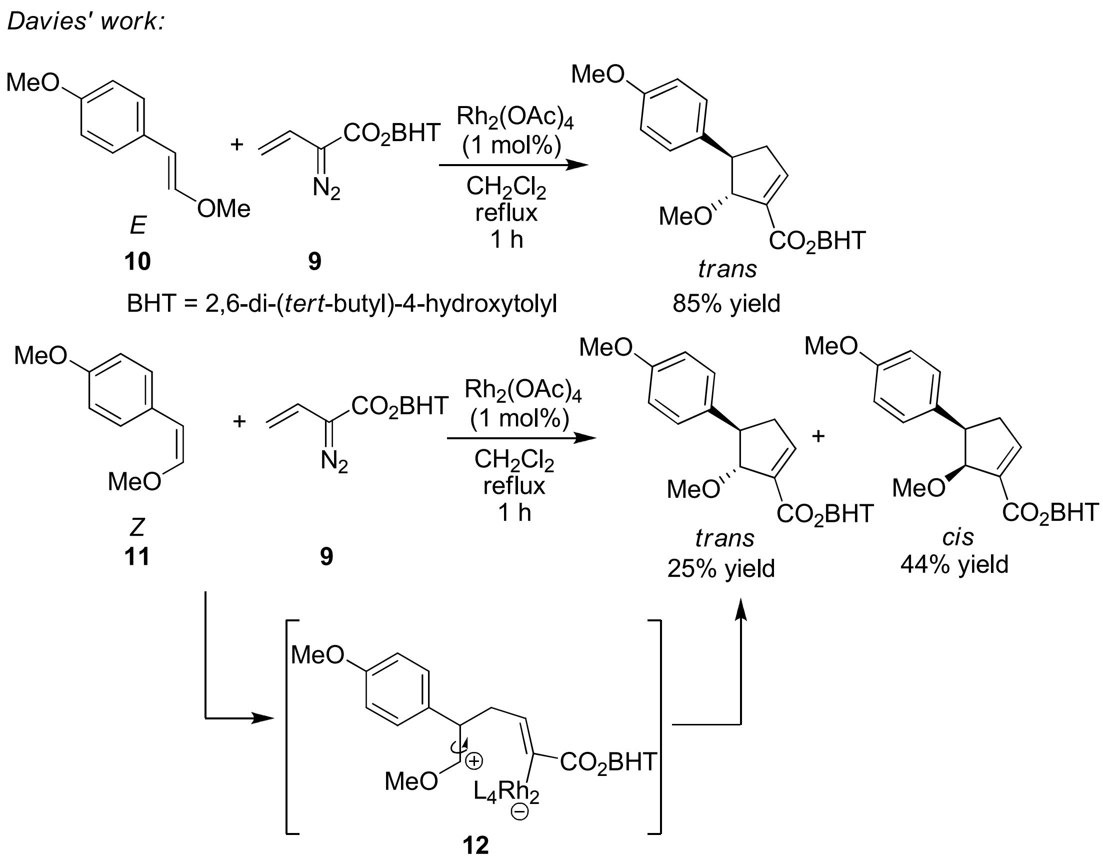
The formation of **7** was proposed to occur through dipolar intermediate **8**, which was formed by addition of **5** to the rhodium vinylcarbene at the vinylogous site (Scheme 2.9). This mechanism is supported by the observation that using a non-polar solvent such as hexane inhibits the formation of **7**, because a dipolar intermediate (e.g., **8**) is expected to be destabilized by non-polar media.



Scheme 2.9 Formation of **7** via the Vinylogous Addition.

Generation of a dipolar intermediate through vinylogous addition was also confirmed in the $Rh_2(OAc)_4$-catalzyed [3+2]-cycloaddition reactions of vinyldiazoacetates with vinyl ethers.[7b] Vinyldiazoacetate **9** was reacted with the *E* and

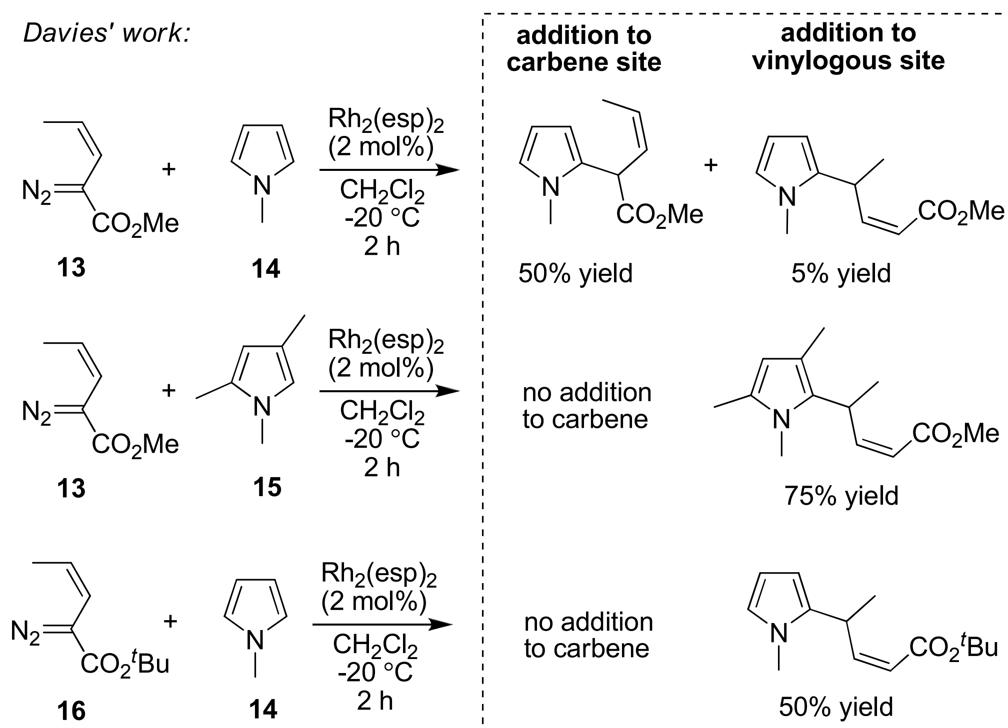
Z vinyl ethers, **10** and **11** in the presence of $Rh_2(OAc)_4$ (Scheme 2.10). Reaction with the *E* vinyl ether (**10**) produced the *trans* product exclusively; however, a mixture of *cis* and *trans* products was formed with the *Z* vinyl ether (**11**). The result from the Z vinyl ether clearly indicates the presence of intermediate **12** in the process that could adjust its conformation to produce the *trans* product (Scheme 2.10).[7b]



Scheme 2.10 [3+2]-Cycloadditions of *E* and *Z* Vinyl Ethers with a Rhodium Vinylcarbene.

The selectivity between the vinylogous site and the carbene site in nucleophilic additions to rhodium vinylcarbenes can be influenced by steric effect from substituents on nucleophiles.[7c] For example, the reaction between methyl 2-diazo-(*Z*)-pent-3-enoate (**13**) and *N*-methylpyrrole (**14**) catalyzed by $Rh_2(esp)_2$[8] (Figure 2.2) produced two substitution products in 55% overall yield (Scheme 2.11).[7c]

The major product accounting for 50% yield was generated from reaction at the carbene site; and the minor product, accounting for 5% yield, was from addition to the vinylogous site. However, when the nucleophile was changed to the 2,4-dimethyl-substituted *N*-methylpyrrole (**15**), regioselectivity shifted to the vinylogous addition completely, and the same outcome was also obtained when the steric bulk of the vinyldiazoacetate was increased by changing from the methyl ester in **13** to the *tert*-butyl ester in **16** (Scheme 2.11).[7c]



Scheme 2.11 Regioselectivity Influenced by the Steric Effect of the Reactants.

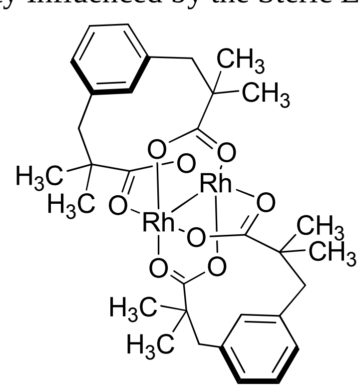
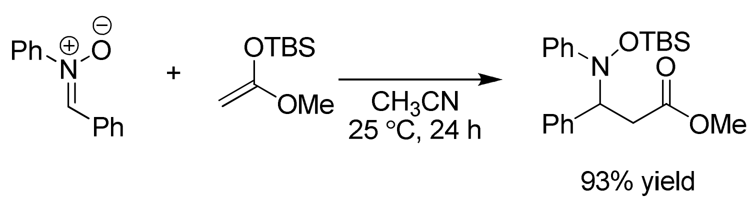


Figure 2.2 $Rh_2(esp)_2$ {Bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionates)]}

1.3 Nitrones

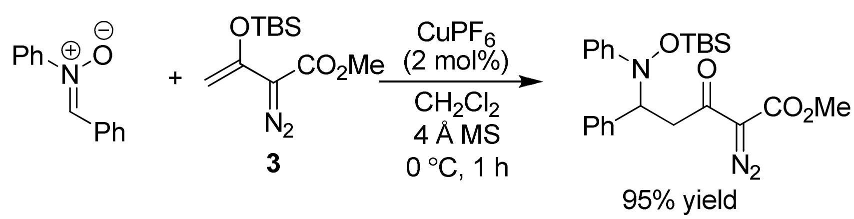
Besides their potential in dipolar cycloaddition reactions, nitrones are also electrophiles. Since Tomoda first performed the nucleophilic addition of silyl ketene acetals to nitrones (Scheme 2.12) in 1982,[9] nucleophilic additions to nitrones have been performed by many groups.[10] Dr. X. Xu in our group first mixed β-siloxy-substituted vinyldiazoacetate **3** with *N*,*α*-diphenylnitrone, and found that nucleophilic addition of **3** to the electron-deficient carbon of the nitrone with TBS transfer occurred in a high yield when Lewis acid $CuPF_6$ was added (Scheme 2.13).[11]

Tomoda's work:



Scheme 2.12 Nucleophilic Addition of a Silyl Ketene Acetal to *N*,*α*-diphenylnitrone.

Doyle's work:

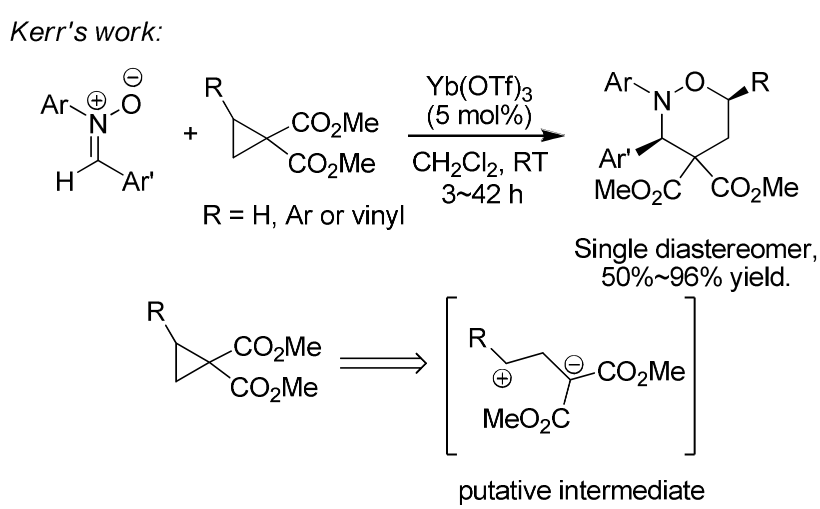


Scheme 2.13 Nucleophilic Addition of Vinyldiazoacetate **3** to *N*,*α*-diphenylnitrone.

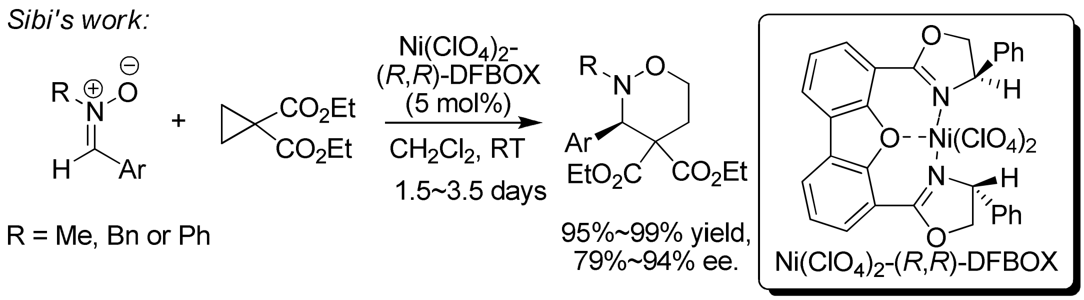
1.4 Previous Reports of [3+3]-Cycloaddition Reactions with Nitrones

A cycloaddition is a reaction in which two or more unsaturated molecules (or parts of the same molecule) combine with the formation of a cyclic adduct in which there is a net reduction of the bond multiplicity.[12] Cycloadditions may be pericyclic reactions or stepwise reactions.[12] Although [3+2]-cycloaddition reactions of nitrones have been studied extensively,[1,2] scarce attention has been given to the [3+3]-cycloaddition that involves a nitrone.

There are only a few reports in the literature that present a [3+3]-cycloaddition process with nitrones. In 2003, Kerr and co-workers developed a [3+3]-cycloaddition reaction of a nitrone with a 1,1-cyclopropane diester to produce a tetrahydro-1,2-oxazine (Scheme 2.14).[13] 1,1-Cyclopropane diesters are known to have dipolar character due to polarization by the esters.[14] Although there are still unanswered questions on the mechanism of this process,[13] the overall outcome is the connection of a dipole donor to a dipole acceptor in a head to tail fashion. Following Kerr's discovery, Sibi developed an enantioselective version of the reaction through the use of Kanemasa's chiral $Ni(ClO_4)_2$-(*R*,*R*)-DFBOX catalyst[15] as the Lewis acid (Scheme 2.15).[16]

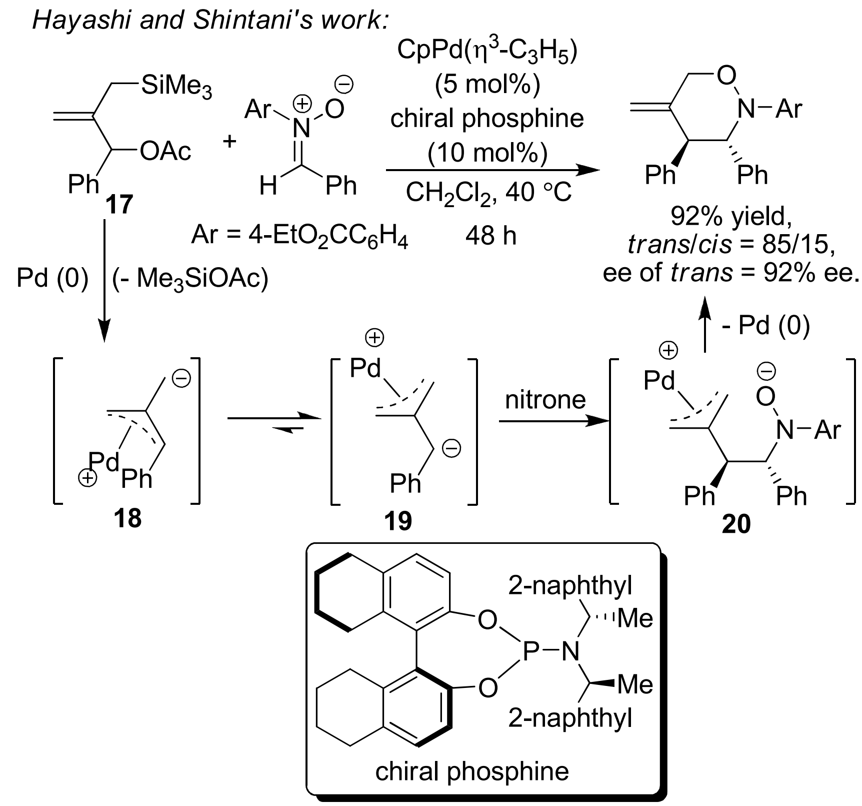


Scheme 2.14 [3+3]-Cycloaddition Reactions of Nitrones with Cyclopropanes.



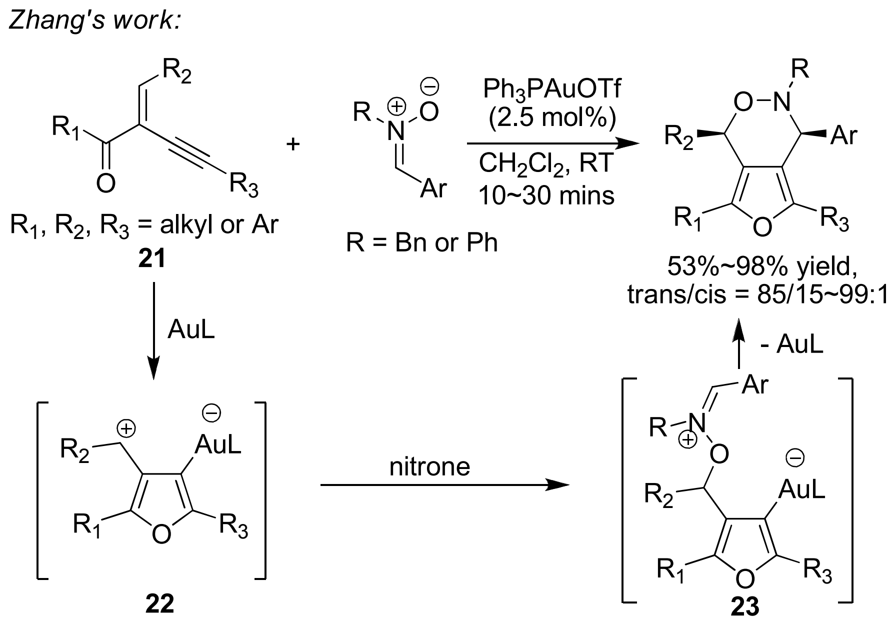
Scheme 2.15 Chiral Lewis Acid-Catalyzed Asymmetric [3+3]-Cycloaddition Reactions of Nitrones with Cyclopropanes.

In 2006, Hayashi and Shintani reported an enantioselective [3+3]-cycladdition reaction of a trimethylenemethane **17** with nitrones catalyzed by a *in situ*-generated chiral Pd(0)-phosphine catalyst (Scheme 2.16).[17] In this reaction, the generation of the Pd-associated dipolar intermediate **18** from **17** by coordination of a Pd catalyst is a well-studied process,[18] the isomerization from **18** to **19** is driven by stabilization of the benzylic anion,[19] and addition occurs by attack of the benzylic anion at the electron-deficient carbon of the nitrone (**19** $\rightarrow$ **20**).

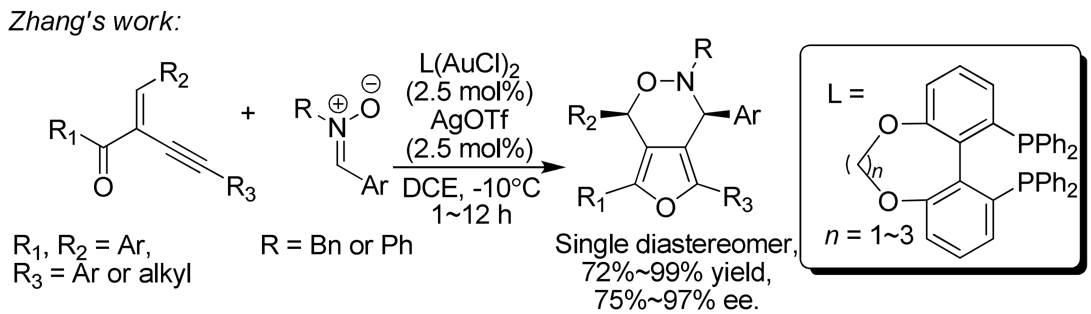


Scheme 2.16 Pd-catalyzed [3+3]-Cycloaddition Reactions of Trimethylenemethane with Azomethine Imines.

In 2009, Zhang and co-workers discovered a gold-catalyzed [3+3]-cycloaddition of 2-(1-alkynyl)-2-alken-1-ones (**21**) with nitrones (Scheme 2.17).[20] They proposed a mechanism[20] (Scheme 2.17) in which 2-(1-alkynyl)-2-alken-1-ones (**21**) first cyclized to generate the putative furanyl gold intermediate **22**, and then the oxygen of the nitrone acted as a nucleophile to attack the carbocation in **22** to generate the intermediate **23**, which cyclized to produce the [3+3]-cycloaddition product.[20] Zhang's group has also achieved the enantioselective version of the reaction by use of the chiral diphosphine ligated Au(I) catalysts (Scheme 2.18).[21]



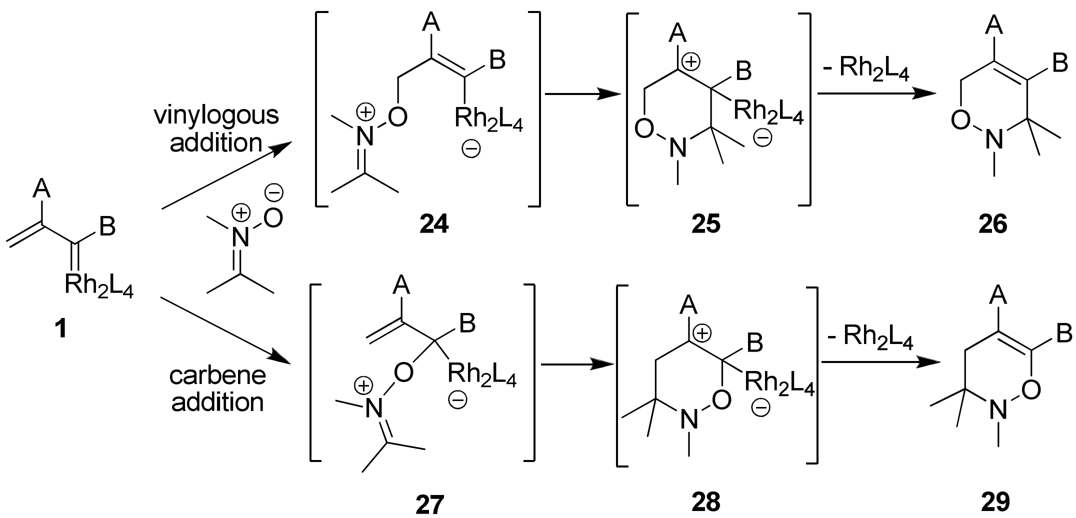
Scheme 2.17 Gold Catalyzed [3+3]-Cycloaddition Reactions of 2-(1-Alkynyl)-2-alken-1-ones with Nitrones.



Scheme 2.18 Enantioselective [3+3]-Cycloaddition Reactions of 2-(1-Alkynyl)-2-alken-1-ones with Nitrones Catalyzed by a Chiral Au(I)-diphosphine Complex.

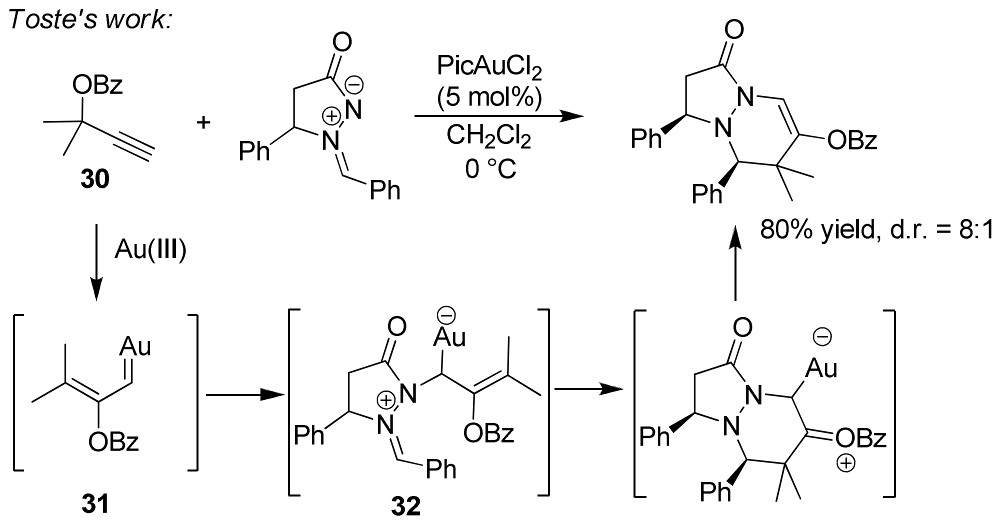
1.5 Our Design of the [3+3] Cycloaddition Reaction of Nitrones with Rhodium Vinylcarbenes

We envisioned that, when a rhodium vinylcarbene (**1**) is treated with a nitrone, a [3+3]-cycloaddition reaction could occur. General representation of this possible [3+3]-cycloaddition process is shown in Scheme 2.19. Considering the electronic nature of the rhodium carbene intermediate (**1**), both the vinylogous carbon and the carbene carbon are activated for nucleophilic attack by oxygen from the nitrone, and either intermediate **24** or **27** can be formed depending on whether the site for addition is at the carbene carbon or at the vinylogous carbon. The following cyclization would form the intermediate **25** or **28**, and then elimination of Rh_2L_4 would produce a product of a six-membered ring (**26** or **29**) that is comprised of three atoms from the nitrone and three atoms from the rhodium vinylcarbene.



Scheme 2.19 Possible [3+3]-Cycloaddition of Nitrones with Rhodium Vinylcarbenes.

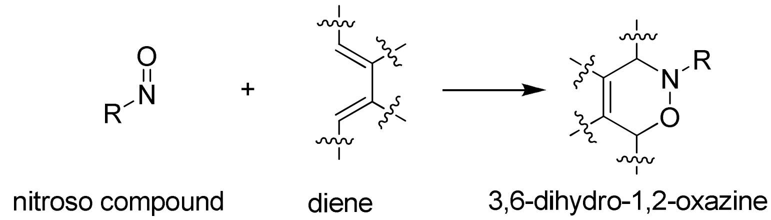
[3+3]-Cycloaddition of a vinylcarbene with a 1,3-dipole is a very undeveloped area. Only a recent communication by Toste has described a [3+3]-cycloaddition process (Scheme 2.20) that involves a putative metal vinylcarbene intermediate (**31**).[22] The metal vinylcarbene (**31**) was generated from the association of a propargyl ester (**30**) with a gold(III) catalyst. The process reported by Toste occurs through attack of the nucleophilic nitrogen of the 1,3-dipole at the carbene site of the gold vinylcarbene (**31** → **32**), resembling the transformation from **27** to **29** in Scheme 2.19.



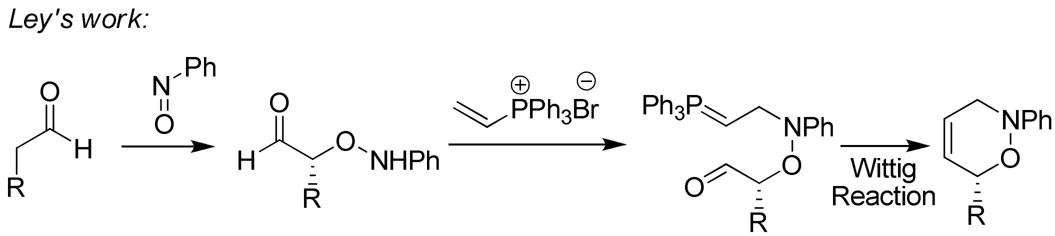
Scheme 2.20 Gold(III)-Catalyzed [3+3]-Cycloaddition Reaction between a Propargyl Ester and an Azomethine Imine.

1.6 Product of the Designed [3+3]-Cycloaddition and Previous Synthesis

Our designed [3+3]-cycloaddition of nitrones with rhodium vinylcarbenes would produce 3,6-dihydro-1,2-oxazines (compound **26** in Scheme 2.19) as the reaction product if the initial oxygen addition occurs at the vinylogous site. Synthesis of 3,6-dihydro-1,2-oxazines has been achieved *via* the hetero-Diels-Alder reaction of a nitroso compound with a diene[23] (Scheme 2.21) and from a tandem one-pot process developed by Ley involving organocatalytic α-oxyamination of an enamine with nitrosobenzene followed by reaction with a vinyl phosphonium salt in an intramolecular Wittig process (Scheme 2.22).[24] Ley's two-step organocatalytic route provides high enantiocontrol and modest to good yields but is limited thus far to nitrosobenzene.

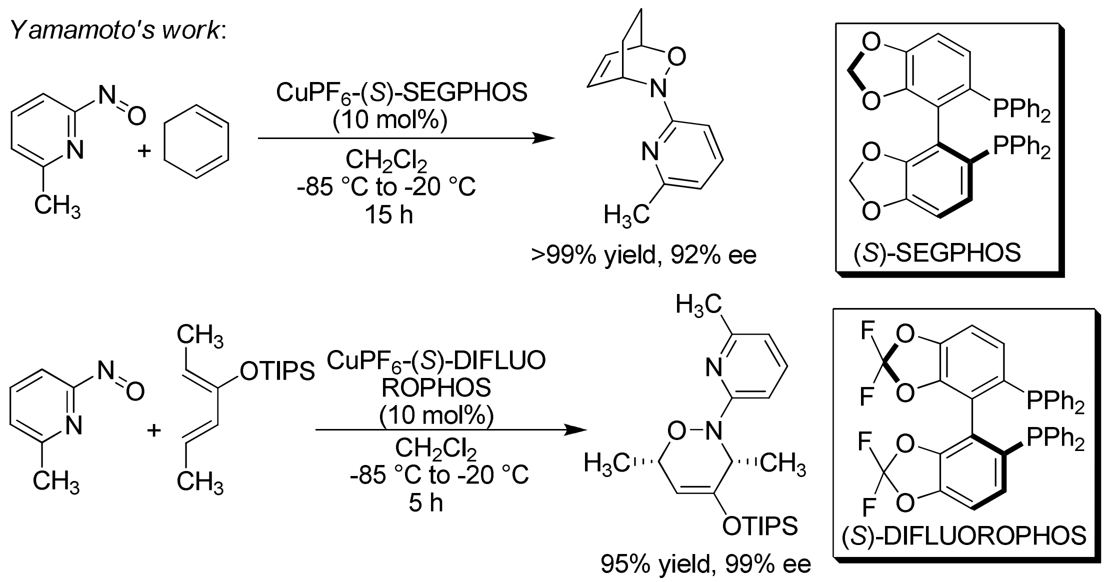


Scheme 2.21 Hetero-Diels-Alder Reactions of Nitroso Compounds with Dienes.



Scheme 2.22 Ley's Tandem Reactions to Prepare Chiral 3,6-Dihydro-1,2-oxazines.

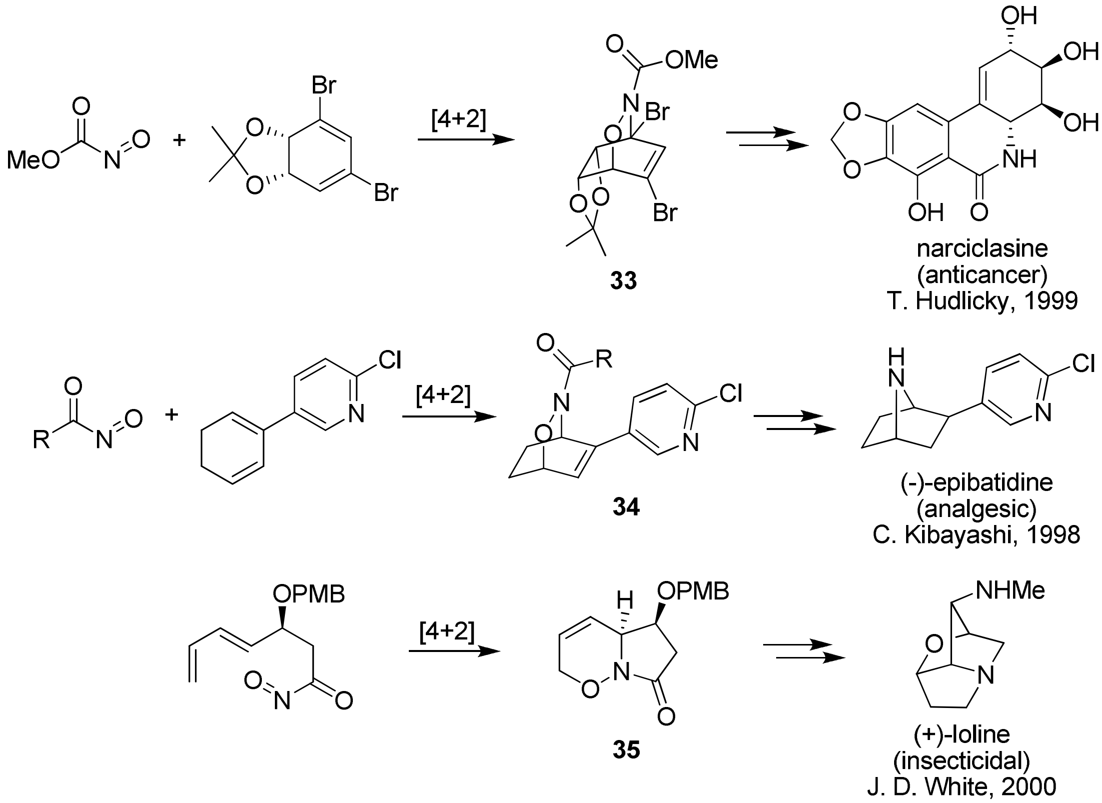
Yamamoto reported the only successful example of a metal-catalyzed enantioselective preparation of 3,6-dihydro-1,2-oxazines, where the Cu(I)/diphosphine complex was used as a Lewis acid to activate the nitroso compounds for [4+2]-cycloaddition with conjugated dienes that occurred in excellent yields and enantioselectivities (Scheme 2.23).[25] However, a relatively high catalyst loading (10 mol%) was required, and only pyridylnitroso compounds produced the 3,6-dihydro-1,2-oxazines with high enantiocontrol, probably due to a need for two-point binding of substrate to catalyst provided by both the nitroso and the pyridyl groups.



Scheme 2.23 Cu(I)/Diphosphine Complexes Catalyzed Hetero-Diels-alder Reactions of Pyridylnitroso Compounds with Cyclic and Acyclic Dienes.

1.7 Synthetic Applications of 3,6-Dihydro-1,2-oxazines

3,6-Dihydro-1,2-oxazines are useful building blocks for the synthesis of natural products and biologically relevant compounds.[23] For example, 3,6-dihydro-1,2-oxazines (**33–35**) have been used as precursors for synthesis of narciclasine,[26] (-)-epibatidine,[27] and (+)-loline[28] (Scheme 2.24). Preparations of these precursors were all achieved with the hetero-Diels-Alder reactions of nitroso compounds with dienes.

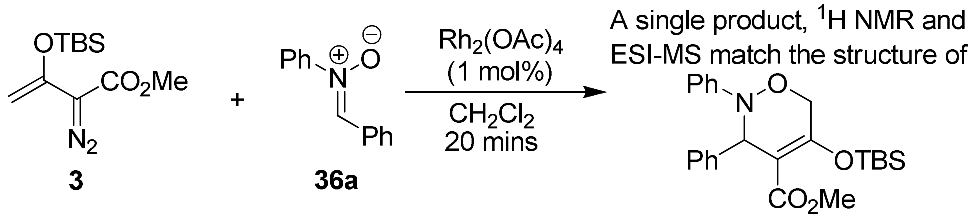


Scheme 2.24 Total Synthesis of Natural Products and Biologically Active Compounds *via* 3,6-Dihydro-1,2-oxazines.

II. Results and Discussion

2.1 Discovery of the [3+3]-Cycloaddition Reaction

We initiated our investigation of a possible [3+3]-cycloaddition reaction using *N*,α-diphenylnitrone and β-TBSO-substituted vinyldiazoacetate **3** (Scheme 2.25). Treatment of 1.5 equivalents of **3** with *N*,α-diphenylnitrone in the presence of 1.0 mol % of rhodium acetate in dichloromethane gave immediate dinitrogen extrusion from **3** and produced a single compound with complete conversion of the nitrone over a reaction time of only 20 minutes. The ^{1}H NMR spectrum (Figure 2.3) of the product showed ten protons from the two phenyl rings, a singlet at δ 5.62, a pair of coupled protons at δ 4.50 and 4.30 with a coupling constant of 16 Hz, three protons from the methyl group at δ 3.67 and protons from the TBS group with lower chemical shifts (δ 1.01, δ 0.27 and δ 0.23). Also, the mass spectrum showed a molecular ion with a mass as the sum of the two reactants plus one proton (ESI-MS and H^+ mode). These spectral data matched the structure of the 3,6-dihydro-1,2-oxazine. Structural confirmation for 3,6-dihydro-1,2-oxazine was obtained from X-ray diffraction of a single crystal from the product of the reaction between *N*-phenyl-α-(*p*-bromophenyl)nitrone and **3** (Figure 2.4).



Scheme 2.25 Reaction of *N*,α-diphenylnitrone with β-TBSO-substituted vinyldiazoacetate **3** catalyzed by $Rh_2(OAc)_4$.

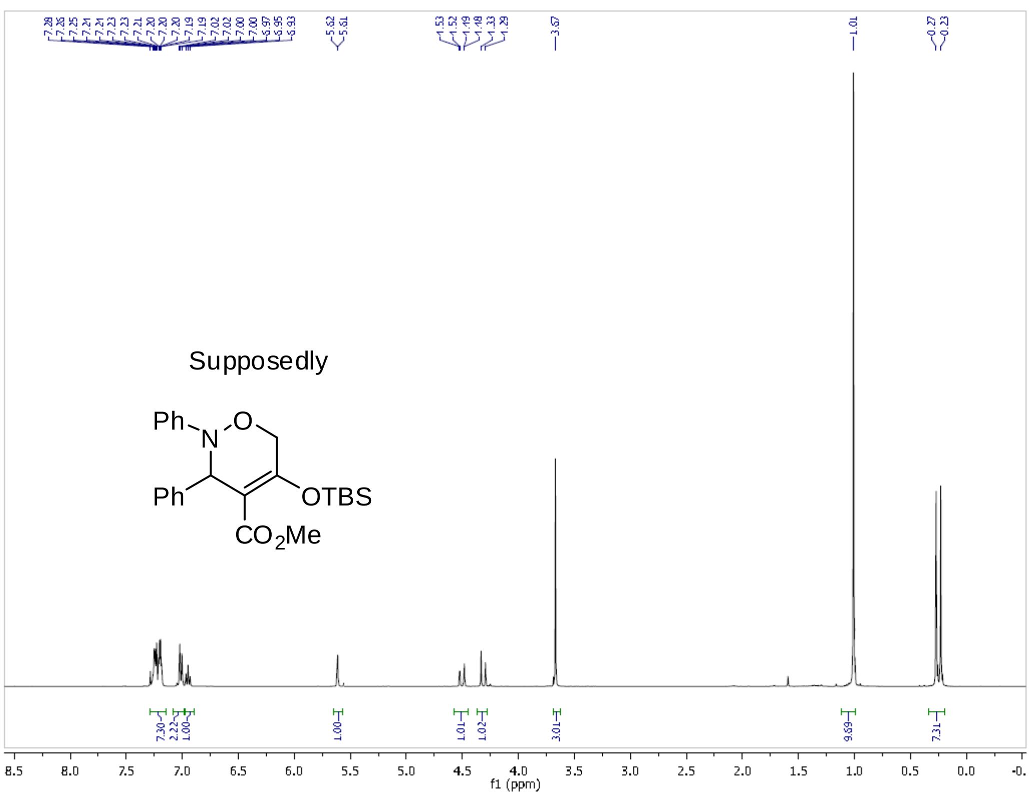


Figure 2.3 ^{1}H NMR Spectrum of the Product from the Reaction between **3** and **36a**.

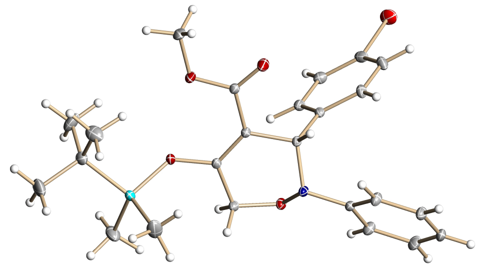
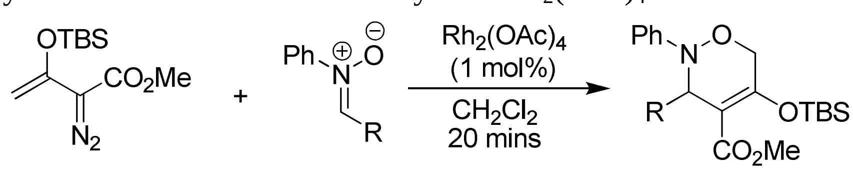


Figure 2.4 X-ray Structure of the Reaction Product from 3 and *N*-Phenyl-α-(*p*-bromophenyl)nitrone.

Reactions with nitrones having various α-substituents were performed, and the results are summarized in Table 2.1. Fast reaction rates and high yields of 3,6-dihydro-1,2-oxazines were obtained with different diarylnitrones having both electron-donating and electron-withdrawing substituents (products **37a–37h**). Reactions with α-2-furyl and α-2-thienyl-substituted nitrones (products **37i** and **37k**) showed slower reaction rates compared to that with N,α-diphenylnitrone, and lower yields were obtained because of incomplete conversion of the nitrones. When the α-cyclohexyl-substituted nitrone was used (product **37l**), [3+3]-cycloaddition still proceeded like those with diarylnitrones and with a fast reaction rate and an excellent yield.

Table 2.1 [3+3]-Cycloaddition Reactions between Acyclic Nitrones **36** and the Siloxyvinyldiazoacetate **3** under the Catalysis of $Rh_2(OAc)_4$.[a]

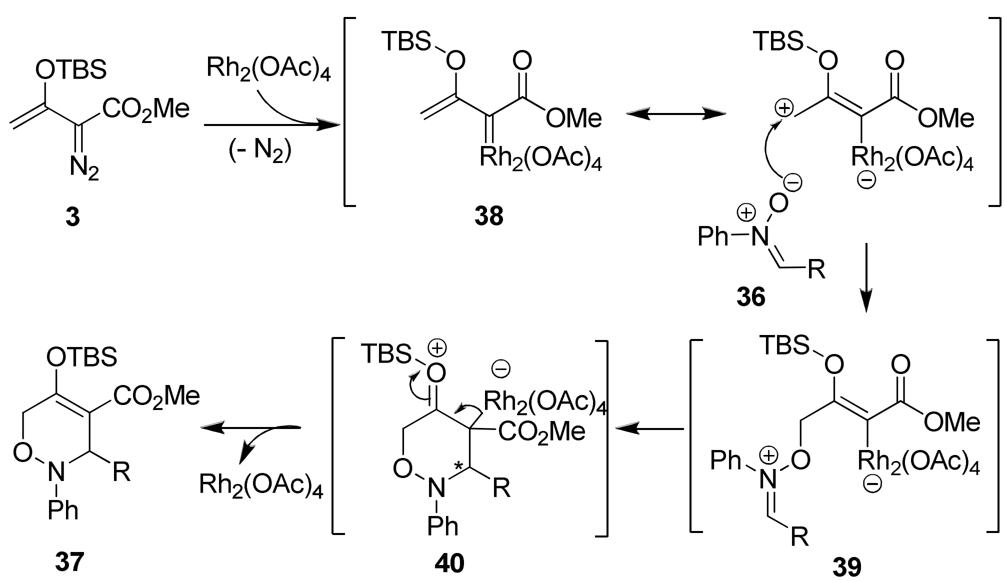


R	37	yield (%)[b]	R	37	yield (%)[b]
C_6H_5	**37a**	97	*p*-MeC_6H_4	**37b**	97
p-$MeOC_6H_4$	**37c**	98	*p*-BrC_6H_4	**37d**	91
p-FC_6H_4	**37e**	92	*m*-MeC_6H_4	**37f**	97
m-ClC_6H_4	**37g**	94	2-naphthyl	**37h**	94
2-furyl	**37i**	78	3-furyl	**37j**	90
2-thienyl	**37k**	81	cyclohexyl	**37l**	97

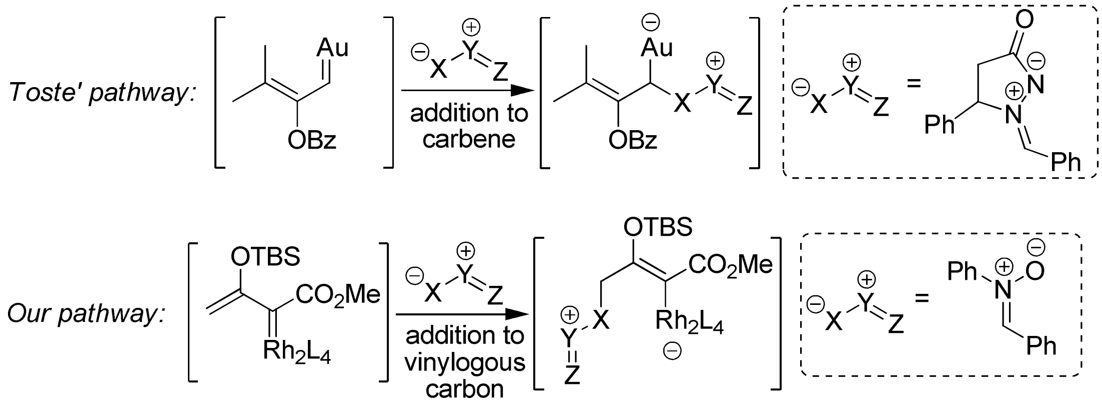
[a] Reactions were performed with 0.25 mmol of nitrone, 0.38 mmol of the vinyldiazoacetate **3**, and 0.0025 mmol of rhodium acetate in 1.0 mL of dichloromethane at room temperature. [b] Yield of the isolated product.

2.2 Proposed Reaction Mechanism

The mechanism of the [3+3]-cycloaddition between nitrones and the rhodium vinylcarbene (Scheme 2.26) is proposed in accord with the general process given in Scheme 2.19 in section 1.5 of this chapter. The rhodium substituent activates the vinylogous carbon of the rhodium vinylcarbene **38** for nucleophilic attack by nitrone **36** at the vinylogous site. Cyclization of **39** forms the $Rh_2(OAc)_4$-ligated intermediate **40**, and elimination of $Rh_2(OAc)_4$ from **40** produces the 3,6-dihydro-1,2-oxazine. The cyclization step (**39** → **40**) is facilitated by the TBSO substituent. In contrast, Toste's [3+3]-cycloaddition of gold vinylcarbenes with azomethine imines occurs with initial nucleophilic attack of the 1,3-dipole at the carbene site (Scheme 2.27),[22] but [3+3]-cycloaddition reactions of the rhodium vinylcarbene with nitrones proceed with initial attack of nitrone at the vinylogous site of the vinylcarbene intermediate.



Scheme 2.26 Mechanism of the [3+3]-Cycloaddition Reaction of the Siloxyvinyldiazoacetate **3** and the Nitrone **36** Catalyzed by Rhodium Acetate.

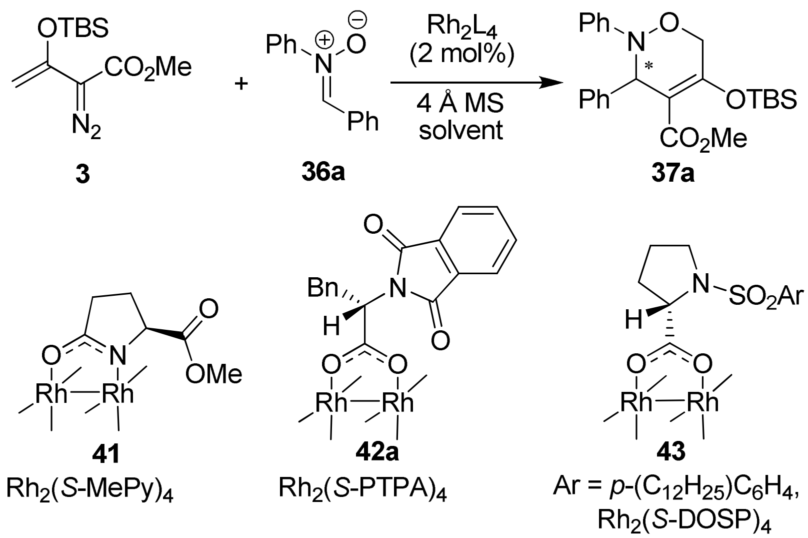


Scheme 2.27 Different Reaction Pathways of the Gold Vinylcarbene and the Rhodium Vinylcarbene.

2.3 Asymmetric [3+3]-Cycloaddition Reactions Catalyzed by Chiral Dirhodium Catalysts

In view of the limited availability of catalytic enantioselective methods with which to access 3,6-dihydro-1,2-oxazines, we sought to employ chiral dirhodium catalysts for the [3+3]-cycloaddition reactions of nitrones with vinyldiazoacetates. During the initial catalyst screening, we used the same conditions from the $Rh_2(OAc)_4$-catalyzed [3+3]-cycloaddition in which a solution of 1.5 equiv of **3** in dichloromethane was added dropwise (complete addition within 1 min) to a solution of *N*,α-diphenylnitrone (**36a**) in dichloromethane in the presence of a dirhodium catalyst (2 mol%). Molecular sieves (4 Å) were added to limit hydrolysis of the nitrone. As can be seen by the data in Table 2.2, chiral dirhodium carboxamidate catalyst $Rh_2(S\text{-MePy})_4$ (**41**),[29] showed no reactivity toward the [3+3]-cycloaddition reaction. However, the chiral phthalimide-amino acid ligated dirhodium catalyst **42a**[30] facilitated the [3+3]-cycloaddition with an excellent yield and a 30% enantiomeric excess. Interestingly, switching the reaction solvent from dichloromethane to toluene significantly increased enantiocontrol from 30% ee to 70% ee using **42a** as the catalyst. Rh_2(*S*-DOSP)$_4$ (**43**)[31] catalyzed the [3+3]-cycloaddition reaction but failed to provide any evidence of enantiocontrol. Optimization of enantiocontrol by varying the reaction temperature revealed that a lower temperature of -15 °C decreased the yield but improved the enantioselectivity with catalyst **42a**.

Table 2.2 Initial Screening of Dirhodium Catalyts.

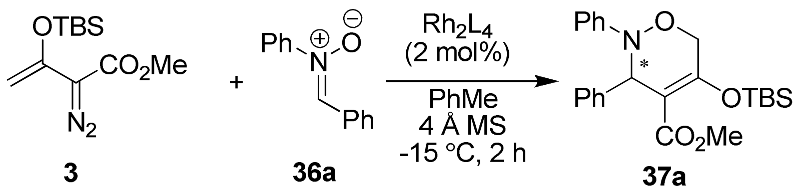


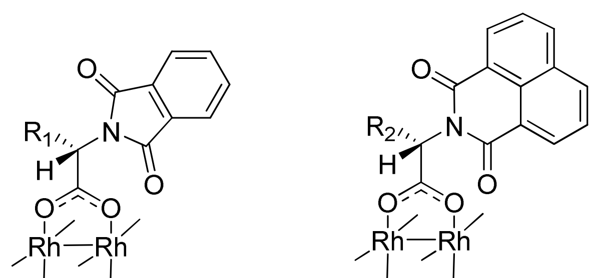
Rh_2L_4	Solvent	T (°C)	time (h)	yield (%)[a]	ee (%)[b]
41	CH_2Cl_2	23	1	0	-
42a	CH_2Cl_2	23	0.5	98	30
42a	PhMe	23	0.5	98	70
43	PhMe	23	1	80	0
42a	PhMe	-15	2	76	80

[a] Yield of the isolated product; the only other nitrone-derived material observed in the reaction mixture was unreacted *N*,α-diphenylnitrone. [b] Determined by HPLC (AD-H column).

Further screening of catalysts was made by using different phthalimide-amino acid-ligated (**42**)[30] and naphthalimide-amino acid-ligated dirhodium catalysts (**44**).[32] Results are summarized in Table 2.3. Surprisingly, the catalyst with the smallest R_1 (**42d**) provided the highest level of enantiocontrol; steric interference by R_1 (for **42**) and R_2 (for **44**) appears to be the cause for the decrease in % ee, and the absence of 3,6-dihydro-1,2-oxazine formation from catalysis by **44b** suggests the absolute limit for catalysis by dirhodium carboxylates with this class of chiral ligand. Notably, bulky substituents in ligands also decreased the reaction rate, especially for Rh_2(*S*-PTTL)$_4$ (**42c**) and Rh_2(S-PTAD)$_4$ (**42e**[33]), which only converted a small portion of the nitrone into the [3+3]-cycloaddition product over 2 h resulting in less than 20% isolated yield and only modest enantiocontrol.

Table 2.3 Further Screening of Dirhodium Catalysts.





42 **44**

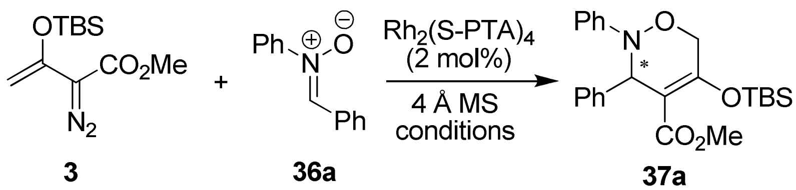
R_1 = Bn, Rh_2(*S*-PTPA)$_4$ (**42a**)
R_1 = *i*-Pr, Rh_2(*S*-PTV)$_4$ (**42b**)
R_1 = *t*-Bu, Rh_2(*S*-PTTL)$_4$ (**42c**)
R_1 = Me, Rh_2(*S*-PTA)$_4$ (**42d**)
R_1 = 1-adamantyl, Rh_2(*S*-PTAD)$_4$ (**42e**)
R_2 = Me, Rh_2(*S*-NTA)$_4$ (**44a**)
R_2 = *t*-Bu, Rh_2(*S*-NTTL)$_4$ (**44b**)

Catalyst	yield (%)[a]	ee (%)[b]
42a	76	80
42b	80	62
42c	15	60
42d	85	87
42e	18	64
44a	50	53
44b	<3	-

[a] Yield of the isolated product; the only other nitrone-derived material observed in the reaction mixture was unreacted *N*,α-diphenylnitrone. [b] Determined by HPLC (AD-H column).

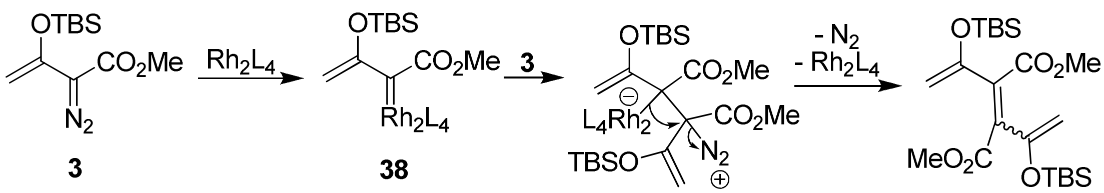
After the screening of catalysts, $Rh_2(S\text{-}PTA)_4$ (**42d**) provided the highest level of enantiocontrol with a high yield of 3,6-dihydro-1,2-oxazine **37a**. To further enhance the enantiocontrol, both solvent and temperature were varied (Table 2.4). Decreasing the reaction temperature to minus 30 °C improved enantioselectivity slightly, but the yield was decreased. Switching the solvent from toluene to a mixed toluene/hexane (2:1) further enhanced the enantiocontrol to 91% ee with a yield of 70%. To identify the reason for the moderate yield, we monitored the reaction with ^{1}H NMR spectroscopy. We found that, **3** (1.5 equiv) was fully consumed over 2 h of the reaction time, but the conversion of nitrone (1.0 equiv) was only 74%. Therefore, there was a competing reaction that consumed **3**. We suspected that this competing reaction was the dimerization of **3** through rhodium catalysis, which is shown in Scheme 2.28. Although we did not successfully isolate the dimerization product drawn in Scheme 2.28, analogous dimerization reactions of diazoacetates have been reported in the literature.[34] To overcome the low yields due to the dimerization of diazo compounds, previous studies have shown that very slow addition of a diazo compound to a reaction mixture is able to diminish the dimerization kinetically because slow addition would maintain a low concentration of the diazo compound in the reaction mixture.[3] Therefore, we also adopted the slow addition methodology. A syringe pump was used so that the addition of **3** was accomplished over a time period of 1 h. With slow addition the yield was improved to 95%, and the enantiomeric excess of 91% was maintained. We also discovered that use of a non-coordinating ether *tert*-butyl methyl ether (TBME) as the solvent improved the enantioselectivity to 93% ee with a yield of 95%.

Table 2.4 Optimization with the Catalyst Rh_2(*S*-PTA)$_4$ (**42d**).



solvent	T (°C)	time (h)	yield (%)[a]	ee (%)[b]
PhMe	-15	2	85	87
PhMe	-30	2	60	89
PhMe/hexanes (2 : 1)	-30	2	70	91
PhMe/hexanes (2 : 1)[c]	-30	2	95	91
TBME[c]	-30	2	95	93

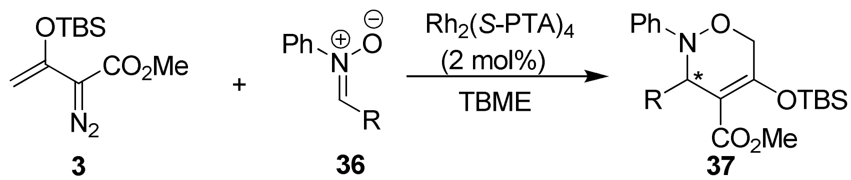
[a] Yield of the isolated product; the only other nitrone-derived material observed in the reaction mixture was unreacted *N*,α-diphenylnitrone. [b] Determined by HPLC (AD-H column). [c] The diazo compound was added dropwise with a syringe pump over a time period of 1 h.



Scheme 2.28 Possible Dimerization of **3** through Catalysis of Rh_2L_4.

With the optimal conditions in hand, the generality of this enantioselective [3+3]-cycloaddition reaction was further investigated by varying the α-substituent of the nitrone, and the results of this investigation are given in Table 2.5. Product yields were high, and 3,6-dihydro-1,2-oxazines **37** were the sole reaction products; however, enantioselectivities of reactions with nitrones having electron-donating or electron-withdrawing groups all occurred with a lower enantiomeric excess than did *N*,α-diphenylnitrone. A reaction temperature of -30 °C was not universally applicable to different nitrones because reaction rates were too slow for several nitrones at -30 °C. Reactions with α-2- and α-3-furyl nitrones (entries 9 and 10) showed significantly low reactivities, and slow reaction rates were observed even at 0 °C, but enantioselectivities with these nitrones were high. When the α-substituent was changed to the aliphatic cyclohexyl group (entry 12), enantioselectivity was also lower than with aryl groups as α-substituents.

Table 2.5 Effects of Nitrone Substituents on Enantiocontrol for the [3+3]-Cycloaddition Reaction.[a]



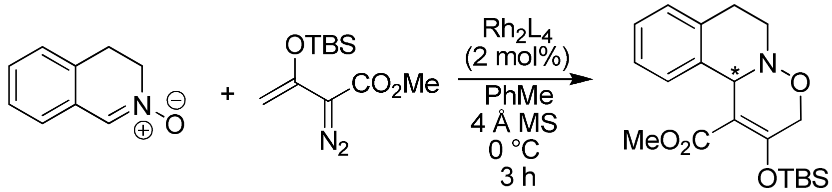
Entry	R	T (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	C_6H_5	-30	2	95	93
2	*p*-MeC_6H_4	-30	2	95	87
3	*p*-$MeOC_6H_4$	-15	3	96	78
4	*p*-BrC_6H_4	-15	4	65	80
5	*p*-FC_6H_4	-15	4	92	77
6	*m*-MeC_6H_4	-30	2	94	90
7	*m*-ClC_6H_4	-15	3	89	85
8	2-naphthyl	0	3	73	80
9	2-furyl	0	3	53	90
10	3-furyl	0	3	66	89
11	2-thienyl	0	3	81	80
12	cyclohexyl	-30	2	85	77

[a] Reactions were performed by slow addition (over 1 hour) of 1.0 mL solution of **5** (0.38 mmol) to the suspension of 0.25 mmol nitrone **36**, 0.0050 mmol catalyst (2.0 mol%), and 100 mg 4 Å MS with 1.0 mL TBME. [b] Yield of the isolated product; the only other nitrone-derived material observed in the reaction mixture was unreacted **36**. [c] Determined by HPLC (AD-H or OD-H column).

Catalytic reactions of **3** with the cyclic nitrone of 3,4-dihydroisoquinoline-*N*-oxide (**45**), which is the geometric equivalent of a *cis*-disubstituted nitrone, were also examined (Table 2.6). In contrast to reactions with acyclic nitrones, catalysis of the reaction between **3** and **45** by Rh_2(*S*-PTA)$_4$ (**42d**) provided the [3+3]-cycloaddition product in high yield but with only a moderate 54% enantiomeric excess. However, the sterically demanding catalyst Rh_2(*S*-PTTL)$_4$ (**42c**) improved enantioselectivity to 80% ee without a significant decrease in product yield. That use of Rh_2(*S*-PTAD)$_4$

(**42e**) had the same degree of enantiocontrol as Rh_2(*S*-PTTL)$_4$, but the yield of **46** in this case was much lower suggesting the subtle nature of steric influences in this catalytic process. *tert*-Butyl methyl ether was not used as the reaction solvent because of the poor solubility of 3,4-dihydroisoquinoline *N*-oxide in this solvent.

Table 2.6 [3+3]-Cycloaddition Reactions of 3,4-Dihydroisoquinoline *N*-oxide with **3**.[a]



45 **3** **46**

catalyst	yield (%)[b]	ee (%)[c]
Rh_2(*S*-PTA)$_4$ (**42d**)	97	54
Rh_2(*S*-PTTL)$_4$ (**42c**)	86	80
Rh_2(*S*-PTAD)$_4$ (**42e**)	50	80
Rh_2(*S*-NTTL)$_4$ (**44b**)	75	60

[a]Reactions were performed by slow addition (over 1 hour) of the diazo compound (0.38 mmol) in 1.0 mL toluene to the suspension of 0.25 mmol 3,4-dihydroisoquinoline *N*-oxide, 0.0050 mmol catalyst (2.0 mol%), and 100 mg 4 Å MS in 1.0 mL toluene. [b] Yield of the isolated product; the only other nitrone-derived material observed in the reaction mixture was unreacted **45**. [c] Determined by HPLC (AD-H column).

The difference in reaction rates with phthalimide-amino acid-ligated dirhodium catalysts (**42**) between acyclic nitrones (**36**) and the cyclic nitrone (**45**) in the [3+3]-cycloaddition process is explained with the models in Figure 2.5. According to the suggested model by Hashimoto,[30] the catalyst is C_2-symmetric, and the vinylcarbene would sit in a plane that is between the two ligand carboxylates. The attack of nitrones at the front side of the rhodium vinylcarbene is hindered by R_1 from ligands. However, with acyclic nitrones (**36**), the approach of nitrone from the back side is possibly hindered by the interaction of R_1 with R (**A** in Figure 2.5), which explains the significantly slower reaction rates when Rh_2(*S*-PTTL)$_4$ (**42c**) (R_1 = *tert*-butyl) was used, compared to those when Rh_2(*S*-PTA)$_4$ (**42d**) (R_1 = methyl) was used.

On the other hand, for 3,4-dihydroisoquinoline-*N*-oxide (**45**) (**B** in Figure 2.5), the *cis*-disubstituted nitrone does not have the substituent interaction depicted in **A** (R = H in this case), so the attack from the back side of the vinylcarbene is facilitated. Therefore, for the reactions with 3,4-dihydroisoquinoline-*N*-oxide (**45**), a bulky R_1 substituent like *tert*-butyl in the catalyst ligand is expected to improve enantiocontrol, while not affecting the yields significantly.

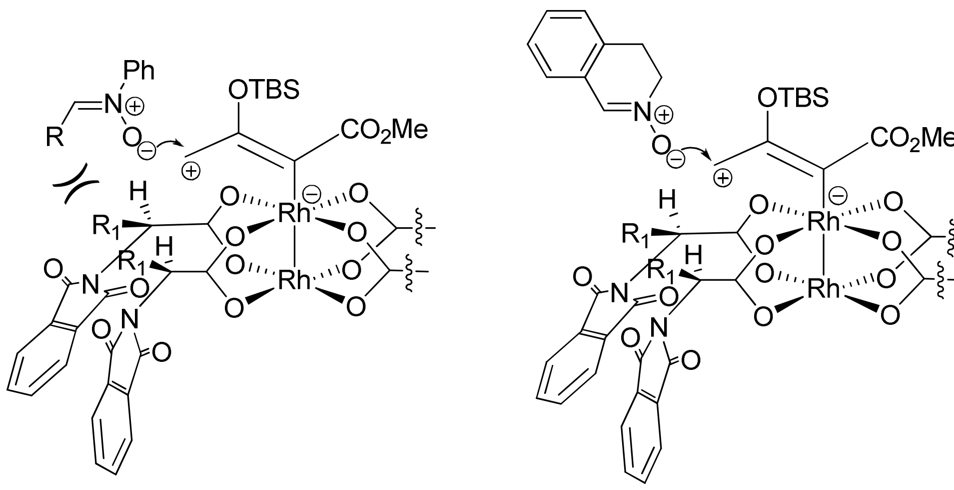
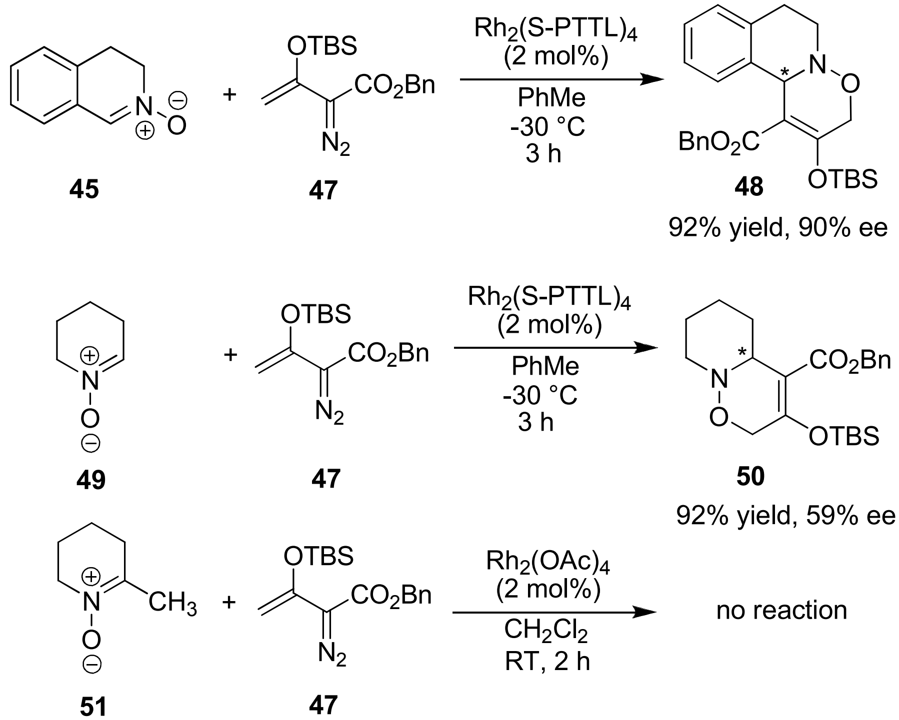


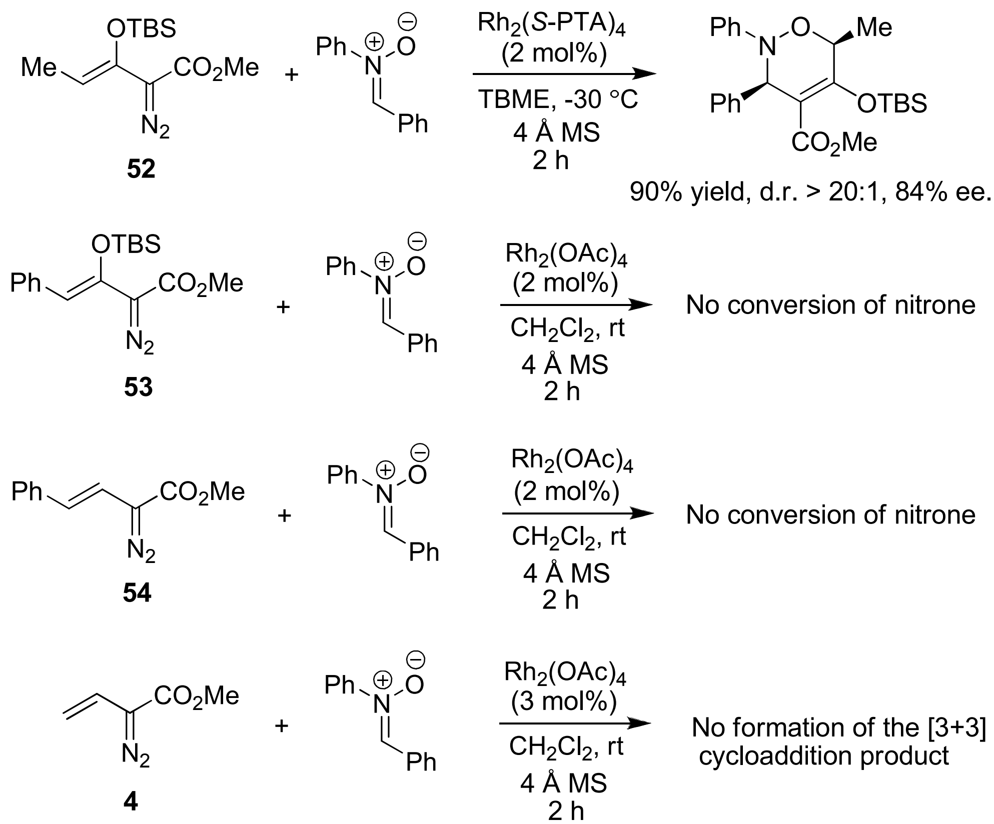
Figure 2.5 Approaching Modes of an Acyclic Nitrone (**A**) and a Cyclic Nitrone (**B**) to the Rhodium Vinylcarbene from **42**.

When the Bn-substituted vinyldiazoacetate **47** was used instead of **3** in the reaction with 3,4-dihydroisoquinoline-*N*-oxide (**45**), and the reaction temperature was decreased to -30 °C (Scheme 2.29), a 90% ee of the cycloadduct (**48**) was obtained. However, when the same conditions were applied to cyclic nitrone **49**, which was prepared from piperidine, the cycloaddition product (**50**) was obtained in only 59% ee, and when the α-disubstituted nitrone **51** was used, no reaction occurred even with the more reactive rhodium acetate (Scheme 2.29). These results again suggest the subtle steric influence of substituents on both the reactivity and selectivity of this transformation.



Scheme 2.29 Reactions between Bn-Substituted Vinyldiazoacetate **47** and Cyclic Nitrones.

Various vinyldiazoacetates with different substitution patterns were also subjected to the catalytic conditions of the [3+3]-cycloaddition reaction with *N*,*α*-diphenylnitrone (Scheme 2.30). The vinyldiazoacetate with a γ-methyl substituent (**52**) was active in enantioselective [3+3]-cycloaddition process producing the 3,6-dihydro-1,2-oxazine as a single *cis*-diastereomer[35] in 90% isolated yield and 84% ee under the catalysis of Rh_2(S-PTA)$_4$ (**42d**). However, when the same conditions were applied to the γ-Ph-substituted vinyldiazoacetate **53**, no reaction of nitrone was observed, and even with rhodium acetate, the nitrone still remained intact. The same outcome was obtained with **54**, which did not have the β-TBSO substituent compared to **53**. Surprisingly, unsubstituted vinyldiazoacetate **4** was able to undergo a totally different reaction pathway to produce a highly functionalized tricyclic compound (discussed in the next chapter). However, the fact that no [3+3]-cycloaddition occurred with **4** clearly verifies the involvement of the TBSO-substituent in the cyclization step as indicated in the reaction mechanism (Scheme 2.26 in section 2.2 of this chapter).



Scheme 2.30 Reactivities of Various Vinyldiazoacetates toward *N*,*α*-Diphenylnitrone.

III. Conclusion

In conclusion, we have developed a general, enantioselective [3+3]-cycloaddition process between the TBSO-activated vinyldiazoacetates and acyclic and cyclic nitrones that occur in high yields and selectivities. The convenience of this methodology, the absence of a background reaction, and the potential suitability of a spectrum of 1,3-dipoles and β-substituted vinyldiazoacetates for this transformation suggest broad applicability. The high level of dependence of catalyst ligands on enantioselectivity in product formation provides opportunities for new catalyst development.

IV. Experimental Section

4.1 Materials

Chiral dirhodium catalysts were prepared according to the reported procedures.[29-33] Purities of the dirhodium carboxylates **42–44** were confirmed by ^{1}H NMR analysis, and purity of Rh_2(*S*-MePy)$_4$ was confirmed by HPLC analysis. The acyclic nitrones (**36**) were prepared with the method reported by Fu[36a] and the cyclic nitrones (**45**, **49**, **51**) were prepared with the method reported by Murahashi.[36b] Vinyldiazoacetates **3**, **4**, **47**, **52** and **54** were prepared with the method reported by Davies,[37] and vinyldiazoacetate **53** was prepared with the method reported by Doyle.[38] Analytically pure solvents from commercial sources were stored with activated 4 Å molecular sieves in a capped round-bottom flask for at least 24 h to diminish the water content.[39] All the other chemicals were obtained from commercial sources and used without further purification.

4.2 General Information

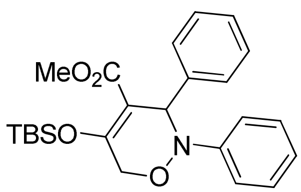
All reactions, unless noted, were carried out under an inert atmosphere of dried nitrogen in flame-dried or oven-dried glassware with magnetic stirring. Analytical thin layer chromatography (TLC) was performed on Dynamic Adsorbents precoated (0.25 mm thickness) silica gel plates with F_{254} indicator. Visualization was accomplished by UV light (254 nm) or with phosphomolybdic acid (PMA) solution in ethanol. Flash chromatography was performed with silica gel (32-63 μm) supplied by Dynamic Adsorbents. ^{1}H NMR spectra were recorded on a Bruker DRX-400 (400 MHz) spectrometer, and chemical shifts were reported in ppm. The peak information was described as: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = composite; coupling constant(s) in Hz. ^{13}C NMR spectra were recorded on a Bruker DRX-400 (100 MHz) or a Bruker DRX-500 (125 MHz) spectrometer with complete proton decoupling. Enantioselectivity was determined on an Agilent 1200 Series HPLC using a Daicel Chiralcel OD-H column (250 x 4.6 mm) or an AD-H column (250 x 4.6 mm). High-resolution mass spectra (HRMS) were performed on JEOL AccuTOF-CS mass spectrometer using CsI as the standard.

Reaction Temperature Control: 23 °C, room temperature; 0 °C, ice bath; -15 °C, NaCl/ice bath; -30 °C, dry ice/*o*-xylene bath.

4.3 Experimental Procedures and Compound Characterizations

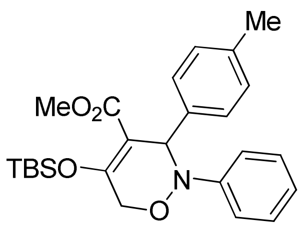
General Procedure for the Asymmetric [3+3]-Cycloaddition Reactions of Nitrones with the TBSO-Substituted Vinyldiazoacetate 3. A 10 mL Schlenk flask charged with a magnetic stir bar and 4 Å molecular sieves (100 mg) was placed under high vacuum and heated by Bunsen burner to dryness. After cooling to room temperature, Rh_2(*S*-PTA)$_4$ (5.4 mg, 2.0 mol%), *N*,α-diphenylnitrone (49.3 mg, 0.250 mmol) and 1.0 mL of *tert*-butyl methyl ether (TBME) were added under the flow of N_2. The resulting green solution was stirred for 5 min and then cooled to -30 °C. Methyl 3-(*tert*-butyldimethylsilyloxy)-2-diazobut-3-enoate (**3**, 96 mg, 0.38 mmol) in

1.0 mL of TBME was added into the flask *via* a syringe pump over a time period of 1 h. After the addition, the mixture was stirred for another one hour at -30 °C. The reaction mixture was then allowed to warm to room temperature. The solution was evaporated under the reduced pressure. The obtained mixture was dissolved in a minimal amount of dichloromethane and loaded onto a silica gel column. Column chromatography with hexane/ethyl acetate (3:1) provided the cycloaddition product which was later analyzed for enantiomeric excess by HPLC (AD-H or OD-H column).



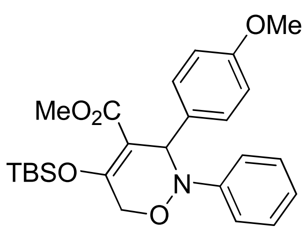
37a

Methyl 5-(*tert*-Butyldimethylsilyloxy)-2,3-diphenyl-3,6-dihydro-*2H*-1,2-oxazine-4-carboxylate. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.19-7.26 (comp, 7H), 7.01 (d, *J* = 8.0 Hz, 2H), 6.95 (t, *J* = 7.2 Hz, 1H), 5.61 (d, *J* = 1.6 Hz, 1H), 4.51 (dd, *J* = 16.0 Hz, 1.6 Hz, 1H), 4.31 (d, *J* = 16.0 Hz, 1H), 3.67 (s, 3H), 1.01 (s, 9H), 0.27 (s, 3H), 0.23 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 165.79, 158.50, 147.98, 138.00, 129.80, 128.98, 127.95, 122.91, 117.76, 109.69, 68.81, 63.55, 51.66, 26.01, 18.80, -3.58, -3.65; HRMS (ESI) calculated for $C_{24}H_{32}NO_4Si$ $[M+H]^+$: 426.2095; found: 426.2088. HPLC conditions for determination of the enantiomeric excess: AD-H column, 254 nm, 1.0 mL/min, Hexane:IPA = 95:5, t_r = 5.9 (major), 6.6 (minor) min; 93% ee.



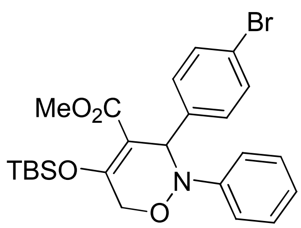
37b

Methyl 5-(*tert*-Butyldimethylsilyloxy)-2-phenyl-3-*p*-tolyl-3,6-dihydro-*2H*-1,2-oxazine-4-carboxylate. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.93-7.30 (comp, 9H), 5.61 (d, *J* = 1.6 Hz, 1H), 4.50 (dd, *J* = 16.0 Hz, 1.6 Hz, 1H), 4.31 (d, *J* = 16.0 Hz, 1H), 3.68 (s, 3H), 2.28 (s, 3H), 1.02 (s, 9H), 0.28 (s, 3H), 0.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 165.81, 158.33, 148.06, 137.51, 135.05, 129.69, 129.00, 128.76, 122.80, 117.69, 109.93, 68.86, 63.13, 51.66, 26.07, 21.55, 18.83, -3.56, -3.61; HRMS (ESI) calculated for $C_{25}H_{34}NO_4Si$ $[M+H]^+$: 440.2252; found: 440.2233. HPLC conditions for determination of the enantiomeric excess: AD-H column, 254 nm, 1.0 mL/min, Hexane:IPA = 97:3, t_r = 6.1 (minor), 8.0 (major) min; 87% ee.



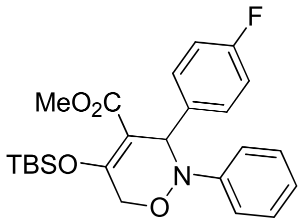
37c

Methyl 5-(*tert*-Butyldimethylsilyloxy)-3-(4-methoxyphenyl)-2-phenyl-3,6-dihydro-*2H*-1,2-oxazine-4-carboxylate. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.19-7.26 (comp, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 2H), 6.95 (t, *J* = 7.6 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 2H), 5.57 (d, *J* = 1.6 Hz, 1H), 4.51 (dd, *J* = 16.0 Hz, 1.6 Hz, 1H), 4.32 (d, *J* = 16.0 Hz, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 1.02 (s, 9H), 0.28 (s, 3H), 0.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 165.85, 159.34, 158.30, 148.13, 130.93, 130.18, 128.99, 122.85, 117.77, 113.35, 110.08, 69.07, 63.15, 55.16, 51.67, 26.07, 18.83, -3.55, -3.63; HRMS (ESI) calculated for $C_{25}H_{34}NO_5Si$ $[M+H]^+$: 456.2201; found: 456.2186. HPLC conditions for determination of the enantiomeric excess: AD-H column, 254 nm, 0.7 mL/min, Hexane:IPA = 97:3, t_r = 14.0 (minor), 16.2 (major) min; 78% ee.



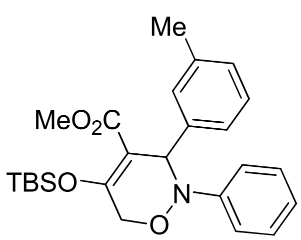
37d

Methyl 3-(4-Bromophenyl)-5-(*tert*-butyldimethylsilyloxy)-2-phenyl-3,6-dihydro-*2H*-1,2-oxazine-4-carboxylate. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.16-7.30 (comp, 4H), 7.07 (d, *J* = 8.4 Hz, 2H), 6.90-6.96 (comp, 3H), 5.51 (d, *J* = 1.6 Hz, 1H), 4.48 (dd, *J* = 16.0 Hz, 1.6 Hz, 1H), 4.28 (d, *J* = 16.0 Hz, 1H), 3.64 (s, 3H), 0.97 (s, 9H), 0.24 (s, 3H), 0.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 165.23, 158.60, 147.38, 136.67, 131.05, 130.68, 128.65, 122.73, 121.70, 117.27, 108.96, 68.75, 62.89, 51.26, 25.58, 18.38, -3.99, -4.06; HRMS (ESI) calculated for $C_{24}H_{31}BrNO_4Si$ $[M+H]^+$: 504.1200; found: 504.1201. HPLC conditions for determination of the enantiomeric excess: AD-H column, 254 nm, 1.0 mL/min, Hexane:IPA = 97:3, t_r = 8.0 (minor), 11.3 (major) min; 80% ee.



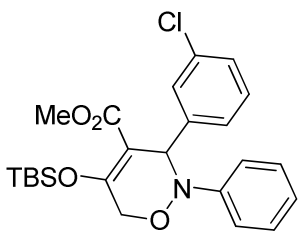
37e

Methyl 5-(*tert*-Butyldimethylsilyloxy)-3-(4-fluorophenyl)-2-phenyl-3,6-dihydro-*2H*-1,2-oxazine-4-carboxylate. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.80-7.23 (comp, 9H), 5.53 (d, *J* = 1.6 Hz, 1H), 4.48 (dd, *J* = 16.0 Hz, 1.6 Hz, 1H), 4.28 (d, *J* = 16.0 Hz, 1H), 3.64 (s, 3H), 0.98 (s, 9H), 0.24 (s, 3H), 0.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 165.27, 162.19 (d, *J* = 244.0 Hz), 158.35, 147.45, 133.32 (d, *J* = 3.2 Hz), 130.92 (d, *J* = 8.0 Hz), 128.56, 122.65, 117.32, 114.30 (d, *J* = 21.1 Hz), 109.22, 68.69, 62.80, 51.22, 25.57, 18.35, -4.02, -4.08; HRMS (ESI) calculated for $C_{24}H_{31}FNO_4Si$ $[M+H]^+$: 444.2001; found: 444.1988. HPLC conditions for determination of the enantiomeric excess: AD-H column, 254 nm, 0.8 mL/min, Hexane:IPA = 97:3, t_r = 10.0 (minor), 11.0 (major) min; 77% ee.



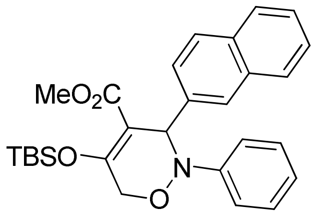
37f

Methyl 5-(*tert*-Butyldimethylsilyloxy)-2-phenyl-3-*m*-tolyl-3,6-dihydro-*2H*-1,2-oxazine-4-carboxylate. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.89-7.24 (comp, 9H), 5.55 (d, *J* = 1.6 Hz, 1H), 4.42 (dd, *J* = 16.0 Hz, 1.6 Hz, 1H), 4.23 (d, *J* = 16.0 Hz, 1H), 3.63 (s, 3H), 2.22 (s, 3H), 0.95 (s, 9H), 0.21 (s, 3H), 0.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 165.38, 157.81, 147.48, 137.60, 136.97, 130.01, 128.54, 128.34, 127.36, 126.41, 122.43, 117.34, 109.25, 67.91, 62.58, 51.20, 25.58, 21.39, 18.35, -1.08, -1.17; HRMS (ESI) calculated for $C_{25}H_{34}NO_4Si$ $[M+H]^+$: 440.2252; found: 440.2253. HPLC conditions for determination of the enantiomeric excess: AD-H column, 254 nm, 0.5 mL/min, Hexane:IPA = 98:2, t_r = 12.4 (major), 18.5 (minor) min; 90% ee.



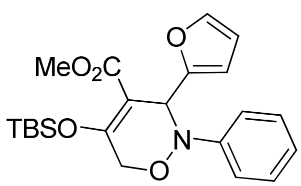
37g

Methyl 5-(*tert*-Butyldimethylsilyloxy)-3-(3-chlorophenyl)-2-phenyl-3,6-dihydro-*2H*-1,2-oxazine-4-carboxylate. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.90-7.24 (comp, 9H), 5.51 (d, *J* = 1.6 Hz, 1H), 4.44 (dd, *J* = 16.0 Hz, 1.6 Hz, 1H), 4.25 (d, *J* = 16.0 Hz, 1H), 3.64 (s, 3H), 0.96 (s, 9H), 0.22 (s, 3H), 0.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 165.17, 158.69, 147.24, 139.75, 133.45, 129.30, 128.67, 128.63, 127.70, 122.77, 117.29, 108.67, 68.42, 62.78, 51.24, 25.55, 18.35, -4.03, -4.10; HRMS (ESI) calculated for $C_{24}H_{31}ClNO_4Si$ $[M+H]^+$: 460.1705; found: 460.1691. HPLC conditions for determination of the enantiomeric excess: OD-H column, 254 nm, 0.4 mL/min, Hexane:IPA = 98:2, t_r = 11.8 (major), 13.7 (minor) min; 85% ee.



37h

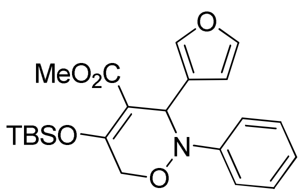
Methyl 5-(*tert*-Butyldimethylsilyloxy)-3-(naphthalen-2-yl)-2-phenyl-3,6-dihydro-*2H*-1,2-oxazine-4-carboxylate. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.31-7.74 (comp, 7H), 7.17 (t, J = 7.6 Hz, 2H), 7.01 (d, J = 8.4 Hz, 2H), 6.88 (m, 1H), 5.75 (s, 1H), 4.50 (d, J = 16.0 Hz, 1H), 4.32 (d, J = 16.0 Hz, 1H), 3.61 (s, 3H), 0.98 (s, 9H), 0.26 (s, 3H), 0.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 165.32, 158.20, 147.50, 132.88, 132.83, 128.61, 128.51, 128.19, 127.53, 127.42, 127.08, 125.65,125.55, 122.53, 117.31, 109.37, 68.39, 63.01, 51.23, 25.55, 18.10, -1.01, -1.11; HRMS (ESI) calculated for $C_{28}H_{34}NO_4Si$ $[M+H]^+$: 476.2252; found: 476.2234. HPLC conditions for determination of the enantiomeric excess: AD-H column, 254 nm, 1.0 mL/min, Hexane:IPA = 95:5, t_r = 7.6 (major), 10.7 (minor) min; 80% ee.



37i

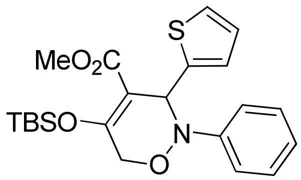
Methyl 5-(*tert*-Butyldimethylsilyloxy)-3-(furan-2-yl)-2-phenyl-3,6-dihydro-*2H*-1,2-oxazine-4-carboxylate. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.20-7.30 (comp, 3H), 7.09 (d, J = 7.6 Hz, 2H), 7.00 (t, J = 7.6 Hz, 1H), 6.21 (m, 1H), 6.13 (d, J = 3.6 Hz, 1H), 5.72 (d, J = 1.6 Hz, 1H), 4.49 (dd, J = 16.0 Hz, 1.6 Hz, 1H), 4.28 (d, J =

16.0 Hz, 1H), 3.73 (s, 3H), 1.00 (s, 9H), 0.26 (s, 3H), 0.23 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 165.50, 159.10, 152.27, 147.82, 142.38, 129.01, 123.07, 117.31, 110.38, 109.65, 107.95, 69.09, 57.25, 51.76, 26.03, 18.82, -3.57, -3.61; HRMS (ESI) calculated for $C_{22}H_{30}NO_5Si$ $[M+H]^+$: 416.1888; found: 416.1863. HPLC conditions for determination of the enantiomeric excess: AD-H column, 254 nm, 0.5 mL/min, Hexane:IPA = 97:3, t_r = 12.8 (minor), 13.7 (major) min; 90% ee.



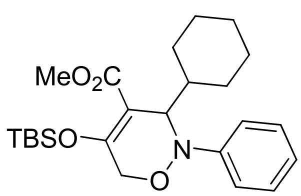
37j

Methyl 5-(*tert*-Butyldimethylsilyloxy)-3-(furan-3-yl)-2-phenyl-3,6-dihydro-*2H*-1,2-oxazine-4-carboxylate. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.21-7.38 (comp, 4H), 7.05 (d, *J* = 8.0 Hz, 2H), 7.00 (t, *J* = 8.0 Hz, 1H), 6.19 (m, 1H), 5.59 (d, *J* = 1.6 Hz, 1H), 4.53 (dd, *J* = 16.0 Hz, 1.6 Hz, 1H), 4.2 (d, *J* = 16.0 Hz, 1H), 3.74 (s, 3H), 1.00 (s, 9H), 0.26 (s, 3H), 0.23 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 166.01, 158.73, 147.95, 142.31, 141.79, 129.23, 122.70, 122.51, 117.01, 111.43, 111.00, 69.11, 55.43, 51.36, 26.02, 18.97, -3.59, -3.63; HRMS (ESI) calculated for $C_{22}H_{30}NO_5Si$ $[M+H]^+$: 416.1888; found: 416.1876. HPLC conditions for determination of the enantiomeric excess: AD-H column, 254 nm, 0.5 mL/min, Hexane:IPA = 97:3, t_r = 12.8 (major), 15.2 (minor) min; 89% ee.



37k

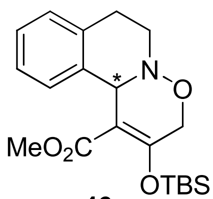
Methyl 5-(*tert*-Butyldimethylsilyloxy)-2-phenyl-3-(thiophen-2-yl)-3,6-dihydro-*2H*-1,2-oxazine-4-carboxylate. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.11-7.28 (comp, 3H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.97 (t, *J* = 8.0 Hz, 1H), 6.78-6.83 (comp, 2H), 5.89 (d, *J* = 1.6 Hz, 1H), 4.57 (dd, *J* = 16.0 Hz, 1.6 Hz, 1H), 4.35 (d, *J* = 16.0 Hz, 1H), 3.72 (s, 3H), 1.01 (s, 9H), 0.28 (s, 3H), 0.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 165.59, 158.93, 147.88, 140.58, 129.03, 127.75, 126.21, 125.80, 122.98, 117.27, 110.90, 69.75, 59.60, 51.71, 26.06, 18.81, -3.47, -3.49; HRMS (ESI) calculated for $C_{22}H_{30}NO_4SSi$ $[M+H]^+$: 432.1659; found: 432.1644. HPLC conditions for determination of the enantiomeric excess: OD-H column, 254 nm, 0.5 mL/min, Hexane:IPA = 97:3, t_r = 9.6 (major), 10.5 (minor) min; 80% ee.



37l

Methyl 5-(*tert*-Butyldimethylsilyloxy)-3-cyclohexyl-2-phenyl-3,6-dihydro-*2H*-1,2-oxazine-4-carboxylate. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.23-7.27 (comp, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.91 (t, *J* = 7.2 Hz, 1H), 4.35 (d, *J* = 8.0 Hz, 1H), 4.03 (d, *J* = 16.0 Hz, 1H), 3.83 (d, *J* = 16.0 Hz, 1H), 3.76 (s, 3H), 2.08 (m, 1H), 1.84 (m, 1H), 1.69 (m, 2H), 1.61 (m, 2H), 1.00-1.25 (comp, 5H), 0.79 (s, 9H), -0.07 (s, 3H), -0.17

(s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 166.91, 153.83, 147.28, 129.10, 121.79, 116.72, 109.83, 62.60, 59.59, 51.47, 42.61, 30.96, 29.93, 26.56, 26.42, 26.29, 25.42, 25.32, 18.08, -4.60, -4.65; HRMS (ESI) calculated for $C_{24}H_{38}NO_4Si$ $[M+H]^+$: 432.2565; found: 432.2564. HPLC conditions for determination of the enantiomeric excess: AD-H column, 254 nm, 0.4 mL/min, Hexane:IPA = 99:1, t_r = 9.7 (minor), 10.1 (major) min; 77% ee.



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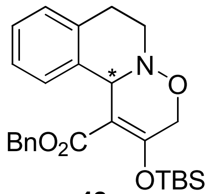
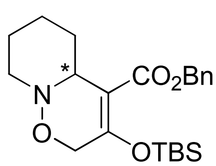
Methyl 2-(*tert*-Butyldimethylsilyloxy)-3,6,7,11*b*-tetrahydro-[1,2]-oxazino[3,2-*a*]isoquinoline-1-carboxylate. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.07-7.24 (comp, 3H), 6.05 (d, *J* = 6.8 Hz, 1H), 5.08 (d, *J* = 1.6 Hz, 1H), 4.40 (dd, *J* = 16.0 Hz, 1.6 Hz, 1H), 3.95 (d, *J* = 16.0 Hz, 1H), 3.81 (s, 3H), 3.63 (m, 1H), 3.40 (m, 1H), 3.20 (m, 1H), 2.57 (m, 1H), 0.93 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 167.25, 159.88, 136.61, 133.79, 128.73, 127.83, 126.81, 126.68, 110.45, 69.82, 58.37, 51.90, 51.24, 26.00, 23.81, 18.76, -3.38, -3.46; HRMS (ESI) calculated for $C_{20}H_{30}NO_4Si$ $[M+H]^+$: 376.1939; found: 376.1930. HPLC conditions for determination of the enantiomeric excess: AD-H column, 254 nm, 1.0 mL/min, Hexane:IPA = 97:3, t_r = 6.3 (major), 8.4 (minor) min; 80% ee.



48

Benzyl 2-(*tert*-Butyldimethylsilyloxy)-3,6,7,11b-tetrahydro-[1,2]oxazino[3,2-a]isoquinoline-1-carboxylate. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.40-7.24 (comp, 5H), 7.13-7.00 (comp, 2H), 7.00-6.95 (m, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.36 (d, J = 12.0 Hz, 1H), 5.19 (d, J = 12.0 Hz, 1H), 5.09 (s, 1H), 4.40 (d, J = 15.6 Hz, 1H), 3.95 (d, J = 15.6 Hz, 1H), 3.66-3.59 (m, 1H), 3.47-3.35 (m, 1H), 3.25-3.15 (m, 1H), 2.55 (dd, J = 4.8, 16.8 Hz, 1H), 0.91 (s, 9H), 0.16 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.73, 159.60, 136.16, 136.06, 133.30, 128.60, 128.40, 128.25, 128.08, 127.48, 126.33, 126.16, 109.98, 69.44, 65.98, 57.95, 50.78, 25.60, 25.43, 23.35, 18.35, -3.80, -3.85; HRMS (ESI) calculated for $C_{26}H_{34}NO_4Si$ $[M+H]^+$: 452.2252; found: 452.2250. HPLC conditions for determination of the enantiomeric excess: AD-H column, 254 nm, 0.8 mL/min, Hexane:IPA = 97:3, t_r = 7.7 (major), 23.5 (minor) min; 90% ee.



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Benzyl 3-(*tert*-Butyldimethylsilyloxy)-2,4a,5,6,7,8-hexahydropyrido[1,2-b][1,2]oxazine-4-carboxylate. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.34-7.26 (comp, 5H), 5.26-5.16 (m, 1H), 5.10 (dd, J = 11.2, 16.4 Hz, 1H), 4.44-4.18 (m, 1H), 3.93 (dd, J = 15.6, 34.0 Hz, 1H), 3.72-3.40 (m, 1H), 3.30 (d, J = 9.6 Hz, 1H), 3.00-2.92 (m, 1H), 2.65-2.50 (m, 1H), 1.80-1.10 (comp, 5H), 0.88 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H); ^{13}C NMR and HRMS spectra were not obtained. HPLC conditions for determination of the enantiomeric excess: AD-H column, 254 nm, 0.7 mL/min, Hexane:IPA = 97:3, t_r = 6.3 (major), 14.8 (minor) min; 59% ee.

NMR graphs and HPLC chromatograms can be obtained from the supporting information of the paper published in the *Journal of the American Chemical Society*: Wang, X.; Xu, X.; Zavalij, P. Y.; Doyle, M. P. *J. Am. Chem. Soc.* **2011**, *133*, 16402.

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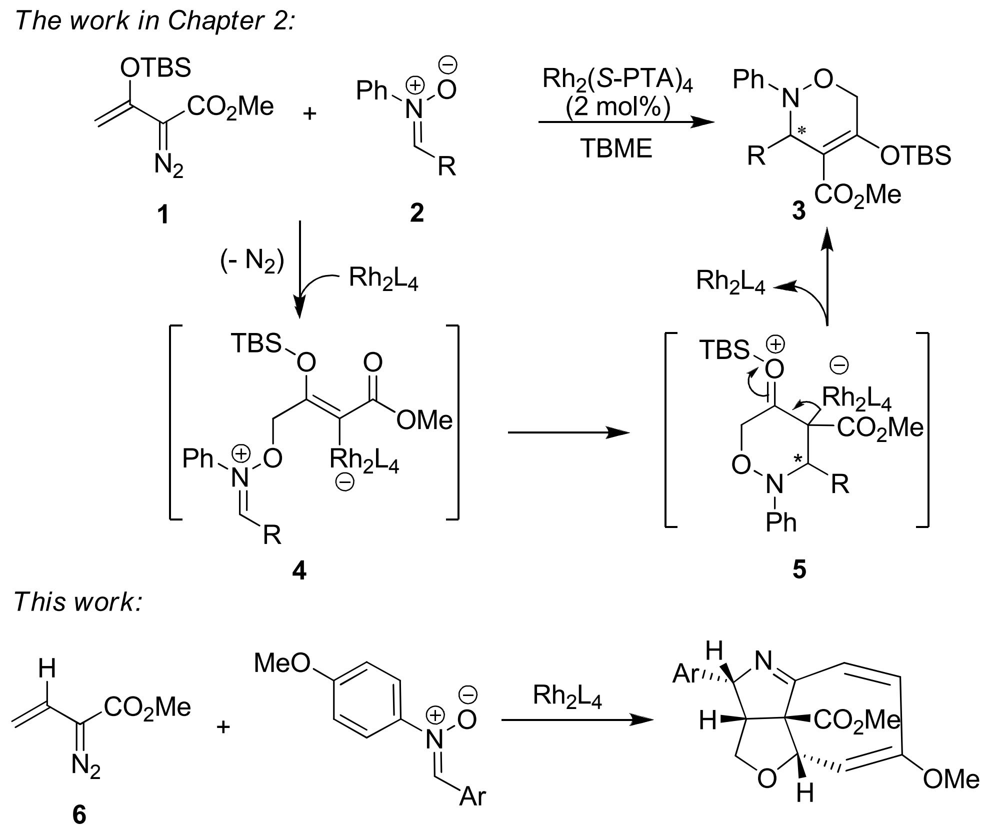
Chapter 3

Highly Regio- and Stereoselective Dirhodium Vinylcarbene-induced Nitrone Cycloaddition with Subsequent Cascade Carbenoid Aromatic Cycloaddition/N-O Cleavage and Rearrangement

I. Introduction

1.1 Discovery of the Cascade Process

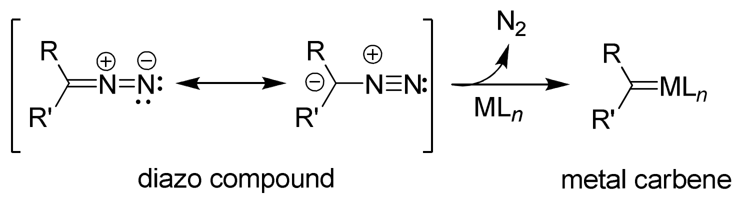
We discovered an efficient and highly enantioselective [3+3]-cycloaddition reaction of nitrones with the rhodium vinycarbene obtained by dinitrogen extrusion from TBS-protected enoldiazoacetate **1** through association with chiral dirhodium(II) carboxylates (Scheme 3.1, announced in the *Journal of the American Chemical Society*[1] and discussed in Chapter 2). This reaction occurred stepwise through vinylogous nucleophilic attack by the nitrone (**2**) on the dirhodium vinylcarbene followed by intramolecular iminium ion addition to the catalyst-activated vinyl ether (**4** → **5**) that, with catalyst dissociation, forms cycloaddition product **3**. During exploration of substrate scope using different vinyldiazoacetates, we discovered that the dirhodium(II) catalyzed reaction of unsubstituted vinyldiazoacetate **6**[2] failed to produce the [3+3]-cycloaddition product, but instead a highly functionalized tricyclic compound was generated through what must be an elaborate cascade process (Scheme 3.1) .



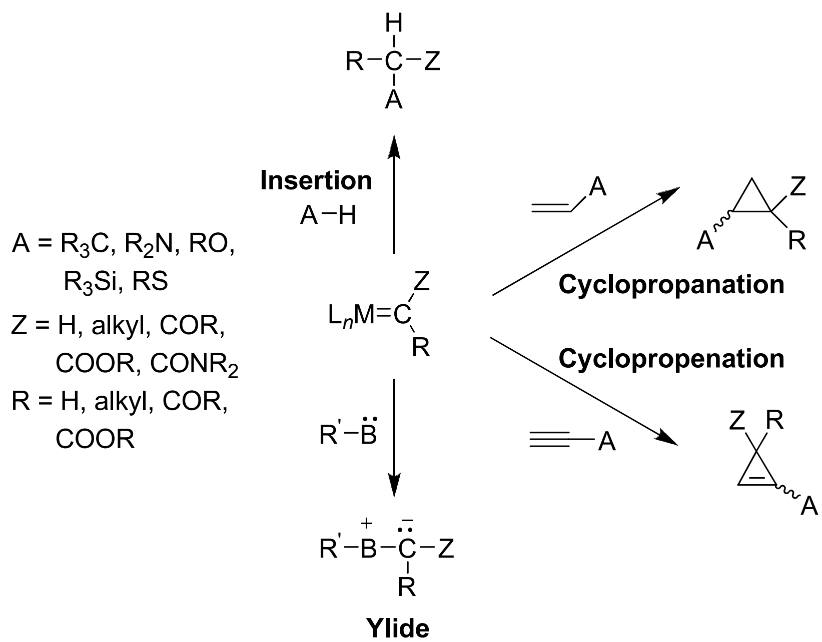
Scheme 3.1 Exploration of the Reavities of Vinyldiazoacetates with Nitrones Leads to the Discovery of a New Cascade Reaction.

<u>1.2 Metal Carbenes and Reactions with Metal Carbenes</u>

Decomposition of a diazo compound by losing gaseous dinitrogen under the catalysis of a transition metal (ML_n) will produce a metal carbene (Scheme 3.2).[3] Common transformations associated with metal carbenes are cyclopropanation, cyclopropenation, insertion and the ylide formation (Scheme 3.3).[4]



Scheme 3.2 Formation of a Metal Carbene from a Diazo Compound and a Transition Metal.

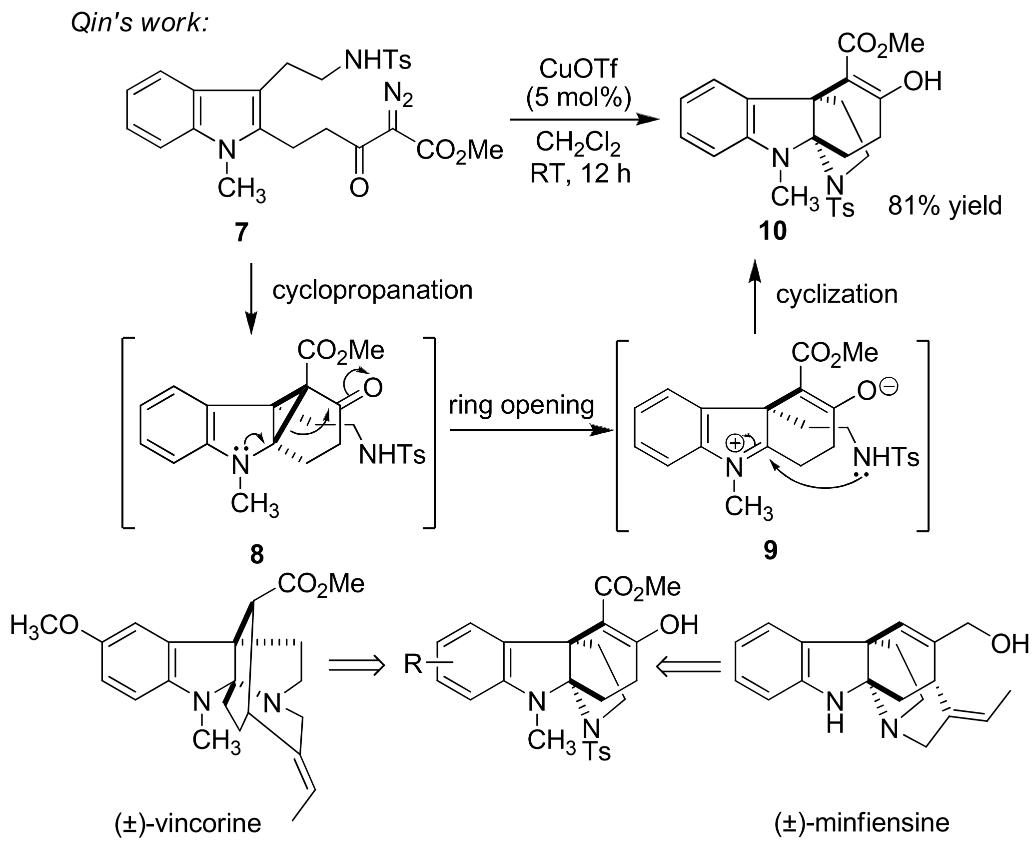


Scheme 3.3 Diverse Transformations with a Metal Carbene.

1.3 Cascade Reactions Involving Metal Carbenes

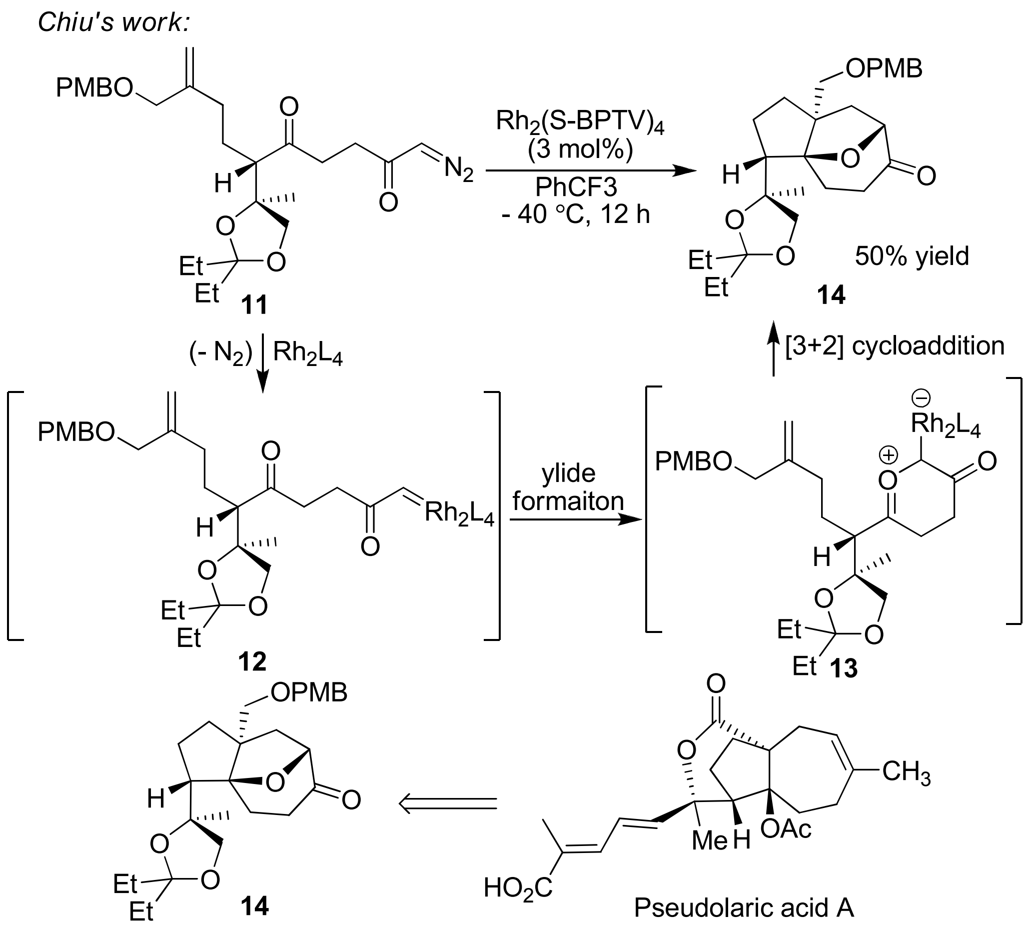
Cascade reactions are tandem reactions that happen consecutively under the same reaction conditions through highly reactive intermediates.[5] Numerous examples of cascade reactions that involve a metal carbene have been reported in the literature, and some of them have proven useful in constructing multicyclic cores for the total synthesis of natural products.[5,6]

Qin and coworkers developed a cascade process of tandem cyclopropanation/ring opening/annulation to assemble a tetracyclic skeleton (**10**) from the disubstituted *N*-methylindole (**7**) via a copper(I)-catalyzed diazo decomposition (Scheme 3.4).[7] The authors suggested a reaction pathway in which a copper(I) triflate-catalyzed intramolecular cyclopropanation first occurred to form intermediate **8** with subsequent indole-induced cyclopropane ring opening and then cyclization of **9** through the indolenium cation to produce the tetracyclic product (**10**).[7] The copper(I)-catalyzed cyclopropanation (**7** → **8**) is a well-studied process that occurs in a stereospecific fashion *via* a copper carbene intermediate.[8] With access to **10** and its analogs, Qin developed the total synthesis of the *Akuammiline* alkaloid (±)-vincorine[7] and the *Strychnos* alkaloid (±)-minfiensine.[9]



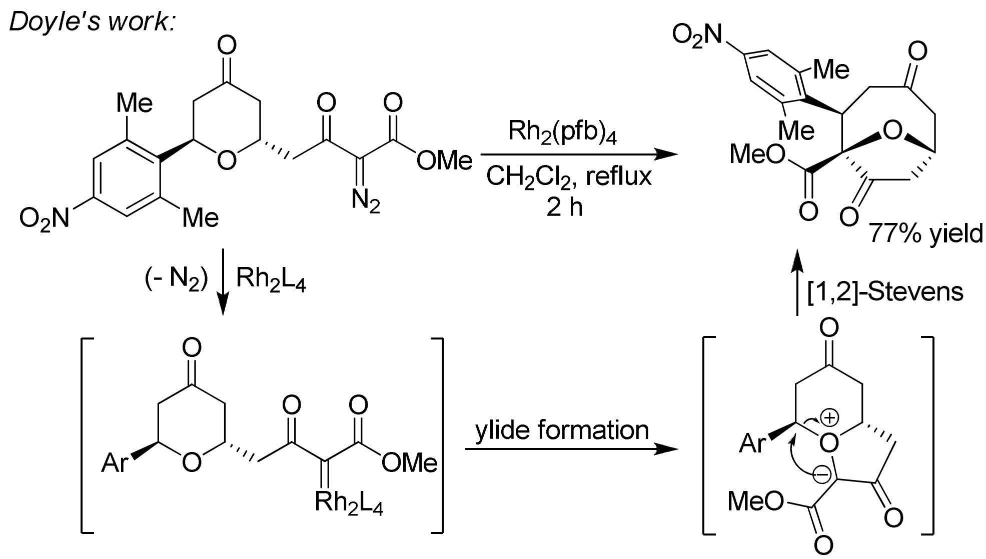
Scheme 3.4 Cascade Process Involving Cyclopropanation of an Indole Core by Copper-catalyzed Diazo Decomposition and Its Applications in Total Synthesis of Natural Products.

Ylide formation (shown in Scheme 3.3) is common in the cascade reactions that involve a metal carbene.[10] Taking the total synthesis of pseudolaric acid A as an example (Scheme 3.5),[11] the [3+2]-cycloaddition of the rhodium-stabilized carbonyl ylide with the terminal alkene in **13** constructs the polycyclic core (**14**) in a single step. Generation of the carbonyl ylide intermediate (**12** → **13**) is a favorable process because six-membered-ring formation is favored both kinetically and thermodynamically.[12]



Scheme 3.5 Intramolecular Carbonyl Ylide Cycloaddition with Alkene as the Key Step in the Total Synthesis of Pseudolaric Acid A.

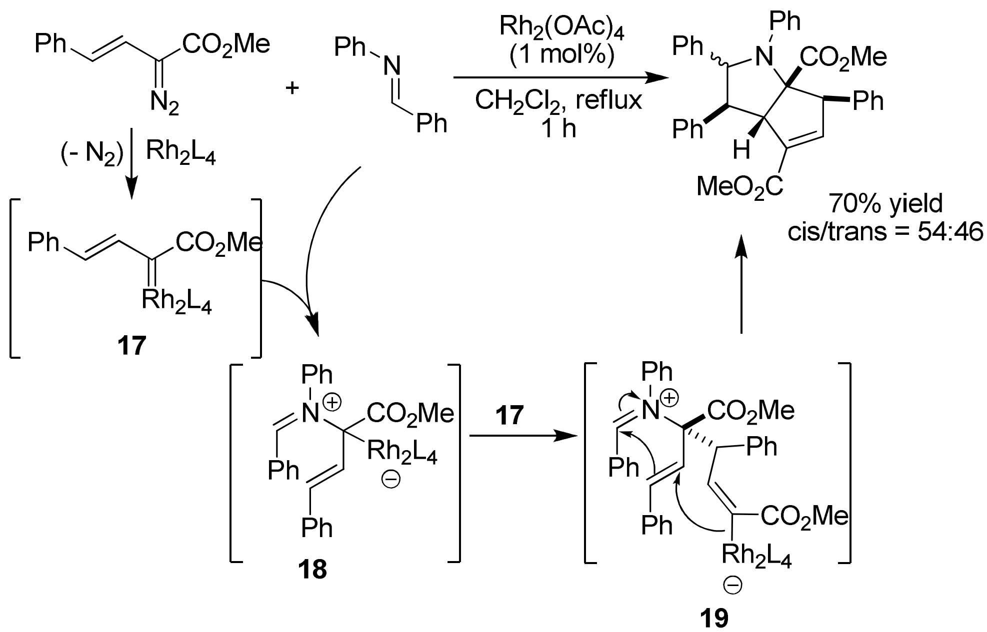
Dr. Jaber and co-workers in our group developed a cascade process that involved the rearrangement of an oxonium ylide (**16**).[13] In this cascade process (Scheme 3.6), attack of the oxygen in the six-membered ring at the rhodium carbene in **15** produces the oxonium ylide (**16**), and then **16** undergoes the [1,2]-Stevens rearrangement to produce an oxygen-bridged bicyclic compound.[13]



Scheme 3.6 Oxonium Ylide/[1,2]-Stevens Rearrangment Cascade.

Dr. Yan and co-workers in our group developed a cascade process involving a rhodium-stabilized azomethine ylide (**18**).[14] In the proposed reaction pathway (Scheme 3.7), rhodium vinylcarbene **17** captures a molecule of *N*,α-diphenylimine to form azomethine ylide **18**, and then **18** captures another molecule of rhodium vinylcarbene **17** through nucleophilic attack at the vinylogous site to produce intermediate **19**, and finally cyclization of **19** produces the nitrogen-fused bicyclic compound.[14]

Doyle's work:



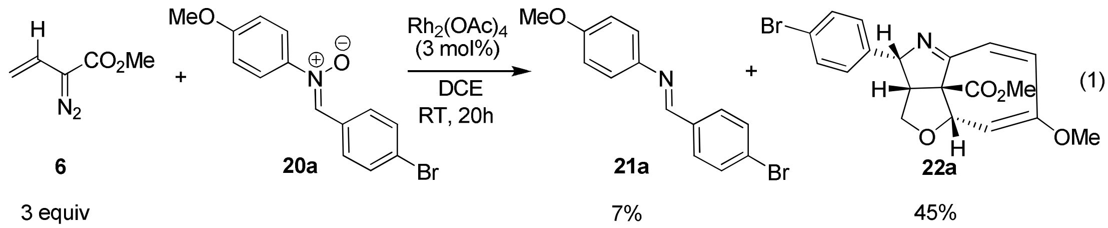
Scheme 3.7 Cascade Process via an Azomethine Ylide.

II. Results and Discussion

<u>2.1 Discovery of the Cascade Process and Optimization of Product Yields by Varying Reaction Conditions</u>

Treatment of methyl 2-diazo-3-butenoate (**6**) with *N*-(4-methoxyphenyl)-α-(4-bromophenyl)nitrone (**20a**) in the presence of rhodium acetate at room temperature gave immediate gas evolution and consumption of nitrone. After a reaction time extending to 20 h two products, accounting for 52% conversion based on **20a**, were isolated. The minor product (7% conversion) was identified as *N*-(4-methoxyphenyl)-α-(4-bromophenyl)imine (**21a**). The NMR spectrum of the major product (45% conversion) indicated a single compound with the loss of resonances due to the original anisyl group and new olefinic protons suggestive of a methoxy-substituted diene, and structural confirmation of this compound as tricyclic **22a** was obtained by

X-ray diffraction of a single crystal (eq 1 and Figure 3.1). This product reveals that extensive rearrangement has occurred and that the carboxylate group from the vinyldiazoacetate is now bound to a quaternary carbon that connects the tricycle.



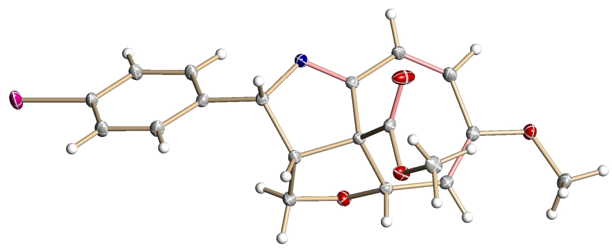
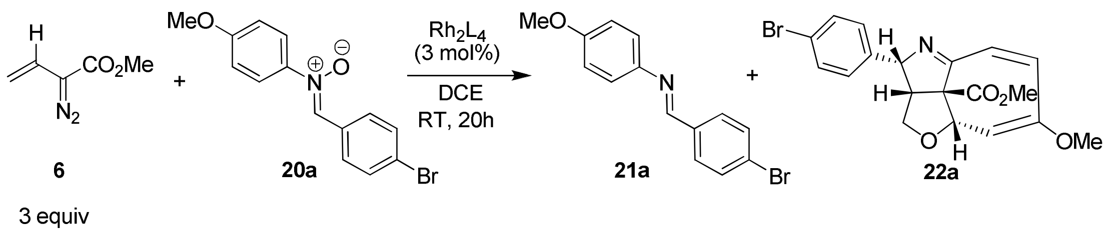


Figure 3.1 X-ray Structure of Compound **22a**.

Different dirhodium catalyts were examined in attempts to increase the yield of tricyclic product **22a** (Table 3.1). Use of rhodium trifluoroacetate $Rh_2(TFA)_4$, which is a stronger Lewis acid than is rhodium acetate,[15] resulted in a significantly lower conversion to the tricyclic product, but there was increased conversion to imine **21a**. Rhodium triphenylacetate $Rh_2(TPA)_4$ and rhodium caprolactamate $Rh_2(CAP)_4$ showed low or negligible reactivities toward this transformation under the same conditions. Rhodium octanoate $Rh_2(OCT)_4$ provided higher conversion, probably due to its higher solubility in 1,2-dichloroethane compared to rhodium acetate.[16] Extending the reaction time or increasing the amount of the vinyldiazoacetate reactant to 10 equivalents did not significantly increase conversion to **22a**. Since unreacted nitrone remained, and neither reactant was an inhibitor for the catalyst, we considered that the formation of a coordinating base could cause inhibition of the catalytic reaction with **6** and incomplete conversion of the nitrone; and both **21a** and **22a**, as well as the pyrazoline formed by intramolecular cycloaddition from **6**,[2] are suitable bases. To solve this problem, acidic 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was used as an additive to capture the basic product.[17] When one equivalent of HFIP was added, and three equivalents of **6** were used, complete conversion of the nitrone was achieved, resulting in 85% conversion to **22a** with 74% yield of the isolated product and the remainder (15% conversion) due to the imine by-product **21a**. An excess of **6** was required due to its relatively low stability.[2] Nitrone **20a** did not react with vinyldiazoacetate **6** in the absence of the dirhodium catalyst.

Table 3.1 Screening of the Reaction Conditions for the Cascade Process.[a]

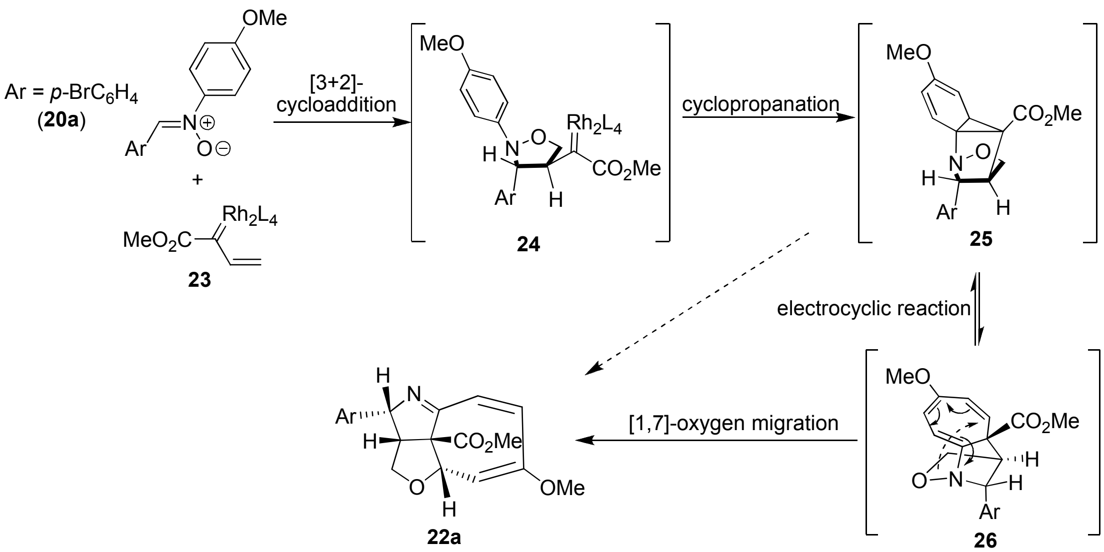


Rh_2L_4	Additive	conversion[b] (%) **21a**	conversion[b] (%) **22a**
$Rh_2(OAc)_4$	4 Å MS	7	45
$Rh_2(TFA)_4$	4 Å MS	24	17
$Rh_2(TPA)_4$	4 Å MS	Trace	10
$Rh_2(CAP)_4$	4 Å MS	Trace	Trace
$Rh_2(OCT)_4$	4 Å MS	9	66
$Rh_2(OCT)_4$ (36 h)	4 Å MS	9	70
$Rh_2(OCT)_4$ (10 eq of **6**)	4 Å MS	10	75
$Rh_2(OCT)_4$	4 Å MS/HFIP	15	85 (74%)[c]

[a] Reactions were performed by addition of a 1.0 mL solution of the vinyldiazoacetate **6** (0.75 mmol) in DCE dropwise over 1 h to the mixture of dirhodium carboxylate catalysts (0.0075 mmol), *N*-(4-methoxyphenyl)-α-(4-bromophenyl)nitrone (0.25 mmol) and 4 Å MS (100 mg) in 1.5 mL of DCE. [b] Conversions were determined by ^{1}H NMR of the reaction mixture before workup. [c] Yield of isolated product after column chromatography is given in parenthesis.

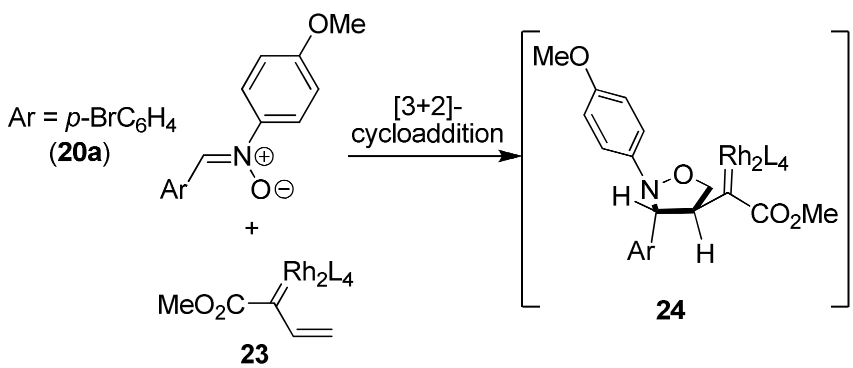
2.2 Reaction Mechanism

We speculate that the overall reaction occurs through a four-step sequential [3+2]-cycloaddition/cyclopropanation/rearrangement pathway (Scheme 3.8) in which the dirhodium carbene intermediate (**23**) activates the adjacent vinyl group for [3+2]-cycloaddition by the nitrone. In [3+2]-cycloaddition reactions between diarylnitrones and electron-deficient alkenes, the concerted reaction prefers *endo* addition which would suggest the exclusive formation of the *trans* isomer **24**.[18] The formation of **22a** is consistent with cycloaddition of nitrone **20a** with metal carbine **23** that forms the electronically favored[18] 3,4-disubstituted regioisomer **24**. Subsequent intramolecular cyclopropanation (aromatic cycloaddition) and electrocyclic opening of the cyclopropane ring by the rhodium carbene on the nitrogen-bound aryl group is proposed to form intermediate **26** that undergoes an unexpected and unique N-O bond cleavage and [1,7]-oxygen migration to **22a** to complete the overall process. In this reaction pathway the dual role of the rhodium carbene, which first activates the conjugated double bond for dipolar cycloaddition, and then undergoes aromatic cycloaddition, is unprecedented, as is the [1,7]-oxygen migration. Alternatively, cleavage of the N-O bond in **25** and attack of oxygen at the cyclopropane with imine formation can lead to **22a** in a single step (shown with the dashed arrow in Scheme 3.8).



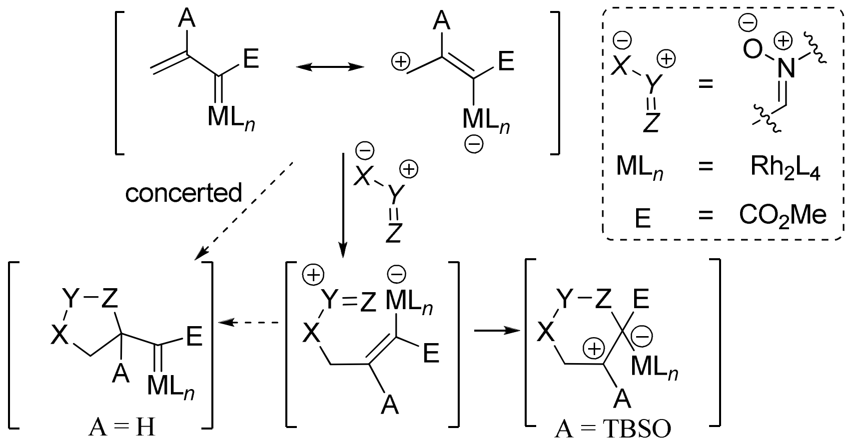
Scheme 3.8 Proposed Reaction Pathway of the Cascade Process.

2.2a [3+2]-Cycloaddition of Nitrones with Rhodium Vinylcarbenes



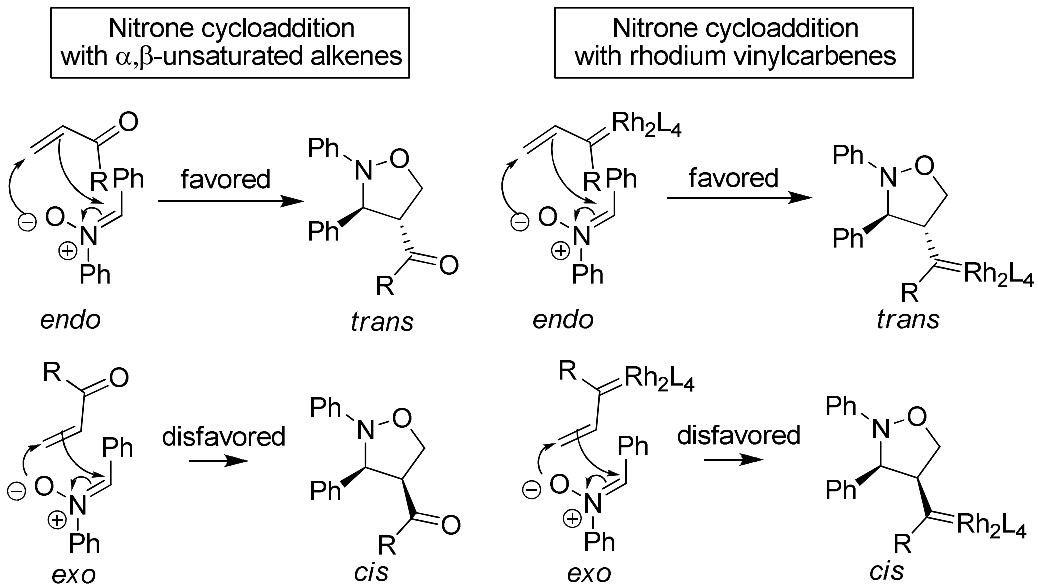
Since nitrone cycloaddition to vinyldiazoacetate **6** does not occur in the absence of catalyst, and dirhodium(II) catalysts are known to undergo rapid dinitrogen extrusion with vinyldiazoacetates, the likely intermediate that allows cycloaddition is the dirhodium vinylcarbene (**23**); but instead of the stepwise [3+3]-cycloaddition,[1] a stepwise or concerted [3+2]-cycloaddition occurs (see Scheme 3.9 for the general representation). Electronic stablization by the TBSO substituent, as well as steric hindrance by the TBS group, might have inhibited the [3+2]-

cycloaddition pathway in the $Rh_2(OAc)_4$-catalyzed [3+3]-cycloaddition reaction of β-TBSO substituted vinyldiazoacetates with nitrones.



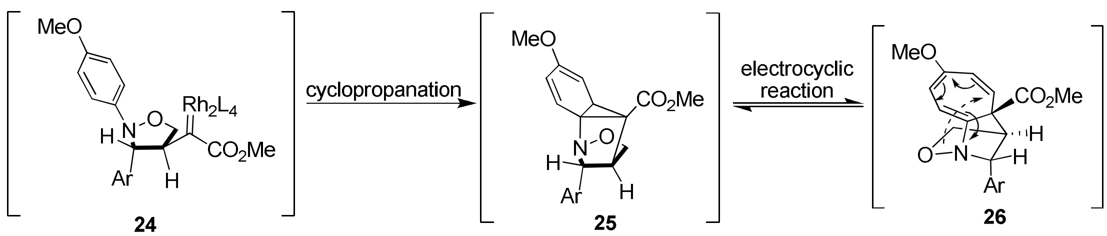
Scheme 3.9 Reaction Pathway Dependent on the Electronic Stabilization by A.

Electron-withdrawing influences by dirhodium catalysts make the C=C double bond in a rhodium vinylcarbene an electron-deficient alkene (discussed in Chapter 2). [3+2]-Cycloaddition of diarylnitrones with α,β-unsaturated alkenes, which are also electron-deficient alkenes, has been well-documented,[18] and the reaction is concerted and occurs preferentially in an *endo* fashion to produce a [3+2]-cycloadduct in which the α-aryl substituent from the nitrone is *trans* to the carbonyl group from the α,β-unsaturated alkene (shown in Scheme 3.10, and also discussed in Chapter 1). Since the cascade process is diastereoselective and only the *trans*-[3+2]-cycloadduct (**24**) would lead to the final product, it is reasonable to deduce that the intial [3+2]-cycloaddition of the cascade process also occurs concertedly in an *endo* fashion (Scheme 3.10).

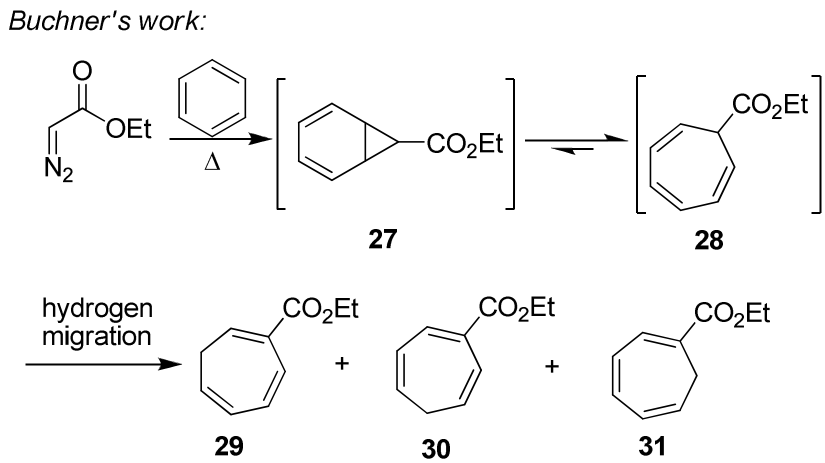


Scheme 3.10 Diastereocontrol in Nitrone Cycloadditions with Electron-deficient Alkenes.

2.2b Buchner Reactions



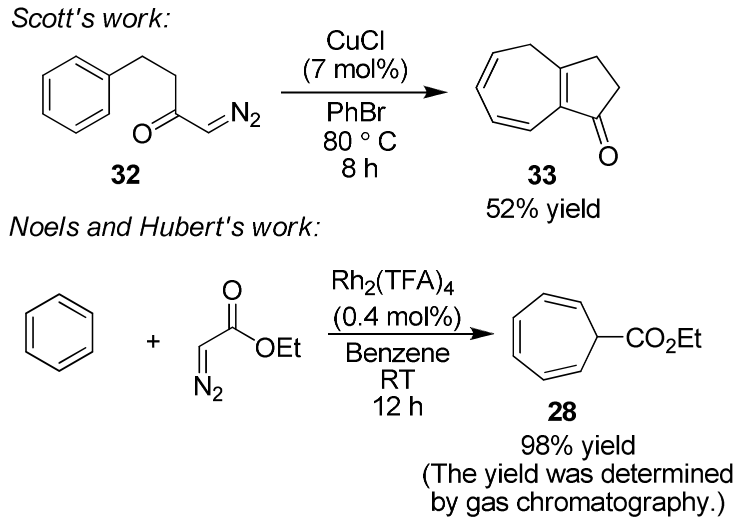
Aromatic cycloaddition by metal carbenes followed by electrocyclic rearrangement to form cycloheptatrienes (e.g., **24** → **26** in our cascade process) is a well-known process, widely recognized as the Buchner reaction.[19] The Buchner reaction was named after the German chemist Eduard Buchner, who thermally reacted ethyl diazoacetate with benzene to prepare what was thought to be norcaradiene **27** (Scheme 3.11).[19a,b] However, the products of the reaction were later determined by Doering and co-workers through modern NMR techniques to be an isomeric mixture of cycloheptatrienes **29–31**.[19c] Cycloheptatrienes **29–31** were obtained from the electrocyclic ring opening of norcaradiene **27** and subsequent [1,3]-, [1,5]- and [1,7]-hydrogen migration from **28** (Scheme 3.11).



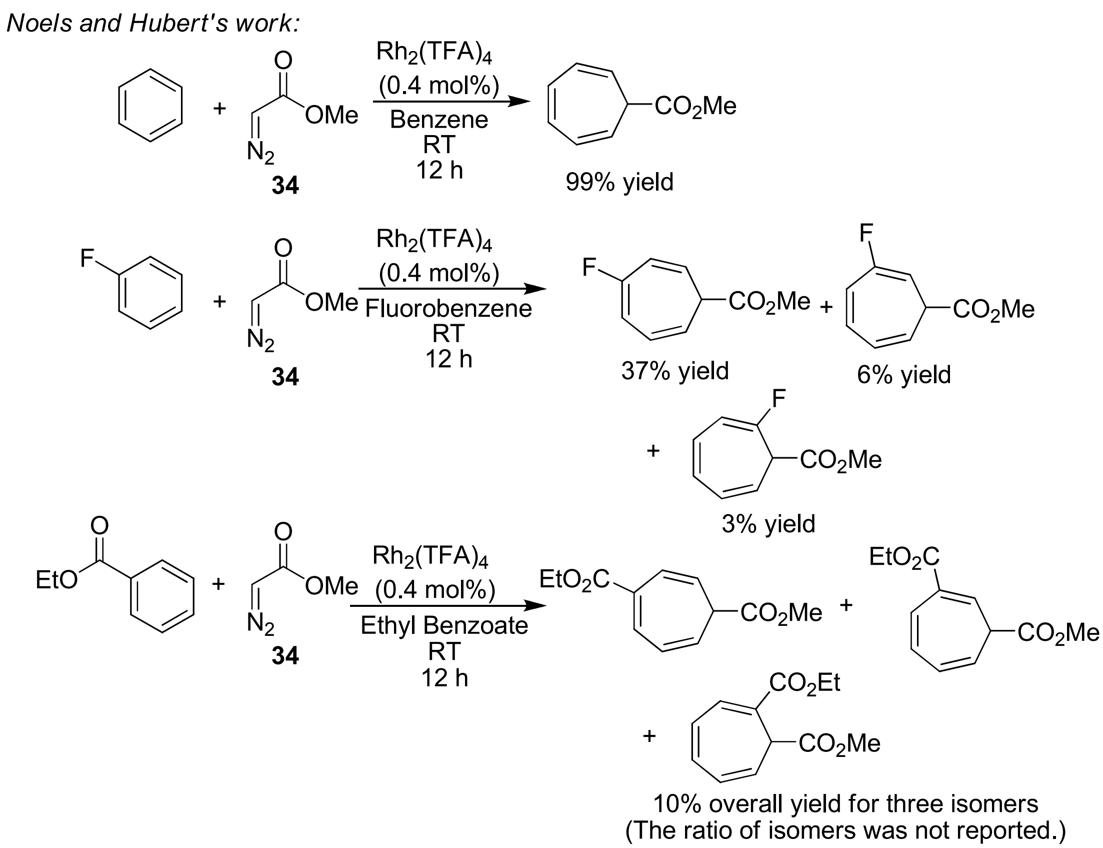
Scheme 3.11 Initial Discovery of the Buchner Reaction.

Early experiments on the Buchner reaction were performed with either photochemical or thermal activation, and the products under these conditions were generally mixtures of cycloheptatrienes (like the results shown in Scheme 3.11).[19] Lack of selectivity and poor yields limited the potential application of the Buchner reaction until transition-metal catalysis was introduced to the reaction in the 1970s, when copper(I) chloride was found by Scott to catalyze the intramolecular Buchner reaction of 1-diazo-4-phenylbutan-2-one (**32**),[20] providing a single cycloheptatriene **33** (Scheme 3.12). In 1980, Noels and Hubert discovered that rhodium trifluoroacetate [$Rh_2(TFA)_4$] was able to catalyze the intermolecular Buchner reaction of ethyl diazoacetate with benzene at room temperature resulting in a 98% yield to cycloheptatriene **28** (Scheme 3.12)[21a] and with no isomerization because of the mild reaction conditions employed in their study. Noels and Hubert also revealed that Buchner reactions catalyzed by dirhodium compounds were disfavored with electron-deficient aromatic rings.[21b] For example, the Buchner reaction of methyl diazoacetate

(**34**) with fluorobenzene occurred with a yield that was much lower than that with benzene; and with more electron-deficient ethyl benzoate the yield was only 10% (Scheme 3.13).[21b]

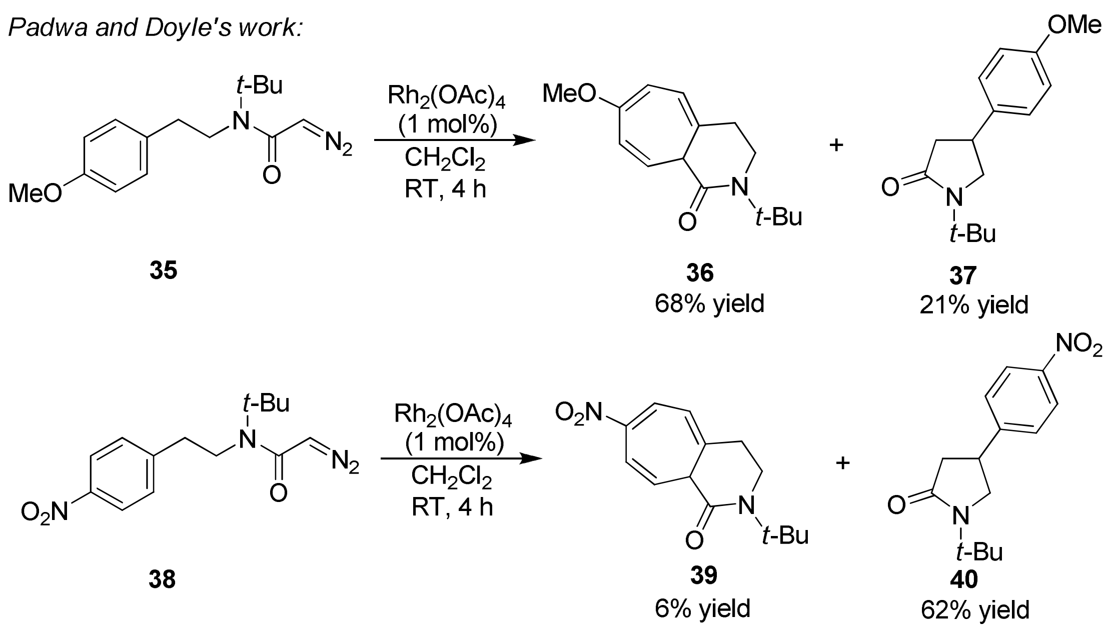


Scheme 3.12 Early Studies on Transition Metal-catalyzed Buchner Reactions.



Scheme 3.13 Buchner Reactions of **34** with Benzene, Fluorobenzene and Ethyl Benzoate Catalyzed by $Rh_2(TFA)_4$ (yields were determined by gas chromatography).

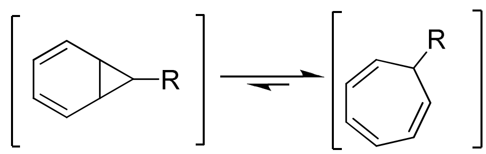
The inhibition of Buchner reaction by electron-deficient aromatic rings was also observed by Padwa and Doyle in intramolecular Buchner reactions (Scheme 3.14).[22] Rhodium acetate-catalyzed decomposition of **35**, which has electron-donating *p*-methoxy substituent on the aromatic ring, provided the Buchner reaction product (**36**) in 68% yield as well as the benzylic C-H insertion product (**37**) in 21% yield; in contrast, when **38** was used, the electron-withdrawing *p*-nitro substituent decreased the electron density of the aromatic ring and resulted in an inhibition of the Buchner reaction that produced **39** in only 6% yield, but the product yield from the benzylic C-H insertion (**40**) was increased to 62% in this case.[22]



Scheme 3.14 Yields of Intramolecular Buchner Reactions Influenced by the Electronic Properties of Aromatic Rings.

Studies of Buchner reactions also revealed that norcaradienes (**41**) were in equilibrium with cycloheptatrienes (**42**) through tautomerization (Scheme 3.15), but in simple unstrained systems, cycloheptatrienes (**42**) were generally favored over norcaradienes (**41**) because of the strain from cyclopropane ring in norcaradienes (**41**).

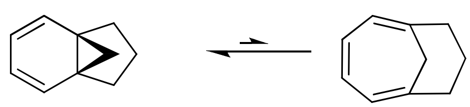
For example, the reactions shown in Scheme 3.12–3.14 did not provide any products of the norcaradiene form under those conditions.[20,21,22] However, for strained systems, the equilibrium of norcaradiene and cycloheptatriene could shift to the norcaradiene side. For example, norcaradiene **43** is stable and does not tautomerize to its cycloheptatriene form (**44**) because of the strong structural stain in **44** (Scheme 3.16).[23]



41 **42**

Scheme 3.15 Tautomerization between Norcaradienes (**41**) and Cycloheptatrienes (**42**).

Vogel's work:

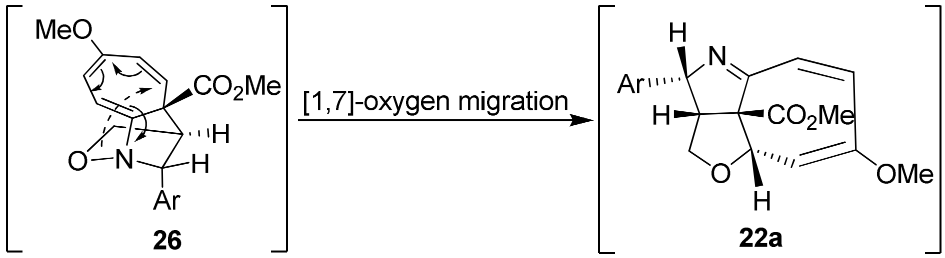


43 **44**
not observed

Scheme 3.16 Equilibrium Favoring the Norcaradiene Form.

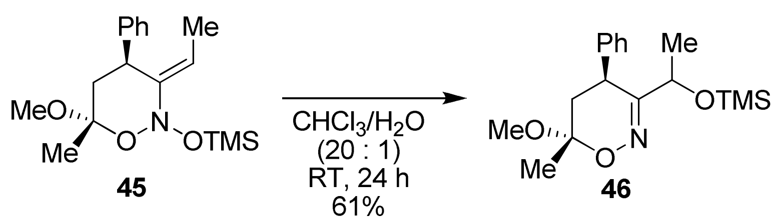
For the Buchner reaction in our cascade process, both the *p*-methoxy and the nitrogen substituents in intermediate **24** are electron-donating, so the Buchner reaction is facilitated electronically.[21,22] We were unable to detect either norcaradiene **25** or cycloheptatriene **26** by NMR spectroscopy under the reaction conditions. However, structures of both norcaradiene **25** and cycloheptatriene **26** are very strained. The strain could be the driving force for the unusual rearrangement step which follows the Buchner reaction in the cascade process.

2.2c N-O Cleavage with Oxygen Migration



The transformation from intermediate **26** to **22a**, which involves cleavage of the N-O bond and subsequent [1,7]-migration of oxygen to the conjugated carbon, is unprecedented. Cleavage of a N-O bond followed by migration of oxygen to conjugated olefinic carbon atoms has been observed in silyl nitroso acetals,[24] but [1,3]-migration was the only process reported. Strain in the intermediate **26** and the proximity of the reacting atoms could be the driving force of this unusual rearrangement.

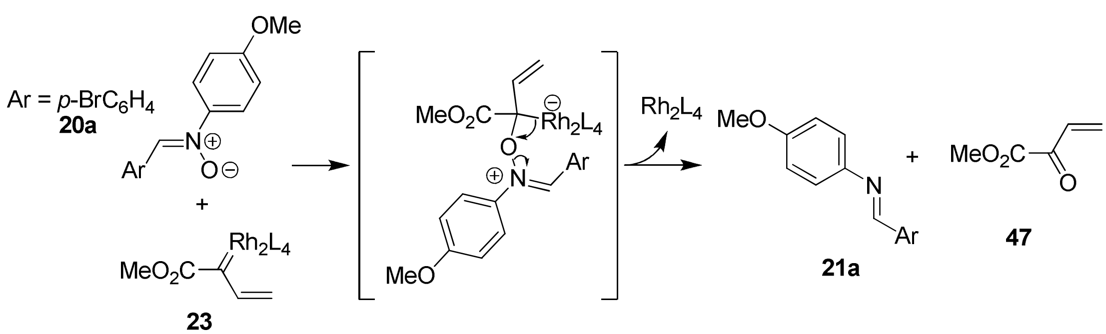
One example of analogous [1,3]-migration in silyl nitroso acetals is shown in Scheme 3.17.[24c] At room temperature, silyl nitroso acetal **45** slowly rearranged into oxazine **46** with a yield of 61% over a reaction time of 24 h. The authors who reported this reaction did suggest some possible reaction mechanisms involving N-O bond cleavage, but no direct evidence was reported to confirm any of them.



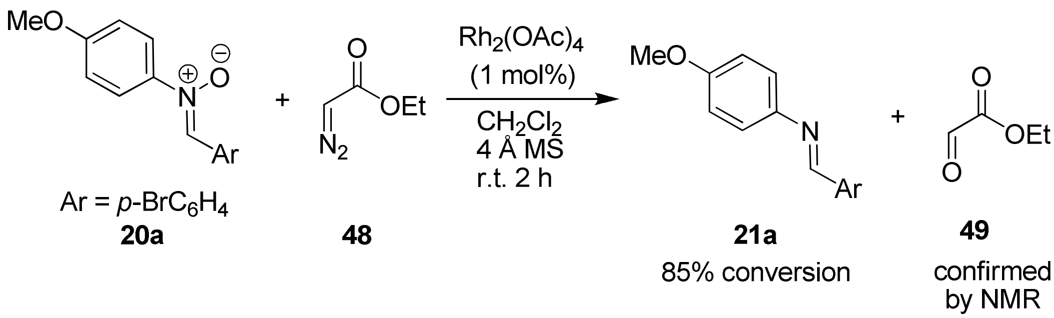
Scheme 3.17 Oxygen Migration with N-O Cleavage in the Nitroso Silyl Acetal.

2.3 Imine Formation

For the formation of the imine by-product (**21a**), we speculate that nucleophilic addition of the nitrone oxygen to the carbene center of the rhodium vinylcarbene occurs first, then subsequent N-O cleavage, facilitated by the elimination of dirhodium catalysts, produces imine **21a** and 2-oxa-3-butenoate (**47**) (Scheme 3.18). However, isolation of 2-oxa-3-butenoate (**47**) from the reaction mixture was not successful, and characterization of **47** has not been reported in the literature. Therefore, we designed an alternative way to validate the mechanism (Scheme 3.19). We reacted ethyl diazoacetate (**48**, 2 equivalents) with nitrone **20a** under the catalysis of $Rh_2(OAc)_4$ (1 mol%). After a reaction time of 2 h, there was an 85% conversion to imine **21a**, and the only other reaction product was ethyl glyoxalate (**49**), which was identified by comparing the ^{1}H NMR spectrum of the reaction mixture with that of **49** from a commercial source.



Scheme 3.18 Mechanism of the Imine Formation.

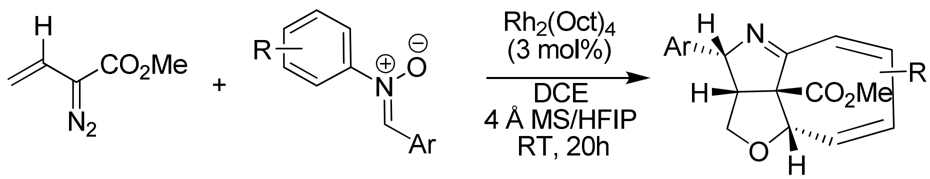


Scheme 3.19 Reactions of Nitrone **20a** with Ethyl Diazoacetate.

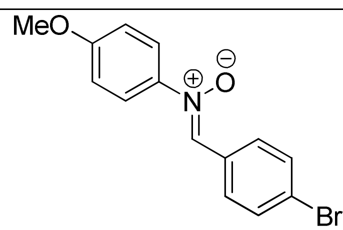
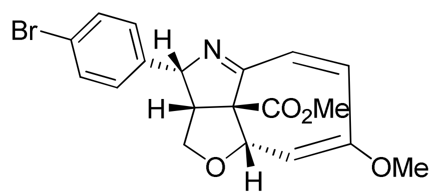
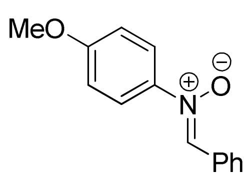
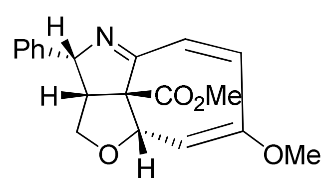
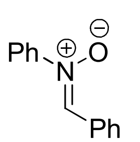
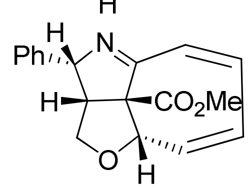
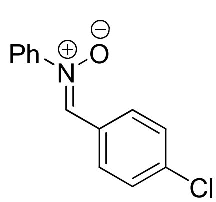
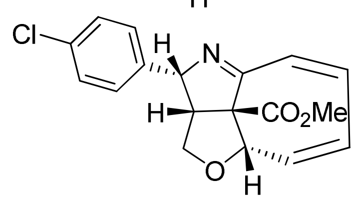
2.4 Scope of Reactions with Diarylnitrone in the Cascade Process

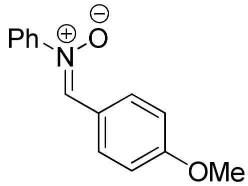
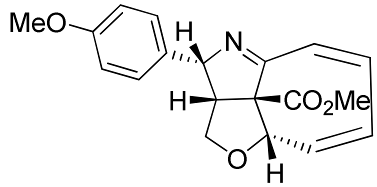
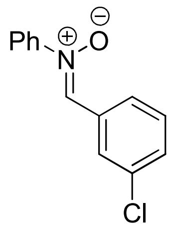
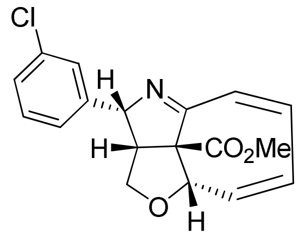
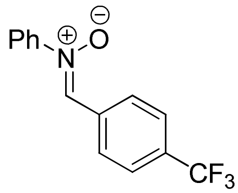
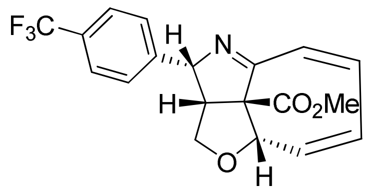
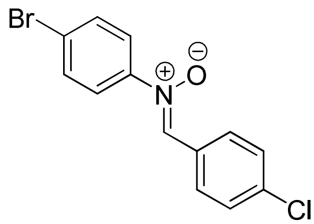
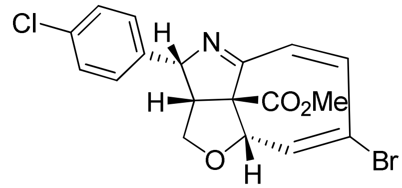
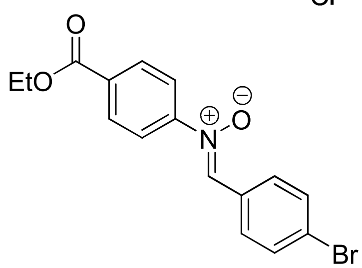
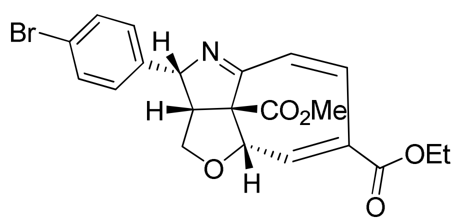
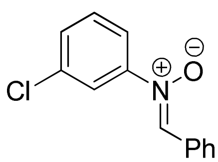
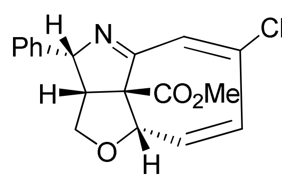
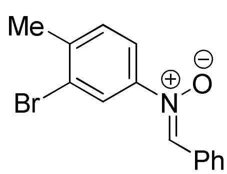
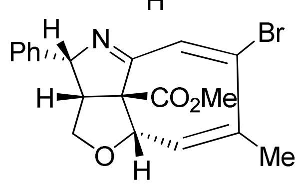
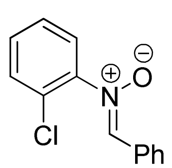
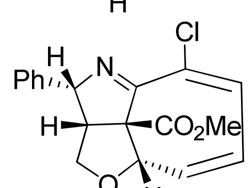
Using the optimized conditions that include HFIP as an additive we investigated the generality of this process with a broad range of nitrones, and the results of this investigation are reported in Table 3.2. With diphenylnitrone (**20c**) an 83% yield of tricyclic product **22c** was produced. Yields for **22** were not obviously dependent on electronic influences from the α-aryl ring since yields ranged from 73% to 85% (products **22c–22g**) with nitrones having electron-donating and electron-withdrawing substituents. Substituents on the *N*-Ar ring were varied in anticipation of activation from electron-donating substituents and inhibition of addition from electron-withdrawing groups.[22] However, reaction occurred even with the nitrone having a strongly electron-withdrawing ester group on the *N*-Ar group (nitrone **20i**). Electron-withdrawing groups on the aromatic ring are known to deactivate the aromatic cycloaddition by metal carbenes,[22] but with these substrates (e.g., with **20i**) the electron-donating nitrogen has an overriding activating influence. Also, with *meta*- and *ortho*-substituents on the *N*-Ar group, cyclopropanation could have occurred on either side of the *N*-Ar bond which would have led to the formation of two regioisomers; however, only a single regioisomer was formed in good yields (products **22j–22l**). A single diastereomer of **22** was obtained in all cases; and formation of the imine by-product, which was observed in the optimization process, was variable depending on the nitrone. Nitrones having the electron-donating methoxy substituent on the *N*-Ar group (nitrones **20a** and **20b**) appeared to produce the imine by-product with larger conversions, while for the reactions that produce **22c–22l**, imine by-products were formed only in trace amounts. Therefore, this multistep cascade process is general and occurs with very high regiocontrol. The resulting products are predisposed for further elaboration.

Table 3.2 Scope of Diarylnitrones.[a]



6 3 equiv | **20** | **22**

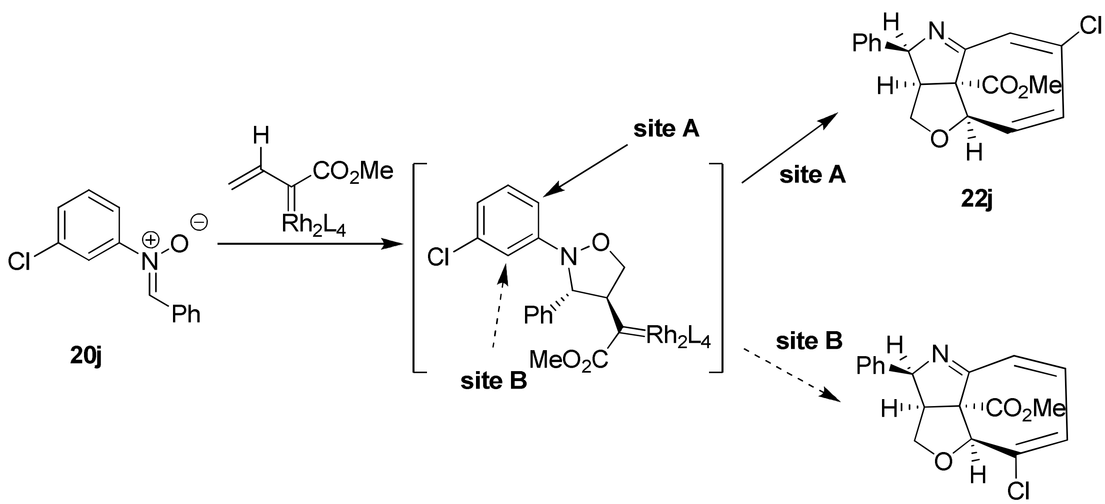
Comp	nitrones, **20**	products, **22**	yield(%)[b]
a			74 (15[c])
b			70 (7[c])
c			83
d			73

e			85
f			75
g			73
h			80
i			60
j			86
k			82
l[d]			88

[a] Reactions were performed by addition of a 1.0 mL solution of vinyldiazoacetate **6** (0.75 mmol) in DCE dropwise over 1 h to the mixture of $Rh_2(OCT)_4$ (0.0075 mmol), nitrone (0.25

mmol), 4 Å MS (100 mg), and HFIP (0.25 mmol) in 1.5 mL of DCE. [b] Yield of isolated product after column chromatography. [c] Conversions to imine by-products is given in parentheses; For reactions with nitrones **20c**–**20l**, conversions to imine by-products were <5%. [d] 6 equiv. of **6** was used, and the reaction time was 48 h.

As discussed earlier, nitrones with *meta*- and *ortho*-substituents on the *N*-Ar group could produce two regioisomers depending on the site of cyclopropanation. The route is shown in Scheme 3.20 using nitrone **20j** as an example, where only cyclopropanation at site A produces **22j**. Confirmation of structure **22j** was easily obtained from the ^{1}H NMR spectrum (Figure 2.2). The olefinic proton region (δ 7.10-5.80) of the ^{1}H NMR spectrum clearly showed a singlet proton (δ 6.99) and a pair of coupled protons (δ 6.28 and 6.18), indicating a diene system of **22j**. During the formation of **22j–22l**, cyclopropanation occured on the less substituted side of the N-aryl bond.



Scheme 3.20 Regioselectivity in the Reaction of **20j**.

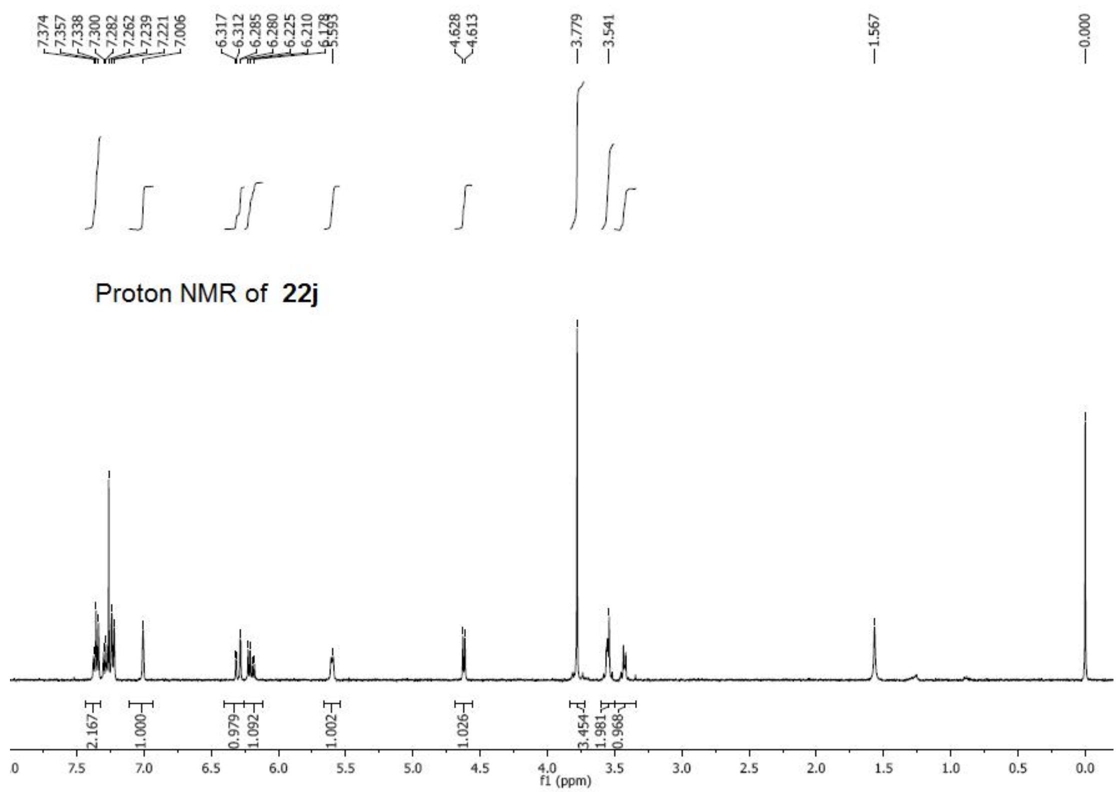
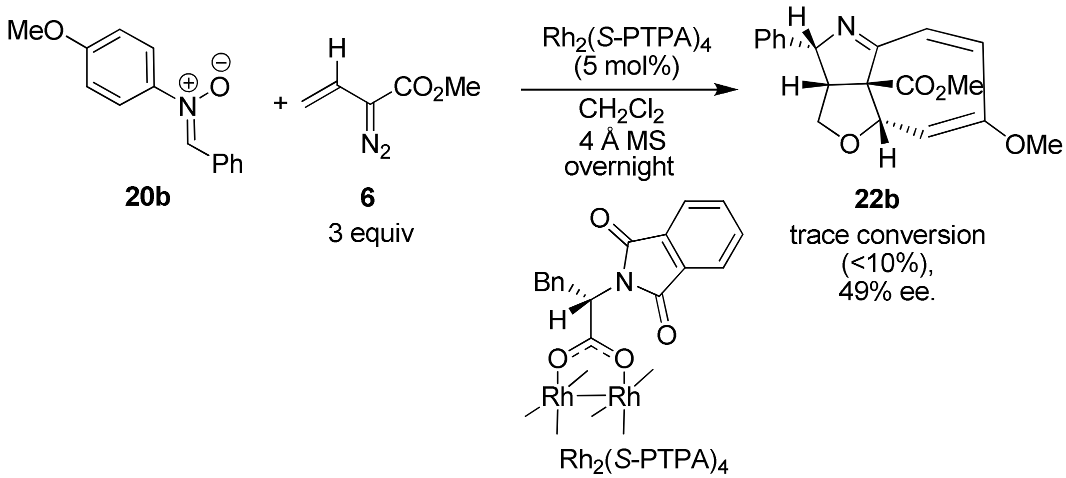


Figure 3.2 ^{1}H NMR of **22j**.

We also investigated chiral dirhodium catalysts for an enantioselective method. With Rh_2(*S*-PTPA)$_4$, the reaction with nitrone **20b** produced **22b** in 49% ee, but with a very low conversion (Scheme 3.21). The extremely poor conversions of nitrone **20b** were also obtained with other Hashimoto's dirhodium catalysts[25] (conversions were all lower than 10%). To obtain a viable enantioselective method for the cascade process, further optimization is necessary.



Scheme 3.21 Rh_2(*S*-PTPA$)_4$-catalyzed Cascade Reaction of **20b**.

III. Conclusion

In conclusion, we have developed a general and highly selective method for the preparation of multifunctionalized tricyclic heterocycles through an abnormal cascade process. To undergo this process a metal vinylcarbene activates the vinyl group for nitrone cycloaddition and then undergoes the Buchner reaction that is linked to a [1,7]-oxygen migration which occurs with N-O bond cleavage. The products of the process, which have both oxygen and nitrogen-fused rings and a quaternary carbon in the middle, are formed with remarkable specificity.

IV. Experimental Section

4.1 Materials

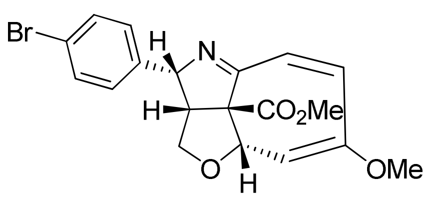
$Rh_2(OAc)_4$ was purchased from Pressure Chemical Co. and $Rh_2(OCT)_4$ was purchased from Johnson Matthey Co.. Other dirhodium catalysts,[15,25] diarylnitrones[26] and methyl 2-diazobut-3-enoate (**6**)[2] were prepared according to the literature procedures. Analytically pure solvents from commercial sources were stored with activated 4 Å molecular sieves in a capped round-bottom flask for at least 24 h to diminish the water content.[27] All the other chemicals were obtained from commercial sources and used without further purification.

4.2 General Information

All reactions, unless noted, were carried out under an inert atmosphere of dried nitrogen in flame-dried or oven-dried glassware with magnetic stirring. Analytical thin layer chromatography (TLC) was performed on Dynamic Adsorbents precoated (0.25 mm thickness) silica gel plates with F_{254} indicator. Visualization was accomplished by UV light (254 nm) or with phosphomolybdic acid (PMA) solution in ethanol. Flash chromatography was performed with silica gel (32-63 μm) supplied by Dynamic Adsorbents. ^{1}H NMR spectra were recorded on a Bruker DRX-400 (400 MHz) spectrometer or a Bruker DRX-500 (500 MHz) spectrometer, and chemical shifts were reported in ppm using tetramethylsilane (δ = 0 ppm for ^{1}H) as the internal standard. The peak information was described as: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = composite; coupling constant(s) in Hz. ^{13}C NMR spectra were recorded on a Bruker DRX-500 (125 MHz) spectrometer with complete proton decoupling and the chemical shifts were reported in ppm using $CDCl_3$ (δ = 77.0 ppm) as the internal standard. IR spectra were recorded on a JASCO FT/IR 4100 spectrometer. Enantioselectivities were determined on an Agilent 1200 Series HPLC using a Daicel Chiralcel OD-H column or an AD-H column. High-resolution mass spectra (HRMS) were performed on JEOL AccuTOF-CS mass spectrometer using CsI as the standard.

4.3 Experimental Procedures and Compound Characterizations

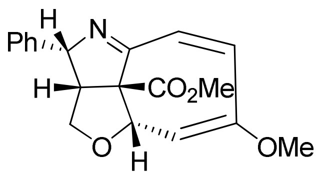
General Procedure for the Cascade Reaction between Diarylnitrones and Methyl 2-Diazobut-3-enoate Catalyzed by $Rh_2(Oct)_4$. A 10 mL Schlenk flask charged with a magnetic stir bar and 4 Å molecular sieves (100 mg) was placed under high vacuum and heated by Bunsen burner to dryness. After cooling to room temperature, $Rh_2(Oct)_4$ (6.0 mg, 3.0 mol%), diarylnitrone (0.250 mmol), 1,1,1,3,3,3-hexafluoro-2-propanol (27 μL, 0.25 mmol) and 1.5 mL of 1,2-dichloroethane were added under a flow of N_2. The resulting green solution was stirred for 5 min, and then the flask was wrapped with aluminum foil to avoid light (based on my own observation that self-polymerization of pure **6** seems to be faster under day-light). Freshly prepared methyl 2-diazobut-3-enoate (**6**) in 1.0 mL of 1,2-dichloroethane was added into the flask *via* a syringe pump over 1 h. After complete addition, the mixture was stirred at room temperature for 20 hours. The solvent from the reaction solution was evaporated under reduced pressure, and the residue was dissolved in a minimal amount of dichloromethane and loaded onto a silica gel column. Column chromatography with hexane/ethyl acetate (3:1) with 5% Et_3N provided the final product that was later analyzed by ^{1}H NMR and ^{13}C NMR spectroscopy.



22a

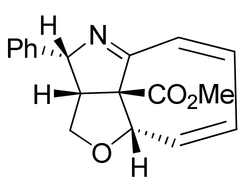
Methyl 5-(4-Bromophenyl)-10-methoxy-2-oxa-6-azatricyclo[5.4.1.0^{4,12}]-dodeca-6,8,10-triene-12-carboxylate (22a). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.48 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 6.73 (d, *J* = 12.8 Hz, 1H), 6.33 (d, *J*

= 12.8 Hz, 1H), 5.49 (d, *J* = 6.7 Hz, 1H), 5.23 (dd, *J* = 1.7, 7.2 Hz, 1H), 4.69 (d, *J* = 7.2 Hz, 1H), 3.74 (s, 3H), 3.61 (s, 3H), 3.60-3.49 (comp, 2H), 3.42-3.35 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 169.88, 167.94, 155.71, 138.07, 133.12, 131.70, 128.98, 126.91, 121.23, 97.30, 78.65, 74.99, 71.95, 68.06, 54.97, 54.62, 52.78; HRMS (ESI) calculated for $C_{19}H_{19}BrNO_4$ $[M+H]^+$: 404.0492; found: 404.0494.



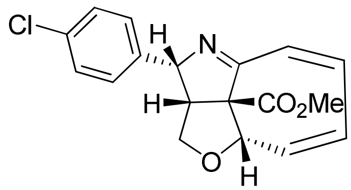
22b

Methyl 10-Methoxy-5-phenyl-2-oxa-6-azatricyclo[5.4.1.0^{4,12}]dodeca-6,8,10-triene-12-carboxylate (22b). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.39-7.24 (comp, 5H), 6.75 (d, *J* = 12.7 Hz, 1H), 6.31 (d, *J* = 12.7 Hz, 1H), 5.54 (d, *J* = 6.0 Hz, 1H), 5.23 (dd, *J* = 1.8, 7.2 Hz, 1H), 4.69 (d, *J* = 7.2 Hz, 1H), 3.75 (s, 3H), 3.61 (s, 3H), 3.58-3.49 (comp, 2H), 3.45-3.36 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.12, 167.58, 155.71, 138.93, 132.86, 128.58, 127.27, 127.23, 127.13, 97.22, 78.66, 75.59, 71.75, 68.23, 55.21, 54.61, 52.79. HRMS (ESI) calculated for $C_{19}H_{20}NO_4$ $[M+H]^+$: 326.1387; found: 326.1396.



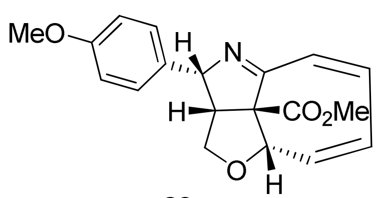
22c

Methyl 5-Phenyl-2-oxa-6-azatricyclo[5.4.1.0^{4,12}]dodeca-6,8,10-triene-12-carboxylate (22c). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.38-7.32 (comp, 2H), 7.29-7.23 (comp, 3H), 6.75 (d, *J* = 11.9 Hz, 1H), 6.47-6.35 (m, 1H), 6.25-6.20 (comp, 2H), 5.61 (d, J = 6.2 Hz, 1H), 4.65-4.60 (m, 1H), 3.75 (s, 3H), 3.58-3.50 (comp, 2H), 3.48-3.39 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.20, 168.09, 138.91, 130.84, 129.76, 128.55, 128.49, 127.97, 127.27, 127.26, 79.95, 76.30, 68.77, 54.95, 52.77 (one carbon was missing due to overlapping signals). HRMS (ESI) calculated for $C_{18}H_{18}NO_3$ $[M+H]^+$: 296.1281; found: 296.1274.



22d

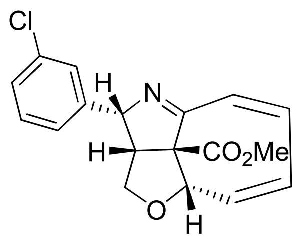
Methyl 5-(4-Chlorophenyl)-2-oxa-6-azatricyclo[5.4.1.0^{4,12}]dodeca-6,8,10-triene-12-carboxylate (22d). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.32 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 6.73 (d, J = 11.8 Hz, 1H), 6.47-6.33 (m, 1H), 6.24-6.22 (comp, 2H), 5.57 (d, J = 6.5 Hz, 1H), 4.60-4.62 (m, 1H), 3.74 (s, 3H), 3.60-3.50 (comp, 2H), 3.41-3.36 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.01, 168.43, 137.55, 133.16, 131.05, 129.82, 128.75, 128.68, 128.33, 127.94, 79.99, 75.69, 72.78, 68.62, 54.83, 52.77. HRMS (ESI) calculated for $C_{18}H_{17}ClNO_3$ $[M+H]^+$: 330.0891; found: 330.0884.



22e

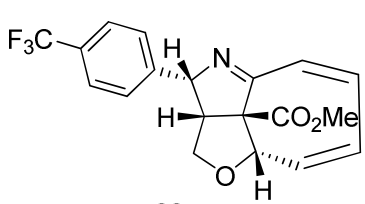
Methyl 5-(4-Methoxyphenyl)-2-oxa-6-azatricyclo[5.4.1.0^{4,12}]dodeca-6,8,10-triene-12-carboxylate (22e). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.15 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 6.73 (d, J = 12.0 Hz, 1H), 6.39 (m, 1H), 6.24-6.21

(comp, 2H), 5.57 (d, *J* = 6.5 Hz, 1H), 4.63-4.61 (m, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 3.56-3.43 (comp, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.29, 167.82, 158.86, 131.08, 130.73, 129.83, 128.57, 128.40, 127.91, 113.97, 80.12, 75.97, 72.69, 68.78, 55.26, 55.14, 52.71. HRMS (ESI) calculated for $C_{19}H_{20}NO_4$ $[M+H]^+$: 326.1387; found: 326.1392.



22f

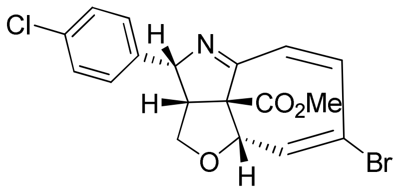
Methyl 5-(3-Chlorophenyl)-2-oxa-6-azatricyclo[5.4.1.0^{4,12}]dodeca-6,8,10-triene-12-carboxylate (22f). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.30-7.24 (comp, 3H), 7.16-7.12 (m, 1H), 6.74 (d, *J* = 11.9 Hz, 1H), 6.44-6.40 (m, 1H), 6.24-6.21 (comp, 2H), 5.57 (d, *J* = 6.6 Hz, 1H), 4.63-4.61 (m, 1H), 3.74 (s, 3H), 3.63-3.52 (comp, 2H), 3.41 (dd, *J* = 2.0, 9.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.93, 168.57, 141.14, 134.66, 131.13, 129.84, 129.81, 128.31, 128.00, 127.55, 127.43, 125.43, 79.87, 75.65, 72.64, 68.65, 54.78, 52.79. HRMS (ESI) calculated for $C_{18}H_{17}ClNO_3$ $[M+H]^+$: 330.0891; found: 330.0902.



22g

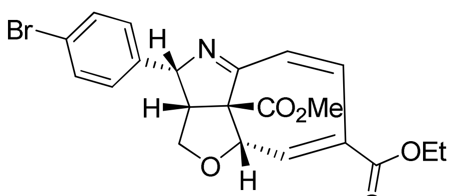
Methyl 5-[4-(Trifluoromethyl)phenyl]-2-oxa-6-azatricyclo[5.4.1.0^{4,12}]-dodeca-6,8,10-triene-12-carboxylate (22g). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.61 (d, *J* = 6.5 Hz, 2H), 7.39 (d, *J* = 6.5 Hz, 2H), 7.74 (d, *J* = 9.6 Hz, 1H), 6.44-6.40

(m, 1H), 6.25-6.22 (comp, 2H), 5.64 (d, J = 4.4 Hz, 1H), 4.63-4.62 (m, 1H), 3.75(s, 3H), 3.60-3.56 (comp, 2H), 3.34-3.32 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) ^{13}C NMR δ 169.87, 168.72, 143.10, 131.24, 129.76, 128.18, 127.99, 127.63, 126.25 (q, J = 270.0 Hz), 125.52 (q, J = 3.8 Hz), 79.82, 75.78, 72.68, 68.54, 54.65, 52.84 (one carbon is missing due to overlapping signals). HRMS (ESI) calculated for $C_{19}H_{17}F_3NO_3$ $[M+H]^+$: 364.1155; found: 364.1156.



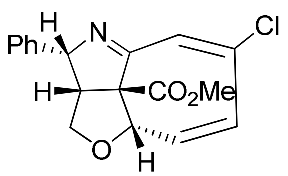
22h

Methyl 10-Bromo-5-(4-chlorophenyl)-2-oxa-6-azatricyclo[5.4.1.0^{4,12}]dodeca-6,8,10-triene-12-carboxylate (22h). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.33 (d, J = 8.3 Hz, 2H), 7.17 (d, J = 8.3 Hz, 2H), 6.73 (d, J = 6.6 Hz, 1H), 6.66-6.58 (comp, 2H), 5.60-5.57 (m, 1H), 4.51 (d, J = 6.6 Hz, 1H), 3.77 (s, 3H), 3.57-3.49 (comp, 2H), 3.38-3.35 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.43, 166.89, 137.02, 136.01, 133.36, 130.85, 128.84, 128.62, 128.07, 122.81, 80.15, 75.86, 72.99, 68.51, 54.67, 53.05. HRMS (ESI) calculated for $C_{18}H_{16}BrClNO_3$ $[M+H]^+$: 407.9997; found: 407.9983.



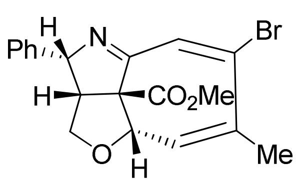
22i

10-Ethyl 12-Methyl 5-(4-Bromophenyl)-2-oxa-6-azatricyclo[5.4.1.0^{4,12}]-dodeca-6,8,10-triene-10,12-dicarboxylate (22i). This compound decomposed under the catalysis of triethylamine, so triethylamine was not used when column chromatography was performed. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.48 (d, *J* = 7.8 Hz, 2H), 7.42 (d, *J* = 6.1 Hz, 1H), 7.15-7.09 (comp, 2H), 7.09 (d, *J* = 12.7 Hz, 1H), 6.81 (d, *J* = 12.7 Hz, 1H), 5.59 (d, *J* = 5.5 Hz, 1H), 4.76 (d, *J* = 6.1 Hz, 1H), 4.28 (q, *J* = 6.3 Hz, 2H), 3.74 (s, 3H), 3.62-3.53 (comp, 2H), 3.41-3.38 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.63, 167.39, 166.34, 137.71, 136.56, 131.74, 130.86, 129.21, 128.99, 128.08, 121.38, 79.25, 76.09, 72.95, 68.90, 61.89, 54.60, 53.02, 14.15. HRMS (ESI) calculated for $C_{21}H_{21}BrNO_5$ $[M+H]^+$: 446.0598; found: 446.0605.



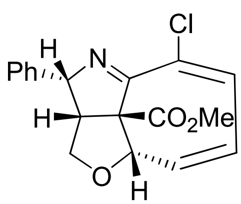
22j

Methyl 9-Chloro-5-phenyl-2-oxa-6-azatricyclo[5.4.1.0^{4,12}]dodeca-6,8,10-triene-12-carboxylate (22j). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.40-7.20 (comp, 5H), 7.00 (s, 1H), 6.30 (dd, *J* = 2.0, 12.8 Hz, 1H), 6.81 (dd, *J* = 5.9, 12.8 Hz, 1H), 5.60-5.58 (m, 1H), 4.61 (d, *J* = 5.9 Hz, 1H), 3.78 (s, 3H), 3.57-3.53 (comp, 2H), 3.44-3.41 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.66, 165.02, 138.51, 137.57, 131.52, 130.05, 128.60, 127.41, 127.18, 126.59, 79.31, 76.42, 72.47, 68.90, 54.85, 53.01. HRMS (ESI) calculated for $C_{18}H_{17}ClNO_3$ $[M+H]^+$: 330.0891; found: 330.0884.



22k

Methyl 9-Bromo-10-methyl-5-phenyl-2-oxa-6-azatricyclo[5.4.1.0^{4,12}]dodeca-6,8,10-triene-12-carboxylate (22k). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.38-7.33 (comp, 2H), 7.31 (d, J = 1.8 Hz, 1H), 7.28-7.27 (m, 1H), 7.22-7.20 (comp, 2H), 6.20 (dd, J = 1.3, 5.6 Hz, 1H), 5.56 (dd, = 1.6, 7.3 Hz, 1H), 4.61 (d, J = 5.6 Hz, 1H), 3.79 (s, 3H), 3.54-3.46 (comp, 2H), 3.34-3.31 (m, 1H), 2.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.93, 165.99, 138.45, 135.09, 132.14, 130.23, 128.56, 127.41, 127.22, 126.88, 79.68, 77.00, 73.64, 68.27, 55.02, 53.03, 29.92. HRMS (ESI) calculated for $C_{19}H_{19}BrNO_3$ $[M+H]^+$: 388.0543; found: 330.0551.



22l

Methyl 8-Chloro-5-phenyl-2-oxa-6-azatricyclo[5.4.1.0^{4,12}]dodeca-6,8,10-triene-12-carboxylate (22l). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.38-7.32 (comp, 2H), 7.28-7.26 (m, 1H), 7.22-7.19 (comp, 2H), 6.69 (d, J = 8.5 Hz, 1H), 6.23 (dd, J = 5.7, 12.2 Hz, 1H), 6.09 (dd, J = 8.5, 12.2 Hz, 1H), 5.70 (d, J = 7.6 Hz, 1H), 4.61 (d, J = 5.7 Hz, 1H), 3.78 (s, 3H), 3.61 (dt, J = 2.3, 7.7 Hz, 1H), 3.56-3.53 (m, 1H), 3.42 (dd, J = 2.3, 9.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.85, 165.79, 138.01, 131.39, 129.54, 128.63, 128.57, 127.51, 127.49, 125.22, 80.51, 76.89, 72.43, 68.85, 55.48, 53.05. HRMS (ESI) calculated for $C_{18}H_{17}ClNO_3$ $[M+H]^+$: 330.0891; found: 330.0880.

NMR graphs can be obtained from the supporting information of the paper published in *Angew. Chem., Int. Ed.*: Wang, X.; Abrahams, Q. M.; Zavalij, P. Y.; Doyle, M. P. *Angew. Chem., Int. Ed.* **2012**, DOI: 10.1002/anie.201201917.

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