Co(II) Based Metalloradical Catalysis: Carbene and Nitrene Transfer Reactions

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Co(II) Based Metalloradical Catalysis:

Carbene and Nitrene Transfer Reactions

by

Joseph B. Gill

A dissertation in partial fulfillment of the requirements for the degree of
Doctor of Philosophy
Department of Chemistry
College of Arts and Sciences
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Dedication

I dedicate this work to my parents: Larry and Karen, siblings: Jason and Jessica, and my partner: Darnell, for their constant support. Without all of you I would never have made it through this journey. Thank you.
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I would like to thank my advisor, Professor X. Peter Zhang, for his support and guidance throughout my time working with him. I cannot express how grateful I am for how much he has taught me in the last few years. I would also like to thank my committee members without whom I would not have been able to finish this journey.

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<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tertiary butyloxy carbonyl</td>
</tr>
<tr>
<td>CDA</td>
<td>α-cyanodiazocetate</td>
</tr>
<tr>
<td>DFT</td>
<td>Density functional theory</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DPPA</td>
<td>Diphenylphosphoryl azide</td>
</tr>
<tr>
<td>EDA</td>
<td>ethyl diazoacetate</td>
</tr>
<tr>
<td>EPR</td>
<td>Electron paramagnetic resonance</td>
</tr>
<tr>
<td>HOMO</td>
<td>Highest occupied molecular orbital</td>
</tr>
<tr>
<td>HRMS</td>
<td>High resolution mass spectroscopy</td>
</tr>
<tr>
<td>IDA</td>
<td>isopropyl diazoacetate</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium diisopropyl amine</td>
</tr>
<tr>
<td>LUMO</td>
<td>Lowest unoccupied molecular orbital</td>
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<tr>
<td>MRC</td>
<td>Metalloradical catalysis</td>
</tr>
<tr>
<td>NDA</td>
<td>α-nitrodiazocetate</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>SOMO</td>
<td>Singly occupied molecular orbital</td>
</tr>
<tr>
<td>tBDA</td>
<td>tertiary butyl diazoacetate</td>
</tr>
<tr>
<td>Acronym</td>
<td>Full Form</td>
</tr>
<tr>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>Tces</td>
<td>Trichloroethoxysulfonyl</td>
</tr>
<tr>
<td>TEMPO</td>
<td>(2,2,6,6-Tetramethylpiperidin-1-yl)oxy</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TPP</td>
<td>tetraphenylporphyrin</td>
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Abstract

Radical chemistry has attracted a large amount of research interest over the last few decades and radical reactions have recently been recognized as powerful tools for organic synthesis. The synthetic applications of radicals have been demonstrated in many fields, including in the synthesis of complex natural products. Radical reactions have a number of inherent synthetic advantages over their ionic counterparts. For example, they typically proceed at fast reaction rates under mild and neutral conditions in a broad spectrum of solvents and show significantly greater functional group tolerance. Furthermore, radical processes have the capability of performing in a cascade fashion, allowing for the rapid construction of complex molecular structures with multiple stereogenic centers. To further enhance the synthetic applications of radical reactions, current efforts are devoted toward the development of effective approaches for the regioselective control of their reactivity as well as stereoselectivity, especially enantioselectivity, a challenging issue that is intrinsically challenged by the “free” nature of radical chemistry.

This research has identified a fundamentally new approach to radical reactions based on the concept of metalloradical catalysis (MRC) for controlling the stereoselectivity of both C- and N-centered radical reactions. Cobalt(II) porphyrins [Co(Por)], are stable metalloradicals, and have been shown to enable the activation of diazo reagents and azides to cleanly generate C- and N-centered radicals, respectively, with \( \text{N}_2 \) as the only byproduct in a controlled and catalytic manner. In addition to the radical nature of [Co(Por)], the low
bond dissociation energy of Co–C/Co–N bonds plays a key role in the successful turnover of the Co(II)-based catalytic carbene and nitrene transfers. Through the support of porphyrin ligands with tunable electronic, steric, and chiral environments, this general concept of Co(II)-based metalloradical catalysis (Co-MRC) has been successfully applied to the development of various radical processes that enable stereoselective carbene and nitrene transfers.
Chapter 1: Overview of Metalloradical Catalysis

1.1 Introduction

Free radicals, often considered to be a class of short-lived and highly reactive compounds, have been used to initiate many types of organic reactions such as substitution, addition, abstraction, and fragmentation. The diverse reaction profile of radical reactivity has led to the development and methodological study of these potentially powerful synthetic intermediates over the past few decades. Radicals have a few synthetic advantages over their ionic counterparts, such as the rates at which they react, the ability to act in neutral conditions, in a wide variety of solvents and a generally large functional group tolerance. Radicals are also capable of performing multiple step cascade type reactions enabling the rapid construction of complex structures.

Scheme 1.1. Radical Reactions: Opportunities and Challenges
Despite the rich chemistry demonstrated by radicals, they are often still considered more challenging and less practical than their closed-shell ionic counterparts. Radicals are, by definition, a high energy species. Often they cannot be prepared in advance or used as starting materials and typically the use of an initiator is required. Classically, radical initiators are unstable molecules used in a stoichiometric fashion resulting in unwanted byproducts. Due to the highly active nature of radicals, the reactivity and selectivity of these reactions have customarily been difficult to control and produced unwanted side reactions such as dimerization or disproportionation. Stereoselectivity has been a particularly challenging area of research due in part to the very small energy difference between stereoisomers. Finding a way to control the selectivity of radical processes would provide particularly meaningful methodologies and provide more opportunities for their application in synthesis.$^1$

Most known catalytic processes are based on the employment of catalysts with closed-shell electronic structures, either as transition metal complexes or small organic molecules, that proceed with catalytic mechanisms consisting of two-electron reactions. The possibility of addressing the aforementioned challenges of radical reactions through catalysis was envisioned through the development of an open-shell transition metal-based catalyst that proceeded with a one-electron catalytic mechanism. The simplest case of this type of catalyst has an electronic configuration with one unpaired electron in a well-defined $d$ orbital, and has been termed a metalloradical. With the appropriate combination of the transition metal ion in the desired oxidation state and the supporting ligand having a suitable coordination environment, it is hypothesized that the original metal radical character could be completely transferred to the organic precursor upon activation,
resulting in catalytic generation of C-, N-, or O-based radicals (Scheme 1.1). These radical intermediates would function in a similar way as free organic radicals but would not be “free” since they remain bound covalently to the metal complex, which potentially allows for the control of both reactivity and selectivity profiles.

More broadly, the above postulated catalysis may represent a new type of catalytic radical transformation, which can be conceptually considered and defined as metalloradical catalysis (MRC). Essentially, MRC entails the use of open-shell transition metal complexes as metalloradical catalysts to facilitate and control chemical reactions through the catalytic transfer of radical character. It may be applied to a vast array of catalytic processes involving radical mechanisms that consist of one-electron steps. MRC represents a fundamentally new approach to controlling the reactivity and selectivity of radical reactions as well as providing a potential solution to controlling stereoselective radical reactions.

1.2 Cobalt(II) Complexes of Porphyrins: Ideal Candidates as Metalloradical Catalysts

Porphyrins, a class of tetradeutate macrocyclic nitrogen ligands, are well known to form stable cobalt (II) porphyrin complexes ([Co(II)(Por)]). The cobalt (II) complexes of porphyrins are stable in their solid forms in open air without noticeable oxidation for an extended period of time. Due to the strong ligand field and planar coordination environment of porphyrins, [Co(II)(Por)] adopt a low-spin ground state with the $(d_{xy})^2(d_{xz,yz})^4(d_{z^2})^1$ electron configuration and are well-defined metalloradicals (Scheme 1.2). With a single unpaired electron located in the $d_{z^2}$ orbital that is perpendicular to the
porphyrin plane, [Co(II)(Por)] are ideal candidates for metalloradical catalysts. Since [Co(II)(Por)] can activate suitable organic molecules to provide carbene or nitrene equivalents, the bonding pictures of potential [Co(II)(Por)] carbene and nitrene intermediate can be constructed accordingly (Scheme 1.2). The $(d_{xy})^2(d_{xz,yz})^4(d_{z^2})^1$ electron configuration of the Co(II) ion would require the parent carbene/nitrene unit to interact with it in the triplet state. The bonding interaction is thus dominated by the formation of a covalent Co–C (or Co–N) bond between the cobalt’s $d_z^2$ orbital and the ligand’s $sp^2$ orbital. Additional bonding interactions between Co-$d_{xz/yz}$ and $p$ orbitals, a common feature in classic metallocarbene complexes, are minimized as a result of the fully-filled $d_{xz/yz}$ and singly-filled $p$ orbitals. On the basis of these bonding pictures, these carbene and nitrene intermediates of [Co(II)(Por)] shown in Scheme 1.2 would be best described as Co(III)-supported organic radicals and have been named Co(III)-carbene radicals and Co(III)-nitrene radicals, respectively. It is expected that Co(III)-carbene radicals and Co(III)-nitrene radicals would function in a similar fashion to free organic radicals with regards to their reactivities, however the porphyrin ligand environment would provide substantial control of the radical’s reactivity and selectivity.

A series of cobalt(II) porphyrins [Co(Por)] have been designed and synthesized as stable metalloradicals. They have been shown to activate diazo reagents and azides for the effective generation of C- and N-centered radicals, respectively, with $N_2$ as the only byproduct in stereocontrolled and catalytic manners. Furthermore, a class of $D_2$-symmetric cobalt(II) complexes of chiral porphyrins [Co(Por*)], have been shown to be highly selective catalysts for a variety of radical-mediated asymmetric reactions, including C-radical-based cyclopropanation, and N-radical-based aziridination, and C–H amination
reactions. These radical processes are well-regulated with respect to reactivity and stereoselectivity. As a result, they provide both practical and effective solutions for several long-standing challenges in traditional $2e^-$ catalytic carbene and nitrene transfer reactions.$^2$

**Scheme 1.2.** [Co(II)Por]-based Metalloradical and Co(III)-supported Organic Radicals

1.3 **Design and Synthesis of $D_2$-Symmetric Chiral Porphyrins with Tunable Environments**

Due to the unique ligand environment and metal coordination modes, [Co(II)(Por)] was anticipated to have several additional catalytic advantages for MRC (Figure 1.1). First, due to the macrocyclic chelation effect of the aromatic ligand [Co(II)(Por)] has excellent thermal and metal coordination. Once inserted into the macrocyclic ring, dissociation of the Co$^{2+}$ ion is, under most reaction conditions, highly unfavorable. This leads to an increased catalyst lifetime and the elimination of metal contamination in the products; a practical issue for many metal-catalyzed processes. Second, being a square planar ligand, [Co(II)(Por)] has no vacant cis-coordination sites available, which avoids unwanted side reactions that stem from cis-site reactivity. Third, it has been well documented that the physical and chemical properties of [Co(II)(Por)] can be systematically tuned by introducing peripheral substituents with varied electronic, steric, and conformational environments on the periphery of the porphyrin ligand. Together, these advantages may
provide [Co(II)(Por)]-based metalloradical catalysis with great structural tunability and potentially high catalytic selectivity.

![Figure 1.1. D2-symmetric Co(II) complexes of porphyrins as metalloradical catalysts.](image)

Despite all the characteristics and advantages of [Co(II)(Por)], one practical issue that might prevent them from being developed into useful metalloradical catalysts is the difficulty associated with preparation of chiral porphyrins via traditional methods. This long-standing issue is presumably the primary reason for the current absence of practical applications of metalloporphyrin-based methodologies in stereoselective organic synthesis. To this end, a general synthetic scheme for the construction of $D_2$-symmetric chiral porphyrins via Pd-catalyzed quadruple amidation reactions with 5,15-bis(2',6'-dibromophenyl)porphyrins (1) as synthons has been developed ([Scheme 1.3]). The synthesis of this class of catalysts starts with preparation of synthon 1, which contains...
different *meso*-aryl or alkyl groups at the 10- and 20-positions, via a MacDonald [2+2] porphyrin synthesis using Lindsey's condition. Then, a combination of Pd(OAc)$_2$ and XantPhos effectively catalyzes the quadruple amidation reactions of synthons with optically pure amides to afford a family of chiral porphyrin ligands (2) in up to 90% yields. With facile metalation as the third major step, $D_2$-symmetric Co(II) complexes of chiral porphyrins, [Co(Por*)], are usually synthesized as stable solids in high overall yields.

This chiral synthesis is modular and has several attractive characteristics. First, the bromoporphyrin synthons are stable and can be prepared on a multigram scale in two steps from readily available starting materials. Second, a wide range of R substituents, including both aryl and alkyl groups, can be introduced into the other two *meso*-positions of the porphyrins from the corresponding aldehydes. This allows for the fine-tuning of their electronics, steric, and solubility. Third, the Pd-catalyzed quadruple amidation reactions are reliable and can be performed in high yields under mild conditions where functional and sensitive groups are well tolerated. Finally, many optically pure chiral amides are commercially available or can be easily prepared from the corresponding chiral acids or esters. This wide availability provides many options to design and synthesize $D_2$-symmetric chiral porphyrins with diverse chiral environments. The combination of these attributes affords a practical approach to construct a “toolbox” of [Co($D_2$-Por*)] with tunable electronic, steric, and chiral environments that can be employed for the development of Co(II)-based metalloradical catalysis.

In addition to the effectiveness of the amidation reactions and the availability of the chiral amides, the quadruple amidated skeleton exhibits several unique features that provide effective control driving catalytic reactions. Starting with 5,10-bis(2',6'-
dibromophenyl)porphyrins (1), the cross-coupling reaction performed on all the ortho-positions of the meso-aryl groups installs chiral amides directed toward the center of the porphyrin. These chiral groups are close enough to dramatically influence the reaction occurring at the metal center. The nearly perpendicular arrangement between all the meso-phenyl rings and the porphyrin plane, as shown by single crystal structures such as P6, enables a chiral pocket-like environment for the metal center (Figure 1.2). The amido groups, which adopt a trans conformation, provide significant rigidity and direct the ortho-chiral R* units toward the center of porphyrins. More importantly, the N–H moiety of the amido units is suitably close to the reaction centers. They serve as effective hydrogen bonding donors and are the key to the distinctive reactivity and selectivity often found in [Co(Por*)]-based metalloradical catalysis (Figure 1.3).

Scheme 1.3. Synthesis of $D_2$-Symmetric Chiral Porphyrins and Their Co(II) Complexes
Figure 1.2. Structure of $D_2$-symmetric Co(II) complexes of porphyrins.

Figure 1.3. Potential H-bonding interaction in Co(II)-based metalloradical catalysis.

1.4 C-Centered Radical Reactions via Co(II)-Based Metalloradical Catalysis (MRC)

Based on the postulated formation of Co(III)-carbene radicals, the metalloradical is expected to transfer the single electron character from its metal center to generate a carbon-based radical following reaction with a suitable carbene precursor. Diazo reagents are a class of organic molecules well known for generating carbene species after the
expulsion of nitrogen gas. In addition to their extensive application as carbene precursors, preparation of different types of diazo reagents has also been well developed over the last few decades. The potential activation of diazo reagents by Co(II)-based metalloradicals would form the hypothesized Co(III)-carbene radicals, by releasing N$_2$ as the only stoichiometric byproduct, which is both thermodynamically favorable and an environmentally friendly process (Scheme 1.4).

**Scheme 1.4.** Postulated Formation of a Co(III)-carbene Radical via the Activation of Diazo Reagents.

![Scheme 1.4](image)

**Figure 1.4.** Co(III)-carbene radical and Fischer-type carbene.

If Co(III)-carbene radicals functioned similar to free carbon radicals, they should be capable of undergoing the common radical reactions, such as radical addition reactions to
multiple bonds. However, in contrast to the electrophilic Fischer-type carbene that is usually formed by Lewis acid metal catalysts, the Co(III)-carbene radicals should be considered an electronically neutral species. Therefore, the reactivity should largely depend on the carbene’s radical character, instead of its electrophilicity (Figure 1.4).

1.5 Radical Cyclopropanation Reactions via Co(II)-based Metalloradical Catalysis (MRC)

Radical addition reactions to double bonds are a common class of fundamental reactions in classical radical transformations. If possible, the addition of the Co(III)-carbene radicals to olefin compounds would break the π bond and transfer the radical to the olefin carbon, forming a typical carbon radical. The highly active carbon radical intermediate is likely to undergo a radical substitution reaction with the homolysis of the weak cobalt-carbon bond (a 3-exo-tet radical cyclization reaction). With the formation of a cyclopropane derivative and the regeneration of the [Co(II)Por] complex, the catalytic cyclopropanation of olefins are anticipated to turnover in a radical-type cycle (Scheme 1.5).

Scheme 1.5. Radical Cyclopropanation by Co(II)-Based Metalloradical Catalysis.
Olefin cyclopropanation reactions with diazo reagents as the carbene source have been studied by using a variety of metal catalysts. The catalytic pathways have typically proceeded through an electrophilic addition of the Fischer-type metalallocarbene to olefin compounds, which is usually an electrophilic [1+2] addition. These types of catalysts, including Rh$_2$(II)- and Cu(I)-based complexes, have been shown to be effective for a wide range of asymmetric cyclopropanation reactions, producing chiral cyclopropane derivatives with high levels of optical purity.$^{2d}$

While many systems have been developed successfully, there are still several major challenges in these 2e$^-$ catalytic systems. First, although the existing catalytic systems generally work well with styrene derivatives and some electron-rich olefins, asymmetric cyclopropanation of electron-deficient olefins has been a major challenge. This lack of reactivity towards electron-deficient substrates is presumably due to the electrophilic nature of the metal-carbene intermediates in the catalytic cycles. Second, acceptor/acceptor-substituted diazo reagents, which contain two adjacent electron-withdrawing groups, generally suffer from a lack of reactivity with Lewis acidic metal catalysts and struggle to form the corresponding metalallocarbene intermediates. Even when they are formed under harsh conditions, their subsequent reactions with olefins often have a lack of enantioselective control due to the high electrophilicity of the acceptor/acceptor-substituted metalallocarbenes.$^{2a,2d}$ Third, dimerization of diazo compounds is a common side reaction in the cyclopropanation systems. The use of excess olefin and the slow addition of the diazo reagents are usually required to minimize this side reaction despite the impracticality of this technique.$^5$
Radical cyclopropanation by Co(II)-based MRC, which is fundamentally different from the previous electrophilic catalytic systems, has been shown to be capable of stereoselectively producing a variety of cyclopropane derivatives. More importantly, this radical system has put forth solutions to the major challenges that are associated with the previous $2e^-$ systems.

### 1.5.1 Asymmetric Olefin Cyclopropanation Reactions via Co(II)-based MRC.

The cyclopropanation of styrene with diazoacetates, the first benchmark reaction, as demonstrated to be highly selective by using cobalt(II) complex of a $D_2$-symmetric chiral porphyrin 3,5-DiBu-ChenPyrin, $[\text{Co(P1)}]$. In addition to the rigidity and the *trans* conformation of the amido groups of the catalyst, it is rationalized that a hydrogen bonding interaction between the chiral cyclopropyl amide N–H element on the P1 ligand with the C=O (CO$_2$R group) unit of the carbene moiety plays an important role. This weak interaction may rigidify the radical intermediates (B and C, **Scheme 1.6**), and also presumably accelerate the reaction rate by lowering their energy.

Using 4-dimethylaminopyridine (DMAP) as a sub-stoichiometric additive, $[\text{Co(P1)}]$ has been experimentally shown to be highly effective for the asymmetric cyclopropanation of styrene with diazoacetates, a representative acceptor-substituted diazo reagent.$^{3d}$ Starting with $t$-butyl diazoacetate, styrene and its derivatives with varied electronic and steric properties can be cyclopropanated in high yields and with excellent *trans*-selectivity and enantiocontrol (**Scheme 1.7**).$^{3d,6}$ This asymmetric system still remains highly *trans*-selective when other diazoacetates, such as less sterically hindered ethyl diazoacetate, were used.$^{3d,7}$
Scheme 1.6. Proposed Stereocontrolled Metalloradical Cyclopropanation with [Co(P1)]

Scheme 1.7. [Co(D2-Por*)]-Catalyzed Asymmetric Cyclopropanation with Diazoacetates

As a unique feature, this [Co(P1)]-based metalloradical-based catalytic system could effectively operate in a one-pot fashion with both alkenes as the limiting regent and without the slow addition of diazo reagent. No significant formation of the dimerization side products were observed in these processes. The employment of stoichiometric olefin and the one-pot protocol were found to be very general and suitable for all the radical cyclopropanation systems subsequently developed. These unique characteristics and
superior performance indicate the [Co(Por)] metalloradical catalysts are highly selective toward cyclopropanation, and suggest that Co-carbene radical species distinctively favor addition to olefins versus dimerization with another diazo molecule.

After the initial results of the Co(II)-based metalloradical cyclopropanation, the potential of this system for solving some of the long-standing problems in carbene cyclopropanation was investigated further. The high reactivity and selectivity in producing pentafluorophenyl cyclopropane 9 affirmed the hypothesis that the Co(II)-based MRC has unusually high activity toward electron-deficient alkenes, which is a major challenge for the other existing electrophilic carbene-based systems. While Fischer-type carbene species generally favor the reactions with electron-rich olefins, the metal-carbene radical may be able to undergo radical additions to a broader range of olefins, including the electron-poor ones. This hypothesis further encouraged exploration of cyclopropanation of other electron-deficient olefins using Co(II)-based MRC. These exciting results indicated a high consistency with the projected reactivity. [Co(P1)]-catalyzed asymmetric cyclopropanation was effectively applied for a wide range of α–β-unsaturated carbonyl compounds and nitriles, forming the corresponding cyclopropane derivatives (13) in high yields and stereoselectivities (Scheme 1.8). Notably, acrylamide (12c) was also shown to be cyclopropanated in high yield and stereocontrol without the support of the N–H bonds.

The exceptional reactivity of the Co(II)-based MRC for electron-deficient olefins suggests there is some nucleophilic character during the carbene transfer, which lends further evidence to the differences between of the radical-type cyclopropanation from the typical electrophilic (Fischer-type) transition-metal carbene-mediated systems and the Zhang group’s MRC system. In collaboration with Prof. de Bruin, a comprehensive study on
the mechanism of [Co(Por)]-catalyzed cyclopropanation of olefins with diazoacetates was carried out. EPR and HRMS experiments in combination with DFT calculations support an unprecedented stepwise radical reaction mechanism for the Co(II)-catalyzed cyclopropanation (Scheme 1.9). DFT calculations suggested the Co(II)-based metalloradical is able to interact with the diazo reagent in its triplet state followed by a β-scission reaction to release nitrogen gas generating an unusual α-metalloalkyl radical (B) as the key intermediate of the catalytic cycle. The net process may be considered as a radical transfer in which the radical character is transferred from the Co-center to the α-carbon atom of the diazo moiety. The [Co(Por)]-supported carbon-based radical B, which was detected experimentally using EPR and HRMS techniques, is capable of performing common radical reactions such as radical addition and substitution. Consequently, radical addition of the α-radical B to the C=C bond of the olefin substrate results in further radical transfer to form the γ-radical intermediate C. Then, C readily undergoes a ring-closure reaction via an intramolecular radical substitution by homolytically breaking the relatively weak Co–C bond and simultaneously regenerating the metalloradical catalyst (Scheme 1.5). Both the α-radical B and γ-radical C are essentially carbon-based radicals, however, they are not “free” as their reactivity and selectivity are well regulated by the electronic, steric, and chiral environments of the covalently-attached [Co(Por)] moiety.

Further calculative studies suggest that the carbene carbon is nucleophilic in nature, which makes the exceptional reactivity toward electron-deficient olefins understandable. Moreover, it is suggested that the charge of the carbene radical carbon could be tunable through the introduction of different α-carbon substituents on the diazo
reagents. Accordingly, the substituents of the diazo reagents may be used as tools for fine-tuning the electronic properties of the carbene radicals and for matching varied substrates in different carbene transformations.

**Scheme 1.8.** Asymmetric Cyclopropanation of Electron-deficient Olefins via MRC

![Scheme 1.8](image)

**Scheme 1.9.** Proposed Stepwise Metalloradical Cyclopropanation (MRC)

![Scheme 1.9](image)
1.5.2 Radical Cyclopropanation Reactions of Acceptor/Acceptor-substituted Diazoe Reagents via Co(II)-based MRC

Acceptor/acceptor-substituted diazo reagents are diazo compounds bearing two electron-withdrawing groups and typically display both low reactivity and poor stereocontrol in transition metal-catalyzed carbene transfer reactions. In principle, Co(II)-based radical type cyclopropanation should provide a possible solution to this challenge because its radical pathways would be much less electronically dependent. However, Co(tetraphenylporphyrin) displayed low reactivity toward acceptor/acceptor-substituted diazo reagents in radical cyclopropanation. It was hypothesized that since the two electron-withdrawing α-substituents of acceptor/acceptor-substituted diazo reagents are usually suitable hydrogen bonding acceptors. The $D_2$-symmetric chiral amidoporphyrins (Figure 1.3) enabled potential double hydrogen bonding interactions between two of the chiral amide N-H moieties on the ligand with both the electron-withdrawing groups of the carbene moiety (Scheme 1.10). By using α-Nitrodiazoacetates (NDAs, such as 19), the hypothesis was experimentally confirmed through the observation that the cyclopropanation was dramatically accelerated and gave well-controlled stereoselectivity when [Co(P1)] was used as the metalloradical catalyst. In addition to the promoted reactivity toward these classically less reactive diazo reagents, the double hydrogen bonding interactions also rigidified the carbene radical intermediate 22 towards its subsequent reaction with the olefin substrate, which afforded the product in a high level of stereocontrol.
The Co(II) complexes of $D_2$-symmetric chiral amidoporphyrins have been demonstrated to be effective catalysts for cyclopropanation with a broad scope of acceptor/acceptor-substituted diazo reagents. $\alpha$-Cyanodiazoacetates (CDAs, such as 24), whose cyano group is considered to be a stronger hydrogen bond acceptor than a nitro group, underwent olefin cyclopropanation with a higher degree of stereoselectivity.
Notably, these cyclopropanation systems with acceptor/acceptor-substituted diazo reagents are also suitable for both aromatic and aliphatic olefins with varied electronic properties, affording densely functionalized cyclopropane products with high optical purity.

1.6 Organic azides as ideal nitrene sources for Co(II)-based MRC

Classic nitrene sources include prepared and \textit{in situ} generated iminiodinane derivatives. These display suitable reactivity toward several Lewis acidic metal catalysts, most notably, Rh(II) complexes.\textsuperscript{2g,20a,21a,21d} Recent efforts have been made to overcome limitations inherent in the use of these hypervalent iodine reagents, including their instability and the generation of ArI as a byproduct. As a result, alternative nitrene sources such as haloamine-T, which proceed under non-oxidative conditions and produce only sodium halides as byproducts, have been pursued to improve catalytic nitrene transfer reactions.\textsuperscript{23}

\textbf{Figure 1.5.} Cobalt supported nitrene radical.

While the above nitrene precursors have been successfully used in several important types of nitrene transformations several drawbacks still remain. Instability of
the nitrene precursor, as well as oxidative and/or basic conditions still bring great challenges to the development of these transformations, such as limited access to derivatives and restricted substrate scope.

![Structural similarity between diazo reagents and azides.](image)

**Figure 1.6.** Structural similarity between diazo reagents and azides.

Organoazides, a class of readily available molecules, exhibit significant similarities in their resonance structures to diazo reagents (**Figure 1.6**). This comparison led to a parallel thinking that azides might potentially function as a new nitrene source and form radical nitrene species with metalloradical catalysts. Analogous to the metal carbene formation from diazo reagents, azide initiated metal nitrene formation simply generates nitrogen gas (N₂) as the byproduct, which is eco-friendly and simplifies the purification. In principle, bases or terminal oxidants could be avoided in the metal nitrene formation step. The resulting neutral and non-oxidative conditions are extremely important for producing wide substrate scopes and high functional group tolerance for nitrene transformations.

### 1.6.1 Radical aziridination reactions with organoazides via Co(II)-based MRC.

The cobalt supported nitrene radical, similarly, should be capable of initiating new types of radical nitrene transformations. Aziridination via MRC could be proposed simply by using cyclopropanation as a template (**Scheme 1.12**). Upon the activation of the
organoaazides by a Co(II) metalloradical, the formed nitrene radical B would undergo an addition reaction to an olefin, producing an aziridine after an intramolecular radical substitution of the γ-radical intermediate C. The stepwise radical-type nitrene transfer pathway, which is supported by density functional theory (DFT) calculations and electron paramagnetic resonance (EPR) spectroscopy studies, is intrinsically different from the existing electrophilic nitrene transfer systems. These radical nitrenes would be expected to exhibit special reactivity and reaction profiles that are associated with the radical pathways.

**Scheme 1.12.** Potential Radical-Mediated Nitrene Transfers via Co(II)-Based MRC.

Initial studies showed that azides could be activated by Co(II)-based metalloradical catalysts and were appropriate nitrene precursors for nitrene transfer reactions. By using structurally simple cobalt(II) tetraphenylporphyrin [Co(TPP)], diphenylphosphoryl azide (DPPA) (41) has been demonstrated to be an effective nitrene source for the aziridination
Although elevated temperatures are typically required for satisfying yields, the demonstration of phosphoryl azide as the nitrone source points to the potential of organoaizides as general nitrone precursors for a variety of nitrone transfer processes via Co(II)-based metalloradical catalysis.

Incorporation of potential hydrogen bonding interactions have been extensively studied through the use of amido-containing cobalt(II) catalysts which enhance the azide activation in MRC nitrone transformations. Several kinds of azides, including sulfonyl azides, have been shown to interact with the amido moiety of the catalyst through hydrogen bonding as the oxygen atoms of the sulfonyl groups are suitable hydrogen bonding acceptors. Guided by this hypothesis, Co(P9) was examined as the catalyst for an aziridination reaction with sulfonyl azides as nitrene sources (Scheme 1.14).\textsuperscript{25} Comparison experiments showed that using a catalyst without an amido moiety afforded the aziridine in 11-24\% yield. However, using catalysts with amido moieties, sulfonyl azides with different electronic and steric properties can be converted to their corresponding aziridines (43) in up to 98\% yield. The dramatic increase of catalytic activity strongly suggests the existence of hydrogen bonding interactions and the potential role it plays to accelerate the reaction.

\textbf{Scheme 1.13.} Azides as Nitrone Sources for Different Nitrone Transfers via Co(II)-Based MRC
**Scheme 1.14.** Hydrogen Bonding Facilitated MRC Olefin Aziridination

\[
\text{Ar-S=O-N}_3 + \text{CH}_2=\text{CH}_2 \rightarrow \text{CH}_2=\text{CH-N}=\text{O-_aromatic} \quad \text{(75-98% yield)}
\]

**Suitable Nitrene Precursor:**

In addition to sulfonyl azides, several other types of azides were activated through similar hydrogen bonding interactions (**Figure 1.7**). Diphenylphosphoryl azide (DPPA) (40) has been successfully activated by the cobalt(II) complex of 3,5-di^Bu-ChenPhyrin, [Co(P1)], resulting in the consequent olefin aziridination in good yields at 40°C. With this chiral catalyst, asymmetric induction was observed in the aziridine products, presumably owing to the rigidification effect of the hydrogen bonding interactions. In principle, the same model of stabilized intermediates could be applied to other organoazides bearing α-electron-withdrawing groups, such as the α-carbonyl azides (model C, **Figure 1.7**).

**Figure 1.7.** General hydrogen bonding interactions in nitrene radical intermediates.
**Scheme 1.15.** Enantioselective Aziridination of Alkenes with TcesN$_3$ Facilitated by Hydrogen Bonding Interactions

$$\ce{\text{Scheme 1.15.} \quad \text{Enantioselective Aziridination of Alkenes with TcesN}_3 \quad \text{Facilitated by Hydrogen Bonding Interactions}}$$

![Scheme 1.15](image)

**Selected examples:**

1. 
   ![Chemical structure](image)  
   - 91% yield  
   - 94% ee

2. 
   ![Chemical structure](image)  
   - 92% yield  
   - 99% ee

3. 
   ![Chemical structure](image)  
   - 88% yield  
   - 81% ee

4. 
   ![Chemical structure](image)  
   - 85% yield  
   - 90% ee

5. 
   ![Chemical structure](image)  
   - 42% yield  
   - 91% ee

6. 
   ![Chemical structure](image)  
   - 53% yield  
   - 87% ee

The further rigidification of the chiral porphyrin ligand has also been shown to be a useful strategy for enhancing the asymmetric induction of aziridination reactions. Trichloroethoxysulfonyl azide (TcesN$_3$) underwent olefin aziridination with Co(P1) with low enantioselectivity.$^{27}$ Highly rigid catalyst Co(P6) (2,6-DiMeO-ZhuPhyrin) appeared to perfectly match this azide, reaching up to 99% enantiomeric excess in olefin aziridination reactions (Scheme 1.15). Since the hydrogen bonding between the azide and the ligand may still play an important role in activating the azide, it is very interesting to note that the N–H moieties of the ligand might weakly interact with both the hydrogen bonding acceptors in the ligand and the nitrene moiety. In this manner, the conformation of the
catalyst would be suitably stabilized. The azide would be activated and regulated for high reactivity as well as selectivity.

Recently, the Zhang research group has explored the application of MRC systems for several more challenging azides beyond electron deficient azides, such as aryl azides and alkyl azides. Aryl azides have been known to have difficulties initiating nitrene transfers presumably owing to their stability. Using the hydrogen bonding stabilized nitrene radical model, fluorine atoms were installed at the ortho-positions of the aryl azides to stabilize the intermediate and effectively pin the cobalt supported nitrene radical into place.\textsuperscript{28} Although non-substituted phenyl azide was ineffective as a nitrene source, 2-fluorophenyl azide afforded the aziridination product with styrene in 52\% yield and 75\% ee in the presence of the optimal catalyst [Co(P10)] (A in \textbf{Scheme 1.16}). More interestingly, 2,6-difluorophenyl azide as the reagent resulted in the aziridination in 80\% yield and 96\% ee. It is obvious that the 2,6-difluorophenyl azide could have double hydrogen bonding interactions, which further lowers the energy barrier of the transition state and further accelerates the reaction rate (B in \textbf{Scheme 1.16}). Notably, 3,4,5-trifluorophenyl azide, which is electronically similar to the above fluorophenyl azides but without the ortho-fluoro moiety, gave no reaction under the same conditions (C in \textbf{Scheme 1.16}), suggesting again the importance of the N–H–F hydrogen bond in the Co(II)-based metalloradical aziridination process. This catalytic system was successfully applied for a variety of 2,6-difluorophenyl azide derivatives. A group of highly fluorinated aziridines have been synthesized from olefins in excellent yields and with up to 98\% ee.
1.6.2 Radical C–H amination reactions with organoazides via Co(II)-based MRC.

Metal-catalyzed C–H amination via nitrene insertion constitutes a general strategy for the direct functionalization of ubiquitous C–H bonds. It holds great promise for the selective synthesis of biologically and pharmaceutically important nitrogen-containing compounds, including chiral amines and N-heterocycles. While significant advancements have been made with existing catalytic systems, important challenges remain in the field that necessitate the development of new types of catalysts for such C–H amination processes, especially processes that are operationally simple while allowing for highly controlled regio-, chemo- and stereo-selectivity.

Scheme 1.16. Enantioselective Aziridination of Alkenes with Fluoroaryl Azides

![Scheme 1.16. Enantioselective Aziridination of Alkenes with Fluoroaryl Azides](image)
Departing from the traditional metal supported nitrene radical, a MRC C–H amination would proceed as illustrated in Scheme 1.17. The key step would be hydrogen atom abstraction from a suitable C–H source with the nitrene radical B, which transfers from an N-centered to a C-centered radical to form a radical intermediate, R’, and amino cobalt complex C. An intermolecular radical substitution would cleave the Co–N bond of C and transfer the radical back to the metal center, releasing the amination product.

The proposed catalytic mechanism associated with the metalloradical nature of [Co(II)(Por)] is fundamentally different from that of known electrophilic nitrene-based systems. This pathway would be a highly attractive way to introduce amine functionality into C–H bonds as the radical H-abstraction is well known as a powerful way to break various C–H bonds, and does not depend on electronic properties of both reagents and C–H bonds as ionic type reactions do. The whole hypothesis is based on the possible similarity between the cobalt nitrene radicals and common organic radicals.

Early results demonstrated C–H amination pathways could be realized with organoazides by using [Co(TPP)] as the catalyst, however, harsh conditions were often necessary. Increased reactivity has once again been observed by using [Co(P9)], which provides potential hydrogen bonding donors. Intramolecular amination of sulfamoyl azide 48, through a selective 1,6-C–H abstraction process, has been discovered to effectively occur under mild conditions (Scheme 1.18). Without using any other reagents or additives, the desired six-membered cyclic sulfamide 49 was produced cleanly in 95% yield.
**Scheme 1.17.** Radical C–H Amination with Organoazides via Co(II)-Based MRC.

This Co(II)-based catalytic system has been applied for various sulfamoyl azides with diverse types of C–H bonds. Generally, this process is highly favored for six-membered ring formations and produces the 1,6-C–H amination product with exclusive
regioselectivity (Scheme 1.19). Remarking, the amination of unactivated primary C–H bonds in azides 50a and 50b can be performed in excellent yields. In addition to non-activated secondary C–H bonds (50c), different adjacent functionalities were well tolerated, including arenes and heteroatoms (51d-f).

Scheme 1.19. Intramolecular C–H Amination with Sulfamoyl Azides Catalyzed by [Co(P9)]

The effective C–H amination reactions of varied C–H bonds clearly indicates that the cobalt nitrene radical involved in the reaction may possess similar reaction profiles to common organic radicals in hydrogen abstraction reactions. The high reactivity toward non-activated C–H bonds suggests that this catalytic system may favor the C–H amination process. Driven by this hypothesis, competition reactions of the cobalt nitrene radical between hydrogen abstraction and other radical reactions such as radical addition were investigated. Allylic C–H bonds are highly challenging because the aziridination of the more
electron-rich C–C π bond is often more favorable than the amination process when using an electrophilic nitrene. In radical processes, the nitrene radical intermediate may prefer the abstraction of the hydrogen rather than the adding to the double bond considering the relatively weak bond dissociation energy (83 kcal/mol) of allylic C–H bonds, along with the higher stability of the resulting allylic radical from the hydrogen abstraction. This work explored the predominance of a highly chemoselective intramolecular allylic C–H amination reaction versus the competitive C=C aziridination (Scheme 1.20). The metalloradical catalyst [Co(P9)] has proven to be highly effective for the intramolecular amination of sulfamoyl azides with different types of allylic C–H bonds (52), including primary C–H bonds (52d), with outstanding chemoselectivity. High-yielding formation of cyclic sulfamides 53e and 53f further demonstrated the superior preference of allylic C–H amination over non-allylic C–H amination and aziridination, respectively.

Scheme 1.20. Intramolecular C–H Amination of Allylic C–H Bonds Catalyzed by [Co(P9)]
Electron-deficient C–H bonds are often the most challenging substrates for catalytic amination as they are generally incompatible with the classical electrophilic metallonitrene-mediated catalytic systems. This challenging issue has been solved through the use of metalloradical catalyst [Co(P9)] under mild and neutral reaction conditions.\textsuperscript{32} The Co(II)-Based metalloradical amination reaction occurred exclusively at C–H bonds located α with respect to electron-withdrawing groups, which include ester, ketone, amide and nitrile functional groups (Scheme 1.21). In addition to secondary C–H bonds, tertiary C–H bonds also displayed excellent reactivity in this catalytic process. Diastereoselectivity has been studied with multisubstituted azides such as 54g, the trans-bis-α-amino acid derivative 55g was produced in 94\% yield and 94:6 diastereomeric ratio.

**Scheme 1.21.** Intramolecular C–H Amination of Electron-deficient C–H Bonds by [Co(P9)]
These results showed that C-H bonds with a wide variety of steric and electronic properties could be intramolecularly aminated by using sulfamoyl azides. An important application of the resulting multifunctionalized cyclic sulfamides is not only that they are potentially valuable heterocycles, but that they also serve as convenient precursors for the preparation of precious 1,3-diamine derivatives by removal of the SO₂ unit.\textsuperscript{30-32} Co(II)-based metalloradical catalysis has been extended to use other types of azides as nitrene precursors for highly selective amination reactions. Phosphoryl azides have emerged out to be a new class of organo azides that are suitable for the selective production of cyclophosphoramidates with 6- and even 7-membered-ring structures.\textsuperscript{33}

\subsection*{1.7 Conclusion}

Metalloradical catalysis (MRC) which utilizes cobalt(II) porphyrins [Co(Por)] that provide stable metalloradical intermediates, enables a fundamentally new approach for controlling stereoselectivity of both C- and N-centered radical reactions. The Co(II)-based metalloradicals have been shown to activate diazo reagents and azides to cleanly generate C- and N-centered radicals, respectively, in a controlled and catalytic manner. The newly generated metal supported carbon-centered radical and nitrogen-centered radicals have demonstrated that the Co(II)-porphyrin catalysts are capable of transferring their radical character to other atoms, producing common organic radical species. These new types of carbene radicals and nitrene radicals, which remain complexed with [Co(Por)], have been shown to undergo common radical reactions such as radical addition, but with the reactivity and stereoselectivity effectively controlled by the porphyrin ligand environment. Through the support of porphyrin ligands with tunable electronic, steric, and chiral
environments, this general concept of Co(II)-based metalloradical catalysis (Co-MRC) has been successfully applied for the development of various radical processes for stereoselective carbene and nitrene transfers. The results of these radical reactions indicate that the Co-MRC system is generally tolerant of various electronic properties in both the substrates and reagents. Moreover, the mild reaction condition and high degree of functional group tolerance are also important features that are presumably related to the radical mechanism.

Cobalt-supported carbene and nitrene radicals have been demonstrated to undergo cyclization reactions with double bonds and triple bonds, leading to radical cyclopropanation, cyclopropenation, and aziridination reactions. A broad range of C–H bonds were shown to undergo amination reactions with nitrene radicals. The Co-MRC promises to address several long standing issues in these systems, such as low reactivity and selectivity of acceptor/acceptor-substituted diazo reagents, electron-deficient olefins and C–H bonds, and poor selectivity of allylic and propargylic C–H bonds. Similar to amination, it is anticipated that carbene radicals will react with C–H bonds through hydrogen abstraction and radical substitution pathways as well as produce C–H alkylation products. These proposed studies may lead to the development of new catalytic C–H functionalization processes that are both mechanistically distinctive and operationally attractive.
1.8 References


(10) (a) Dzik, W. I.; Zhang, X. P.; de Bruin, B.: Inorg. Chem. 2011, 50, 9896-9903;


Chapter 2: Stereoselective Intermolecular Cyclopropanation via Co(II) based Metalloradical Catalysis

2.1 Introduction

Asymmetric cyclopropanation via metal mediated carbene transfer reactions have gained a large amount of attention in the past decades. Many different transition metals have been shown to be quite adept at this transformation including Cu, Ru, Rh, Os and Fe. While great strides have undoubtedly been achieved in this area, the vast majority of systems have been focused on the formation of the more thermodynamically stable trans-isomer.

Scheme 2.1. Co(II) Catalyzed Metalloradical Cyclopropanation
In the past there have been very few systems that are able to access the cis-cyclopropane in high yield and stereoselectivity\textsuperscript{7a}, and no systems exist to date that are able to achieve both isomers in high selectivity by tuning the electronics and steric of the ligand environment about the metal center. It was postulated that as an open-shell catalytic mechanism, such as Co(II) would be a prime candidate for a diastereomeric optimization study.

The general catalytic cycle, as shown in Scheme 2.1, begins with the decomposition of the diazo compound. Next, a cobalt supported $\alpha$-alkyl radical forms. Then, a radical addition to an olefin results in the formation of a $\gamma$-alkyl radical. The $\gamma$-alkyl radical will then undergo a 3-exo-tet radical ring-closure to afford the desired cyclopropane. It is anticipated that the olefin approaches the $\alpha$-alkyl radical in a very specific orientation to avoid unfavorable steric interactions leading to the formation of the $\gamma$-alkyl radical conformation shown in Conformer A in Scheme 2.2. Through a low energy $\sigma$-bond rotation, it is expected that the $\gamma$-alkyl radical interconverts between the two conformations quite readily, which could lead to cis- and trans-isomers of the cyclopropane. However, Conformer B, which leads to the trans-cyclopropane, is postulated to be more thermodynamically stable and is purportedly the reason this system has, in the past, had a very high trans-selectivity. It has been hypothesized that if a catalyst were designed with enough rigidity and steric bulk, it would be theoretically possible to shut down the $\sigma$-bond rotation and obtain the cis-isomer in high selectivity.
2.2 Results and Discussion

Previously, the Zhang group reported a Co(II)-Porphyrin based metalloradical cyclopropanation that produced high yields and selectivity often aided by a sub-stoichiometric additive, and produced the anticipated trans isomer when [Co(P1)] was employed as the optimized catalyst. It was noted, however, that in the case of one type of catalyst, [Co(P2)], there was a reversal of selectivity from the trans isomer towards the cis isomer. Supposing that the intramolecular hydrogen bonding in the P2 ligand was the factor that added the rigidity desired efforts were made to probe other experiments that could exploit this effect and give a higher selectivity. The first of these experiments explored the use of different catalysts both with and without the aforementioned intramolecular hydrogen bonding.

By excluding the additive, the switch in stereochemistry was able to be repeatedly observed. The employment of Co(3,5-DiBu-ChenPhyrin) [Co(P1)] for the cyclopropanation of styrene with ethyl diazoacetate (EDA) produced, as expected, the preferential formation of the trans cyclopropane in a 16:84 ratio and with a 22% ee for the cis-isomer. When Co(3,5-DiBu-RuppelPhyrin) [Co(P2)] was employed, the diastereoselective ratio of
cyclopropanes increased to 65:35 favoring cis-isomer and the ee for the cis-isomer increased to 39%.

Co(3,5-Di'Bu-ZhuPhyrin) [Co(P3)] was hypothesized to have a significantly more rigid structure which caused the intramolecular hydrogen bonding to be stronger. This catalyst produced a 54:46 diastereomeric ratio, slightly favoring the cis isomer, with an improved 64% ee. Encouraged by this result, we increased the steric environment around the metal center, replacing the 3,5-DitBu-Ph groups with 2,6-DiMeO-Ph groups. The use of Co(2,6-DiMeO-ZhuPhyrin) [Co(P4)] resulted in an increase in both diastereoselectivity, 77:23 favoring the cis-isomer, and enantioselectivity, 81%. With these results in hand, the focus shifted to understanding the mechanistic model of the catalytic system. Experiments were needed to test the hypothesis that the catalyst design could be refined to achieve a higher diastereomeric and enantiomeric selectivity of [Co(P4)].

As described in Scheme 2.1 and Scheme 2.2, the added rigidity of the chiral arms were indeed shown to inhibit the σ-bond rotation that leads to Conformer B and allowed for the cis-cyclopropane to be obtained with high selectivity. A series of catalysts were synthesized that were modeled after [Co(P3)], and they bore larger differing steric groups in place of one methyl group in the chiral arm (Figure 2.2). It is worth noticing that all of the new porphyrin ligands performed better than [Co(P3)]. This confirmed the hypothesis that the rigidity of the intramolecular hydrogen bonding was causing the cis-isomer to be the major cyclopropane observed (Figure 2.1).
**Figure 2.1.** Catalytic Screening of Ethyl Diazoacetate and Styrene with Various Co(II) Porphyrins

It was noticed that Co(\( \text{P7} \)) gave an unusually high diastereoselectivity. This lead to experimentation with several substrates to determine the scope of the catalyst and determine how general this catalyst was for the cyclopropanation process. Co(\( \text{P7} \)) was able to maintain high diastereomeric ratios for halogenated, electron rich and electron deficient
styrenes. Unfortunately, only one substrate (Figure 2.3, entry 4) was able to achieve a moderate enantioselectivity.

**Figure 2.2.** Structure of Co(II) Porphyrin Catalysts Screened for Stereoselective Cyclopropanation.
<table>
<thead>
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<th>Yield</th>
<th>Diastereomeric Ratio</th>
<th>Enantiomeric Excess</th>
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</thead>
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<td>1</td>
<td>59%</td>
<td>92:8</td>
<td>59%</td>
</tr>
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</table>

\(^{a}\) Reactions carried out in one-pot protocol in toluene using 1 mol % catalyst under N\(_2\) for 24 h with [olefin] = 0.20 M and [diazo] = 0.24 M.

\(^{b}\) Isolated yields.

\(^{c}\) Diastereomeric ratio determined by \(^{1}\)HMR.

\(^{d}\) Enantiomeric excess determined by chiral HPLC.

**Figure 2.3.** Substrate Scope for Stereoselective Cyclopropanation of Ethyl Diazoacetate with Various Styrene Derivatives Using [Co(P7)].

Drawing on the evidence that the chiral arm of the porphyrin plays a large role in increasing *cis*-selectivity, [Co(P6)] was selected for further tuning through the modification of the diazo reagent (See **Figure 2.4**). By increasing the size of the diazo ester from an ethyl group to a butyl group, an increase in the ee from 81% to 98% was observed for the *cis* isomer, however the increased enantioselectivity came at the expense of the diastereoselectivity which fell to 32:68 favoring the trans-isomer once again. By decreasing the ester size to a phenyl group the *cis* isomer was obtained in a 60:40 ratio, albeit with a slight loss in enantioselectivity to 86%.
Figure 2.4. Catalytic Screening of Various Diazoacetates for Stereoselective Cyclopropanation.

Both isopropyl and isobutyl diazoacetates were synthesized to vary and compare the sterics in the range between commercially available ethyl and 4-Butyl diazoacetate. The isobutyl diazoacetate performed similarly to ethyl diazoacetate yielding a 70:30 cis:trans ratio and an 86% cis ee. However, isopropyl diazoacetate significantly improved the selectivity and yielded an 81:19 cis:trans ratio with a 91% ee. These results coincided very well with the proposed mechanistic model where if the ester became too rigid or large, the trans product was anticipated to become more predominant, presumably due to an unfavorable steric interaction in the final ring-closing step of the mechanistic cycle. This unfavorable steric interaction should slow down the final 3-exo-tet cyclization allowing for
α-bond rotation to occur. With these results, isopropyl diazoacetate was chosen as the diazo reagent that best matched the chiral pocket of the catalyst and provided the greatest increase in both the diastereo- and enantioselectivity.

Using isopropyl diazoacetate as the carbene source, it was possible to favor the cis-cyclopropanation of various styrene derivatives bearing neutral steric substituents (Figure 2.5, entries 1-6) with very high enantioselectivity while maintaining a very high diastereoselectivity. Various halogenated styrenes (entries 7-11) also performed very well in this catalytic system and reached up to 94% ee for both the p-bromo and p-chloro substrates. The system was also tolerant of strong electron donating and withdrawing substituents (entries 12-14). The system is also tolerant of heteroaromatic styrene derivatives, as evidenced in entry 15, affording the desired cis-cyclopropanes in very high enantio- and diastereoselectivities.

These results are very promising preliminarily evidence that the metalloradical catalytic system operates with a fundamentally different mechanism than the previously reported closed shell Lewis acidic metallocarbene systems. In principle, Co(II)-based metalloradical catalysis proceeds through a step-wise mechanism that substantiates the idea that this catalytic system can be tuned, whether electronically or sterically, to allow for the formation of both sets of diastereomeric products. These results indicate that accessing the previously unobtained two stereoisomers in any of the previously published metalloradical cyclopropanation reactions should be an achievable goal for the Zhang research group.
**Figure 2.5.** Substrate Scope for Stereoselective Cyclopropanation of Isopropyl Diazoacetate With Various Styrene Derivatives.
2.3 Experimental Data

N,N′-ditosylhydrazine

Pyridine (75 mmol) was added to a mixture of p-toluenesulfonyl hydrazide (50 mmol) and p-toluenesulfonyl chloride (75 mmol) in CH₂Cl₂ (50 mL). This mixture was stirred at room temperature for 1.5 h. Diethyl ether (200 mL) and water (100 mL) were added and the resultant mixture was stirred at 0 °C for an additional 15 min. The mixture was filtered and washed with cold diethyl ether. The solid was recrystallized from CH₃OH to yield N,N′-ditosylhydrazine as a white solid (75% Yield) known compound⁸; ¹H NMR (400 MHz, DMSO) δ 9.54 (s, 1H), 7.61 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 2.35 (s, 3H). ¹³C NMR (100 MHz, DMSO) δ 143.8, 135.9, 129.8, 128.2, 21.5.

Phenyl Diazaoacetate

Phenyl 2-bromoacetate (2.5 mmol) and N,N′-ditosylhydrazine (5 mmol) were dissolved in THF (20 mL) and cooled to 0 °C. DBU (2.5 mmol) was added dropwise and the mixture was stirred for 30 minutes at room temperature. The reaction was quenched with saturated NaHCO₃ and extracted with diethyl ether. The organic layers were then washed with water and brine, dried over Na₂SO₄ and concentrated. The residue was purified by
flash column chromatography to yield the product as a yellow oil (48% yield), known compound⁸; ¹H NMR (400 MHz, CDCl₃) δ 7.38 (t, J = 7.6 Hz, 2H), 7.23 (t, J = 7.2 Hz, 1H), 7.14 (d, J = 8 Hz, 2H), 4.95 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 150.5, 129.4, 125.9, 121.6, 115.31, 46.85.

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\text{Isobutyl Diazoacetate}
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NaHCO₃ (6 mmol) was added to a solution of isobutanol (2 mmol) in CH₃CN (10 mL). Bromoacetyl chloride (3 mmol) was added dropwise at 0 °C. The reaction was brought to room temperature and allowed to stir for 30 min. The reaction was quenched with water and extracted with CH₂Cl₂. The organic layers were then washed with water and brine, combined and dried over Na₂SO₄, and concentrated to afford isobutyl 2-bromoacetate as a brown oil which was used without further purification.

Isobutyl 2-bromoacetate (2 mmol) and N,N'-ditosylhydrazine (4 mmol) were dissolved in THF (20 mL) and cooled to 0 °C. DBU (2.5 mmol) was added dropwise and the mixture was stirred for 30 minutes at room temperature. The reaction was quenched with saturated NaHCO₃ and extracted with diethyl ether. The organic layers were then washed with water and brine, dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography to yield the product as a yellow oil (73% yield over two steps), known compound⁹. ¹H NMR (400 MHz, CDCl₃) δ 4.71 (s, 1H), 3.91 (d, J = 6.7 Hz, 2H), 1.90 (m, 1H), 0.89 (d, J = 6.7 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 166.9, 70.8, 46.0, 27.8, 19.0.
Isopropyl Diazoacetate

Isopropyl 2-bromoacetate (2.5 mmol) and N,N’-ditosylhydrazine (5 mmol) were dissolved in THF (20 mL) and cooled to 0 °C. DBU (2.5 mmol) was added dropwise and the mixture was stirred for 30 minutes at room temperature. The reaction was quenched with saturated NaHCO₃ and extracted with diethyl ether. The organic layers were then washed with water and brine, dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography to yield the product as a yellow oil (87% yield), known compound[^10]; ^1H NMR (400 MHz, CDCl₃) δ 5.10 – 4.96 (m, 1H), 4.66 (s, 1H), 4.66 (s, 1H), 1.20 (d, J = 6.3 Hz, 6H). ^13C NMR (100 MHz, CDCl₃) δ 166.4, 68.2, 46.2, 21.9. IR (neat cm⁻¹): 2105, 1684, 1377, 1193, 1104.

### 2.3.1 Cyclopropane Synthesis and Characterization

An oven dried Schlenk tube was charged with catalyst (0.002 mmol) then evacuated and back filled with nitrogen gas. The Teflon screw cap was replaced with a rubber septum and 0.25 mL of dry toluene was added, followed by olefin (0.2 mmol) and diazo (0.24 mmol) in single portion fashion followed by the remaining solvent (total 0.5 mL). The Schlenk tube was then purged with nitrogen for 1 minute and the rubber septum was replaced with the Teflon screw cap. The Schlenk tube was then placed in an oil bath at the desired temperature for 48 h. Once the reaction was complete, the mixture was
concentrated and purified by flash column chromatography. The product was then concentrated to afford the pure compound.

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\text{Ethyl 2-phenylcyclopropane-1-carboxylate} \text{ was synthesized according to the general procedure as a colorless oil (80\% yield, 77:23 cis:trans ratio), known compound}^{7b}; [\alpha]^{20}_D = +10.707 \text{ (c} = 0.61, \text{ CHCl}_3); ^1\text{H NMR} (400 \text{ MHz, CDCl}_3) \delta \text{ ppm 7.27} - 7.15 \text{ (m, 5H), 3.85 (q, } J = 7.1 \text{ Hz, 2H), 2.56 (dd, } J = 16.6, 8.9 \text{ Hz, 1H), 2.06 (ddd, } J = 9.2, 7.8, 5.7 \text{ Hz, 1H), 1.69 (dt, } J = 7.5, 5.3 \text{ Hz, 1H), 1.30 (ddd, } J = 8.5, 7.9, 5.1 \text{ Hz, 1H), 0.95 (t, } J = 7.1 \text{ Hz, 3H); } ^{13}\text{C NMR (100 MHz CDCl}_3) \delta \text{ ppm 170.94, 136.52, 129.26, 127.83, 126.58, 60.13, 25.42, 21.77, 13.98, 11.07; IR (neat, cm}^{-1}\text{): 1715, 1265, 1192, 1107; HPLC (Chiral OJ-H, 1.0\% 2-propanol-hexane rate 0.8 ml/min): Cis-isomer: Major } t = 13.8 \text{ min., Minor } t = 31.2 \text{ min. e.e. 81\%; Trans-isomer: Major } t = 18.9 \text{ min., Minor } t = 10.5 \text{ min. e.e. 94\%. }
\]

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\text{Tert-butyl 2-phenylcyclopropane-1-carboxylate} \text{ was synthesized according to the general procedure as a colorless oil (95\% Yield; 32:68 cis:trans ratio), known compound}^{7b}; ^1\text{H NMR} (400 \text{ MHz, CDCl}_3) \delta \text{ ppm 7.17-7.27 (m, 5H), 2.52 (m,1H), 1.99 (m, 1H), 1.65 (m, 1H), 1.24 (m, 1H), 1.13 (s, 9H); } ^{13}\text{C NMR (100 MHz CDCl}_3) \delta \text{ ppm 170.1, 136.8, 129.5, 127.8, 126.5, 80.0, 27.7, 25.0, 22.7, 10.5; HPLC (Chiral AD-H, 0.5\% 2-propanol-hexane rate 0.7 ml/min): Cis-isomer: Major } t = 8.1 \text{ min., Minor } t = 8.6 \text{ min. e.e. 98\%; Trans-isomer: Major } t =
Phenyl 2-phenylcyclopropane-1-carboxylate was synthesized according to the general procedure as a colorless oil (73% Yield; 60:40 cis:trans ratio), known compound\textsuperscript{11}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ ppm 7.42-7.12 (m, 10 H), 2.77 (dd, $J = 16.8$, 8.5 Hz, 1H), 2.39-2.29 (m, 1H), 1.92 (dt, $J = 7.4$, 5.5 Hz, 1H), 1.54-1.43 (m, 1H); \textsuperscript{13}C NMR (100 MHz CDCl\textsubscript{3}) δ ppm 170.1, 133.6, 132.8, 132.1, 127.6, 127.2, 126.9, 126.1, 125.1, 24.34, 21.36, 19.35; IHPLC (Chiral OJ-H, 0.5% 2-propanol-hexane rate 0.8 ml/min): Cis-isomer: Major $t = 9.9$ min., Minor $t = 8.6$ min. e.e. 86%; Trans-isomer: Major $t = 12.6$ min., Minor $t = 11.3$ min. e.e. 78%.

Isobutyl 2-phenylcyclopropane-1-carboxylate was synthesized according to the general procedure as a colorless oil (95% Yield; 70:30 cis:trans ratio), known compound\textsuperscript{12}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ ppm 7.32 – 7.13 (m, 5H), 3.64 (dd, $J = 10.6$, 6.7 Hz, 1H), 3.53 (dd, $J = 10.6$, 6.7 Hz, 1H), 2.56 (dd, $J = 16.7$, 8.7 Hz, 1H), 2.15 – 2.04 (m, 1H), 1.97 – 1.87 (m, 1H), 1.69 (dt, $J = 7.4$, 5.4 Hz, 1H), 1.31 (dt, $J = 8.2$, 5.0 Hz, 1H), 0.74 (d, $J = 6.7$ Hz, 6H); \textsuperscript{13}C NMR (100 MHz CDCl\textsubscript{3}) δ ppm 171.0, 136.6, 129.2, 127.9, 126.6, 70.4, 27.5, 25. 4, 21.8, 18.9, 11.1; HPLC (Chiral OD-H, 1.0% 2-propanol-hexane rate 0.8 ml/min): Cis-isomer: Major $t = 8.0$ min., Minor $t = 6.9$ min. e.e. 86%; Trans-isomer: Major $t = 7.7$ min., Minor $t = 6.6$ min. e.e. 74%.
**Isopropyl 2-phenylcyclopropane-1-carboxylate** was synthesized according to the general procedure as a colorless oil (73% Yield; 81:19 cis:trans ratio), known compound\(^{13}\); 
\[\alpha\]\(^{20}\)_D = +34.616° (c = 1.28, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 7.29 – 7.14 (m, 5H), 4.71 (sept, \(J = 6.3\) Hz, 1H), 2.55 (dd, \(J = 16.6, 8.9\) Hz, 1H), 2.03 (ddd, \(J = 9.3, 7.8, 5.6\) Hz, 1H), 1.73 – 1.65 (m, 1H), 1.33 – 1.26 (m, 1H), 0.96 (d, \(J = 6.3\) Hz, 3H), 0.89 (d, \(J = 6.3\) Hz, 3H); \(^{13}\)C NMR (100 MHz CDCl\(_3\)) \(\delta\) ppm 170.45, 136.60, 129.35, 127.81, 126.55, 67.40, 25.28, 21.98, 21.74, 21.30, 10.77; IR (neat, cm\(^{-1}\)): 1715, 1265, 1192, 1107; HPLC (Chiral OJ-H, 0.5% 2-propanol-hexane rate 0.8 ml/min): Cis-isomer: Major \(t = 9.9\) min., Minor \(t = 11.3\) min. e.e. 91%; Trans-isomer: Major \(t = 12.8\) min., Minor \(t = 8.6\) min. e.e. 73%.

**Isopropyl 2-(p-tolyl)cyclopropane-1-carboxylate** was synthesized according to the general procedure as a colorless oil (88% Yield; 87:13 cis:trans ratio), \[\alpha\]\(^{20}\)_D = +18.398° (c = 1.42, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 7.15 (d, \(J = 8.0\) Hz, 2H), 7.05 (d, \(J = 8.1\) Hz, 2H), 4.74 (sept, \(J = 6.2\) Hz, 1H), 2.52 (dd, \(J = 16.6, 8.5\) Hz, 1H), 2.29 (s, 3H), 2.01 (ddd, \(J = 9.3, 7.8, 5.6\) Hz, 1H), 1.66 (dt, \(J = 7.4, 5.3\) Hz, 1H), 1.28 (dd, \(J = 5.9, 2.8\) Hz, 1H), 0.99 (d, \(J = 6.2\) Hz, 3H), 0.97 (d, \(J = 6.2\) Hz, 3H); \(^{13}\)C NMR (100 MHz CDCl\(_3\)) \(\delta\) ppm 170.68, 138.21, 135.00, 129.34, 129.13, 126.71, 125.31, 67.25, 24.35, 21.60, 21.21, 19.35, 10.93; IR (neat, cm\(^{-1}\)):
Isopropyl 2-(m-tolyl)cyclopropane-1-carboxylate was synthesized according to the general procedure as a colorless oil (63% Yield; 67:33 cis:trans ratio), $[\alpha]^{20}_D = +65.074$ (c = 0.735, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.20 (dd, $J = 11.5, 7.0$ Hz, 1H), 7.17 – 7.07 (m, 3H), 4.70 (sept, $J = 6.1$ Hz, 1H), 2.43 (dd, $J = 16.8, 8.5$ Hz, 1H), 2.35 (s, 3H), 2.17 – 2.09 (m, 1H), 1.75 (dt, $J = 7.5, 5.3$ Hz, 1H), 1.38 – 1.28 (m, 1H), 0.94 (d, $J = 6.3$ Hz, 3H), 0.83 (d, $J = 6.3$ Hz, 3H); $^{13}$C NMR (100 MHz CDCl$_3$) $\delta$ ppm 170.67, 138.20, 134.98, 129.32, 129.11, 126.69, 125.30, 67.23, 24.34, 21.59, 21.36, 21.19, 10.92; IR (neat, cm$^{-1}$): 1715, 1183 1106, 1026; HRMS m/z calcd for [M+H]$^+$ 218.1307, obsd 218.1296; HPLC (Chiral AD-H, 0.5% 2-propanol-hexane rate 1.0 ml/min): Cis-isomer: Major t = 7.5 min., Minor t =8.0 min. e.e. 90%; Trans-isomer: Major t = 6.0 min., Minor t =6.2 min. e.e. 83%.

Isopropyl 2-(o-tolyl)cyclopropane-1-carboxylate was synthesized according to the general procedure as a colorless oil (82% Yield; 89:11 cis:trans ratio), $[\alpha]^{20}_D = +45.217^\circ$ (c =
Isopropyl 2-(4-(tert-butyl)phenyl)cyclopropane-1-carboxylate was synthesized according to the general procedure as a colorless oil (66% Yield; 80:20 cis:trans ratio), $[\alpha]^{20}_{D} = +22.650^\circ$ (c = 0.59, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm $7.26$ (d, $J = 9.2$ Hz, 2H), $7.18$ (d, $J = 8.2$ Hz, 2H), $4.70$ (sept, $J = 6.2$ Hz, 1H), $2.52$ (dd, $J = 16.7$, 8.6 Hz, 1H), $2.01$ (ddd, $J = 9.3$, 7.8, 5.7 Hz, 1H), $1.68$ (dt, $J = 7.4$, 5.4 Hz, 1H), $1.60 - 1.52$ (m, 1H), $1.27$ (s, 9H), $0.93$ (d, $J = 6.3$ Hz, 3H), $0.81$ (d, $J = 6.3$ Hz, 3H); $^{13}$C NMR (100 MHz CDCl$_3$) $\delta$ ppm $170.56$, $149.35$, $133.54$, $128.97$, $124.71$, $67.30$, $31.31$, $24.82$, $22.02$, $21.87$, $21.69$, $21.18$, $10.73$; IR (neat, cm$^{-1}$): $1717$, $1265$, $1190$, $1108$; HRMS m/z calcd for [M+H]$^+$ $260.1726$, obsd $260.1776$; GC (Chiral DexCB, initial temperature 50 °C - 200 °C, 5 °C/min): Cis-isomer: Major $t = 29.8$ min., Minor $t = 30.0$ min. e.e. 87%. 

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\text{O} \quad \text{O} \\
\text{Isopropyl} \quad 2-(4-(\text{tert-butyl)phenyl)cyclopropane-1-carboxylate}
\]
Isopropyl 2-methyl-2-phenylcyclopropane-1-carboxylate was synthesized according to the general procedure as a colorless oil (85% Yield; 88:12 cis:trans ratio), $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.30 – 7.26 (m, 3H), 7.24 (d, $J$ = 0.9 Hz, 2H), 4.73 – 4.61 (m, 1H), 1.93 (dd, $J$ = 8.3, 6.0 Hz, 1H), 1.86 (dd, $J$ = 7.7, 5.4 Hz, 1H), 1.76 (t, $J$ = 5.0 Hz, 1H), 1.44 (d, $J$ = 2.8 Hz, 1H), 1.02 (d, $J$ = 6.2 Hz, 3H), 0.82 (d, $J$ = 6.3 Hz, 3H); $^{13}$C NMR (100 MHz CDCl$_3$) $\delta$ ppm 170.70, 141.89, 128.82, 128.38, 128.09, 127.18, 67.24, 31.89, 28.77, 28.59, 21.82, 21.19, 19.18; HPLC (Chiral OD-H, 2% 2-propanol-hexane rate 0.8 ml/min): Cis-isomer: Major $t$ = 6.3 min., Minor $t$=5.9 min. e.e. 83%.

Isopropyl 2-(naphthalen-2-yl)cyclopropane-1-carboxylate was synthesized according to the general procedure as a colorless oil (53% Yield; 86:14 cis:trans ratio), $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.79 – 7.70 (m, 3H), 7.45 – 7.34 (m, 4H), 4.72 – 4.58 (m, 1H), 2.69 (dd, $J$ = 16.9, 8.4 Hz, 1H), 2.10 (ddd, $J$ = 9.3, 7.8, 5.6 Hz, 1H), 1.82 (dt, $J$ = 7.4, 5.5 Hz, 1H), 1.36 (ddd, $J$ = 8.5, 7.9, 5.1 Hz, 1H), 0.91 (d, $J$ = 6.2 Hz, 3H), 0.79 (d, $J$ = 6.3 Hz, 3H); $^{13}$C NMR (100 MHz CDCl$_3$) $\delta$ ppm 170.43, 134.18, 133.18, 132.39, 127.92, 127.77, 127.59, 127.54, 127.33, 125.83, 125.38, 67.44, 25.53, 22.16, 21.77, 21.32, 11.07; HPLC (Chiral AD-H, 1.0% 2-propanol-hexane rate 0.8 ml/min): Cis-isomer: Major $t$ = 11.0 min., Minor $t$=8.3 min. e.e. 85%.
Isopropyl 2-(4-fluorophenyl)cyclopropane-1-carboxylate was synthesized according to the general procedure as a colorless oil (85% Yield; 88:12 cis:trans ratio), \([\alpha]_{20}^{D} = +26.455^\circ\) (c = 0.395, CHCl₃); \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) ppm 7.19 (dt, \(J = 4.8, 4.3\) Hz, 2H), 6.97 – 6.88 (m, 2H), 4.71 (sept, \(J = 6.3\) Hz, 1H), 2.49 (dd, \(J = 16.6, 8.6\) Hz, 1H), 2.01 (ddd, \(J = 9.3, 7.8, 5.6\) Hz, 1H), 1.63 (dt, \(J = 7.4, 5.4\) Hz, 1H), 1.27 (ddd, \(J = 8.7, 6.8, 4.1\) Hz, 1H), 0.97 (d, \(J = 6.3\) Hz, 3H), 0.93 (d, \(J = 6.3\) Hz, 3H); \(^{13}\)C NMR (100 MHz CDCl₃) \(\delta\) ppm 170.32, 130.78 (d, \(J = 8.0\) Hz), 127.68 (d, \(J = 8.0\) Hz), 115.21 (d, \(J = 21.4\) Hz), 114.64 (d, \(J = 21.4\) Hz), 67.52, 24.49. 21.76, 21.37, 11.03; \(^{19}\)F NMR (376 MHz, CDCl₃) \(\delta\) -116.40 (tt, \(J = 8.8, 5.4\) Hz); IR (neat, cm⁻¹): 1712, 1514, 1107, 1024; HPLC (Chiral AD-H, 0.5% 2-propanol-hexane rate 0.8 ml/min): Cis-isomer: Major \(t = 7.8\) min., Minor \(t = 7.3\) min. e.e. 83%; Trans-isomer: Major \(t = 6.9\) min., Minor \(t = 6.4\) min. e.e. 82%.

Isopropyl 2-(4-chlorophenyl)cyclopropane-1-carboxylate was synthesized according to the general procedure as a colorless oil (90% Yield; 90:10 cis:trans ratio), \([\alpha]_{20}^{D} = +15.124^\circ\) (c = 0.485, CHCl₃); \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) ppm 7.23 – 7.14 (m, 4H), 4.72 (sept, \(J = 6.2\) Hz, 1H), 2.48 (dd, \(J = 16.6, 8.6\) Hz, 1H), 2.03 (ddd, \(J = 9.3, 7.8, 5.7\) Hz, 1H), 1.64 (dt, \(J = 7.4, 5.4\) Hz, 1H), 1.32 – 1.25 (m, 1H), 0.97 (d, \(J = 6.3\) Hz, 3H), 0.94 (d, \(J = 6.3\) Hz, 3H); \(^{13}\)C NMR (100 MHz CDCl₃) \(\delta\) ppm 170.21, 135.15, 132.32, 130.66, 127.94, 67.61, 24.63,
Isopropyl 2-(4-bromophenyl)cyclopropane-1-carboxylate was synthesized according to the general procedure as a colorless oil (88% Yield; 90:10 cis:trans ratio), \([\alpha]^{20}_D=+10.048^\circ\) (c = 0.38, CHCl₃); \(^1\)H NMR (400 MHz, CDCl₃) δ ppm 7.35 (d, \(J = 8.3\) Hz, 2H), 7.11 (d, \(J = 8.5\) Hz, 2H), 4.72 (sept, \(J = 6.2\) Hz, 1H), 2.46 (dd, \(J = 16.7, 8.7\) Hz, 1H), 2.03 (ddd, \(J = 9.3, 7.8, 5.7\) Hz, 1H), 1.63 (dt, \(J = 7.4, 5.4\) Hz, 1H), 1.29 (td, \(J = 8.2, 5.4\) Hz, 1H), 0.97 (d, \(J = 6.3\) Hz, 3H), 0.94 (d, \(J = 6.3\) Hz, 3H); \(^13\)C NMR (100 MHz CDCl₃) δ ppm 170.19, 135.68, 131.04, 130.88, 127.86, 67.63, 24.69, 21.98, 21.80, 21.38, 10.98; IR (neat, cm⁻¹): 1699, 1204, 1108, 1024; HPLC (Chiral OJ-H, 1.0% 2-propanol-hexane rate 0.8 ml/min): Cis-isomer: Major t = 9.2 min., Minor t = 8.3 min. e.e. 93%; Trans-isomer: Major t = 11.4 min., Minor t = 10.2 min. e.e. 78%.

Isopropyl 2-(3-bromophenyl)cyclopropane-1-carboxylate was synthesized according to the general procedure as a colorless oil (73% Yield; 77:23 cis:trans ratio), \([\alpha]^{20}_D=+30.142^\circ\) (c = 0.83, CHCl₃); \(^1\)H NMR (400 MHz, CDCl₃) δ ppm 7.40 (s, 1H), 7.31 (dt, \(J = 7.8, 7.4\) Hz, 2H), 7.16 (br s, 1H), 7.07 (d, \(J = 8.3\) Hz, 2H), 6.91 (d, \(J = 8.3\) Hz, 2H), 4.61 (sept, \(J = 6.2\) Hz, 1H), 2.64 (dd, \(J = 16.7, 8.3\) Hz, 1H), 2.14 (ddd, \(J = 9.3, 7.8, 5.7\) Hz, 1H), 1.63 (dt, \(J = 7.4, 5.4\) Hz, 1H), 1.29 (td, \(J = 8.2, 5.4\) Hz, 1H), 0.96 (d, \(J = 6.3\) Hz, 3H), 0.94 (d, \(J = 6.3\) Hz, 3H); \(^13\)C NMR (100 MHz CDCl₃) δ ppm 170.19, 135.68, 131.04, 130.88, 127.86, 67.63, 24.69, 21.98, 21.80, 21.38, 10.98; IR (neat, cm⁻¹): 1699, 1204, 1108, 1024; HPLC (Chiral OJ-H, 1.0% 2-propanol-hexane rate 0.8 ml/min): Cis-isomer: Major t = 9.2 min., Minor t = 8.3 min. e.e. 93%; Trans-isomer: Major t = 11.4 min., Minor t = 10.2 min. e.e. 78%.

22.00, 21.79, 21.39, 11.01; IR (neat, cm⁻¹): 1719, 1495, 1395, 1186; HPLC (Chiral OJ-H, 1.0% 2-propanol-hexane rate 0.8 ml/min): Cis-isomer: Major t = 8.7 min., Minor t = 7.9 min. e.e. 94%; Trans-isomer: Major t = 10.4 min., Minor t = 9.1 min. e.e. 62%.
Isopropyl 2-(2-bromophenyl)cyclopropane-1-carboxylate was synthesized according to the general procedure as a colorless oil (87% Yield; 89:11 cis:trans ratio). $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 7.49 (dd, $J = 7.9, 1.1$ Hz, 1H), 7.32 – 7.18 (m, 3H), 4.74 (sept, $J = 6.2$ Hz, 1H), 2.50 (dd, $J = 16.7, 8.5$ Hz, 1H), 2.18 (ddd, $J = 9.0, 8.0, 5.6$ Hz, 1H), 1.68 (dt, $J = 7.6, 5.3$ Hz, 1H), 1.39 (td, $J = 8.2, 5.0$ Hz, 1H), 1.00 (d, $J = 6.2$ Hz, 3H), 0.95 (d, $J = 6.3$ Hz, 3H); $^{13}$C NMR (100 MHz CDCl$_3$) δ ppm 170.5, 136.6, 132.6, 131.9, 131.1, 128.2, 126.7, 67.4, 26.9, 21.9, 21.6, 21.3, 12.1; HPLC (Chiral OJ-H, 1% 2-propanol-hexane rate 0.8 ml/min): Cis-isomer: Major $t = 9.7$ min., Minor $t = 14.2$ min. e.e. 91%.

Isopropyl 2-(4-methoxyphenyl)cyclopropane-1-carboxylate was synthesized according to the general procedure as a colorless oil (57% Yield; 80:20 cis:trans ratio),
[α]$_D^{20}$ = +30.341 (c = 0.765, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 7.18 (d, $J$ = 8.5 Hz, 2H), 6.80 (d, $J$ = 8.8 Hz, 2H), 4.74 (sept, $J$ = 6.2 Hz, 1H), 3.77 (s, 3H), 2.50 (dd, $J$ = 16.6, 8.6 Hz, 1H), 2.00 (ddd, $J$ = 9.2, 7.8, 5.6 Hz, 1H), 1.75 – 1.54 (m, 1H), 1.39 – 1.19 (m, 2H), 0.99 (d, $J$ = 6.3 Hz, 3H), 0.95 (d, $J$ = 6.3 Hz, 3H); $^{13}$C NMR (100 MHz CDCl$_3$) δ ppm 170.55, 158.26, 130.29, 127.26, 113.26, 67.34, 55.17, 24.65, 21.87, 21.81, 21.40, 10.94; IR (neat, cm$^{-1}$): 1716, 1516, 1248, 1177, 1028; HRMS m/z calcd for [M+H]$^+$ 234.1256, obsd 234.125; HPLC (Chiral OD-H, 1.0% 2-propanol-hexane rate 0.8 ml/min): Cis-isomer: Major $t$ = 10.9 min., Minor $t$ = 9.3 min. e.e. 82%.

Isopropyl 2-(4-nitrophenyl)cyclopropane-1-carboxylate was synthesized according to the general procedure as a colorless oil (90% Yield; 85:15 cis:trans ratio), $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 8.10 (d, $J$ = 8.8 Hz, 1H), 7.40 (d, $J$ = 8.8, 1H), 4.79 – 4.64 (m, 1H), 2.58 (dd, $J$ = 16.8, 8.5 Hz, 1H), 2.14 (ddd, $J$ = 9.3, 7.9, 5.7 Hz, 1H), 1.78 – 1.70 (m, 1H), 1.45 – 1.36 (m, 1H), 0.97 (d, $J$ = 4.7 Hz, 3H), 0.96 (d, $J$ = 4.6 Hz, 3H); $^{13}$C NMR (100 MHz CDCl$_3$) δ ppm 169.81, 146.64, 144.63, 130.15, 123.01, 67.96, 24.97, 22.59, 21.77, 21.45, 11.55; HPLC (Chiral OJ-H, 1% 2-propanol-hexane rate 0.8 ml/min): Cis-isomer: Major $t$ = 44.4 min., Minor $t$ = 29.5 min. e.e. 92%; Trans-isomer: Major $t$ = 50.3 min., Minor $t$ = 59.0 min. e.e. 82%.
**Isopropyl 2-(4-(trifluoromethyl)phenyl)cyclopropane-1-carboxylate** was synthesized according to the general procedure as a colorless oil (79% Yield; 83:17 cis:trans ratio), $[\alpha]^{20}_D = +34.400$ (c = 2.43, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.51 (d, $J = 8.2$ Hz, 2H), 7.38 (d, $J = 8.2$ Hz, 2H), 4.73 (sept, $J = 6.3$ Hz, 1H), 2.58 (dd, $J = 16.9$, 8.4 Hz, 1H), 2.11 (ddd, $J = 9.3$, 7.9, 5.7 Hz, 1H), 1.73 (dt, $J = 7.4$, 5.4 Hz, 1H), 1.41 – 1.32 (m, 1H), 1.30 – 1.22 (m, 1H), 0.97 (d, $J = 6.3$ Hz, 3H), 0.93 (d, $J = 6.3$ Hz, 3H); $^{13}$C NMR (100 MHz CDCl$_3$) $\delta$ ppm 170.30, 141.61, 130.42, 68.48, 22.94, 22.46, 22.04, 11.80; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -62.50 (s); HPLC (Chiral OD-H, 2% 2-propanol-hexane rate 0.8 ml/min): Cis-isomer: Major t = 6.3 min., Minor t = 5.9 min. e.e. 94%; Trans-isomer: Major t = 7.5 min., Minor t = 6.9 min. e.e. 83%.

**Isopropyl 2-(pyridin-2-yl)cyclopropane-1-carboxylate** was synthesized according to the general procedure as a colorless oil (97% Yield; 89:11 cis:trans ratio), $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 8.46 (ddd, $J = 4.9$, 1.8, 0.9 Hz, 1H), 7.55 (td, $J = 7.7$, 1.8 Hz, 1H), 7.25 – 7.19 (m, 1H), 7.07 (ddd, $J = 7.5$, 4.9, 0.7 Hz, 1H), 4.79 – 4.62 (m, 1H), 2.67 (dd, $J = 16.5$, 8.9 Hz, 1H), 2.11 (ddd, $J = 9.4$, 7.9, 5.8 Hz, 1H), 1.80 (ddd, $J = 7.4$, 5.8, 5.1 Hz, 1H), 1.36 (ddd, $J = 8.6$, 8.0, 5.0 Hz, 1H), 0.95 (d, $J = 6.3$ Hz, 6H); $^{13}$C NMR (100 MHz CDCl$_3$) $\delta$ ppm 170.4, 156.8, 148.8, 135.8, 123.6, 121.5, 67.5, 27.0, 21.6, 21.4, 11.3; HPLC (Chiral OD-H, 2.0% 2-propanol-hexane rate 0.8 ml/min): Cis-isomer: Major t = 17.2 min., Minor t = 14.9 min. e.e. 91%.
2.4 References


Chapter 3: Asymmetric Intramolecular C-H Amination of Sulfonyl Azides via Co(II)-Based Metalloradical Catalysis: Enantioselective Synthesis of 5-Membered Chiral Sultams under Mild Conditions

3.1 Introduction

Catalytic C–H amination via metal nitrenoid insertion has been widely recognized as a general approach for the direct conversion of C–H bonds to C–N bonds and represents the development of a powerful technology for amine synthesis.\textsuperscript{1} Since the first demonstration of asymmetric induction in C–H amination via nitrone insertion in 1997,\textsuperscript{2} vast efforts have been devoted to the development of efficient catalytic systems for stereoselective inter- and intramolecular C–H amination.\textsuperscript{3,4} Recently, considerable advancements have been achieved for enantioselective intramolecular C–H amination due to the advent of new chiral catalysts\textsuperscript{4} and the invention of \textit{in-situ} generated aryliminodiiodanes.\textsuperscript{5} This type of intramolecular transformation offers a streamlined the synthesis of optically pure N-heterocycles that are valuable chiral synthons or useful in area including medicinal chemistry and materials. Despite the progress, enantioselective amination has been limited in its ability to accommodate benzylic C–H bonds containing electron donating substituents.\textsuperscript{3d, 4b} Due to the electrophilic nature of most metallonitrene species, asymmetric amination of benzylic C–H bonds substituted with electron-withdrawing groups are generally problematic. Moreover, enantioselective amination of allylic C–H
substrates has proven to be challenging, although several chemoselective catalytic protocols have been developed.\textsuperscript{4b-c, 6} Furthermore, most catalytic systems are known to be less effective in promoting C–H amination reactions that form of five membered sulfone-containing heterocycles, including sultams and their related cyclic counterparts such as sulfates and sulfamidates, owing to their increased ring strain versus the six-membered counterpart.\textsuperscript{4a, 7}

The sulfonamide moiety has been well documented as an important pharmacophore in medicinal chemistry and its cyclic analogue has attracted great attention in the synthetic community.\textsuperscript{8} Among different approaches to synthesize enantioenriched sultams, catalytic intramolecular C–H amination via metal nitrenoid insertion offers a direct method to accessing this important class of compounds. Although metal complexes based on Cu,\textsuperscript{9} Ru,\textsuperscript{10} Rh,\textsuperscript{11} and Co\textsuperscript{12} have been shown to catalyze the cyclization of suitable nitrene precursors via intramolecular C–H amination to generate sultams, the enantioselective variant of this process remains underdeveloped. Very recently, Ir(III) complexes of chiral salens were successfully applied by the Katsuki group to catalyze the cyclization of arylsulfonyl azides, generating corresponding benzosultams in good to high enantioselectivity.\textsuperscript{4d} However, the Ir(III)-based catalytic system is mainly restricted to benzylic C–H bonds of arylsulfonyl azides and its application to alkylsulfonyl azides was demonstrated with only a single cyclic substrate with 87\% ee. Consequently, there is a need to develop more general and effective catalytic systems for asymmetric intramolecular C–H amination that can be employed for the enantioselective synthesis of valuable chiral sultams with diverse structural features.
Scheme 3.1. Ligand Effect on Co(II)-Catalyzed Asymmetric Intramolecular C-H Amination of Arylsulfanyl Azide.

3.2 Results and Discussion

Previous effort from the Zhang laboratory has shown that the cobalt (II) metalloradical complex of tetraphenylporphyrin, [Co(TPP)], is capable of catalyzing the intramolecular C–H amination of arylsulfanyl azides at elevated temperature to generate benzosultams.\textsuperscript{12} Subsequent development of $D_{2h}$-symmetric achiral amidoporphyrins to replace TPP allowed Co(II)-based system for the intramolecular C–H amination of a broad range of azide substrates at lower temperature and with enhanced reactivity. This is postulated to be a result of the hydrogen-bonding interactions between the S=O group of the sulfonyl unit and the N–H group of the amide moiety of the porphyrin ligand.\textsuperscript{6c, 13}

In view of the availability of $D_2$-symmetric chiral amidoporphyrins with tunable
electronic, steric, and chiral environments,\textsuperscript{14} and the efficacy of these amidoporphyrins as ligands for cyclopropanation and aziridination, these Co(II)-based metalloradical systems were applied to enantioselective intramolecular C–H amination\textsuperscript{15}. As a result, an effective catalytic system was developed using cobalt(II) complexes of D\textsubscript{2}-symmetric chiral amidoporphyrins \([\text{Co}(\text{D}_2\text{-Por*})]\) for the highly enantioselective intramolecular C–H amination of sulfonyl azides. In addition to arylsulfonyl azides, this Co(II)-catalyzed asymmetric system is also suitable for alkylsulfonyl azides. This allows for the selective amination of allylic as well as benzylic C–H bonds to generate a range of 5-membered chiral sultams in high yields and enantioselectivity. Additional practical features associated with the use of azides as the nitrone source include that these Co(II)-catalyzed reactions can be operated under neutral and nonoxidative conditions without the need of any additives and generate the environmentally benign N\textsubscript{2} gas as the only byproduct. Furthermore, experimental evidence has been provided to shed light on the unique radical mechanism of this metalloradical amination process.

At the outset of this project, 2-ethylbenzenesulfonyl azide (1a) was selected as the model substrate, since it was able to be readily prepared from its corresponding arylsulfonyl chloride via azide substitution. This was followed by the identification of a suitable D\textsubscript{2}-symmetric chiral amidoporphyrin ligand to support this Co(II)-based catalytic system for its asymmetric intramolecular C–H amination reaction (Scheme 3.1). Among the different metalloradical catalysts [Co(D\textsubscript{2}-Por*)] selected,\textsuperscript{14} the Co(II) complex of 3,5-Di\textsuperscript{i}Bu-ChenPhyrin, [Co(P1)], was found to be effective in catalyzing the intramolecular C–H amination of azide 1a, generating the 5-membered benzosultam 2a in 93% yield, however only 15% ee was observed. The regioselectivity at the benzylic C–H position appeared to be
exclusive from any amination at the homobenzylic position as no 6-membered product was observed. Dramatic improvement in the enantioselectivity of the catalytic reaction was achieved when the catalyst was replaced with Co(II) complex of 2,6-DiMeOZhuPhyrin,\textsuperscript{16} [Co(P6)], where the D\textsubscript{2}-symmetric chiral amidoporphyrin P6 has a chiral environment with enhanced rigidity and steric hindrance. Under the same reaction conditions, the [Co(P6)]-catalyzed reaction afforded benzosultam 2a in 90\% ee while maintaining the high yield (94\%) and benzylic C–H activation.

The metalloradical catalyst [Co(P6)] was shown to be generally effective for asymmetric intramolecular C–H amination of various arylsulfonyl azides under the optimized conditions (Figure 3.1). Like azide 1a, the derivatives of 2-ethylarenesulfonyl azides which contained different aryl substituents with electron-donating as well as electron withdrawing groups were also suitable substrates for [Co(P6)]-catalyzed amination system, giving the corresponding 5-membered benzosultams 2a–2d in high yields and enantioselectivity (Figure 3.1, entries 1–4). Furthermore, the Co(II)-based metalloradical amination could be effectively applied for 2-ethylarenesulfonyl azides bearing strong electron-withdrawing substituents such as cyano, nitro, and ester groups. This allowed for the high-yielding highly asymmetric production of functional benzosultams 2e–2g (Figure 3.1, entries 5–7). The absolute configuration of the newly generated chiral center in 2g was established as [R] by X-ray crystal structural analysis.
**Figure 3.1.** [Co(P6)] Catalyzed Enantioselective Intramolecular C–H Amination of Various Arylsulfonaryl Azides.

The intramolecular C–H amination reactions of these more electron deficient substrates were performed with both high efficiency and stereoselectivity at relatively low temperatures. This reactivity profile is in stark contrast to other catalytic systems that experience significant decreases in both reactivity and enantioselectivity during the
amination of benzylic C–H bonds containing strong electron-withdrawing aryl substituents. The complete regioselectivity at the benzylic position was also observed in the other 2-alkylarenesulfonyl azides as demonstrated for high-yielding formation of 5-membered benzosultam 2h from 2-pentyl-5-(methoxycarbonyl)benzenesulfonyl azide, albeit with lower enantioselectivity (Figure 3.1, entry 8). As expected, C–H bonds at bis-benzylic positions could also be aminated by [Co(6)], as exemplified by the reaction of 2-benzylbenzenesulfonyl azide, resulting in the formation of 2i, but in a relatively lower yield and moderate enantioselectivity (Figure 3.1, entry 9).

Subsequent experiments indicated that asymmetric intramolecular C–H amination of alkylsulfonyl azides behaves differently from arylsulfonyl azides because of their high flexibility. As illustrated in Scheme 3.2 with substrate 3-phenylpropylsulfonyl azide (3a), catalyst [Co(6)] was much less effective in catalyzing the intramolecular C–H amination reaction of this alkylsulfonyl azide which afforded the corresponding 5-membered sultam 4a in only 10% yield despite having a 90% ee. Catalyst [Co(1)] was found to be much more effective for this reaction, generating the desired 4a in 97% yield, but with only 48% ee (Scheme 3.2). When the cobalt(II) complex of the new-generation D2-symmetric chiral amidoporphyrin 3,5-Di‘Bu-QingPhyrin, [Co(12)], was used as the catalyst, the enantioselectivity of the cyclization reaction was increased to 69% ee while maintaining an excellent yield (99%).
Scheme 3.2. Ligand Effect on Co(II)-Catalyzed Asymmetric Intramolecular C–H Amination of Alkylsulfanyl Azide.

These results prompted the development of new metalloradical catalysts with the combined benefits of these existing catalysts. This effort led to the design and synthesis of D$_2$-symmetric chiral amidoporphyrin 2,6-DiMeO-(4'-Me)QingPhyrin (Scheme 3.2, P13). Cobalt(II) complex of 2,6-DiMeO-(4'-Me)QingPhyrin, [Co(P13)], whose structure and
stereochemistry were established by X-ray crystallographic analysis (see Supporting Information for details), was found to be a superior metalloradical catalyst for the asymmetric intramolecular C–H amination of alkylsulfonyl azide 3a. The [Co(P13)]-catalyzed reaction displayed both high efficiency and excellent stereoselectivity, affording sultam 4a in 92% yield with 94% ee (Scheme 3.2).

The new metalloradical catalyst [Co(P13)] was shown to be generally effective for the asymmetric intramolecular C–H amination of alkylsulfonyl azides as exemplified by reactions of different propylsulfonyl azide derivatives under the optimized conditions (Figure 3.2). Similar to the amination reaction of 3a, the [Co(P13)]-based catalytic system performed equally well for 3-arylpropylsulfonyl azides with various aryl substituents at the ortho-, meta- or para-positions and produced the corresponding 5-membered sultams in high yields and with excellent enantioselectivity (Figure 3.2, entries 2–4). Co(P13)]-catalyzed amination resembled the [Co(P6)]-based catalytic system for arylsulfonyl azides 1 (Figure 3.1) in that electron-deficient C–H bonds were well tolerated as exemplified with reactions of azides 3 which bear strong electron withdrawing substituents such as trifluoromethyl and nitro groups on the phenyl ring (Figure 3.2, entries 5–6). The absolute configuration of the newly generated chiral center in sultam 4f was established as [S] by X-ray crystal structural analysis.

The alkylsulfonyl azide derived from indole was intramolecularly aminated to give the desired indole-based sultam 4g in a nearly quantitative yield with almost total control of enantioselectivity (Figure 3.2, entry 7). Furthermore, catalyst [Co(P13)] was shown to be capable of catalyzing the chemoselective intramolecular amination of allylic C–H substrates without any complication from the competitive intramolecular aziridination. For
example, sulfonyl azides derived from both terminal and internal olefins could be selectively aminated at the allylic C–H positions. These provided the corresponding vinyl-substituted sultams in high yields with excellent chemo- and enantioselectivity (Figure 3.2, entries 8 and 9).

![Chemical reaction diagram]

---

*Reactions were carried out on 0.25 mmol scale at 40 °C for 18 h using 2 mol % catalyst loading under N₂ atmosphere. Concentration: 0.10 M in benzene; Isolated yields; % ee determined by chiral HPLC. "[S] absolute configuration determined by X-ray analysis. *Reactions carried out on 0.10 mmol scale at 0 °C for 24 h using 5 mol % catalyst loading in chlorobenzene. *% ee determined via derivatization.

**Figure 3.2.** [Co(P13)] Catalyzed Enantioselective Intramolecular C–H Amination of Various Alkylsulfonyl Azides.
**Scheme 3.3.** Proposed Mechanistic Cycle for Stepwise Radical Co(II)-Catalyzed Intramolecular C–H Amination of Sulfonyl Azides.

The catalytic reaction in **Scheme 3.3** displayed the characteristic profile of reactivity and selectivity of Co(II)-based metalloradical catalysis (MRC).\(^{6c, 13}\) Accordingly, a stepwise radical mechanism was proposed for the [Co(D\(_2\)-Por\(^\ast\))]-catalyzed asymmetric intramolecular C–H amination of sulfonyl azides that involve the unique Co(III)-nitrene radical intermediate.\(^{18}\) As illustrated in **Scheme 3.3**, the activation of sulfonyl azides by metalloradical catalyst (P)Co• transfers the radical character from the Co(II)-center to the N atom and then releases of N\(_2\) to generate an α-metalloamino radical (intermediate A). Subsequent intramolecular 1,5-H abstraction by the Co-supported, N-centered radical results in a second radical transfer from the N-atom to the C-atom to form C-centered radical intermediate B. As a consequence of the low bond dissociation energy of the Co–N
bond, intermediate B undergoes a facile 5-exo-tet radical cyclization to furnish the sultam product and complete the catalytic cycle through the third radical transfer to regenerate the metalloradical catalyst (P)Co• (Scheme 3.3).

Scheme 3.4. Supporting Evidence for Stepwise Radical Co(II)-Catalyzed Intramolecular C–H Amination of Sulfonyl Azides.

a. Kinetic Isotope Effect

\[
\text{Ph} \begin{array}{c}
\text{SO}_2\text{N}_3 \\
\text{3j}
\end{array} \xrightarrow{[\text{Co(P14)}] \text{(2 mol %)}} \begin{array}{c}
\text{HN} \begin{array}{c}
\text{D} \\
\text{4j-H}
\end{array} + \\
\text{HN} \begin{array}{c}
\text{D} \\
\text{4j-D}
\end{array}
\end{array}
\text{C}_6\text{H}_6, \; 40 ^\circ \text{C} \; 75\% \text{ yield}
\]

\[k_{\text{H}}/k_{\text{D}} = 6.7\]

b. Trapping of Radical Intermediate

\[
\text{Ph} \begin{array}{c}
\text{N}_3 \text{SO}_2 \\
\text{(E)-3i}
\end{array} \xrightarrow{[\text{Co(P13)}] \text{(2 mol %)}} \begin{array}{c}
\text{Ph} \begin{array}{c}
\text{HN} \text{SO}_2\text{NH}_2 \\
\text{(E)-5i}
\end{array} + \\
\text{HF} \begin{array}{c}
\text{D} \\
\text{(E)-5i}
\end{array}
\end{array}
\text{C}_6\text{H}_6, \; 40 ^\circ \text{C}
\]

(E)-5i

10% yield
0% ee

(E)-5i

72% yield
72% ee

c. Complete Olefin Isomerization

\[
\text{Ph} \begin{array}{c}
\text{N}_3 \text{SO}_2 \\
\text{(Z)-4i}
\end{array} \xrightarrow{[\text{Co(P13)}] \text{(2 mol %)}} \begin{array}{c}
\text{Ph} \begin{array}{c}
\text{HN} \text{SO}_2 \\
\text{(E)-4i}
\end{array}
\end{array}
\text{C}_6\text{H}_6, \; 40 ^\circ \text{C}
\]

(E)-4i

86% yield, 82% ee

To further investigate proposed radical mechanism, several mechanistic experiments were carried out for the Co(II)-based C–H amination (Scheme 3.4a-c). First, the kinetic isotopic effect (KIE) was measured for the MRC intramolecular C–H amination.
using the mono-deuterated azide 3j as the substrate under the typical catalytic conditions (Scheme 3.4a). Using the Co(II) complex of D_{2h}-symmetric amidoporphyrin 3,5-di{Bu-IbuPhyrin, [Co(P14)], as an achiral catalyst, the reaction provided both C–H and C–D amination products 4j-H and 4j-D, respectively. Analysis of the product mixture by \(^1\)H-\(^1\)H-NMR provided an intramolecular KIE of 6.7. This high degree of primary KIE implicates that the H-atom abstraction that forms N-radical Intermediate A is the rate-limiting step of the catalytic process.\(^{6c}\)

In an effort to trap radical intermediates formed in the catalytic cycle, the amination of allylic C–H bonds of azide (E)-3i by [Co(P13)] was then carried out in the presence of 5 equiv. TEMPO (Scheme 3.4b). While sultam (E)-4i was still produced as the major product, the isolation of compound (E)-5i without the observation of other trapping products not only supports the existence of the C-radical intermediate B but also indicates the steric protection of N-radical A from being affected by external radicals such as TEMPO.\(^{13a}\) Furthermore, the fact that there was no chiral induction in (E)-5i although significant enantiomeric excess was observed for (E)-4i may suggest that asymmetric induction is primarily determined in the final radical cyclization step.

The existence of intermediate B was further evidenced through the observation of exclusive formation of (E)-4i from the amination of allylic C–H bonds of azide (Z)-3i (Scheme 3.4c). The significant ee observed for (E)-4i from this isomerization-amination process further supports the radical cyclization present during the asymmetric induction step.

The successful development of asymmetric intramolecular C–H aminations of both arylsulfonyl and alkylsulfonyl azides via Co(II)-based metalloradical catalysis provides a
practical method to access optically active stultams bearing various functionalities, which should find interesting applications in medicinal chemistry. In view of recent attention to enantiopure fused sultams for their broad inhibitory properties against a variety of important enzymes, the resulting enantioenriched sultam 4a was demonstrated to serve as a useful chiral synthon for the effective synthesis of fused tricyclic sultam 7 through a sequence of N-methylation, selenylation, elimination and Diels-Alder reactions without the erosion of the original enantiomeric purity (Scheme 3.5). In addition to other characterizations, the stereochemistry of the endo-stereoisomer 7 was unambiguously established by X-ray structural analysis.

**Scheme 3.5.** Enantioselective Synthesis of Fused-Tricyclic Sultam Based on Co(II)-Catalyzed Asymmetric Amination

\[
\text{HN} \quad \text{SO} \quad \text{Ph} \\
4a \quad 94\% \text{ ee}
\]

\[
\overset{\text{MeI, K}_2\text{CO}_3}{\text{HN} \quad \text{SO}} \quad \overset{\text{18-Crown-6}}{\text{PH}} \quad 98\% \text{ yield}
\]

\[
\overset{\text{LDA, PhSeBr}}{\text{HN} \quad \text{SO}} \quad \overset{-78 \degree C}{\text{PH}} \quad 72\% \text{ yield}
\]

\[
\overset{\text{Et}_2\text{AlCl}}{\text{HN} \quad \text{SO}} \quad \overset{\text{80 \degree C}}{\text{PH}} \quad 90\% \text{ yield}
\]

**7** \( \text{endo: exo} = 4:1 \) \( \text{d.r.} > 20:1; 94\% \text{ ee} \)

In summary, a Co(II)-based catalytic system was developed for the highly enantioselective C–H amination of both arylsulfonyl and alkylsulfonyl azides under neutral and nonoxidative conditions. The Co(II)-based metalloradical catalysis is highlighted by the
selective amination of allylic C–H bonds as well as benzylic C–H bonds bearing strong electron-withdrawing substituents, through the production of functionalized 5-membered chiral sultams in high yields and enantioselectivities. This represents, to date, the most general and selective catalytic system for asymmetric intramolecular C–H amination. Several examples of experimental evidences have been provided to support the unique stepwise radical mechanism of this metalloradical amination which involves H-atom abstraction during the key Co(III)-nitrène radical intermediate which is the rate-limiting step. In addition to directly trapping the subsequent C-centered radical intermediate, new fundamental understanding of the key step in the asymmetric induction for catalytic process has been developed.

3.3 Experimental Data

\[
\begin{align*}
\text{COP1} + \text{DMAP} & \quad \rightarrow \quad \text{HOEt} \\
\text{NH}_2 & \quad \rightarrow \quad \text{NH}_{2} \\
\end{align*}
\]

(1R,2R)-2-methyl-2-(p-tolyl)cyclopropanecarboxamide was synthesized according to the reported procedure\textsuperscript{17}. [Co(3,5-di‘Bu-ChenPhyrin)]\textsuperscript{14} (27.2 mg, 0.02 mmol, 0.01 eq) and DMAP (122 mg, 1 mmol, 0.5 eq) were placed in an oven dried, resealable Schlenk tube. The tube was capped with a Teflon screw cap, evacuated, and backfilled with nitrogen. The screw cap was replaced with a rubber septum. Toluene (8 ml) and \( p,\alpha \)-dimethylstyrene (1.32 g, 10 mmol, 5 eq) were added via syringe. After the solution was
cooled to -60 °C, EDA (228 mg, 2 mmol, 1 eq) was added dropwise followed by addition of 1 mL of toluene. The tube was purged with nitrogen for 1 min and its contents were stirred at -60 °C for one day, then -40 °C for one day, -20 °C for one day and 0 °C for one day. After the reaction finished, the resulting mixture was purified by flash silica gel chromatography to give the (1R,2R)-ethyl 2-methyl-2-(p-tolyl)cyclopropanecarboxylate (392 mg, 90%). $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 7.21 (d, $J = 8.0$ Hz, 2H), 7.12 (d, $J = 8.2$ Hz, 2H), 4.21 (dq, $J = 7.1$, 3.1 Hz, 2H), 2.34 (s, 3H), 1.96 (dd, $J = 8.3$, 6.0 Hz, 1H), 1.53 (s, 3H), 1.49-1.37 (m, 2H), 1.31 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (CDCl$_3$) δ ppm 172.2, 143.0, 136.0, 129.1, 127.2, 60.4, 30.3, 27.8, 20.9, 20.8, 19.9, 14.4; IR (neat, cm$^{-1}$): 1715; HRMS m/z calcd for [M+H]$^+$ 219.1385, obsd 219.1388.

The ester above (392 mg, 1.8 mmol) was dissolved in methanol (15 mL) and the solution was added to a solution of KOH (1g, 18 mmol, 10 eq) in water (3 mL). The reaction mixture was stirred overnight prior to being cooled to 0 °C. 6 M HCl (4 mL) was added and the reaction mixture was extracted with DCM (20 mL X 3). The organic layers were combined, dried, and evaporated. The residue was dissolved in DCM (10 mL) and the solution was cooled to 0 °C. Oxalyl chloride (360 mg, 0.25 mL, 2.8 mmol, 1.5 eq) was added dropwise and followed by the addition of 1 drop of DMF. The reaction mixture was allowed to warm to r.t. and stirred for 3 h. The volatile in the reaction mixture was removed under vacuum and the residue was dissolved in DCM (4 mL). The solution was added slowly at 0 °C to a solution of 7 M NH$_3$ in methanol (4 mL) and the reaction mixture was allowed to warm to r.t.. The stirring was continued overnight prior to the removal of the volatiles and the residue was purified by flash silica gel chromatography (eluent ethyl acetate) to give the title compound (276 mg, 73%) as white solid. m.p. 164-165 °C; $^1$H NMR (250 MHz,
CD$_3$COCD$_3$ δ ppm 7.08 (d, $J = 8.6$ Hz, 2H), 6.98 (d, $J = 8.6$ Hz, 2H), 6.40-6.09 (m, 1H), 2.13 (s, 3H), 1.77 (dd, $J = 8.3$, 5.9 Hz, 1H), 1.31 (s, 3H), 1.24-1.12 (m, 1H), 1.06 (dd, $J = 8.3$, 4.2 Hz, 1H); $^{13}$C NMR (CD$_3$COCD$_3$) δ ppm 171.9, 143.8, 135.2, 128.8, 126.8, 29.2, 28.0, 20.0, 18.8, 18.6; IR (neat, cm$^{-1}$): 1633; HRMS m/z calcd for [M+H]$^+$ 190.1226, obsd 190.1228; [α]$^D_{20}$ = -224° (c = 0.2, CHCl$_3$); HPLC (Chiral OJ-H, 20% 2-propanol-hexane rate 0.7 ml/min): Major t = 12.95 min., Minor t =11.77 min. e.e. 98%.

**2,6-DiMeO-(4’-Me)QingPhyrin (P13)** was synthesized according to the reported procedure$^{14}$. 2,6-DiMeO-BromoSynthon (210 mg, 0.2 mmol, 1 eq), chiral amide (453 mg, 2.4 mmol, 12 eq), Pd(OAc)$_2$ (18 mg, 0.08 mmol, 0.4eq), Xantphos (94 mg, 0.16 mmol, 0.8 eq) and Cs$_2$CO$_3$ (1.045 g, 3.2 mmol, 16 eq) were placed in an oven dried, resealable Schlenk tube. The tube was capped with a Teflon screw cap, evacuated, and backfilled with nitrogen. The screw cap was replaced with a rubber septum. Dioxane (6 mL) was added via syringe and the tube was purged with nitrogen for 1 min. The reaction mixture was stirred at 100 °C for three days prior to being cooled to r.t. The reaction mixture was filtered through a short pad of Celite. The solvent was removed and the residue was purified by
flash silica gel chromatography (eluent: hexanes/ethyl acetate 2:1) to give the title compound (178 mg, 60%). \(^1\)H NMR (250 MHz, CDCl\(_3\)) \(\delta\) ppm 8.89 (s, 8H), 8.74-8.37 (m, 4H), 8.00-7.79 (m, 4H), 7.70 (s, 2H), 6.90 (d, \(J = 8.5\) Hz, 4H), 6.83-6.43 (m, 4H), 5.69-4.87 (m, 16H), 2.96 (s, 12H), 1.49 (s, 12H), 1.05-0.90 (m, 16H), 0.56-0.13 (m, 4H), 0.08-0.49 (m, 4H), -2.00 (br, 2H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) ppm 168.8, 160.4, 141.9, 139.0, 134.7, 133.0, 130.8, 130.6, 130.2, 128.4, 127.8, 125.9, 120.7, 117.8, 116.6, 114.9, 106.5, 103.9, 55.0, 29.8, 29.7, 620.3, 19.7, 18.2; UV–Vis (CHCl\(_3\)), \(\lambda_{\text{max}}\) nm (log \(\varepsilon\)): 421(5.53), 515(4.34), 545(3.81), 590(3.85), 643(3.55); HRMS m/z calcd for [M+H]\(^{+}\) 1483.6954, obsd 1483.6966.

\[\text{[Co(2,6-DiMeO-(4'-Me)QingPhyrin)]}\] was synthesized according to the reported procedure\(^{14}\). 2,6-DiMeO-(4'-Me)QingPhyrin (140 mg, 0.1 mmol) and CoCl\(_2\) (130 mg, 1 mmol) were placed in an oven dried, resealable Schlenk tube. The tube was capped with a Teflon screw cap, evacuated, and backfilled with nitrogen. The screw cap was replaced with a rubber septum. 2,6-lutidine (52 mg, 56 \(\mu\)l, 0.05 mmol) and THF (4 mL) were added and
the tube was purged with nitrogen for 1 min. The reaction mixture was stirred at 100 °C for 12 h prior to being cooled to r.t. The reaction mixture was diluted with DCM and washed with brine. The organic layer was separated, dried, and concentrated. The residue was purified by flash silica gel chromatography to give the title compound (130 mg, 93%). UV–vis (CHCl₃), λmax nm (log ε): 413(5.27), 536(4.18); HRMS m/z calcd for [M+H]+ 1540.6130, obsd 1540.6119.

3.3.1 Aryl/alkyl Sulfonyl Azide Synthesis and Characterization

CAUTION: Organic azides are known to be potentially explosive compounds. While we did not encounter any issues during their synthesis, proper precautions were taken. All azidation reactions and subsequent workups were performed behind a blast shield. Once isolated, organic azides were stored in a -20 °C freezer.

**Procedure A:** To a solution of sulfonyl chloride (1 mmol, 1 eq.) in acetone-water (5 mL/5 mL) was added NaN₃ (97.5 mg, 1.5 mmol, 1.5 eq) in one portion and the reaction mixture was stirred for 3 h. The majority of the acetone was removed under vacuum and the crude was extracted with EtOAc (3 x 5 mL). The organic layers were combined, dried, and concentrated in vacuum. The crude product was purified by flash column chromatography to afford the product.

**Procedure B:** To a solution of sulfonyl amide (1 mmol, 1 eq.) in DCM (5 mL) and DBU (0.15 mL) was added a solution of TfN₃ (~0.45 M in hexanes, 3 mL) and the reaction
mixture was stirred for 10 min prior to being quenched with the addition of 1 M HCl (2 mL). The reaction mixture was extracted with DCM (3 x 5 mL) and the organic layers were combined, dried, and concentrated in vacuo. The crude product was purified by flash column chromatography to afford the product.

\[ \text{SO}_2\text{N}_3 \]

2-Ethylbenzenesulfonyl azide (1a): synthesized from the sulfonyl amide\textsuperscript{11} following Procedure B (16:1, hexanes: ethyl acetate, yield: 155 mg, 97%, known compound\textsuperscript{4d}). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) ppm 8.01 (d, \( J = 8.0 \) Hz, 1H), 7.61 (t, \( J = 7.6 \) Hz, 1H), 7.45 (d, \( J = 7.6 \) Hz, 1H), 7.37 (t, \( J = 7.6 \) Hz, 1H), 3.03 (q, \( J = 7.4 \) Hz, 2H), 1.30 (t, \( J = 7.6 \) Hz, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) \( \delta \) ppm 144.6, 136.4, 134.8, 131.4, 129.4, 126.4, 26.1, 15.2; IR(neat, cm\textsuperscript{-1}): 2125, 1364, 1169.

\[ \text{SO}_2\text{N}_3 \]

4-Methyl-2-ethylbenzenesulfonyl azide (1b): synthesized from the sulfonyl amide\textsuperscript{11} following Procedure B (16:1, hexanes: ethyl acetate, yield: 176 mg, 88%) as colorless oil. \textsuperscript{1}H NMR (250 MHz, CDCl\textsubscript{3}) \( \delta \) ppm 7.82 (d, \( J = 8.2 \) Hz, 1H), 7.18 (s, 1H), 7.10 (d, \( J = 8.2 \) Hz, 1H), 2.91 (q, \( J = 7.5 \) Hz, 2H), 2.35 (s, 3H), 1.22 (t, \( J = 7.5 \) Hz, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) \( \delta \) ppm 146.1, 144.5, 133.4, 132.2, 129.7, 127.1, 26.1, 21.6, 15.4; IR(neat, cm\textsuperscript{-1}): 2125, 1364,
1169; HRMS m/z calcd for [M+Na]⁺ 248.0470, obsd 248.0464.

![Image of compound SO₂N₃PhCH₃]

**2-Ethyl-5-(methyl(phenyl)amino)benzenesulfonyl azide (1c):** synthesized following Procedure B (2:1, hexanes: ethyl acetate, 240mg, 86%) as a colorless oil. $^1$H NMR (400 MHz, CDCl₃) δ ppm 7.51 (d, $J = 2.68$ Hz, 1H), 7.39-7.31 (m, 2H), 7.27-7.20 (m, 1H), 7.16-7.04 (m, 4H), 3.32 (d, $J = 9.4$ Hz, 3H), 2.92 (q, $J = 7.4$ Hz, 2H), 1.28 (q, $J = 7.4$ Hz, 3H); $^{13}$C NMR (CDCl₃) δ ppm 147.7, 147.4, 136.7, 134.0, 132.1, 129.8, 124.3, 123.7, 123.1, 116.6, 40.4, 25.3, 15.6; IR: 2123, 1364, 1167; HRMS m/z calcd for [M+Na]⁺ 339.9892, obsd 339.9897.

![Image of compound BrSO₂N₃]

**4-Bromo-2-ethylbenzenesulfonfyl azide (1d):** synthesized following Procedure A (16:1, hexanes: ethyl acetate, yield: 280 mg, 97%, known compound$^{12}$). $^1$H NMR (250 MHz, CDCl₃) δ ppm 7.82 (d, $J = 8.5$ Hz, 1H), 7.54 (d, $J = 1.7$ Hz, 1H), 7.46 (dd, $J = 8.5$, 1.7 Hz, 1H), 2.94 (q, $J = 7.5$ Hz, 2H), 1.22 (t, $J = 7.5$, 3H); $^{13}$C NMR (CDCl₃) δ ppm 146.4, 135.5, 134.4, 130.9, 130.2, 129.7, 26.0, 14.9; IR (neat, cm⁻¹): 2126, 1364, 1164.
5-Cyano-2-ethylbenzenesulfonyl azide (1e): synthesized from 5-cyano-2-ethylbenzene-1-sulfonyl chloride\textsuperscript{24} following Procedure A (8:1, hexanes: ethyl acetate, yield 70 mg, 95%). \textsuperscript{1}H NMR (250 MHz, CDCl\textsubscript{3}) δ ppm 8.26 (d, $J = 1.5$ Hz, 1H), 7.83 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.56 (d, $J = 8.0$ Hz, 1H), 3.04 (q, $J = 7.5$ Hz, 2H), 1.25 (t, $J = 7.5$ Hz, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) δ ppm 149.3, 143.4, 137.9, 132.8, 132.4, 116.5, 111.2, 26.1, 14.6; IR (neat, cm\textsuperscript{-1}): 2233, 2163, 1356, 1162; HRMS m/z calcd for [M+H]\textsuperscript{+} 237.0446, obsd 237.0447.

5-Nitro-2-ethylbenzenesulfonyl azide (1f): synthesized following Procedure A (8:1, hexanes: ethyl acetate, yield: 200 mg, 78%, known compound\textsuperscript{12}). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ ppm 8.87 (d, $J = 2.4$ Hz, 1H), 8.46 (dd, $J = 8.5, 2.4$ Hz, 1H), 7.84-7.57 (m, 1H), 3.14 (q, $J = 7.5$ Hz, 2H), 1.31 (q, $J = 7.5$ Hz, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) δ ppm 151.7, 145.8, 138.1, 132.6, 128.8, 124.6, 124.5, 26.4, 14.8; IR (neat, cm\textsuperscript{-1}): 2141, 1522, 1349, 1168.
Methyl 3-(azidosulfonyl)-4-ethylbenzoate (1g): 3-(chlorosulfonyl)-4-ethylbenzoic acid\textsuperscript{25} (1.25 g, 5 mmol) was refluxed in \( \text{SOCl}_2 \) (5 mL) for 1 h. The solvent was removed \textit{in vacuo}. The residue was then cooled to 0 °C and pre-cooled CH\textsubscript{3}OH (25 mL) was added. The reaction mixture was then allowed to warm to rt and stirred for 1 h. The solvent was removed \textit{in vacuo} and the residue was purified by flash column chromatography (8:1, hexanes: ethyl acetate) to afford methyl ester (840 mg, 64%) as a colorless oil. Then, \textbf{Procedure A} was followed to afford the title compound (8:1, hexanes: ethyl acetate, 267 mg, 99%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) ppm 8.68 (s, 1H), 8.27 (d, \( J = 8.0 \) Hz, 1H), 7.56 (d, \( J = 8.0 \) Hz, 1H), 3.96 (s, 3H), 3.10 \( (q, J = 7.5 \) Hz, 2H), 1.35 \( (t, J = 7.5 \) Hz, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) \( \delta \) ppm 165.1, 149.5, 137.0, 135.4, 131.7, 130.6, 128.8, 52.7, 26.4, 15.0; IR (neat, cm\textsuperscript{-1}): 2134, 1720, 1362, 1163, HRMS m/z calcd for [M+Na]\textsuperscript{+} 292.0368, obsd 292.0370.

Methyl 3-(azidosulfonyl)-4-pentylbenzoate (1g) was prepared following same procedure as above. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) ppm 8.65 (s, 1H), 8.22 (d, \( J = 8.0 \) Hz, 1H), 7.52 (d, \( J = 8.0 \) Hz, 1H), 3.95 (d, \( J = 13.2 \) Hz, 4H), 3.11-2.78 (m, 3H), 1.82-1.58 (m, 3H), 1.58-1.15 (m, 6H), 0.89 \( (t, J = 6.8 \) Hz, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) \( \delta \) ppm 165.0, 148.4, 137.0, 135.1,
132.3, 130.5, 128.7, 52.5, 33.2, 31.8, 30.8, 22.3, 13.9; IR (neat, cm⁻¹): 2133, 1721, 1362, 1163; HRMS m/z calcd for [M+Na]⁺ 334.0837, obsd 334.0840.

**2-Benzylbenzenesulfonyl azide (1h)** was synthesized from the sulfonyl amide¹¹ following **Procedure B** (16:1, hexanes: ethyl acetate, yield: 266 mg, 97%). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.11 (dd, J = 8.0, 1.4 Hz, 1H), 7.58 (dt, J = 7.6, 1.4 Hz, 12 1H), 7.50-7.38 (m, 1H), 7.37-7.30 (m, 2H), 7.30-7.23 (m, 2H), 7.19 (d, J = 6.9 Hz, 2H), 4.44 (s, 2H); ¹³C NMR (CDCl₃) δ ppm 141.2, 138.7, 136.8, 134.6, 132.7, 129.5, 129.3, 129.3, 128.7, 126.8, 126.7, 38.1; IR(neat, cm⁻¹): 2125, 1364, 1169; HRMS m/z calcd for [M+Na]⁺ 296.0470, obsd 296.0471.

**3-Phenylpropane-1-sulfonyl azide (3a)** was obtained from 3-phenylpropane-1-sulfonyl chloride²⁶ using **Procedure A** (8:1, hexanes: ethyl acetate, 306 mg, 91 % yield, known compound²⁷). ¹H NMR (250 MHz, CDCl₃) δ ppm 7.61-7.05 (m, 5H), 3.44-3.11 (m, 2H), 2.84 (t, J = 7.3 Hz, 2H), 2.32-2.26 (m, 2H); ¹³C NMR (CDCl₃) δ ppm 139.3, 128.8, 128.5, 126.8, 55.1, 33.7, 24.9; IR (neat, cm⁻¹): 2132, 1364, 1155.
3-phenylpropane-1-sulfonyl azide-3-d (3j) was obtained from 3-phenylpropane-1-sulfonyl chloride-3-d using Procedure A (8:1, hexanes: ethyl acetate, 51 mg, 98 % yield); \(^1\)H NMR (250 MHz, CDCl\(_3\)) \(\delta\) ppm 7.22-7.15 (m, 5H), 3.31-3.04 (m, 2H), 2.70 (dd, \(J = 9.6, 4.9\) Hz, 1H), 2.19-2.10 (m, 2H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) ppm 139.2, 128.8, 128.4, 126.8, 55.0, 33.4 (t), 24.8; IR (neat, cm\(^{-1}\)): 2132, 1362, 1157; HRMS m/z calcd for [M+Na]\(^+\) 249.0532, obsd 249.0535.

3-(4-Methoxyphenyl)propane-1-sulfonyl azide (3b) was obtained from 3-(4-methoxyphenyl)propane-1-sulfonyl chloride\(^{26}\) using Procedure A (8:1, hexanes: ethyl acetate, 300 mg, 84 % yield). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 7.08 (d, \(J = 8.4\) Hz, 2H), 6.84 (d, \(J = 8.4\) Hz, 2H), 3.78 (s, 3H), 3.36-3.16 (m, 2H), 2.73 (t, \(J = 7.3\) Hz, 2H), 2.22-2.16 (m, 2H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) ppm 158.4, 131.1, 129.3, 114.2, 55.3, 55.0, 32.8, 25.0; IR (neat, cm\(^{-1}\)): 2133, 1364, 1156; HRMS m/z calcd for [M+Na]\(^+\) 278.0575, obsd 278.0578.

3-(2-Bromophenyl)propane-1-sulfonyl azide (3c) was obtained from 3-(2-bromophenyl)propane-1-sulfonyl chloride\(^{26}\) using Procedure A (8:1, hexanes: ethyl acetate, 208 mg, 90 % yield). \(^1\)H NMR (250 MHz, CDCl3) \(\delta\) ppm 7.48 (d, \(J = 7.8\) Hz, 1H), 7.32-
7.10 (m, 2H), 7.10-6.89 (m, 1H), 3.47-3.12 (m, 2H), 2.86 (t, \( J = 7.5 \) Hz, 2H), 2.22-2.09 (m, 2H); \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) ppm 138.8, 133.2, 130.5, 128.6, 127.9, 124.4, 55.0, 34.0, 23.6; IR (neat, cm\(^{-1}\)): 2132, 1367, 1157; HRMS m/z calcd for [M+Na]\(^+\) 325.9275, obsd 325.9278.

\[
\text{Cl} \quad \text{SO}_2\text{N}_3 \\
\text{Cl} 
\]

**3-(3,5-Dichlorophenyl)propane-1-sulfonyl azide (3d)** was obtained from 3-(3,5-dichlorophenyl)propane-1-sulfonyl chloride\(^{26}\) using **Procedure A** (8:1, hexanes: ethyl acetate, 296 mg, 90 % yield). \(^1\)H NMR (250 MHz, CDCl\(_3\)) \( \delta \) ppm 7.28 (s, 1H), 7.12 (s, 2H), 3.46-3.22 (m, 2H), 2.78 (t, \( J = 7.6 \) Hz, 2H), 2.37-2.13 (m, 2H); \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) 142.8, 135.2, 127.0, 127.0, 54.8, 33.2, 24.6; IR (neat, cm\(^{-1}\)): 2134, 1365, 1157; HRMS m/z calcd for [M+Na]\(^+\) 315.9690, obsd 315.9677.

\[
\text{O}_2\text{N} \quad \text{SO}_2\text{N}_3 \\
\]

**3-(4-Nitrophenyl)propane-1-sulfonyl azide (3e)** was obtained from 3-(4-nitrophenyl)propane-1-sulfonyl chloride\(^{26}\) using **Procedure A** (4:1, hexanes: ethyl acetate, 200 mg, 95% yield). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) ppm 8.15 (d, \( J = 8.6 \) Hz, 2H), 7.35 (d, \( J = 8.5 \) Hz, 2H), 3.32 (dd, \( J = 13.8, 6.3 \) Hz, 2H), 2.91 (t, \( J = 7.6 \) Hz, 2H), 2.32-2.26 (m, 2H); \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) ppm 147.0, 146.8, 129.3, 124.0, 54.7, 33.5, 24.5; IR (neat, cm\(^{-1}\)): 2132, 1523, 1364, 1156; HRMS m/z calcd for [M+Na]\(^+\) 293.0320, obsd 293.0316.
3-(4-(trifluoromethyl)phenyl)propane-1-sulfonyl azide (3f) was obtained from 3-(4-(trifluoromethyl)phenyl)propane-1-sulfonyl chloride\textsuperscript{26} using **Procedure A** (8:1, hexanes: ethyl acetate, 89 mg, 90% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.56 (d, $J = 8.0$ Hz, 2H), 7.28 (d, $J = 8.0$ Hz, 2H), 3.39-3.19 (m, 2H), 2.85 (t, $J = 7.5$ Hz, 2H), 2.29-2.22 (m, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ ppm 143.4, 129.1 (q, $J = 32$ Hz), 128.7, 125.7 (q, $J = 3.7$ Hz), 124.3 (q, $J = 260$ Hz), 54.8, 33.4, 24.6; $^{19}$F NMR $\delta$ ppm -62.5; IR (neat, cm$^{-1}$): 2133, 1383, 1162; HRMS m/z calcd for [M+Na]$^+$ 316.0344, obsd 316.0337.

Then, azide intermediate (142 mg, 0.54 mmol) was dissolved in CH$_3$CN (4 mL) and treated with Boc$_2$O (141 mg, 0.64 mmol) and DMAP (3 mg). After stirring at rt for 12 h, more Boc$_2$O (141 mg, 0.64 mmol) and DMAP (3 mg) was added and the reaction mixture was stirred for another 1 h. The reaction was quenched with the addition of water. The reaction mixture was extracted with DCM and washed with water. The organic layers were combined, dried and concentrated to afford crude oil which was purified by flash column chromatography (8:1, hexanes: ethyl acetate) to afford the azide (187 mg, 95%). $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ ppm 8.07 (d, $J = 8.0$ Hz, 1H), 7.42 (dd, $J = 7.1$, 1.1 Hz, 1H), 7.34 (s, 1H), 7.30-7.12 (m, 2H),

**tert-Butyl 3-(3-azidosulfonyl)propyl-1H-indole-1-carboxylate (3g):** 3-(1H-indol-3-yl)propane-1-sulfonyl azide was obtained from 3-(1H-indol-3-yl)propane-1-sulfonyl chloride\textsuperscript{26} using **Procedure A** (4:1, hexanes: ethyl acetate, 142 mg, 98 % yield).
3.43-3.18 (m, 2H), 2.83 (t, J = 7.2 Hz, 2H), 2.38-2.17 (m, 2H), 1.60 (s, 9H); $^{13}$C NMR (CDCl$_3$) δ ppm 149.6, 135.6, 129.9, 124.7, 123.1, 122.7, 118.7, 118.0, 115.5, 83.8, 55.2, 28.3, 23.2, 23.1; IR (neat, cm$^{-1}$): 2133, 1715; HRMS m/z calcd for [M+Na]$^+$ 387.1103, obsd 387.1100.

\[ \text{SO}_2\text{N}_3 \]

**Pent-4-ene-1-sulfonyl azide (3h)** was obtained from pent-4-ene-1-sulfonyl chloride$^{26}$ using **Procedure A** (8:1, hexanes: ethyl acetate, 120 mg, 95 % yield). $^1$H NMR (250 MHz, CDCl$_3$) δ ppm 5.74 (ddd, J = 13.4, 9.8, 6.7 Hz, 1H), 5.23-4.98 (m, 2H), 3.47-3.16 (m, 2H); $^{13}$C NMR (CDCl$_3$) δ ppm 135.6, 117.1, 55.0, 31.6, 22.4; IR (neat, cm$^{-1}$): 2132, 1364, 1155; HRMS m/z calcd for [M+Na]$^+$ 198.0313, obsd 198.0314.

\[ \text{SO}_2\text{N}_3 \]

**E)-5-Phenylpent-4-ene-1-sulfonyl azide (3i)** was obtained from (E)-5-phenylpent-4-ene-1-sulfonyl chloride$^{26}$ using **Procedure A** (8:1, hexanes: ethyl acetate, 300 mg, 92 % yield). $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 7.33-7.26 (m, 5H), 6.45 (d, J = 15.8 Hz, 1H), 6.13 (td, J = 15.8, 7.0 Hz, 1H), 3.50-3.29 (m, 2H), 2.41 (dq, J = 7.0, 1.2 Hz, 2H), 2.20-2.05 (m, 2H); $^{13}$C NMR (CDCl$_3$) δ ppm 136.9, 132.4, 128.7, 127.6, 127.2, 126.2, 55.2, 31.1, 23.0; IR (neat, cm$^{-1}$): 2133, 1367, 1156; HRMS m/z calcd for [M+Na]$^+$ 274.0626, obsd 274.0622.
(Z)-5-Phenylpent-4-ene-1-sulfonyl azide (Z-3i) was obtained using Procedure B (8:1, hexanes: ethyl acetate, 70 mg, 90% yield). \( ^1H \) NMR (250 MHz, CDCl\(_3\)) \( \delta \) ppm 7.34-7.27 (m, 5H), 6.57 (d, \( J = 11.5 \) Hz, 1H), 5.74-5.43 (m, 1H), 3.47-3.07 (m, 2H), 2.50 (dt, \( J = 7.2, 1.6 \) Hz, 2H), 2.15-1.95 (m, 2H), 2.70-2.60 (m, 1H); \( ^{13}C \) NMR (CDCl\(_3\)) \( \delta \) ppm 136.8, 131.5, 129.3, 128.7, 128.4, 127.1, 55.3, 26.5, 23.5; IR (neat, cm\(^{-1}\)): 2132, 1367, 1156; HRMS m/z calcd for [M+Na]\(^+\) 274.0626, obsd 274.0625.

3.3.2 Benzosultam Synthesis and Characterization

An oven dried Schlenk tube, that was previously evacuated and backfilled with nitrogen gas, was charged with azide (if solid, 0.1 mmol), catalyst (0.004 mmol). The Schlenk tube was then evacuated and backfilled with nitrogen. The Teflon screw cap was replaced with a rubber septum and 0.15 ml of CHCl\(_3\) (purchased from Sigma-Aldrich, CHROMASOLV\® HPLC grade, contains 0.5-1.0% ethanol as stabilizer) was added followed by azide (if liquid, 0.1 mmol) and the remaining solvent (total 0.25 mL). The Schlenk tube was then purged with nitrogen for 1 minute and the rubber septum was replaced with a Teflon screw cap. The Schlenk tube was then placed in an oil bath for 48 h at the desired temperature. Following completion of the reaction, the reaction mixture was concentrated and purified via flash chromatography. The fractions containing product were collected and concentrated by rotary evaporation to afford the pure compound.
(R)-3-Methyl-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide was synthesized by the general procedure at 80 °C as white solid (pure dichloromethane, 18 mg, 94%), known compound\textsuperscript{4d}; [α]\textsubscript{D}° = +31° (c = 1.0, CHCl\textsubscript{3}); \textsuperscript{1}H NMR (250 MHz, CDCl\textsubscript{3}) δ ppm 7.77 (d, J = 7.6 Hz, 1H), 7.63 (t, J = 7.6 Hz, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 5.07 (s, 1H), 4.91-4.68 (m, 1H), 1.62 (d, J = 6.5 Hz, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) δ ppm 141.8, 135.4, 133.3, 129.2, 123.9, 121.2, 53.4, 21.5; IR (neat, cm\textsuperscript{-1}): 1287, 1169; HPLC (Chiral OD-H, 10% 2-propanol-hexane rate 0.7 ml/min): Major t = 43.35 min., Minor t = 32.41 min. e.e. 90%.

(R)-3,6-Dimethyl-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide was synthesized by the general procedure at 80 °C (15:1, dichloromethane: ethyl acetate, 18 mg, 96%); [α]\textsubscript{D}° = +30° (c = 1.0, CHCl\textsubscript{3}); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ ppm 7.63 (d, J =8.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.16 (s, 1H), 5.01-4.51 (m, 2H), 2.45 (s, 3H), 1.57(d, J = 6.8 Hz, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) δ ppm 143.2, 141.0, 131.7, 123.1, 119.9, 52.2, 20.8, 20.5; IR (neat, cm\textsuperscript{-1}): 1285, 1180; HRMS m/z calcd for [M+Na]\textsuperscript{+} 220.0403, obsd 220.0406; HPLC (Chiral OD-H, 10% 2-propanol-hexane rate 0.7 ml/min): Major t = 35.14 min., Minor t = 32.79 min. e.e. 90%.
(R)-3-Methyl-6-(methyl(phenyl)amino)-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide was synthesized by the general procedure at 80 °C as yellow oil (dichloromethane, 26 mg, 90%); [α]_{20}^{D} = +30° (c = 1.0, CHCl₃); $^1$H NMR (400 MHz, CDCl₃) δ ppm 7.22-7.07 (m, 5H), 7.42-7.32 (m, 2H), 7.01 (dd, J = 8.6, 2.3 Hz, 1H), 4.87-4.50 (m, 2H), 3.51-3.19 (m, 3H), 1.54 (d, J = 6.4 Hz, 3H); $^{13}$C NMR (CDCl₃) δ ppm 150.2, 147.6, 136.3, 130.8, 129.9, 125.0, 125.0, 123.9, 121.4, 106.0, 52.9, 40.5, 21.7; IR (neat, cm⁻¹): 1495, 1289, 1167; HRMS m/z calcd for [M+H]⁺ 289.1005, obsd 289.0999; HPLC (Chiral OD-H, 10% 2-propanol-hexane rate 0.7 ml/min): Major t = 40.44 min., Minor t = 37.00 min. e.e. 88%

(R)-5-Bromo-3-methyl-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide was synthesized by the general procedure at 80 °C as white solid (pure dichloromethane, 18 mg, 99%), known compound¹²; m.p. 125-126 °C; [α]_{20}^{D} = +33° (c = 0.7, CHCl₃); $^1$H NMR (250 MHz, CDCl₃) δ ppm 7.70-7.57 (m, 2H), 7.54 (d, J = 0.5 Hz, 1H), 5.11-4.88 (m, 1H), 4.74 (dd, J = 12.1, 6.4 Hz, 1H), 1.60 (d, J = 6.7 Hz, 3H); $^{13}$C NMR (CDCl₃) δ ppm 143.9, 134.6, 132.6, 128.0, 127.3, 122.6, 53.0, 21.2; IR (neat, cm⁻¹): 1287, 1156; HPLC (Chiral OD-H, 20% 2-propanol-hexane rate 0.7 ml/min): Major t = 19.25 min., Minor t = 15.01 min. e.e. 88%.
(R)-3-Methyl-2,3-dihydrobenzo[d]isothiazole-6-carbonitrile 1,1-dioxide was synthesized by the general procedure at 50 °C as white solid (15:1, dichloromethane: ethyl acetate, 20 mg, 93%); m.p. 154-155 °C; [α]$_{20}^{D}$ = +23° (c = 1.0, CHCl$_3$); $^1$H NMR (250 MHz, CDCl$_3$) δ ppm 7.99 (s, 1H), 7.83 (dd, J = 8.0, 1.4 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 4.93 (s, 1H), 4.85-4.59 (m, 1H), 1.59 (d, J = 6.8 Hz, 3H); $^{13}$C NMR (CDCl$_3$) δ ppm 146.2, 137.2, 136.4, 125.6, 125.3, 116.9, 113.7, 53.5, 21.0; IR (neat, cm$^{-1}$): 1296, 1158; HRMS m/z calcd for [M+Na]$^+$ 231.0198, obsd 231.0194; HPLC (Chiral OD-H, 20% 2-propanol-hexane rate 0.7 ml/min): Major t = 31.52 min., Minor t = 26.98 min. e.e. 93%.

(R)-3-Methyl-6-nitro-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide was synthesized by the general procedure at 50 °C as white solid (15:1, dichloromethane: ethyl acetate, 22 mg, 96%), known compound$^{12}$. m.p. 175-176 °C; [α]$_{20}^{D}$ = +25° (c = 0.5, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 8.55 (d, J = 1.8 Hz, 1H), 8.46 (dd, J = 8.5, 2.0 Hz, 1H), 7.61 (d, J = 8.5 Hz, 1H), 5.41 (s, 1H), 5.00-4.78 (m, 1H), 1.67 (d, J = 6.8 Hz, 3H); $^{13}$C NMR (CDCl$_3$) δ ppm 148.4, 147.9, 137.3, 128.1, 125.4, 117.3, 53.4, 21.0; IR (neat, cm$^{-1}$): 1529, 1352, 1163; HPLC (Chiral OD-H, 20% 2-propanol-hexane rate 0.7 ml/min): Major t = 27.02 min., Minor t = 23.78 min. e.e. 93%.
(R)-Methyl 3-methyl-2,3-dihydrobenzo[d]isothiazole-6-carboxylate 1,1-dioxide was synthesized by the general procedure at 50 °C as white solid (15:1, dichloromethane: ethyl acetate, 18 mg, 75%), known compound\(^{4d}\); \([\alpha]^{20}_D = +12^\circ\) (c = 0.5, CHCl\(_3\)). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 8.40 (s, 1H), 8.28 (dd, J = 8.1, 1.3 Hz, 1H), 7.47 (d, J = 8.1 Hz, 1H), 4.98 (d, J = 3.7 Hz, 1H), 4.90-4.78 (m, 1H), 3.96 (s, 3H), 1.64 (d, J = 6.8 Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) ppm 165.1, 146.1, 136.3, 134.3, 131.6, 124.2, 122.9, 53.4, 52.8, 21.2; IR (neat, cm\(^{-1}\)): 1729, 1298, 1168; HRMS m/z calcd for [M+H]\(^+\) 242.0482, obsd 242.0482; HPLC (Chiral OD-H, 20% 2-propanol-hexane rate 0.7 ml/min): Major t = 20.04 min., Minor t =17.28 min .e.e. 90%.

(R)-Methyl 3-butyl-2,3-dihydrobenzo[d]isothiazole-6-carboxylate 1,1-dioxide was synthesized by the general procedure at 80 °C as a colorless oil (pure DCM, 25 mg, 88%); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 8.39 (s, 1H), 8.25 (d, J = 7.8 Hz, 1H), 7.44 (d, J = 7.8 Hz, 1H), 4.87-4.63 (m, 2H), 3.94 (s, 3H), 2.09-1.88 (m, 1H), 1.89-1.69 (m, 1H), 1.54-1.24 (m, 5H), 0.91 (t, J = 6.8 Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\)) 165.0, 145.1, 136.3, 134.0, 131.5, 124.3, 122.9, 57.9, 52.7, 35.2, 27.8, 22.3, 13.8; IR (neat, cm\(^{-1}\)): 1724, 1162; HRMS m/z calcd for [M+Na]\(^+\) 306.0770, obsd 306.0774; HPLC (Chiral OJ-H, 20% 2-propanol-hexane rate 0.7 ml/min):
Major $t = 26.90 \text{ min.}$, Minor $t = 21.65 \text{ min.}$ e.e. 60%.

(R)-3-Phenyl-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide was synthesized by the general procedure at 80 °C from 2-benzylbenzen-1-sulfonyl azide as white solid (15:1, dichloromethane: ethyl acetate, 18 mg, 73%); m.p. 135-136 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 7.83 (d, $J = 8.0$ Hz, 1H), 7.64-7.49 (m, 2H), 7.48-7.32 (m, 5H), 7.15 (d, $J = 8.0$ Hz, 1H), 5.72 (d, $J = 4.0$ Hz, 1H), 4.98 (s, 1H); $^{13}$C NMR (CDCl$_3$) δ ppm 139.8, 138.6, 133.3, 129.5, 129.3, 129.1, 127.6, 125.3, 121.1, 61.4; IR (neat, cm$^{-1}$): 1055; HRMS m/z calcd for [M+Na]$^+$ 268.0403, obsd 268.0407; HPLC (Chiral OD-H, 20% 2-propanol-hexane rate 0.7 ml/min): Major $t = 42.85 \text{ min.}$, Minor $t = 37.00 \text{ min.}$ e.e. 68%.

3.3.3 Sultam Synthesis and Characterization

An oven dried Schlenk tube, that was previously charged with azide (if solid, 0.25 mmol), catalyst (7.7mg, 0.005 mmol), evacuated and backfilled with nitrogen gas. The Teflon screw cap was replaced with a rubber septum and 1.0 ml of solvent was added followed by azide (if liquid, 0.25 mmol) and the remaining solvent (total 2.5mL). The Schlenk tube was then purged with nitrogen for 2 minutes and the rubber septum was replaced with a Teflon screw cap. The Schlenk tube was then placed in an oil bath for the desired time and temperature. Following completion of the reaction, the reaction mixture was purified via flash chromatography. The fractions containing product were collected
and concentrated by rotary evaporation to afford the pure compound.

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\text{(S)-3-Phenylisothiazolidine 1,1-dioxide} \text{ was synthesized by the general procedure as white solid (46 mg, 92% yield). (15:1, dichloromethane: ethyl acetate). m.p. 88-89 °C; } [\alpha]^{20}_D = -36^\circ (c = 1.0, \text{CHCl}_3); \text{ } ^1\text{H NMR (400 MHz, CDCl}_3) \delta \text{ ppm 7.63-7.26 (m, 5H), 4.88-4.52 (m, 2H), 3.46-3.25 (m, 1H), 3.17 (dd, } J = 12.6, 10.6, 7.6 \text{ Hz, 1H), 2.78-2.70 (m, 1H), 2.41-2.33 (m, 1H); } ^{13}\text{C NMR (CDCl}_3) \delta \text{ ppm 140.2, 128.9, 128.4, 126.0, 58.1, 48.2, 32.1; IR (neat, cm}^{-1}: 1290, 1141; \text{ HRMS m/z calcd for } [\text{M+Na}]^+ 220.0408, \text{ obsd 220.0407; HPLC analysis: ee = 94%. Chiral OD-H (20% 2-propanol-80% hexanes, 0.7 ml/min): Major } t = 26.34 \text{ min., Minor } t = 34.18 \text{ min.}
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\text{(S)-3-(4-Methoxyphenyl)isothiazolidine 1,1-dioxide} \text{ was synthesized by the general procedure as white solid (52 mg, 99% yield). (15:1, dichloromethane: ethyl acetate). m.p. 90-91 °C; } [\alpha]^{20}_D = -42^\circ (c = 1.0, \text{CHCl}_3); \text{ } ^1\text{H NMR (400 MHz, CDCl}_3) \delta \text{ ppm 7.29 (d, } J = 8.4 \text{ Hz, 2H), 6.86 (d, } J = 8.4 \text{ Hz, 2H), 4.78-4.51 (m, 2H), 3.77 (s, 3H), 3.39-3.24 (m, 1H), 3.17 (dd, } J = 12.6, 10.5, 7.6 \text{ Hz, 1H), 2.73-2.68 (m, 1H), 2.47-2.26 (m, 1H); } ^{13}\text{C NMR (CDCl}_3) \delta \text{ ppm 159.6, 132.0, 127.3, 114.3, 57.8, 55.3, 48.3, 32.2; IR (neat, cm}^{-1}: 1248, 1142; \text{ HRMS}
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m/z calcd for [M+Na]^+ 250.0508, obsd 250.0513; HPLC analysis: ee = 95%. (Chiral AD-H, 20% 2-propanol-hexane rate 0.7 ml/min): Major t = 19.57 min, Minor t = 18.03 min.

(S)-3-(2-Bromophenyl)isothiazolidine 1,1-dioxide was synthesized by the general procedure as white solid (65 mg, 96% yield). (15:1, dichloromethane: ethyl acetate). m.p. 93-94 °C; [α]^20_D = -78° (c = 1.0, CHCl₃); ¹H NMR (250 MHz, CDCl₃) δ ppm 7.66 (dd, J = 7.8, 1.6 Hz, 1H), 7.47 (dd, J = 7.9, 1.2 Hz, 1H), 7.31 (dt, J = 7.9, 1.0 Hz, 1H), 7.17-7.04 (m, 1H), 5.21-4.96 (m, 1H), 4.61 (dd, J = 4.8, 0.8 Hz, 1H), 3.24 (dd, J = 7.2, 3.8 Hz, 1H), 3.19-3.03 (m, 1H), 3.03-2.85 (m, 1H), 2.30-2.03 (m, 1H); ¹³C NMR (CDCl₃) δ ppm 139.6, 133.0, 129.7, 128.3, 127.5, 121.7, 57.1, 47.8, 30.0; IR (neat, cm⁻¹): 1295, 1143; HRMS m/z calcd for [M+Na]^+ 297.9508, obsd 297.9508; HPLC analysis: ee = 96% (Chiral OD-H, 20% 2-propanol-hexane rate 0.7 ml/min): Major t = 23.22 min, Minor t = 28.85 min.

(S)-3-(3,5-Dichlorophenyl)isothiazolidine 1,1-dioxide was synthesized by the general procedure as white solid (63 mg, 95% yield). (15:1, dichloromethane: ethyl acetate). m.p. 142-143 °C; [α]^20_D = -50° (c = 0.6, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ ppm
7.28 (s, 3H); 5.01 (d, J = 5.7 Hz, 1H), 4.67 (td, J = 9.0, 6.5 Hz, 1H), 3.32 (ddd, J = 12.5, 7.5, 3.2 Hz, 1H), 3.25-3.06 (m, 1H), 2.87-2.67 (m, 1H), 2.42-2.21 (m, 1H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) δ ppm 144.0, 135.5, 128.4, 124.5, 56.8, 48.0, 31.7; IR (neat, cm$^{-1}$): 1142; HRMS m/z calcd for [M+Na]$^+$ 287.9623 obsd 287.9629; HPLC analysis: ee = 96% (Chiral OD-H, 20% 2-propanol-hexane rate 0.8 ml/min): Major t = 23.00 min., Minor t = 17.54 min.

**S)-3-(4-Trifluoromethylphenyl)isothiazolidine 1,1-dioxide** was synthesized by the general procedure (61 mg, 96% yield). (15:1, dichloromethane: ethyl acetate). [$\alpha$]$^{20}_D$ = -30° (c = 0.4, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 7.62 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 8.2 Hz, 2H), 5.04 (d, J = 5.3 Hz, 1H), 4.80 (td, J = 8.9, 6.5 Hz, 1H), 3.39-3.29 (m, 1H), 3.27-3.09 (m, 1H), 2.91-2.71 (m, 1H), 2.43-2.22 (m, 1H); $^{13}$C NMR (CDCl$_3$) δ ppm 144.5, 130.5 (q, J = 32 Hz), 126.4, 125.9 (q, J = 4.0 Hz), 124.0 (q, J = 260 Hz), 57.4, 48.0, 31.9; $^{19}$F NMR (376 MHz, CDCl$_3$) δ ppm -62.7; IR (neat, cm$^{-1}$): 1298, 1142; HRMS m/z calcd for [M+Na]$^+$ 288.0277, obsd 288.0284; HPLC analysis: ee = 96% (Chiral OD-H, 10% 2-propanol-hexane rate 1.0 ml/min): Major t = 39.58 min., Minor t = 29.17 min.

**S)-3-(4-Nitrophenyl)isothiazolidine 1,1-dioxide** was synthesized by the general procedure as off-white solid (56 mg, 92% yield). (15:1, dichloromethane: ethyl acetate).
m.p. 132-133 °C; [α]^{20}_D = -68^\circ \ (c = 0.5, \ CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ ppm 8.20 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H), 5.02 (d, J = 5.6 Hz, 1H), 4.96-4.69 (m, 1H), 3.35 (ddd, J = 12.2, 7.4, 3.0 Hz, 1H), 3.19 (ddd, J = 12.3, 11.9, 7.4 Hz, 1H), 2.90-2.80 (m, 1H), 2.38-2.28 (m, 1H); ^13C NMR (CDCl_3) δ ppm 151.1, 148.3, 128.1, 124.6, 57.5, 49.0, 32.7; IR (neat, cm\textsuperscript{-1}): 1524, 1350, 1140; HRMS m/z calcd for [M+Na]^+ 265.0254, obsd 265.0259; HPLC analysis: ee = 93%. (Chiral AD-H, 20% 2-propanol-hexane rate 0.7 ml/min): Major t = 36.37 min., Minor t = 21.86 min.

(S)-tert-butyl 3-(1,1-dioxidothiazolidin-3-yl)-1H-indole-1-carboxylate was synthesized by the general procedure as white solid (82mg, 98% yield). (15:1, dichloromethane: ethyl acetate). m.p. 112-113 °C; [α]^{20}_D = -21^\circ \ (c = 1.0, \ CHCl_3); ^1H NMR (250 MHz, CDCl_3) δ ppm 8.08 (d, J = 8.2 Hz, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.55 (s, 1H), 7.35-7.24 (m, 1H), 7.24-7.18 (m, 1H), 4.90 (dd, J = 6.2, 2.4 Hz, 1H), 4.48 (d, J = 5.8 Hz, 1H), 3.39-3.25 (m, 1H), 3.25-3.11 (m, 1H), 2.74 (dd, J = 6.6, 4.8 Hz, 1H), 2.68-2.46 (m, 1H), 1.60 (s, 9H); ^13C NMR (CDCl_3) δ ppm 149.4, 136.0, 127.7, 125.1, 123.2, 123.0, 119.3, 119.2, 115.6, 84.3, 51.7, 47.9, 30.1, 28.2; IR (neat, cm\textsuperscript{-1}): 1734, 1371, 1156; HRMS m/z calcd for [M+Na]^+ 359.1036, obsd 359.1038; HPLC analysis: ee = 99% (Chiral OD-H, 20% 2-propanol-hexane rate 0.7 ml/min): Major t = 24.80 min, Minor t = 33.0 min.
(S)-3-vinylisothiazolidine 1,1-dioxide was synthesized by the general procedure (13 mg, 92% yield). (15:1, dichloromethane: ethyl acetate). $[\alpha]^{20}_D = +34^\circ$ (c = 1.6, CHCl$_3$); $^1$H NMR (250 MHz, CDCl$_3$) δ ppm 5.82 (ddd, J = 16.9, 10.2, 6.6 Hz, 1H), 5.32 (d, J = 17.0 Hz, 1H), 5.20 (d, J = 10.2 Hz, 1H), 4.62 (s, 1H), 4.25-3.99 (m, 1H), 3.29-2.94 (m, 2H), 2.68-2.45 (m, 1H), 2.31-2.05 (m, 1H); $^{13}$C NMR (CDCl$_3$) δ ppm 136.6, 117.6, 56.4, 47.4, 29.6; IR (neat, cm$^{-1}$): 1295, 1141; HRMS m/z calcd for [M+Na]$^+$ 170.0205, obsd 170.0201.

(S)-2-benzyl-3-vinylisothiazolidine 1,1-dioxide To a solution of substrate (10 mg) in CH$_3$CN (2 mL) was added 18-crown-ether (10 mg), BnBr (20 mg) and powdered K$_2$CO$_3$ (60 mg). The reaction mixture was stirred for 12 h prior to being filtered. The filtrate was concentrated in vacuo and the crude product was purified by flash column chromatography (4:1, hexanes: ethyl acetate) to afford the product (12 mg, 90%). $[\alpha]^{20}_D = +46^\circ$ (c = 1.0, CHCl$_3$); $^1$H NMR (250 MHz, CDCl$_3$) δ ppm 7.35-7.27 (m, 5H), 5.83-5.56 (m, 1H), 5.36-5.07 (m, 2H), 4.39 (d, J = 15.2 Hz, 1H), 4.09 (d, J = 15.2 Hz, 1H), 3.84-3.61 (m, 1H), 3.25 (dd, J = 7.8, 5.2 Hz, 1H), 3.17-2.96 (m, 1H), 2.47 (d, J = 7.2 Hz, 1H), 2.17 (d, J = 6.8 Hz, 1H); $^{13}$C NMR (CDCl$_3$) δ ppm 136.2, 135.8, 128.8, 128.4, 127.6, 119.4, 59.9, 46.9, 45.7, 25.7; IR (neat, cm$^{-1}$): 1303, 1140; HRMS m/z calcd for [M+Na]$^+$ 260.0721, obsd 260.0723; HPLC analysis: ee = 93% (Chiral OJ-H, 10% 2-propanol-hexane rate 1.0 ml/min): Major t = 27.8 min., Minor t
(S,E)-3-styrylisothiazolidine 1,1-dioxide was synthesized by the general procedure as white solid (22 mg, 98% yield). (15:1, dichloromethane: ethyl acetate). m.p. 110-112 °C; $\alpha^{20} = -5^\circ$ (c = 1.0, CHCl$_3$); $^1$H NMR (250 MHz, CDCl$_3$) δ ppm 7.63-7.14 (m, 5H), 6.65 (d, J = 15.8 Hz, 1H), 6.18 (dd, J = 15.8, 7.3 Hz, 1H), 4.76 (d, J = 4.9 Hz, 1H), 4.34 (td, J = 13.7, 7.0 Hz, 1H), 3.43-3.02 (m, 2H), 2.75-2.49 (m, 1H), 2.32 (ddd, J = 17.9, 13.4, 8.4 Hz, 1H); $^{13}$C NMR (CDCl$_3$) δ ppm 135.7, 132.6, 128.8, 128.3, 127.6, 126.7, 56.9, 47.7, 29.9; IR (neat, cm$^{-1}$): 1302, 1143; HRMS m/z calcd for [M+Na]$^+$ 246.0565, obsd 246.0569; HPLC analysis: ee = 90% (Chiral AD-H, 20% 2-propanol-hexane rate 0.7 ml/min): Major $t$ = 17.0 min., Minor $t$ = 15.1 min.

3.3.4 Kinetic Isotope Experiment

An oven dried Schlenk tube that was previously charged with Co(P12) (2.5 mg, 0.0018 mmol), evacuated and backfilled with nitrogen gas. The Teflon screw cap was replaced with a rubber septum and 0.7 ml of benzene was added followed by azide 3j (20 mg, 0.088 mmol) and the remaining solvent (total 1.0 mL). The Schlenk tube was then
purged with nitrogen for 2 minutes and the rubber septum was replaced with a Teflon screw cap. The Schlenk tube was then placed in an oil bath (40 °C) for 24 h. The reaction mixture was purified via flash chromatography (eluent: 15:1, dichloromethane: ethyl acetate) to afford a mixture of 4j-H and 4j-D (13 mg, 75%), which was subject to NMR analysis. However, there is an overlap of NH proton and benzylic proton. This problem was solved by simply adding one drop of D₂O to the CDCl₃ solution for NH proton exchange. The complete disappearance of NH proton allows accurate integration of benzylic proton and calculation of the ratio of 4j-H and 4j-D. ¹H NMR (250 MHz, CDCl₃) δ ppm 7.32-7.27 (m, 5H), 4.60 (s, 1H), 3.37-3.01 (m, 2H), 2.78-2.59 (m, 1H), 2.42-2.19 (m, 1H); ¹³C NMR (CDCl₃) δ ppm 140.1, 129.0, 128.5, 126.1, 57.7(triplet), 48.2, 32.0; IR (neat, cm⁻¹): 1290, 1141; HRMS m/z calcd for [M+Na]⁺ 221.0468, obsd 221.0465.

### 3.3.5 Radical Trap Experiment

An oven dried Schlenk tube that was previously charged with Co(P11) (3.1 mg, 0.002 mmol), evacuated and backfilled with nitrogen gas. The Teflon screw cap was replaced with a rubber septum and 0.7 ml of solvent was added followed by TEMPO (78 mg, 0.5 mmol), azide (E)-3i (25.1 mg, 0.1 mmol) and the remaining solvent (total 1.0 mL). The Schlenk tube then purged with nitrogen for 2 minutes and the rubber septum was replaced with a Teflon screw cap. The Schlenk tube was then placed in an oil bath (40 °C)
for 24 h. The reaction mixture was purified via flash chromatography (eluent: 15:1, dichloromethane: ethyl acetate) to afford (E)-5i (4 mg, 10%) and (E)-4i (18 mg, 72%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.36-7.26 (m, 5H), 6.47 (d, $J = 16.0$ Hz, 1H), 6.17 (dd, $J = 16.0$, 8.5 Hz, 1H), 4.57 (s, 2H), 4.50-4.38 (m, 1H), 3.34-3.12 (m, 2H), 2.41-2.25 (m, 1H), 2.25-2.11 (m, 1H), 1.67-1.35 (m, 6H), 1.23 (s, 3H), 1.15 (s, 4H), 1.09 (s, 6H); $^{13}$C NMR (CDCl$_3$) $\delta$ ppm 136.6, 132.2, 130.5, 128.6, 127.7, 126.5, 82.7, 51.8, 40.1, 36.5, 34.9, 29.1, 20.5, 17.2; HRMS m/z calcd for [M+H]$^+$ 381.2212, obsd 381.2209; HPLC analysis: ee = 0% (Chiral OD-H, 20% 2-propanol-hexane rate 0.8ml/min): first peak $t$ = 15.1 min., second peak $t$ =18.0 min.

3.3.6 Olefin Isomerization Experiment

\[
\begin{align*}
\text{Ph} & \quad \text{N}_3 \quad \text{S}^\ominus \quad \text{O}^\ominus \\
& \quad \text{[Co(P11)] (2 mol %)} \\
& \quad \text{C}_6\text{H}_6, \text{ 40 °C} \\
& \quad \text{Ph} & \quad \text{HN} \quad \text{S}^\ominus \quad \text{O}^\ominus \\
& \quad \text{86% yield, 82% ee}
\end{align*}
\]

An oven dried Schlenk tube that was previously charged with Co(P11) (3.1 mg, 0.002 mmol), evacuated and backfilled with nitrogen gas. The Teflon screw cap was replaced with a rubber septum and 0.7 ml of solvent was added followed by azide (Z)-3i (25.1 mg, 0.1 mmol) and the remaining solvent (total 1.0 mL). The Schlenk tube then purged with nitrogen for 2 minutes and the rubber septum was replaced with a Teflon screw cap. The Schlenk tube was then placed in an oil bath (40 °C) for 24 h. The reaction mixture was purified via flash chromatography (eluent: 15:1, dichloromethane: ethyl acetate) to afford (E)-4i (19 mg, 86%). Characterization data are identical to 4i.
3.3.7 Tricyclic Sultam Synthesis and Characterization

To a solution of 4a (310 mg, 1.6 mmol) in CH₃CN (10 mL) was added 18-crown-ether (338 mg, 1.3 mmol), CH₃I (909 mg, 6.4 mmol) and powdered K₂CO₃ (883 mg, 6.4 mmol). The reaction mixture was stirred for 12 h prior to being filtered. The filtrate was concentrated in vacuo and the crude product was purified by flash column chromatography (4:1, hexanes: ethyl acetate) to afford the product (331 mg, 98%) as white solid. m.p. 85-86 °C; ¹H NMR (250 MHz, CDCl₃) δ ppm 7.38-7.28 (m, 5H), 4.13 (dd, J = 8.7, 6.6 Hz, 1H), 3.50-3.30 (m, 1H), 3.21 (td, J = 12.8, 8.6 Hz, 1H), 2.74-2.56 (m, 1H), 2.51 (s, 3H), 2.35-2.16 (m, 1H); ¹³C NMR (CDCl₃) δ ppm 139.2, 129.2, 128.7, 126.8, 64.1, 46.4, 29.2, 28.8; IR (neat, cm⁻¹): 1362, 1144; HRMS m/z calcd for [M+Na]+ 234.0565, obsd 234.0560.

To a solution of N-Me-4a (63 mg, 0.3 mmol) in THF (4 mL) at -78 °C under N₂ was added dropwise freshly opened LDA (2.0 M, 0.3 mL, 0.6 mmol). The reaction mixture was stirred for 30 min at -78 °C prior to the addition of a solution of PhSeBr (93 mg, 0.3 mmol) in THF (2 mL). The reaction mixture was stirred for 10 min at -78 °C prior to being quenched with saturated NH₄Cl solution. The reaction mixture was extracted with EtOAc (3 x 10 mL) and the organic layers were combined, dried, and concentrated in vacuum. The
crude product was purified by flash column chromatography (8:1 to 4:1, hexanes: ethyl acetate) to afford the monoselenated product (91 mg, 83%) as a colorless oil, which was subsequently dissolved in DCM (8 mL) and cooled to 0°C. To the reaction mixture was added 30% H₂O₂ (135 mg) prior to being allowed to warm to r.t. After stirring one hour, the reaction mixture was diluted with H₂O (10 mL), and extracted with DCM (3 x 10 mL). The organic layers were combined, dried, and concentrated in vacuo. The crude product was purified by flash column chromatography (4:1, hexanes: ethyl acetate) to afford the product (40 mg, 90%) as a white solid. m.p. 135-136 °C; [α]²⁰₀ = -296° (c =1.7, CHCl₃); ¹H NMR (250 MHz, CDCl₃) δ ppm 7.33-7.26 (m, 5H), 6.70-6.65 (m, 2H); 4.82 (s, 1H), 2.64 (s, 3H); ¹³C NMR (CDCl₃) δ ppm 139.3, 134.8, 129.3, 129.3, 127.4, 125.9, 67.9, 27.3; HRMS m/z calcd for [M+Na]+ 232.0408 obsd 232.0411; HPLC analysis: ee = 94% (Chiral OD-H, 10% 2-propanol-hexane rate 1.0 ml/min): Major t = 60.16 min., Minor t = 40.58 min.

To a solution of 6 (17 mg, 0.08 mmol) in toluene (1 mL) under N₂ was added cyclopentadiene (42 mg, 0.64 mmol) and a solution of AlEt₂Cl (1 M in hexanes, 0.1 mL) at -78 °C. The reaction mixture was allowed to warm up to r.t. and heated up to 80°C for 24 h. The reaction mixture was cooled to r.t. prior to being quenched with saturated NaHCO₃ solution. The reaction mixture was extracted with DCM (3 x 5 mL) and the organic layers were combined, dried, and concentrated in vacuum. The crude product was purified by
flash column chromatography (8:1 to 4:1, hexanes: ethyl acetate) to afford the endo-7 (16 mg, 72%) as a white solid and exo-7 (4 mg, 18%) as an oil. endo-7: m.p. 130-131 °C; [α]^{20}_{D} = -14° (c =0.5, CHCl₃); ^1H NMR (400 MHz, CDCl₃) δ ppm 7.36-7.26 (m, 5H), 6.60 (dd, J = 5.6, 3.0 Hz, 1H), 6.32 (dd, J = 5.6, 3.1 Hz, 1H), 3.96 (dd, J = 10.5, 3.7 Hz, 1H), 3.51 (d, J = 6.8 Hz, 1H), 3.41 (s, 1H), 3.22 (ddd, J = 10.6, 6.8, 3.9 Hz, 1H), 3.02 (s, 1H), 2.35 (s, 4H), 1.76 (td, J = 8.8, 1.7 Hz, 1H), 1.49 (d, J = 9.3 Hz, 1H); ^13C NMR (CDCl₃) δ ppm 139.5, 137.2, 133.7, 129.0, 128.4, 127.1, 66.9, 63.6, 52.8, 52.4, 45.1, 44.4, 28.1; IR (neat, cm⁻¹): 1368, 1142; HRMS m/z calcd for [M+Na]+ 298.0878; obsd 298.0875; HPLC analysis: ee = 94% (Chiral AD-H,10% 2-propanol-hexane rate 1.0 ml/min): Major t = 12.46 min., Minor t =14.28 min. exo-7: [α]^{20}_{D} = -72° (c =0.3, CHCl₃); ^1H NMR (400 MHz, CDCl₃) δ ppm 7.45-7.30 (m, 5H), 6.16 (s, 2H), 3.55 (dd, J = 7.7, 2.6 Hz, 1H), 3.40 (s, 1H), 3.31 (d, J = 9.2 Hz, 1H), 2.80 (s, 1H), 2.54 (t, J = 8.4 Hz, 1H), 2.39 (d, J = 3.0 Hz, 3H), 2.17 (d, J = 9.6 Hz, 1H), 1.68 (d, J = 10.2 Hz, 1H); ^13C NMR (CDCl₃) δ ppm 139.9, 139.0, 136.4, 129.1, 128.7, 127.5, 68.1, 61.8, 52.7, 44.4, 44.2, 43.5, 28.4; IR (neat, cm⁻¹): 1363, 1143; HRMS m/z calcd for [M+Na]+ 298.0878; obsd 298.0876; HPLC analysis: ee = 94% (Chiral OD-H,10% 2-propanol-hexane rate 1.0 ml/min): Major t = 10.03 min., Minor t =11.10 min.

3.4 References


(15) This project was initiated shortly after our first report on Co(II)-based non-asymmetric system for intramolecular C–H amination of arylsulfonyl azides in 2007 (see ref. 12). It took us several years of systematic efforts to complete the project as presented in this manuscript. While this project was in the final stage of development, Katsuki and coworkers reported an asymmetric version of the catalytic transformation by a Ir(III)-based catalytic system (see ref. 4d).


