INVESTIGATIONS IN TITANIUM-CATALYZED AND -MEDIATED BOND FORMING REACTIONS

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ABSTRACT

Nitrogen containing compounds, such as isoxazoles, enamines, amines, and a variety of heterocycles have incredible values and potentials in pharmaceutical industry.¹ These compounds are prevalent in many pharmaceuticals, organic dyes, solar cells, and natural products. However, conventional pyridine syntheses often have limitation, such as limited substrate scope, low regioselectivity, or harsh reaction conditions. Therefore, new synthetic routes into these nitrogen containing compounds are highly desirable. Our group has been exploring synthetic routes using titanium metal reagents or catalysts to synthesize a wide variety of nitrogen containing compounds. One of the synthetic routes developed in our group is titanium-mediated pyridine synthesis via inverse electron-demand *hetero*-Diels-Alder reaction (**Chapter 2**). Also, our group previously developed a tool to help us evaluate ligand effects to high valent metal, and with this tool we have been exploring and developing new asymmetric ligands for titanium catalysts (**Chapter 3**).

To My Family and Friends

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LIST OF SYMBOLS AND ABBREVIATIONS

%Vbur	Percent Buried Volume
3CC	Three-Component Coupling
Boc	<i>tert</i> -Butoxycarbonyl
dtbpy	4,4'-tert-butyl-2,2'-bipyridine
СНО	Aldehyde
DMF	Dimethylformamide
DME	Dimethoxyethane
DMSO	Dimethyl sulfoxide
Et2O	Diethyl ether
Equiv.	Equivalent
GC/FID	Gas Chromatography Flame Ionization Detector
GC/MS	Gas Chromatography Mass Spectrometry
h	Hour(s)
IEDDA	Inverse-Electron Demand Diels-Alder
H2 <i>dpm</i>	5,5-dimethyldipyrrolylmethane
H2dpma	N,N-(dipyrrolyl-α-methyl)-N-methylamine
Ind	Indole
LDP	Ligand Donor Parameter
min	Minute(s)
MSU	Michigan State University
M.W.	Molecular weight
NMR	Nuclear magnetic resonance
OAc	Acetate
RT	Room temperature
S	Second(s)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

Chapter 1. Introduction to Synthesis and Catalysis Using Titanium Metal Complexes 1.1 Background

Heterocyclic frameworks containing nitrogen atoms are crucial due to a diverse range of applications, such as organic dyes for solar cells and natural products. In particular, *N*-heterocycles are significant structural components in pharmaceuticals.¹ In 2018, Douguet and colleagues published datasets of FDA-Approved drugs with a molecular weight less than 2000², revealing that nitrogen-heterocycles continue to play a significant role in the pharmaceutical industry. As of July 2022, the database has 2056 drugs including many drugs with *N*-heterocycles, such as pyridines (223), piperidines (216), pyrimidines (190), and pyrazoles (18).



Figure 1.1 Classification of U.S. FDA-Approved drugs in 2022.¹

The formation of heterocyclic scaffolds through chemical reactions, such as C-C and C-N bond forming reactions, has been explored using rare and late transition metals like palladium, iridium, rhodium, and etc. However, the high production costs associated with low natural abundance of these late transition metals bring high cost to produce heterocycles. In contrast, early transition metals are more readily available and less expensive. From this perspective, the development of chemical reactions using early transition metals is important.

1.2 Titanium-Mediated N-Heterocycle Synthesis

Titanium, the second most abundant transition metal and ninth most abundant element in crustal rocks, is non-toxic as well as highly available.³ Due to these reasons, titanium complexes are also highly attractive reagents or catalysts in a view of green chemistry. Consequently, titanium

chemistry has attracted significant attention, leading to the development of essential reactions such as olefin polymerization and Sharpless epoxidation. Titanium chemistry has contributed to the synthesis of N-heterocycles, as demonstrated by many examples of titanium-mediated C-N and C-C bond formation for N-heterocycle synthesis.



Scheme 1.1 Examples of titanium-mediated N-heterocycle synthesis.

In 1989, Ohta and coworkers discovered the IEDDA (Inverse Electron Demand *hetero*-Diels-Alder) reaction of isoxazoles and enamines for synthesizing substituted pyridines in the presence of TiCl₄ and Zn (**Scheme 1.1a**).⁴ In this reaction, the isoxazole undergoes [4 + 2]-cycloaddition with the enamine. It was proposed that subsequent steps after cycloaddition lead to pyridine-*N*-oxide as an intermediate, and this pyridine-*N*-oxide is then reduced by TiCl₄ and Zn in the reaction to produce substituted pyridines. With this strategy, all substituents on pyridines can be controlled with excellent regioselectivity. A titanium-mediated multi-component coupling reaction to form pyridines was reported by Urabe and coworkers in 2005 (**Scheme 1.1b**).⁵ The coupling of two acetylenes with a reduced Ti species generates titanocyclopentadiene, the titanocyclopentadiene reacts with nitriles and forms substituted pyridines. An efficient synthesis of 2,3-disubstituted indoles from 2-nitrophenyl-substituted alkenes by aqueous TiCl₃ was recently reported (**Scheme 1.1c**).⁶ This is an intramolecular reaction between a nitro group and an alkene on the same aromatic ring. Once TiCl₃ reduces the nitro group on the benzene rings, the alkene

attacks nitrogen to form indole-N-oxide in situ. The indole-N-oxide is reduced by TiCl₃ again to produce 2,3-disubstituted indoles. These synthetic methods include simple coupling reactions or reduction but are very effective for the synthesis of N-heterocycles. Other than classic titanium-mediated reactions, many novel synthetic methods utilizing titanium redox chemistry also have been developed in recent years.⁷

The research in the Odom group has been focused on C-N bond forming reactions and Nheterocycle synthesis. I have conducted a study on the IEDDA reaction of isoxazoles and enamines originally reported by the Ohta group.⁴ The reaction conditions are optimized using various reagents to broaden the substrate scope, and a mechanistic study was conducted using DFT calculations (**Chapter 2**).⁸ The Odom research group developed various titanium catalysts and their applications in catalysis, such as hydroamination and iminoamination reactions, that prove to be advantageous in N-heterocycle synthesis as well.³

1.3 Titanium Catalysis for C-N Bond formation

Titanium-catalyzed reactions have been investigated and applied in academia and industry for various purposes; however, they are not as extensively utilized as late transition metal catalysts in terms of the diversity of catalytic chemistry. Therefore, the Odom research group has focused on studying titanium catalysis forming C-N bonds. These C-N bond forming reactions are important starting points for *N*-heterocycle synthesis.

The hydroamination of alkynes using titanium catalysts has been a very important topic of interest for our group. Our group found that $Ti(NMe_2)_4$, a commercially available compound, proved to be effective as a precatalyst for hydroamination of alkynes.⁹ This transformation is a 100% atom-economical process to generate imines from alkynes and amines. Since, our group has been designing ligands for titanium(IV) catalysts to achieve faster reaction rates as well as broader substrate scope. Furthermore, the Odom group developed titanium-catalyzed multicomponent coupling reactions from anilines, alkynes, and isonitriles to produce α,β -unsaturated imines.¹⁰



Figure 1.2 The multicomponent coupling reaction and various N-heterocycle synthesis developed in the Odom group.

These α,β -unsaturated imines, accessed via multicomponent coupling strategies, have similar reactivity with 1,3-dicarbonyl compounds and are employed as intermediates for various *N*-heterocycle syntheses developed in the Odom group. This multicomponent coupling reaction has enabled the synthesis of various *N*-heterocycles, branching out into many different pathways.³ 1.3.1 Titanium-Catalzyed Intermolecular Hydroamination of Alkynes

(a) Proposed Mechanism for Titanium-Catalyzed Intermolecular hydroamination



(b) Synthesis for Titanium Precatalysts from the Odom group



Figure 1.3 Proposed mechanism for titanium-catalyzed intermolecular hydroamination and synthetic routes for titanium precatalysts with H₂dpma and H₂dpm.

In 2001, the Odom group discovered that the commercially available reagent Ti(NMe₂)₄ is a catalyst for hydroamination of alkynes, which is cheaper and more stable than previously reported precatalysts, such as zirconocene- and titanocene-based catalysts.⁹ Comparing to titanocene-based catalysts, Ti(NMe₂)₄ provides faster reaction rates in many cases. The reaction mechanism (**Figure 1.4**) is originally established by Bergman and coworkers for zirconocenebased catalysts.^{11,12} The titanium precatalyst reacts with an amine to form a titanium imido complex, the active catalyst, and the titanium imido complex and alkyne undergo [2 + 2]cycloaddition to form a four-membered titanium metallacycle. Lastly, another amine binds to the metal center and protons from the amines are transferred to release the enamine product. The protonolysis of the titanium-carbon bond is believed to be the rate determining step in the catalytic cycle. Also, dimerization of the titanium imido complex, the active catalyst, is believed to be inhibiting the catalysis.

Although Ti(NMe₂)₄ provides relatively good reactivity and substrate scope, multiple pyrrole-based ancillary ligands have been developed to improve the catalytic activity. The first pyrrole-based ancillary ligand in the Odom group was H₂dpma (*N*,*N*-di(pyrrolyl- α -methyl-*N*-methylamine), synthesized via Mannich condensation of pyrrole, formaldehyde and methylamine hydrochloride.¹² Another representative pyrrole-based ancillary ligand in the Odom group is H₂dpm (5,5-dimethyldipyrrolylmethane), synthesized via Friedel-Crafts reaction of pyrrole and acetone with a catalytic amount of trifluoroacetic acid (**Figure 1.5**).¹⁴

With our titanium catalysts, hydroamination between primary amines and alkynes provide good regioselectivity to produce Markovnikov products in the most cases.^{13,14} However, the regioselectivity varies depending on precatalyst. For example, hydroamination between aniline and 1-hexyne with $Ti(dpma)(NMe_2)_2$ is higly selective for the Markonikov product (>50:1), whereas the same reaction with $Ti(dpm)(NMe_2)_2$ provide a selectivity of 6:1. Moreover, these precatalysts brought the opposite results in terms of regioselectivity for hydroamination between aniline and 1-phenylproypne. The reaction with $Ti(dpma)(NMe_2)_2$ is selective for the anti-Markonikov product (1:19) however, $Ti(dpm)(NMe_2)_2$ provides an excellent regioselectivity of 50:1. Other than H₂dpma and H₂dpm, various pyrrole-, indole-, or phenol-based bidentate ancillary ligands were synthesized in the Odom group to investigate ligand effects on titanium-catalyzed hydroamination of alkynes.

1.3.2 Titanium-Catalyzed Iminoamination

According to the Bergman hydroamination mechanism, the protonolysis of the titaniumcarbon bond is slow from the four-membered titanium metallacycle from [2 + 2]-cycloaddition. The titanium metallacycle has a reactive titanium-carbon bond, and our group tried to utilize the bond to form another compound with an isonitrile before the slow step of proton transfer to release the enamine product. This led to the discovery of a three-component coupling reaction, which forms a new C-C and C-N bond by using a primary amine, an alkyne, and an isonitrile.¹⁰



Scheme 1.2 Proposed mechanism for titanium-catalyzed iminoamination.

The mechanism of the three-component coupling reaction involves a titanium metallacycle as one of intermediates. It is proposed that isonitrile 1,1-inserts into the reactive titanium-carbon bond of the titanium metallacycle. Then protonolysis produces the 1,3-diimine product. The final product is produced through the formal addition of an iminyl and amino group to the C-C triple bond, resulting in iminoamination. Ti(NMe₂)₂(H₂dpma) and Ti(NMe₂)₂(H₂dpm) are employed for iminoamination, and with these catalysts, iminoamination usually gives around 70% yield.

1.4 Titanium-Catalyzed iminoamination for N-Heterocycle Synthesis

The 1,3-diimines from alkyne iminoamination offer a convenient route to synthesize complex structures that would otherwise require multiple steps using alternative methods. These versatile 1,3-diimines find extensive use in the synthesis of various *N*-heterocyclic compounds. Typically, the iminoamination product is not isolated but instead used in a one-pot procedure to build *N*-heterocycles, enabling the fast and convenient synthesis of various heterocyclic cores in an one-pot reaction sequence.



Figure 1.4 Synthetic route for N-heterocycles using titanium-catalyzed iminoamination.

These 1,3-diimines, with amines as leaving groups on both ends, exhibit comparable reactivity to 1,3-dicarbonyl compounds. As a result, they are utilized as intermediates in the synthesis of various N-heterocycles. Typically, reagents utilized as the 4th component in the synthesis of N-heterocycles contain functional groups that facilitate cyclization, which connect to each end of 1,3-diimines.

1.4.1 [3 + n]-Heterocyclizations: Isoxazole, Pyrimidine, and Pyrazole Synthesis

The process of (3+n)-heterocyclizations involves utilizing 1,3-diimines as a three-carbon backbone and a fourth component as a linker to connect the 1- and 3-positions of the backbone. This results in the formation of heterocyclic products by removing two amines from the 1,3-diimine as leaving groups. With this strategy, pyrazoles, pyrimidines, and isoxazoles can be easily prepared by a one-pot titanium catalyzed iminoamination reactions (**Figure 1.6**).

Pyrazoles can be prepared by a one-pot iminoamination reaction followed by addition of hydrazine hydrate or monosubstituted hydrazines in pyridine as a solvent and base in the reaction. Although the yields from the one-pot synthesis for pyrazoles are not high, various pyrazoles are easily prepared from simple and common reagents compared to other multistep synthesis.



Figure 1.5 Synthetic routes for isoxazoles, pyrimidines, pyrroles, and pyrazoles using titaniumcatalyzed iminoamination.

In this reaction, a mixture of two regioisomers could be produced as final products if internal alkynes are used for iminoamination and monosubstituted hydrazine is used as 4^{th} component. However, the unsubstituted NH₂ group prefers to attack on the sterically less hindered carbon of the backbone so that 1,4,5-trisubstituted pyrazole is produced as the major product with good regioselectivity. For example (**Eq 1.1**), a one-pot synthesis (using aniline, 1-phenylpropyne, and *tert*-butyl isocyanide for imminoamination and phenylhydrazine as 4^{th} component) gives 1,4-diphenyl-3-methylpyrazole as a major product (9:1).¹⁵



Pyrimidines and isoxazole can be prepared in a similar manner to the pyrazole synthesis but, instead of hydrazines, amidine and hydroxylamine are used as 4th component.¹⁶ In the isoxazole synthesis, products were synthesized in a regioselective manner because the NH₂ group of hydroxylamine selectively attacks the sterically less hindered carbon of 1,3-diimines.¹⁷ Moreover, symmetric amidines do not bring any issue in regioselectivity in the pyrimidine synthesis.

1.4.2 [4 + 2]-Heterocyclizations: Pyridine and Quinoline Synthesis

The process of [4 + 2]-heterocyclizations also involves utilizing 1,3-diimines as a threecarbon backbone and a fourth component as a linker to connect the 1- and 3-positions of the backbone. However, this process only loses one amine, and the other amine becomes a part of sixmembered heterocycle product. With this strategy, various quinolines and 2-amino-3cyanopyridines can be easily synthesized by a one-pot titanium-catalyzed iminoamination reaction.



Figure 1.6 Synthesis of substituted quinolines using a one-pot titanium-catalyzed iminoamination.

In the case of quinoline synthesis, an aniline is used as a primary amine to produce 1,3diimine, and electrophilic cyclization leads to quinoline derivatives in the presence of acetic acid.¹⁸ The only byproduct from this reaction is the amine derived from isonitrile. In this reaction, anilines should have at least one *ortho*-hydrogen for cyclization. Moreover, this synthetic method is not only limited to quinolines but also other fused-ring systems including other heterocycles, such as thiophenes, pyrroles.

Another one-pot synthesis was developed for the synthesis of 2-amino-3-cyanopyridines.¹⁹ The reaction between imminoamination and malononitrile in the presence of DBU produced 1,2dihydro-2-imino-3-pyridinecarbonitrile intermediate. A Dimroth rearrangement occurs from this intermediate to synthesize 2-amino-5-cyanopyridines as the final products (**Figure 1.8**). The intermediate can be isolated using triethylamine instead of DBU as well. More than twenty examples of 2-amino-3-cyanopyridines were synthesized using this method. The exploration of NRF2 inhibitors was sparked by one of the products in this project.^{20,21} (a) Synthesis of 2-amino-3-cyanopyridines using an one-pot titanium catalyzed iminoamination



(b) Proposed Mechanism for pyridine synthesis from 1,3-diimine and malononitrile



Figure 1.7 Synthesis of 2-amino-3-cyanopyridines using a one-pot titanium-catalyzed iminoamination and proposed mechanism for pyridine synthesis from 1,3-diimines and malononitrile.

In conclusion, the utilization of titanium-catalyzed iminoamination products allowed for the synthesis of a diverse range of heterocycles in one-pot syntheses. These syntheses efficiently transform commercially accessible starting materials to various *N*-heterocyclic compounds. Now our group's research has focused on the improvement in the activity of titanium catalysts by modifying ligand properties as well as the application of *N*-heterocycles.

1.5 Titanium Catalyst Development: Asymmetric Ancillary Ligands for Titanium Catalysis

The most common approach for catalyst development involves modifying ligands to alter reactivity. Nonetheless, quantified data is necessary to make this process effective since ligand design involves multiple variables, including electronic and steric effects, which can make it challenging. To provide a better approach to investigate electronic effects of anionic ligands, the Odom group developed an experimentally-defined parameter for the electron donation of ancillary ligands towards a high oxidation state transition metal center.



Figure 1.8 Chromium system for the measurement of LDP of ligand X, and a space-filling model of the chromium complex with a pyrrole(red) for X ligand.²⁴ The blue sphere is positioned 3.5 Å away from the metal center, while the overlapped region(purple) between the blue sphere and the red area (representing pyrrole) is the volume occupied by pyrrole within the 3.5 Å sphere.

To parameterize donor effects of ligands, the Odom group synthesized chromium(VI) complexes, $NCr(N'Pr_2)_2X$, with mono-anionic ligands X^{22} In this system, the electron donation competition between the amido ligand and the X ligand influences the Cr-N'Pr₂ bond's single or double bond character. When X is a good donor ligand, the amide ligand donates less electron to the metal, and the Cr-N bond will have more single bond character. In contrast, a poor donating X ligand provides an amide ligand with more double bond character. As a result, the rotational enthalpic barrier of the Cr-N bond can be used as a parameter for the X ligand's donor ability towards the metal center.

Using Spin-Saturation Transfer (SST), the Cr-N bond rotation rate can be determined. The enthalpic barrier for rotation (Δ H[‡]) can be obtained from this rate. This value of Δ H has been referred to as the Ligand Donation Parameter (LDP), allowing direct and quantitative comparison of the electronic donor ability between various ligands towards an early transition metal. A high LDP indicates weak donor ability to the metal center by the ligand, while a low LDP suggests that

the ligand is a strong donor. In the previous study from the Odom group, donor abilities of various ligands were evaluated with this technique (**Figure 1.10**).²²



Figure 1.9 Ligand Donor Parameters (kcal/mol) for various X in NCr(NⁱPr₂)₂X.²²

To quantify the ligand steric effects, web-based software made by Cavallo and coworkers is used.²³ With crystal structure data of chromium(VI) complexes, the percentage of the coordination sphere taken up by the ligand within 3.5 angstrom radius from the metal can be measured. Considering a sphere with a radius of 3.5 Å around the metal, the software demonstrates a strong correlation with Tolman's cone angle in some cases. Using this tool, the steric effect is taken into account by using this measured volume (percent buried volume or %V_{bur}). This %V_{bur} steric effect was used with LDP in a simple model (**Eq. 1.2**).

$$k_{obs} \times 10^4 = 1.34 + 1.61(LDP) - 2.25(\% V_{bur})$$
 (Eq. 1.2)

The Odom group studied a series of catalysts with using these techniques, LDP and $%V_{bur}$.²⁴ Various titanium catalysts were synthesized with symmetric ancillary ligands, and experimental reaction rates for hydroamination with these catalysts were successfully modelled

using LDP and $%V_{bur}$. Based on the model, catalysts with electron-deficient and small ligands provide faster reaction rates than those with electron-rich and sterically bulky ligands. With this model, it is possible to predict reaction rates of catalysts with only LDP and $%V_{bur}$ values. Furthermore, the database of LDP and $%V_{bur}$ can be useful to improve other early transition metal catalysis with ancillary ligands.

Despite successfully modeling the titanium-catalyzed reaction, one limitation in improving catalysts is that all ancillary ligands were symmetric in the previous study. To investigate the ligand effects of asymmetric ancillary ligands, multiple titanium catalysts were synthesized and a new model was obtained (vide infra).

1.6 Conclusion

Titanium, an Earth abundant transition metal, is non-toxic and provides attractive reagents or catalysts, and various synthetic methods for *N*-heterocycle synthesis using titanium reagents were developed. Using these synthetic methods, various nitrogen-containing heterocyclic compounds are easily accessed. Taking advantage of properties of titanium complexes, the Odom group has been focusing on titanium-catalyzed and titanium-mediated reactions for nitrogen-containing heterocyclic compounds. During my doctoral study, I have studied titanium-mediated Diels-Alder reactions from isoxazoles and enamines, and unsymmetrical ancillary ligand effect for titanium-catalyzed hydroamination to improve titanium catalysis. Furthermore, I have worked on exploration and development of NRF2 inhibitors derived from titanium-catalyzed iminoamination reactions.

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Chapter 2. Titanium-Mediated Pyridine Syntheses from Isoxazoles via inverse electrondemand *hetero*-Diels-Alder reaction (IEDDA)

2.1 Introduction

Pyridines, six-membered heterocyclic aromatic compounds containing one nitrogen atom, attract significant attention in various fields. Pyridine scaffolds occur in many important compounds, including agrochemicals, pharmaceuticals, and vitamins (**Figure 2.1**).¹ According to the database published by Douguet and colleagues, 223 drugs have pyridine moieties among 2056 drugs approved by FDA as of July 2022.²



Figure 2.1 Examples of bioactive substituted pyridines.

Pyridines (or bipyridines) have been widely used as ligand for various catalysts due to their robust redox stability and ease of functionalization. For instance, various types of pyridine or bipyridine ligands are predominantly used in such reactions as iridium-catalyzed C-H borylation, and photocatalysis.^{4,5} Given the importance of substituted pyridines, chemists have been studying preparation of highly substituted pyridines for over a century. For example the Hantzsch synthesis was published in 1881.⁶

2.1.1 Condensation Strategy to Substituted Pyridines

(a) Condensation of 1,5-dicarbonyl



(b) Hantzsch Synthesis



Figure 2.2 Preparation of substituted pyridines using a condensation approach.

One of the most common synthetic methods for substituted pyridines is the condensation of carbonyl compounds. In the case of condensation of 1,5-dicarbonyl and Hantzsch synthesis⁶ (**Figure 2.2**), ammonia reacts with ketones or aldehydes, and generates 1,4-dihydropyridines as intermediates. These intermediates can be oxidized to generate substituted pyridines. Although these methods are widely used, limitations still exist. For example, pyridines generated from Hantzsch synthesis must have ester groups in the 3- and 5-positions on the pyridine.

2.1.2 Cycloaddition Strategy to Substituted Pyridines



Figure 2.3 Preparation of substituted pyridines using cycloaddition of 1-azadiene.⁷

Cycloaddition between 1-azadiene and an alkene or alkyne, followed by subsequent oxidation is a straightforward synthetic route to access substituted pyridines. In 1994, Menendez and coworkers published a reaction between 1-azadienes and electron-deficient dienophiles to form pyridines using ultrasound.⁷ In the case of the reaction between 1-azadiene and dienophile, 1-azadiene undergoes [4 + 2]-cycloaddition with a dienophile, and 1,4-dihydropyridine is formed. Subsequent oxidation leads to pyridines from 1,4-dihydropyridines by losing amine. Many of Diels-Alder reactions with 1-azadiene have developed. However, this pathway often requires harsh reaction conditions and is disfavored because conformational (*s*-cis $\leq s$ -trans) and tautomeric

equilibria (imine \rightleftharpoons enamine) of 1-azadienes lower the concentration of reactive species. In addition, the high electronegativity of the nitrogen in 1-azadiene lowers the reactivity of 1-azadiene in the case of "normal" electron demand Diels-Alder reactions.⁷

2.1.3 Inverse-Electron Demand Diels-Alder (IEDDA) Reactions to Substituted Pyridines

IEDDA with cyclic 1- or 2-azadienes is a rapid synthetic pathway to substituted pyridines. Isoxazole and oxazole are cyclic 1- and 2-azadienes, respectively. In 1984, Weinreb and coworkers published a paper including a IEDDA reaction between oxazole and olefin for the Kondrat'eva synthesis.⁸ In the case of the reaction with oxazole, oxazole undergoes [4 + 2]-cycloaddition, and a norbornene-like intermediate is formed. Depending on the reaction conditions, it is suggested that three distinct final products may be generated from the same intermediate. Although cycloaddition with oxazole is a less energy demanding reaction than isoxazole, this reaction might not be selective to form a single product.⁹

(a) Inverse Electron Demand Diels-Alder reaction with oxazole



(b) Inverse Electron Demand Diels-Alder reaction with Isoxazole



Figure 2.4 Preparation of substituted pyridines using IEDDA of cyclic 1- and 2-azadienes.

Another pathway to build substituted pyridines is an IEDDA reaction with isoxazole. This reaction was first reported by Ohta and coworkers in 1989 using titanium tetrachloride (TiCl₄) and zinc as reductant.¹⁰ In this work, it is proposed that isoxazole undergoes [4 + 2]-cycloaddition to form the [2.2.1]-oxazabicyclic intermediate, and then amine loss and reduction from this intermediate leads to substituted pyridines. This reaction of isoxazoles with electron-rich olefins not only changes isoxazoles to pyridines with removal of the oxygen atom in isoxazole but also

adds new substituents in a regioselective manner in the pyridine core. This type of "scaffold hopping" reaction is an appealing synthetic method because the core structure of heterocycles can be switched to another core structure while leaving the substituents the same or adding complexity to it.¹⁵⁻¹⁹ For instance, one can change the core structure by adding or deleting a nitrogen atom to convert cyclic compounds to other cyclic compounds.²⁰⁻²² These "scaffold hopping" reactions enable rapid exploration of structural relationships to biological activity.¹⁷

The Odom group has been exploring a novel class NRF2 (Nuclear factor-erythroid factor 2-related factor 2) inhibitors with 2-amino-3-cyanopyridines.^{23,24} This synthetic approach could be highly efficient to generate diverse pyridine compounds that function as NRF2 inhibitors, particularly when combined with our group's established synthetic method for 3,4-disubstituted isoxazoles.^{25,26}

The previous work showed that IEDDA reaction between isoxazoles and enamines has an excellent regioselectivity so that substituents at all positions of pyridines can be utilized.^{10,11} However, this method still has limitations such as air-sensitive reagents and poor yields, and the substrate scope was limited to isoxazoles with simple alkyl groups. Therefore, I have re-visited this chemistry to reoptimize the reaction conditions and to develop a more reliable method using bench-stable reagents with an easier reaction setup.¹² In addition, we put effort to understand the mechanism of the reaction using Density Function Theory (DFT), the effects of solvents on the reaction using the Solvent Model based on the SMD method, and the role of TiCl₄ as a possible Lewis acid in the reaction.

2.2 Experimental Results and Discussion

The previous work by Ohta and coworkers proposed that pyridine-N-oxide is a possible intermediate and can be reduced to form pyridines in the presence of TiCl₄ and zinc dust,¹⁰ however, TiCl₄ is known to be highly corrosive and reactive. It readily undergoes rapid hydrolysis through a vigorous exothermic reaction. Instead of reactive TiCl₄, commercially available and more bench stable TiCl₄(THF)₂ was used for optimization of this reaction. In addition, various reductants were employed in the optimization process, apart from zinc dust.

Table 2.1 Optimization of pyridine synthesis using TiCl₄(THF)₂ and reductants.¹²

		$\frac{\text{TiCl}_4(\text{THF})_2 (\text{y equiv})}{\text{Ti powder (z equiv)}}$	$\hat{\mathbf{D}}$	
	1a 2a x equiv		3a	
Entry	x / y / z	Reductant	GC % Yield	
1	4 / 1 / 1	Ti powder	80	
2	3 / 1 / 1	Ti powder	69	
3	2 / 1 / 1	Ti powder	58	
4	4 / 2 / 1	Ti powder	69	
5	4 / 1 / 2	Ti powder	68	
6	2 / 1 / 1	Zn dust	61	
7	2 / 1 / 1	Al pellets	45	
8	2 / 1 / 2.2	Mg turning	38	
9	4 / 1 / 1	Sn powder	65ª	
10	4 / 2 / 1.5	Rieke Zn	53ª	
11	4 / 2 / 1.2	Ti powder	53ª	
12	4 / 2 / 1.2	Zn dust	46ª	

^aTHF was used in place of dioxane as solvent.

For the optimization reaction, isoxazole and 1-pyrrolidino-1-cyclohexene were used. In this reaction, 1 equivalent of TiCl₄(THF)₂, 1 equivalent of titanium powder, and 4 equivalent of enamine in dioxane gave the highest yield (**Table 2.1, Entry 1**). With these conditions, various isoxazoles and enamines were investigated. To see the substrate scope of isoxazoles, a large series of isoxazoles were reacted with 1-pyrrolidino-1-cyclohexene (**Scheme 2.1**). These reactions gave good yields in general. Many common functional groups in the 3- and 4-positions of the isoxazoles are tolerated in this reaction, such as alkyls, aryls, acylamines, and halides. Furthermore, 3,4-dimethyl-1,2,5-oxadiazole (dimethylfurazane) was also employed for this reaction to produce 2,3-dimethylpyrazine.



Scheme 2.1 Pyridine synthesis with 1-pyrrolidino-1-cyclohexene. Isolated yields are reported.

Unfortunately, the yield is significantly reduced when isoxazoles have substituents in the 5-position(\mathbb{R}^3) or large substituents in the 4-position(\mathbb{R}^2). In this reaction, enamine attacks into 5-position of isoxazole and undergoes [4 + 2]-cycloaddition; therefore, it is assumed that steric protection from the 5-position or a bulky group in the 4-position of isoxazole leads to reduced yield. Only a trace amount of product was formed from the reaction with an ester group in either the 3- or 5-position of isoxazole, and no product from 3,5-dimethylisoxazole was observed by GC-MS. In previous reports, the IEDDA of isoxazoles showed excellent regioselectivity with a single product formed.^{10,11} In order to study the regioselectivity as well as substrate scope of enamines in the reaction, a few monoaryl enamines were investigated, such 2-phenyl-1-(1-pyrrolidinyl)ethene (**2b**) and 2-methyl-1-phenyl-1-(1-pyrrolidinyl) (**2b**) (Scheme 2.2). Reactions with these enamines produced products selectively with excellent regioselectivity.



Scheme 2.2 Pyridine synthesis with monoaryl enamines. Isolated yields are reported.

These monoaryl enamine reactions include 1-phenyl-1-(1-pyrrolidinyl)ethene (2c) as well. Considering steric effects from substituents in the 2-position of enamine, 1-phenyl-1-(1pyrrolidinyl)ethene (2c) was expected to be more reactive than 2-phenyl-1-(1-pyrrolidinyl)ethene (2b); however, 1-phenyl-1-(1-pyrrolidinyl)ethene (2c) did not give any pyridine products. Similarly, reaction between 4-bromoisoxazole and 1-methyl-1-(1-pyrroldinyl)ethene generates 3bromo-5-methylpyridine in 50% GC yield. However, the reaction between 4-bromoisoxazole and 2-methyl-1-(1-pyrroldinyl)ethene did not give the corresponding pyridine. (Scheme 2.6 in Experimental Details). This result aligns with the findings from Mayr and colleagues regarding the nucleophilicity of enamines in relation to their substitution patterns in 2003.¹³ These results suggested that internal alkenes (e.g. 2-phenyl-1-(1-pyrrolidinyl)ethene) have higher nucleophilicity than terminal alkenes (e.g. 1-(1-pyrrolidinyl)ethene) Enamines with higher nucleophilicity are more reactive for this reaction.



Figure 2.5 (a) Reactions between isoxazole¹² (**a**) and monoaryl enamines (**2b**, **2c**, and **2d**). (**b**) Relative reactivity between internal and terminal alkenes (1-phenyl-1-(1-piperidinyl)ethene vs. 2-phenyl-1-(1-piperidinyl)ethene).¹³

Moreover, pyrrolidine-based enamines provide higher nucleophilicity than piperidine- and morpholine-based enamines. These results are consistent with our findings for this reaction. In addition, in 2013, Houk and coworkers published a computational study on the mechanism of 1,3-dipolar cycloaddition of phenyl azides with enamines, showing that the energy barrier with internal alkene is slightly lower than terminal alkene.¹⁴



Scheme 2.3 Pyridine synthesis with diaryl enamines. Isolated yields are reported.

A couple of diaryl enamines were investigated as well. Reactions with 1-(1,2diphenylvinyl)pyrrolidine and 1-(1,2-di-*p*-tolylvinyl)pyrrolidine gave excellent yields (**Scheme 2.3**). Using this method, multi-arylated pyridines were synthesized with excellent regioselectivity.

Lastly, the mechanism of the reaction was also experimentally investigated. In 1992, Nesi and coworkers reported [4 + 2]-cycloaddition of 4-nitro-3-phenylisoxazole-5-carboxylates with enamines, and it is shown that pyridine-*N*-oxide was isolated as an intermediate and then reduced to generate pyridines.¹¹ In our reaction conditions, pyridine-*N*-oxides were not observed by any means; therefore, it was hypothesized that tetrahydroquinoline-*N*-oxide, the intermediate of the reaction, was produced for reduction. Therefore, ethereal solvents that are likely to act as a radical donor was removed from the reaction to prevent radical reaction. TiCl₄ and benzene were used in place of TiCl₄(THF)₂ and dioxane, respectively. However, 5,6,7,8-tetrahydroquinoline (**3a**) was only observed by GCMS and GCFID (**Scheme 2.4, Eq. 2.1**). Another possible assumption is that enamine acts as reductant. Therefore, an excess of isoxazole was employed in case some enamine is used in side reactions (**Scheme 2.4, Eq. 2.2**). However, pyridine-*N*-oxide intermediate were never observed.



Scheme 2.4 The reaction of isoxazole and 1-(1-cyclohexenyl)pyrrolidine with TiCl₄ in benzene.2.3 Computational Results and Discussion

The investigation of the reaction mechanism was not only conducted using experimental methods but also computational methods. Density Functional Theory, B3LYPD3 with aug-cc-pVDZ, was employed to study the mechanism. The investigation was initiated by gas phase calculations and using the Solvent Model based on Density (SMD) method to study the effects of

solvents on the reaction was modelled for the experimental solvent, 1,4-dioxane. In addition, the effect of Lewis acids on the reaction were investigated using TiCl₄.



Scheme 2.5 The IEDDA (inverse-electron demand hetero-Diels Alder) reaction of isoxazole with enamine produces substituted pyridines after *in situ* reduction in the presence of reductant.¹² Depending on whether ring-opening or amine loss occurs first, the reaction mechanism can be divided into two main pathways after cycloaddition.

2.3.1 Cycloaddition

Despite the proposal of two potential pathways, pathways A and B share a [4 + 2]-cycloaddition step. Hence, the investigation was initiated with the cycloaddition. The cycloaddition step gives us four possible isomers: endo and exo of **I1** and **I1***. However, the energy difference between endo and exo was typically within ~3 kcal/mol, hence only endo isomers (all intermediates and transition states) will be shown to simplify the figures and discussion.

In the calculations modelling 1,4-dioxane solution, the cycloaddition between isoxazole and enamine followed a concerted mechanism to form a [2.2.1]-oxazabicyclic intermediate. The activation energy for the formation of I1 is 14 kcal/mol lower than I1* (Figure 2.3), and this is consistent with the experimental data. In the case of TS1, nucleophilic attack of the β -carbon of the enamine builds up negative charge stabilized by electronegative nitrogen. However, the negative charge is developed on the carbon in TS1*, and cannot be as stabilized. Therefore, the final product derived from I1 is the only one observed experimentally.



Reaction Coordinate

Figure 2.6 Free energy profile for cycloaddition between isoxazole and enamine in 1,4-dioxane with (blue) and without TiCl₄ (black).¹² [M] = TiCl₄. The dotted line represents the pathway of cycloaddition leading to the regioisomer that is not experimentally observed.

Although the cycloaddition step occurs via a more or less concerted mechanism, the transition states were asynchronous, and the symmetry of the transition states are changed when incorporating solvent models into the calculations (vide infra). (The transition states for the cycloaddition step are "synchronous" when two equal bonds are being made between isoxazole and enamine, and "asynchronous" when different amounts of bond making occurs in the two new bonds between isoxazole and enamine.) To quantify the trend in the symmetry of the transition state (TS), we used bond length ratios τ (**Eq 2.3**). The ratio τ can serve as a means of distinguishing the symmetry character of the transition state. Subjectively, when $\tau \leq 0.7$, the transition state looks asynchronous, and, when $\tau > 0.7$, the transition state looks synchronous. Based on the calculations, the τ values are lower and the transition states become slightly less synchronous when the dielectric constant of solvent is higher in the case of TS1-endo. However, the τ values of TS1*-endo remains

relatively consistent across different solvents. The τ values and energy barriers for other pathways are available in the Computation Details.



	Gas Phase	Heptane	1,4- Dioxane	THF	DCM	Ethanol	H ₂ O
k	0	1.92	2.21	7.52	8.93	24.6	78.5
TS1-endo	0.693	0.678	0.676	0.682	0.684	0.692	0.695
TS1*-endo	0.909	0.896	0.893	0.882	0.878	0.885	0.845

Figure 2.7 The τ value for cycloaddition in different solvents with their dielectric constant (k).

Lastly, the effect of Lewis acid was investigated by including TiCl₄ in the calculations. The reaction of the enamine with the isoxazole was found to occur in a stepwise fashion (C–C bond formation followed by C–N bond formation) in the presence of TiCl₄ (**Figure 2.3**). Moreover, the activation energy for this stepwise mechanism is ~24 kcal/mol lower when TiCl₄ is included. The cycloaddition product is also substantially stabilized by TiCl₄ and is ~14 kcal/mol lower in free energy.

2.3.2 Two pathway: Ring opening and Amine loss

Two possible pathways from the [2.2.1]-oxazabicyclic intermediate (I1 or I1_M) were investigated (Reaction pathways from I1* are not considered any longer after cycloaddition.) Pathway A is initial amine loss followed by ring opening, and Pathway B is ring opening followed by amine loss. Energy diagram for Pathway A and B are shown in Figure 2.5 and Figure 2.6, respectively.



Reaction Coordinate

Figure 2.8 Free energy profile for pathway A in 1,4-dioxane with (blue) and without TiCl₄ (black). [M] = TiCl₄. The transition states and intermediate are marked with α in pathway A.¹²

The first step of Pathway A was found to be very high energy. The amine loss step and the ring opening step require ~60 kcal/mol and ~33 kcal/mol as activation energy, respectively. In fact, the transition state for amine loss was stabilized by ~19 kcal/mol in the presence of TiCl₄. However, the Lewis acid effect is insignificant for the amine loss step. In addition, the ring opening step was endergonic, and the intermediate is 27 kcal/mol higher in energy than the cycloaddition product. Consequently, Pathway A cannot be considered as a reasonable reaction mechanism due to its energetically demanding transition states and intermediate.

In contrast, Pathway B is found to be more reasonable. Ring opening barriers (35.9 and 27.3 kcal/mol with and without TiCl₄) are close to the ones in Pathway A. In addition, when

pyrrolidine is employed instead of NH₂ in the calculations, the ring opening barrier dropped to ~20 kcal/mol in the presence of TiCl₄ in Pathway B. The amine loss barrier without TiCl₄ is ~27 kcal/mol and is far more reasonable than amine loss in Pathway A (63.8 and 62.0 kcal/mol without and with TiCl₄). Amine loss may be easier because of aromatization of the pyridine once the ring is open. Unfortunately, the transition state for amine loss after ring opening in the presence of TiCl₄ (TS2_M_ β) was not located. However, the energy difference between the intermediates with and without the metal are only ~13 kcal/mol. Therefore, it is also reasonable to consider that amine loss could occur after decoordination of TiCl₄.



Figure 2.9 Free energy profile for pathway B in 1,4-dioxane with (blue) and without TiCl₄ (black). [M] = TiCl₄. The cycloaddition product and intermediate are marked with β in pathway B.¹²

The calculations suggest that the reaction mechanism can be changed and has lower energy barriers due to the Lewis acidic effect of TiCl₄. Especially, the energy barriers for cycloaddition dropped significantly with the stepwise mechanism with TiCl₄. Based on the calculations, a reasonable pathway after cycloaddition is ring opening followed by amine loss.

2.4 Conclusions

By re-visiting the inverse-electron demand hetero-Diels–Alder reaction between isoxazoles and enamines, the reaction was successfully re-optimized with $TiCl_4(THF)_2$ and titanium powder in 1,4-dioxane to give a single observable regioisomer for the product with good
to excellent yields. The reaction tolerates many common functional groups, but requires isoxazoles without substitution in the 5-position. In this reaction, the nucleophilicity of enamine plays a crucial role, and more nucleophilic enamines give much better reactivity.

The mechanism was investigated using DFT (B3LYPD3, aug-cc-PVDZ, SMD-1,4dioxane). The mechanistic study showed that cycloaddition between isoxazole and enamine has a stepwise mechanism with energetically accessible barriers in the presence of TiCl₄ (~18 kcal/mol). In contrast, cycloaddition between isoxazole and enamine has an energy demanding concerted mechanism without TiCl₄ (~40 kcal/mol). In addition, the reasonable reaction pathway after cycloaddition is ring-opening followed by amine loss. Unfortunately, it is difficult to find the moment of reduction in the reaction. The absence of any observation of pyridine-N-oxide could imply two potential explanations. First, the reduction of pyridine-*N*-oxide may be faster than its production. Second, the intermediate imine-N-oxide (**I2_M_β, Figure 2.6**) could be reduced before amine loss, resulting in the absence of pyridine-N-oxide.



Scheme 2.6 The reaction mechanism based on DFT results.

Overall, the inverse-electron demand hetero-Diels–Alder reaction between isoxazoles and enamine is a fascinating reaction to produce substituted pyridines, with additional substitution possibly being added in the process. The reaction is highly regioselective and tolerates many common functional groups. In addition, the reaction mechanism was elucidated, except for the reduction, using DFT calculations.

2.5 Experimental Details

General Considerations

Syntheses and handling of materials were carried out under an inert nitrogen atmosphere, either in a MBraun glovebox or by standard Schlenk techniques, except as noted and for column chromatography and preparation of GC samples. The ¹H and ¹³C{¹H} NMR spectra were recorded on Agilent DDR2 500 MHz NMR spectrometer equipped with a 5 mm PFG OneProbe operating at 499.84 MHz (¹H) and 125.73 MHz (¹³C), respectively. The chemical shifts (δ) for ¹H and ¹³C NMR spectra are given in ppm relative to residual protio signals of the solvent (CDCl₃: $\delta_{\rm H} = 7.26$ ppm ¹H NMR, $\delta_{\rm C} = 77.16$ ppm ¹³C NMR and C₆D₆: $\delta_{\rm H} = 7.16$ ppm ¹H NMR, $\delta_{\rm C} = 128.06$ ppm ¹³C NMR). GCMS data was collected on an Agilent 5973 MSD with a 6890N series GC. GCFID data were collected on a Hewlett Packard 6890 series GC system and standardized against dodecane as an internal standard. 5,6,7,8-Tetrahydroquinoline was used for reaction optimization, and the yield was quantified in situ utilizing GCFID standardized calibration curves. Pyrrolidine, cyclohexanone, and TiCl₄ were purchased from Acros Organics and used as received. 5,6,7,8-Tetrahydroquinoline, isoxazole (**1a**). 3-aminoisoxazole, 4-bromoisoxazole (1c), 3methylisoxazole (1e), 3-bromo-5-methylpyridine (3u), 3-bromo-6-methylpyridine (3v) were purchased from Fisher Scientific and used as received. Zinc and titanium powder were purchased and stored under N2 from Alfa Aesar and used as received. All materials were purchased commercially, dried prior to use, and stored under N₂. 1,4-Dioxane was dried over Na/benzophenone and distilled under N2. CDCl3 and C6D6 were purchased commercially and dried over P₂O₅ and CaH₂, respectively, and distilled under N₂. All the glassware was dried in the oven at 140 °C overnight before use. TiCl₄(THF)₂,²⁷ 4-(p-tolyl)-isoxazole (1b),²⁸ 3-(Nacetylamino)isoxazole (1d),²⁹ other isoxazoles (1f and 1g),³⁰ enamines (2a-c, 2g, 2f),³¹ and diarylenamines $(2d, 2e)^{32}$ were prepared according to the literature procedures.

Procedure for GC-FID calibration (n-dodecane vs substituted pyridines)

Pyridine solution (0.4 M) in dioxane and n-dodecane solution (1.6 M) in dioxane were prepared in two 5 mL volumetric flasks separately (0.266 g of 5,6,7,8-tetrahydroquinoline (**3a**), 0.3441 g for 3-bromo-5-methylpyridine (**3u**), 0.3441 g of 3-bromo-6-methylpyridine (**3v**), and 1.36 g of dodecane). Then, 0.2, 0.4, 0.6, 0.8 mL of the pyridine solution was transferred into 4 different GC vials, and 0.2 mL of the n-dodecane solution was transferred to each vial. The solution in every vial was diluted to 1 mL with dioxane. All samples were analyzed by GC-FID. Ethyl acetate and

DCM were used as wash solvents to prevent any contamination between samples. The integrations of peaks were calculated and inserted into the equation to plot the graph.



Figure 2.10 GC-FID calibration curve: n-dodecane vs. 5,6,7,8-tetrahydroquinoline.



Figure 2.11 GC-FID calibration curve: n-dodecane vs. 3-bromo-5-methylpyridine.



Figure 2.12 GC-FID calibration curve: n-dodecane vs. 3-bromo-6-methylpyridine.



Reactions of 4-bromoisoxazoles with terminal and intermal enamines

Scheme 2.7 Reactions of 4-bromoisoxazoles (2c) with enamines 2g and 2h.

A 15 mL pressure tube was charged with $TiCl_4(THF)_2$ (0.334 g, 1 mmol, 1 equiv), titanium powder (0.056 g, 1.0 mmol, 1.0 equiv), and dioxane (0.5 mL). The solution was stirred for 1 h over which solids form, and then 1 mL dioxane was added to the solution and stirring was continued for an additional 1 h. In 15 mL pressure tube, 4-bromoisoxazole (1c, 0.069 g, 1 mmol), dodecane (0.170 g), and corresponding enamine (2g or 2h, 0.45 g, 4 mmol, 4 equiv) were added to the solution in dioxane (1 mL). The pressure tube was sealed and transferred from the glovebox to a preheated 100 °C aluminum block. The reaction was heated with stirring for 12 h. After heating, the pressure tube was cooled to room temperature for 10 min. 0.3~0.35 mL) of reaction mixture was taken into a GC vial and diluted to 1 mL. Yield was calculated based on the GC-FID calibration curves above. The diluted reaction mixtures were analyzed by GCMS and GCFID.

The top reaction between 4-bromoisoxazole (1c) and 1-methyl-1-(1-pyrroldinyl)ethene (2g) results in 50% GC yield of 3-bromo-5-methylpyridine (3u). However, the bottom reaction between 4-bromoisoxazole (1c) and 2-methyl-1-(1-pyrroldinyl)ethene (2h) did not give the corresponding pyridine (3v). As we mentioned in the paper, terminal enamines are less reactive and less nucleophilic.

Reactions of isoxazole with 1-(1-cyclohexenyl)pyrrolidine in benzene



Scheme 2.8 The reaction of isoxazole with 1-(1-cyclohexenyl)pyrrolidine in benzene.

A 15 mL pressure tube was charged with TiCl₄ (0.190 g, 1 mmol, 1 equiv) and benzene (1.5 mL). To the reaction mixture, isoxazole (**1a**, 0.069 g, 1 mmol), dodecane (0.170 g), and 1-(1-cyclohexenyl)pyrrolidine (**2a**, 0.605 g, 4 mmol, 4 equiv) in benzene (1 mL) were added. The pressure tube was sealed and transferred from the glovebox to a preheated 100 °C aluminum block. The reaction was heated with stirring for 12 h. After heating, the pressure tube was cooled to room temperature for 10 min. $0.3\sim0.35$ mL) of reaction mixture was taken into a GC vial and diluted to 1 mL. Yield was calculated based on the GC-FID calibration curves above.

Reactions of isoxazole with 1-(1-cyclohexenyl)pyrrolidine in benzene



Scheme 2.9 The reaction of isoxazole with 1-(1-cyclohexenyl)pyrrolidine in benzene.

A 15 mL pressure tube was charged with TiCl₄ (0.190 g, 1 mmol, 1 equiv) and benzene (1.5 mL). To the reaction mixture, isoxazole (**1a**, 0.276 g, 4 mmol), dodecane (0.170 g), and 1-(1-

cyclohexenyl)pyrrolidine (**2a**, 0.151 g, 1 mmol, 0.25 equiv) in benzene (1 mL) were added. The pressure tube was sealed and transferred from the glovebox to a preheated 100 °C aluminum block. The reaction was heated with stirring for 12 h. After heating, the pressure tube was cooled to room temperature for 10 min. $0.3\sim0.35$ mL) of reaction mixture was taken into a GC vial and diluted to 1 mL. The sample was analyzed by GCMS.

Synthesis of Pyridine Derivatives

Synthesis of 5,6,7,8-tetrahydroquinoline

A 15 mL pressure tube was charged with TiCl₄(THF)₂ (0.334 g, 1 mmol, 1 equiv), titanium powder (0.056 g, 1.0 mmol, 1.0 equiv), and dioxane (0.5 mL). The solution was stirred for 1 h over which solids form, and then 1 mL dioxane was added to the solution and stirring was continued for an additional 1 h. Isoxazole (1a, 0.069 g, 1 mmol) and 1-(1-cyclohexenyl)pyrrolidine (2a, 0.605 g, 4 mmol, 4 equiv) were added to the solution in dioxane (1 mL). The pressure tube was sealed and transferred from the glovebox to a preheated 100 °C aluminum block. The reaction was heated with stirring for 12 h. After heating, the pressure tube was cooled to room temperature for 10 min. Then, 2 mL of 20% aqueous K₂CO₃ was added, and the mixture was stirred for 5 min. After stirring, solids were removed by vacuum filtration and were washed with CH₂Cl₂ (~10 mL). The filtrate was dried with Na₂SO₄ and filtered through a piece of cotton. The solvent was removed under reduced pressure. The product was purified by silica gel auto-column chromatography, eluted with hexane to get a colorless oil (101 mg, 76%). ¹H NMR (CDCl₃, 500 MHz): δ 8.34 (d, J = 4.0 Hz, 1H), 7.33 (d, J = 3.0 Hz, 1H), 7.01 (dd, J = 4.0 Hz, 3.0 Hz, 1H), 2.92 (t, J = 6.5 Hz, 2H), 2.76 (t, J = 6.5 Hz, 2H), 1.94-1.85 (m, 2H), 1.84-1.75 (m, 2H). ${}^{13}C{}^{1}H{}$ NMR (CDCl₃, 126 MHz): δ 157.496, 146.886, 136.878, 132.392, 120.981, 32.622, 28.880, 23.187, 22.797. MS (EI): m/z 133 (M^+) . The ¹H and ¹³C{¹H} NMR spectroscopy of the compound matches that in the literature.³³ Synthesis of 3-(4-tolyl)-5,6,7,8-tetrahydroquinoline



A 15 mL pressure tube was charged with $TiCl_4(THF)_2$ (0.334 g, 1 mmol, 1 equiv), titanium powder (0.056 g, 1.0 mmol, 1.0 equiv), and dioxane (0.5 mL). The solution was stirred for 1 h over which

solids form, and then 1 mL dioxane was added to the solution and stirring was continued for an additional 1 h. 4-Tolylisoxazole (**1b**, 0.160 g, 1 mmol) and 1-(1-cyclohexenyl)pyrrolidine (**2a**, 0.605 g, 4 mmol, 4 equiv) were added to the solution in dioxane (1 mL). The pressure tube was sealed and transferred from the glovebox to a preheated 100 °C aluminum block. The reaction was heated with stirring for 12 h. After heating, the pressure tube was cooled to room temperature over 10 min. Then, 2 mL of 20% aqueous K₂CO₃ was added, and the mixture was stirred for 5 min. After stirring, solids were removed by vacuum filtration and were washed with CH₂Cl₂ (~10 mL). The filtrate was dried with Na₂SO₄ and filtered through a piece of cotton. The solvent was removed under reduced pressure. The product was purified by a silica gel auto-column chromatography, eluted with hexane and ethyl acetate (8:2) to get a colorless solid (92 mg, 41%). Mp = 58-60 °C. ¹H NMR (CDCl₃, 500 MHz): δ 8.57 (s, 1H), 7.53 (s, 1H), 7.46 (d, J = 8.5 Hz, 2H), 7.26 (d, J = 8.5 Hz, 2H), 2.96 (t, J = 6.0 Hz, 4H), 2.83 (t, J = 6.0 Hz, 4H), 2.40 (s, 3H), 1.96-1.91 (m, 4H), 1.90-1.82 (m, 4H). ¹³C{¹H} NMR (CDCl₃, 126 MHz): δ 156.077, 145.154, 137.682, 135.308, 135.128, 134.024, 132.206, 129.820, 126.935, 32.307, 29.006, 23.278, 22.880, 21.282. MS (EI): m/z 223 (M⁺).

Synthesis of 3-bromo-5,6,7,8-tetrahydroquinoline



A 15 mL pressure tube was charged with TiCl₄(THF)₂ (0.334 g, 1 mmol, 1 equiv), titanium powder (0.056 g, 1.0 mmol, 1.0 equiv), and dioxane (0.5 mL). The solution was stirred for 1 h over which solids form, and then 1 mL dioxane was added to the solution and stirring was continued for an additional 1 h. 4-Bromoisoxazole (**1c**, 0.148 g, 1 mmol) and 1-(1-cyclohexenyl) pyrrolidine (0.605 g, 4 mmol, 4 equiv) were added to the solution in dioxane (1 mL). The pressure tube was sealed and transferred from the glovebox to a preheated 100 °C aluminum block. The reaction was heated with stirring for 12 h. After heating, the pressure tube was cooled to room temperature over 10 min. Then, 2 mL of 20% aqueous K₂CO₃ was added, and the mixture was stirred for 5 min. After stirring, solids were removed by vacuum filtration and were washed with CH₂Cl₂ (~10 mL). The filtrate was dried with Na₂SO₄ and filtered through a piece of cotton. The solvent was removed under reduced pressure. The product was purified by a silica gel auto-column chromatography, eluted with hexane and ethyl acetate (9:1) to get a colorless oil (150 mg, 70%). ¹H NMR (CDCl₃, 500 MHz): δ 8.39 (s, 1H), 7.49 (s, 1H), 2.85 (t, J = 6.5 Hz, 4H), 2.75 (t, J = 6.5 Hz, 4H), 1.92-1.82

(m, 4H), 1.81-1.73 (m, 4H). ${}^{13}C{}^{1}H$ NMR (CDCl₃, 126 MHz): δ 156.097, 147.707, 139.047, 134.312, 117.332, 32.103, 28.753, 22.920, 22.388. MS (EI): m/z 211 (M⁺). The ¹H and ¹³C{}^{1}H NMR spectroscopy of the compound matches that in the literature.³⁴

Synthesis of 2-(N-acetoamino)-5,6,7,8-tetrahydroquinoline

$$\operatorname{All}_{H}^{\circ}$$

A 15 mL pressure tube was charged with TiCl₄(THF)₂ (0.334 g, 1 mmol, 1 equiv), titanium powder (0.056 g, 1.0 mmol, 1.0 equiv), and dioxane (0.5 mL). The solution was stirred for 1 h over which solids form, and then 1 mL dioxane was added to the solution and stirring was continued for an additional 1 h. 3-(N-acetoamino)isoxazole (1d, 0.126 g, 1 mmol) and 1-(1cyclohexenyl)pyrrolidine (2a, 0.605 g, 4 mmol, 4 equiv) were added to the solution in dioxane (1 mL). The pressure tube was sealed and transferred from the glovebox to a preheated 100 °C aluminum block. The reaction was heated with stirring for 12 h. After heating, the pressure tube was cooled to room temperature over 10 min. Then, 2 mL of 20% aqueous K₂CO₃ was added, and the mixture was stirred for 5 min. After stirring, solids were removed by vacuum filtration and were washed with CH₂Cl₂ (~10 mL). The filtrate was dried with Na₂SO₄ and filtered through a piece of cotton. The solvent was removed under reduced pressure. The product was purified by a silica gel auto-column chromatography, eluted with hexane and ethyl acetate (6:4) to get an amber solid (40 mg, 21%). m.p. = 127-129 °C. ¹H NMR (DMSO, 500 MHz): δ 10.35 (s, 1H), δ 7.80 (d, J = 8.5 Hz, 1H), 7.7.41 (d, J = 8.5 Hz, 1H), 2.71 (t, J = 6.5 Hz, 4H), 2.66 (t, J = 6.5 Hz, 4H), 2.04 (s, 3H), 1.84-1.75 (m, 4H), 1.75-1.66 (m, 4H). ${}^{13}C{}^{1}H{}$ NMR (DMSO, 126 MHz): δ 154.603, 149.499, 138.633, 126.907, 110.851, 31.509, 27.380, 23.810, 22.590, 22.371. MS (EI): m/z 190 $(M^{+}).$

Synthesis of 2-methyl-5,6,7,8-tetrahydroquinoline

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A 15 mL pressure tube was charged with $TiCl_4(THF)_2$ (0.334 g, 1 mmol, 1 equiv), titanium powder (0.056 g, 1.0 mmol, 1.0 equiv), and dioxane (0.5 mL). The solution was stirred for 1 h over which solids form, and then 1 mL dioxane was added to the solution and stirring was continued for an additional 1 h. 3-Methylisoxazole (1e, 0.083 g, 1 mmol) and 1-(1-cyclohexenyl)pyrrolidine (2a, 0.605 g, 4 mmol, 4 equiv) were added to the solution in dioxane (1 mL). The pressure tube was sealed and transferred from the glovebox to a preheated 100 °C aluminum block. The reaction was heated with stirring for 12 h. After heating, the pressure tube was cooled to room temperature over 10 min. Then, 2 mL of 20% aqueous K₂CO₃ was added, and the mixture was stirred for 5 min. After stirring, solids were removed by vacuum filtration and were washed with CH₂Cl₂ (~10 mL). The filtrate was dried with Na₂SO₄ and filtered through a piece of cotton. The solvent was removed under reduced pressure. The product was purified by a silica gel auto-column chromatography, eluted with hexane to get a yellow oil (108 mg, 73%). ¹H NMR (CDCl₃, 500 MHz): δ 7.23 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 2.87 (t, J = 6.5 Hz, 4H), 2.71 (t, J = 6.5 Hz, 4H), 2.48 (s, 3H), 1.91-1.84 (m, 4H), 1.82-1.74 (m, 4H). ¹³C {¹H} NMR (CDCl₃, 126 MHz): δ 156.548, 155.159, 137.592, 129.057, 120.575, 32.690, 28.516, 24.292, 23.332, 22.933. MS (EI): m/z 147 (M⁺). The ¹H and ¹³C {¹H} NMR spectroscopy of the compound matches that in the literature.³⁵ Synthesis of *3-ethyl-2-(thiopheny-2-yl)-5,6,7,8-eterahydroquinoline*



A 15 mL pressure tube was charged with TiCl₄(THF)₂ (0.334 g, 1 mmol, 1 equiv), titanium powder (0.056 g, 1.0 mmol, 1.0 equiv), and dioxane (0.5 mL). The solution was stirred for 1 h over which solids form, and then 1 mL dioxane was added to the solution and stirring was continued for an additional 1 h. 4-Ethyl-3-(thiopheny-2-yl)-isoxazole (**1f**, 0.180 g, 1 mmol) and 1-(1-cyclohexenyl)pyrrolidine (**2a**, 0.605 g, 4 mmol, 4 equiv) were added to the solution in dioxane (1 mL). The pressure tube was sealed and transferred from the glovebox to a preheated 100 °C aluminum block. The reaction was heated with stirring for 12 h. After heating, the pressure tube was cooled to room temperature over 10 min. Then, 2 mL of 20% aqueous K₂CO₃ was added, and the mixture was stirred for 5 min. After stirring, solids were removed by vacuum filtration and were washed with CH₂Cl₂ (~10 mL). The filtrate was dried with Na₂SO₄ and filtered through a piece of cotton. The solvent was removed under reduced pressure. The product was purified by a silica gel auto-column thromatography, eluted with hexane and ethyl acetate (8:2) to get an amber oil (176 mg, 72%). ¹H NMR (CDCl₃, 500 MHz): δ 7.36 (d, J = 3.5 Hz, 1H), 7.35 (d, J = 3.5 Hz, 1H), 7.25 (s, 1H), 7.08 (dd, J = 5.0 Hz, 4.0 Hz, 1H), 2.92 (t, J = 6.5 Hz, 4H), 2.81 (q, J = 6.0 Hz, 4H), 2.77 (t, J = 6.5 Hz, 4H), 2.17 (s, 1H), 1.93-1.86 (m, 4H), 1.85-1.77 (m, 4H), 1.25 (t, 6.0 Hz).

¹³C{¹H} NMR (CDCl₃, 126 MHz): δ 154.574, 148.344, 137.987, 133.565, 131.122, 127.383, 126.582, 126.253, 32.274, 28.581, 25.890, 23.381, 22.949, 14.960. MS (EI): m/z 243 (M⁺). Synthesis of *3-methyl-2-(4-tolyl)-5,6,7,8-tetrahydroquinoline*.



A 15 mL pressure tube was charged with TiCl₄(THF)₂ (0.334 g, 1 mmol, 1 equiv), titanium powder (0.056 g, 1.0 mmol, 1.0 equiv), and dioxane (0.5 mL). The solution was stirred for 1 h over which solids form, and then 1 mL dioxane was added to the solution and stirring was continued for an additional 1 h. 4-methyl-3-(4-tolyl)-isoxazole (1g, 0.187 g, 1 mmol) and 1-(1cyclohexenyl)pyrrolidine (2a, 0.605 g, 4 mmol, 4 equiv) were added to the solution in dioxane (1 mL). The pressure tube was sealed and transferred from the glovebox to a preheated 100 °C aluminum block. The reaction was heated with stirring for 12 h. After heating, the pressure tube was cooled to room temperature over 10 min. Then, 2 mL of 20% aqueous K₂CO₃ was added, and the mixture was stirred for 5 min. After stirring, solids were removed by vacuum filtration and were washed with CH_2Cl_2 (~10 mL). The filtrate was dried with Na_2SO_4 and filtered through a piece of cotton. The solvent was removed under reduced pressure. The product was purified by a silica gel auto-column chromatography, eluted with hexane and ethyl acetate (8:2) to get an amber oil (194 mg, 82%). ¹H NMR (CDCl₃, 500 MHz): δ 7.37 (d, J = 8.0 Hz, 2H), 7.24 (s, 1H), 7.23 (d, J = 3.0 Hz, 2H), 2.93 (t, J = 7.0 Hz, 4H), 2.77 (t, J = 7.0 Hz, 4H), 2.39 (s, 3H), 2.26 (s, 3H), 1.94-1.86 (m, 4H), 1.85-1.77 (m, 4H). ¹³C{¹H} NMR (CDCl₃, 126 MHz): δ 155.970, 154.424, 139.233, 137.327, 130.520, 129.002, 128.922, 127.756, 32.389, 28.517, 23.482, 22.980, 21.400, 19.701. MS (EI): $m/z 237 (M^+)$.

Synthesis of 2,3-dimethyl-5,6,7,8-tetrahydroquinoxaline.



A 15 mL pressure tube was charged with TiCl₄(THF)₂ (0.334 g, 1 mmol, 1 equiv), titanium powder (0.056 g, 1.0 mmol, 1.0 equiv), and dioxane (0.5 mL). The solution was stirred for 1 h over which solids form, and then 1 mL dioxane was added to the solution and stirring was continued for an additional 1 h. 3,4-dimethyl-1,2,5-oxadiazole (**1h**, 0.98 g, 1 mmol) and 1-(1-cyclohexenyl)pyrrolidine (**2a**, 0.605 g, 4 mmol, 4 equiv) were added to the solution in dioxane (1 mL). The pressure tube was sealed and transferred from the glovebox to a preheated 100 °C

aluminum block. The reaction was heated with stirring for 12 h. After heating, the pressure tube was cooled to room temperature over 10 min. Then, 2 mL of 20% aqueous K₂CO₃ was added, and the mixture was stirred for 5 min. After stirring, solids were removed by vacuum filtration and were washed with CH₂Cl₂ (~10 mL). The filtrate was dried with Na₂SO₄ and filtered through a piece of cotton. The solvent was removed under reduced pressure. The product was purified by a silica gel auto-column chromatography, eluted with hexane and ethyl acetate (8:2) to get a colorless oil (31 mg, 19%). ¹H NMR (CDCl₃, 500 MHz): δ 2.61 (t, J = 6.0 Hz, 4H), 2.51 (t, J = 6.0 Hz, 4H), 2.36 (s, 3H), 1.85-1.79 (m, 4H), 1.78-1.71 (m, 4H). ¹³C{¹H} NMR (CDCl₃, 126 MHz): δ 116.106, 25.135, 23.551, 23.035, 22.940, 22.796. MS (EI): m/z 162 (M⁺).

Synthesis of *3-phenylpyridine*

A 15 mL pressure tube was charged with TiCl₄(THF)₂ (0.334 g, 1 mmol, 1 equiv), titanium powder (0.056 g, 1.0 mmol, 1.0 equiv), and dioxane (0.5 mL). The solution was stirred for 1 h over which solids form, and then 1 mL dioxane was added to the solution and stirring was continued for an additional 1 h. Isoxazole (1a, 0.069 g, 1 mmol) and 1-pyrrolidinyl-2-phenylethene (2b, 0.693 g, 4 mmol, 4 equiv) were added to the solution in dioxane (1 mL). The pressure tube was sealed and transferred from the glovebox to a preheated 100 °C aluminum block. The reaction was heated with stirring for 12 h. After heating, the pressure tube was cooled to room temperature over 10 min. Then, 2 mL of 20% aqueous K₂CO₃ was added, and the mixture was stirred for 5 min. After stirring, solids were removed by vacuum filtration and were washed with CH₂Cl₂ (~10 mL). The filtrate was dried with Na₂SO₄ and filtered through a piece of cotton. The solvent was removed under reduced pressure. The product was purified by a silica gel auto-column chromatography, eluted with hexane and ethyl acetate (9:1) to get a yellow oil (131 mg, 84%). ¹H NMR (CDCl₃, 500 MHz): δ 8.85 (s, 1H), δ 8.59 (d, J = 5.0 Hz, 1H), 7.88 (d, J = 5.0 Hz, 1H), 7.59 (d, J = 7.5 Hz, 2H), 7.49 (t, J = 7.5 Hz, 2H), 7.41 (t, J = 7.5 Hz, 2H), 7.37 (dd, J = 8.0 Hz, 4.5 Hz). ¹³C{¹H} NMR (CDCl₃, 126 MHz): δ 148.605, 148.472, 137.988, 136.769, 134.505, 129.216, 128.233, 127.292, 123.694. MS (EI): m/z 155 (M⁺). The ¹H and ¹³C{¹H} NMR spectroscopy of the compound matches that in the literature.³⁶

Synthesis of 3-bromo-5-phenylpyridine



A 15 mL pressure tube was charged with TiCl₄(THF)₂ (0.334 g, 1 mmol, 1 equiv), titanium powder (0.056 g, 1.0 mmol, 1.0 equiv), and dioxane (0.5 mL). The solution was stirred for 1 h over which solids form, and then 1 mL dioxane was added to the solution and stirring was continued for an additional 1 h. 4-Bromoisoxazole (1c, 0.148 g, 1 mmol) and 1-pyrrolidinyl-2-phenylethene (2b, 0.693 g, 4 mmol, 4 equiv) were added to the solution in dioxane (1 mL). The pressure tube was sealed and transferred from the glovebox to a preheated 100 °C aluminum block. The reaction was heated with stirring for 12 h. After heating, the pressure tube was cooled to room temperature over 10 min. Then, 2 mL of 20% aqueous K₂CO₃ was added, and the mixture was stirred for 5 min. After stirring, solids were removed by vacuum filtration and were washed with CH₂Cl₂ (~10 mL). The filtrate was dried with Na₂SO₄ and filtered through a piece of cotton. The solvent was removed under reduced pressure. The product was purified by a silica gel auto-column chromatography, eluted with hexane and ethyl acetate (9:1) to get white solid (133 mg, 86%). m.p. = 47-49 °C, 1 H NMR (CDCl₃, 500 MHz): δ 8.76 (s, 1H), 8.66 (s, 1H), 8.03 (s, 1H), 7.57 (d, J = 7.0 Hz, 2H), 7.50 (t, J = 7.5 Hz, 2H), 7.44 (t, J = 7.5 Hz, 1H). ¹³C{¹H} NMR (CDCl₃, 126 MHz): δ 148.001, 145.823, 140.878, 139.599, 138.077, 129.015, 128.962, 128.434, 119.083. MS (EI): m/z 211 (M⁺). The ¹H and ${}^{13}C{}^{1}H$ NMR spectroscopy of the compound matches that in the literature³⁷

Synthesis of 3-(4-tolyl)-5-phenylpyridine



A 15 mL pressure tube was charged with TiCl₄(THF)₂ (0.334 g, 1 mmol, 1 equiv), titanium powder (0.056 g, 1.0 mmol, 1.0 equiv), and dioxane (0.5 mL). The solution was stirred for 1 h over which solids form, and then 1 mL dioxane was added to the solution and stirring was continued for an additional 1 h. 4-Tolyl)isoxazole (**1b**, 0.159 g, 1 mmol) and 1-pyrrolidinyl-2-phenylethene (**2b**, 0.693 g, 4 mmol, 4 equiv) were added to the solution in dioxane (1 mL). The pressure tube was sealed and transferred from the glovebox to a preheated 100 °C aluminum block. The reaction was heated with stirring for 12 h. After heating, the pressure tube was cooled to room temperature over 10 min. Then, 2 mL of 20% aqueous K₂CO₃ was added, and the mixture was stirred for 5 min.

After stirring, solids were removed by vacuum filtration and were washed with CH_2Cl_2 (~10 mL). The filtrate was dried with Na_2SO_4 and filtered through a piece of cotton. The solvent was removed under reduced pressure. The product was purified by a silica gel auto-column chromatography, eluted with hexane and ethyl acetate (9:1) to get white solid (197 mg, 80%). m.p. = 128-130 °C. ¹H NMR (CDCl₃, 500 MHz): δ 8.81 (d, 2.0 Hz, 1H), 8.80 (d, 2.0 Hz, 1H), 8.07 (s, 1H), 7.65 (d, J = 7.0 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H), 7.51 (t, 8.0 Hz, 2H), 7.46 (t, J = 8.0 Hz, 1H), 7.32 (d, J = 7.0 Hz, 2H), 2.43 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 126 MHz): δ 145.154, 137.682, 135.308, 135.128, 134.024, 132.206, 129.820, 126.935, 32.307, 29.006, 22.278, 22.879, 21.282. MS (EI): m/z 245 (M⁺).

Synthesis of 3-methyl-2-phenylpyridine



A 15 mL pressure tube was charged with TiCl₄(THF)₂ (0.334 g, 1 mmol, 1 equiv), titanium powder (0.056 g, 1.0 mmol, 1.0 equiv), and dioxane (0.5 mL). The solution was stirred for 1 h over which solids form, and then 1 mL dioxane was added to the solution and stirring was continued for an additional 1 h. Isoxazole (1a, 0.069 g, 1 mmol) and 1-(1-phenylprop-1-en-1-yl)pyrrolidine (2c, 0.750 g, 4 mmol, 4 equiv) were added to the solution in dioxane (1 mL). The pressure tube was sealed and transferred from the glovebox to a preheated 100 °C aluminum block. The reaction was heated with stirring for 12 h. After heating, the pressure tube was cooled to room temperature over 10 min. Then, 2 mL of 20% aqueous K₂CO₃ was added, and the mixture was stirred for 5 min. After stirring, solids were removed by vacuum filtration and were washed with CH₂Cl₂ (~10 mL). The filtrate was dried with Na₂SO₄ and filtered through a piece of cotton. The solvent was removed under reduced pressure. The product was purified by a silica gel auto-column chromatography, eluted with hexane and ethyl acetate (9:1) to get a colorless oil (113 mg, 67%). ¹H NMR (CDCl₃, 500 MHz): δ 8.53 (d, J = 4.5 Hz, 1H), 7.60 (d, J = 7.5 Hz, 1 Hz), 7.53 (d, J = 7.0 Hz, 2H), 7.45 (t, J = 7.0 Hz, 2H, 7.39(t, J = 7.0 Hz, 2H), 2.36 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 126 MHz): δ 158.794, 147.082, 140.695, 138.662, 130.973, 129.067, 128.286, 128.058, 122.210, 20.211. MS (EI): m/z 169 (M⁺). The ¹H and ¹³C{¹H} NMR spectroscopy of the compound matches that in the literature.³⁸

Synthesis of 3-bromo-5-methyl-6-phenylpyridine



A 15 mL pressure tube was charged with TiCl₄(THF)₂ (0.334 g, 1 mmol, 1 equiv), titanium powder (0.056 g, 1.0 mmol, 1.0 equiv), and dioxane (0.5 mL). The solution was stirred for 1 h over which solids form, and then 1 mL dioxane was added to the solution and stirring was continued for an additional 1 h. 4-Bromoisoxazole (1c, 0.148 g, 1 mmol) and 1-(1-phenylprop-1-en-1yl)pyrrolidine (2c, 0.750 g, 4 mmol, 4 equiv) were added to the solution in dioxane (1 mL). The pressure tube was sealed and transferred from the glovebox to a preheated 100 °C aluminum block. The reaction was heated with stirring for 12 h. After heating, the pressure tube was cooled to room temperature over 10 min. Then, 2 mL of 20% aqueous K₂CO₃ was added, and the mixture was stirred for 5 min. After stirring, solids were removed by vacuum filtration and were washed with CH₂Cl₂ (~10 mL). The filtrate was dried with Na₂SO₄ and filtered through a piece of cotton. The solvent was removed under reduced pressure. The product was purified by a silica gel auto-column chromatography, eluted with hexane and ethyl acetate (8:2) to get a colorless oil (208 mg, 84%). ¹H NMR (CDCl₃, 500 MHz): δ 8.58 (s, 1H), δ 7.74 (s, 1H), 7.50 (s, J = 7.0 Hz, 2H), 7.45 (t, J = 7.0 Hz, 2H), 7.41 (t, J = 7.0 Hz, 1H), 2.35 (s, 3H). ${}^{13}C{}^{1}H$ NMR (CDCl₃, 126 MHz): δ 147.847, 145.669, 140.766, 137.962, 132.781, 128.880, 128.827, 128.303, 128.283, 118.949, 19.982. MS (EI): m/z 247 (M⁺). The ¹H and ¹³C{¹H} NMR spectroscopy of the compound matches that in the literature.39

Synthesis of 3-methyl-2-phenyl-5-(4-tolyl)pyridine



A 15 mL pressure tube was charged with $TiCl_4(THF)_2$ (0.334 g, 1 mmol, 1 equiv), titanium powder (0.056 g, 1.0 mmol, 1.0 equiv), and dioxane (0.5 mL). The solution was stirred for 1 h over which solids form, and then 1 mL dioxane was added to the solution and stirring was continued for an additional 1 h. (4-Tolyl)isoxazole (**1b**, 0.159 g, 1 mmol) and 1-(1-phenylprop-1-en-1yl)pyrrolidine (**2c**, 0.750 g, 4 mmol, 4 equiv) were added to the solution in dioxane (1 mL). The pressure tube was sealed and transferred from the glovebox to a preheated 100 °C aluminum block. The reaction was heated with stirring for 12 h. After heating, the pressure tube was cooled to room temperature over 10 min. Then, 2 mL of 20% aqueous K₂CO₃ was added, and the mixture was stirred for 5 min. After stirring, solids were removed by vacuum filtration and were washed with CH₂Cl₂ (~10 mL). The filtrate was dried with Na₂SO₄ and filtered through a piece of cotton. The solvent was removed under reduced pressure. The product was purified by a silica gel auto-column chromatography, eluted with hexane and ethyl acetate (8:2) to get a white solid (200 mg, 77%). m.p. = 80-81 °C. ¹H NMR (CDCl₃, 500 MHz): δ 8.76 (s, 1H), δ 8.66 (s, 1H), 8.03 (s, 1H), 7.57 (d, J = 7.0 Hz, 2H), 7.49 (t, J = 7.0 Hz, 2H), (t, J = 7.0 Hz, 2H). ¹³C{¹H} NMR (CDCl₃, 126 MHz): δ 159.562, 147.642, 139.605, 137.960, 135.045, 134.966, 134.358, 129.907, 129.278, 128.787, 126.988, 126.587, 123.133, 44.429, 21.294 . MS (EI): m/z 259 (M⁺).

Synthesis of 2-(N-acetoamino)-5-methyl-6-phenylpyridine



A 15 mL pressure tube was charged with TiCl₄(THF)₂ (0.334 g, 1 mmol, 1 equiv), titanium powder (0.056 g, 1.0 mmol, 1.0 equiv), and dioxane (0.5 mL). The solution was stirred for 1 h over which solids form, and then 1 mL dioxane was added to the solution and stirring was continued for an additional 1 h. 3-(N-Acetoamino)isoxazole (1d, 0.126 g, 1 mmol) and 1-(1-phenylprop-1-en-1yl)pyrrolidine (2c, 0.750 g, 4 mmol, 4 equiv) were added to the solution in dioxane (1 mL). The pressure tube was sealed and transferred from the glovebox to a preheated 100 °C aluminum block. The reaction was heated with stirring for 12 h. After heating, the pressure tube was cooled to room temperature over 10 min. Then, 2 mL of 20% aqueous K₂CO₃ was added, and the mixture was stirred for 5 min. After stirring, solids were removed by vacuum filtration and were washed with CH₂Cl₂ (~10 mL). The filtrate was dried with Na₂SO₄ and filtered through a piece of cotton. The solvent was removed under reduced pressure. The product was purified by a silica gel auto-column chromatography, eluted with hexane and ethyl acetate (7:3) to get an amber solid (147 mg, 65%). m.p. = 159 °C, ¹H NMR (CDCl₃, 500 MHz): δ 7.99 (s br, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.29 (m, 4H), 7.20 (t, J = 7.0 Hz, 1H), 2.10 (s, 3H), 1.90 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 126 MHz): δ 168.761, 156.566, 148.985, 141.148, 140.033, 128.870, 128.410, 128.263, 128.806, 112.552, 24.690, 19.325. MS (EI): m/z 226 (M⁺).

Synthesis of 2,3-diphenylpyridine



A 15 mL pressure tube was charged with TiCl₄(THF)₂ (0.334 g, 1 mmol, 1 equiv), titanium powder (0.056 g, 1.0 mmol, 1.0 equiv), and dioxane (0.5 mL). The solution was stirred for 1 h over which solids form, and then 1 mL dioxane was added to the solution and stirring was continued for an additional 1 h. Isoxazole (1a, 0.069 g, 1 mmol) and 1-(1,2-diphenylvinyl)pyrrolidine (2d, 1 g, 4 mmol, 4 equiv) were added to the solution in dioxane (1 mL). The pressure tube was sealed and transferred from the glovebox to a preheated 100 °C aluminum block. The reaction was heated with stirring for 12 h. After heating, the pressure tube was cooled to room temperature over 10 min. Then, 2 mL of 20% aqueous K₂CO₃ was added, and the mixture was stirred for 5 min. After stirring, solids were removed by vacuum filtration and were washed with CH₂Cl₂ (~10 mL). The filtrate was dried with Na₂SO₄ and filtered through a piece of cotton. The solvent was removed under reduced pressure. The product was purified by a silica gel auto-column chromatography, eluted with hexane and ethyl acetate (9:1) to get white solid (207 mg, 90%). m.p. = 56-58 °C, 1 H NMR (CDCl₃, 500 MHz): δ 8.71 (dd, J = 5.0 Hz, 2.0 Hz, 1H), 7.74 (dd, J = 5.0 Hz, 2.0 Hz, 1H), 7.39-7.32 (m, 2H), 7.31-7.23 (m, 6H), 7.21-7.17 (m, 2H). ¹³C{¹H} NMR (CDCl₃, 126 MHz): δ 157.227, 148.372, 140.107, 139.956, 138.791, 136.271, 130.016, 129.684, 128.462, 128.036, 127.960, 127.376, 122.248. MS (EI): m/z 231 (M⁺). The ¹H and ¹³C{¹H} NMR spectroscopy of the compound matches that in the literature.⁴⁰

Synthesis of 3-bromo-5,6-diphenylpyridine



A 15 mL pressure tube was charged with $TiCl_4(THF)_2$ (0.334 g, 1 mmol, 1 equiv), titanium powder (0.056 g, 1.0 mmol, 1.0 equiv), and dioxane (0.5 mL). The solution was stirred for 1 h over which solids form, and then 1 mL dioxane was added to the solution and stirring was continued for an additional 1 h. 4-Bromoisoxazole (**1c**, 0.148 g, 1 mmol) and 1-(1,2-diphenylvinyl)pyrrolidine (**2d**, 1 g, 4 mmol, 4 equiv) were added to the solution in dioxane (1 mL). The pressure tube was sealed and transferred from the glovebox to a preheated 100 °C aluminum block. The reaction was heated with stirring for 12 h. After heating, the pressure tube was cooled to room temperature over 10 min. Then, 2 mL of 20% aqueous K₂CO₃ was added, and the mixture was stirred for 5 min. After stirring, solids were removed by vacuum filtration and were washed with CH₂Cl₂ (~10 mL). The filtrate was dried with Na₂SO₄ and filtered through a piece of cotton. The solvent was removed under reduced pressure. The product was purified by a silica gel auto-column chromatography, eluted with hexane and dichloromethane (9:1 to 4:6) to get white solid (273 mg, 88%). m.p. = 103-105 °C. ¹H NMR (CDCl₃, 500 MHz): δ 8.74 (s, 1H), 7.88 (s, 1H), 7.34-7.20 (m, 8H), 7.19-7.13 (m, 2H). ¹³C{¹H} NMR (CDCl₃, 126 MHz): δ 155.631, 149.103, 140.831, 138.905, 138.512, 137.616, 129.745, 129.423, 128.509, 128.180, 128.029, 127.801, 119.043. MS (EI): m/z 310 (M⁺). Synthesis of *3-methyl-5,6-diphenyl-2-(4-tolyl)pyridine*



A 15 mL pressure tube was charged with TiCl₄(THF)₂ (0.334 g, 1 mmol, 1 equiv), titanium powder (0.056 g, 1.0 mmol, 1.0 equiv), and dioxane (0.5 mL). The solution was stirred for 1 h over which solids form, and then 1 mL dioxane was added to the solution and stirring was continued for an additional 1 h. 4-Methyl-3-(4-tolyl)isoxazole (0.174 g, 1 mmol) and 1-(1,2diphenylvinyl)pyrrolidine (2d, 1g, 4 mmol, 4 equiv) were added to the solution in dioxane (1 mL). The pressure tube was sealed and transferred from the glovebox to a preheated 100 °C aluminum block. The reaction was heated with stirring for 12 h. After heating, the pressure tube was cooled to room temperature over 10 min. Then, 2 mL of 20% aqueous K₂CO₃ was added, and the mixture was stirred for 5 min. After stirring, solids were removed by vacuum filtration and were washed with CH₂Cl₂ (~10 mL). The filtrate was dried with Na₂SO₄ and filtered through a piece of cotton. The solvent was removed under reduced pressure. The product was purified by a silica gel autocolumn chromatography, eluted with hexane and dichloromethane (9:1 to 4:6) to get white solid (306 mg, 91%). m.p. = 119-122 °C. ¹H NMR (CDCl₃, 500 MHz): δ 8.76 (s, 1H), δ 8.66 (s, 1H), 8.03 (s, 1H), 7.57 (d, J = 7.0 Hz, 2H), 7.49 (t, J = 7.0 Hz, 2H), (t, J = 7.0 Hz, 2H). ${}^{13}C{}^{1}H$ NMR (CDCl₃, 126 MHz): δ 148.001, 145.823, 140.878, 139.599, 138.077, 129.015, 128.962, 128.434, 119.083. MS (EI): m/z 334 (M⁺).

Synthesis of 2,3-di-(4-tolyl)pyridine



A 15 mL pressure tube was charged with TiCl₄(THF)₂ (0.334 g, 1 mmol, 1 equiv), titanium powder (0.056 g, 1.0 mmol, 1.0 equiv), and dioxane (0.5 mL). The solution was stirred for 1 h over which solids form, and then 1 mL dioxane was added to the solution and stirring was continued for an additional 1 h. Isoxazole (1a, 0.069 g, 1 mmol) and 1-(1,2-di(4-tolyl)vinyl)pyrrolidine (2e, 1 g, 4 mmol, 4 equiv) were added to the solution in dioxane (1 mL). The pressure tube was sealed and transferred from the glovebox to a preheated 100 °C aluminum block. The reaction was heated with stirring for 12 h. After heating, the pressure tube was cooled to room temperature over 10 min. Then, 2 mL of 20% aqueous K₂CO₃ was added, and the mixture was stirred for 5 min. After stirring, solids were removed by vacuum filtration and were washed with CH₂Cl₂ (~10 mL). The filtrate was dried with Na₂SO₄ and filtered through a piece of cotton. The solvent was removed under reduced pressure. The product was purified by a silica gel auto-column chromatography, eluted with hexane and ethyl acetate (9:1) to get a colorless oil (174 mg, 67%). ¹H NMR (CDCl₃, 500 MHz): δ 8.73 (d, J = 5.0 Hz, 1H), δ 7.76 (d, J = 8.0 Hz, 1H), 7.40-7.30 (m, 3H), 7.20-7.10 (m, 6H), 2.42 (s, 3H), 2.19 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 126 MHz): δ 157.209, 148.179, 138.696, 137.608, 137.474, 137.271, 137.001, 136.002, 129.862, 129.485, 129.182, 128.741, 121.935, 21.393, 21.312. MS (EI): m/z 259 (M⁺). The ¹H and ¹³C{¹H} NMR spectroscopy of the compound matches that in the literature.⁴¹

Synthesis of 3-bromo-5,6-di-(4-tolyl)pyridine



A 15 mL pressure tube was charged with $TiCl_4(THF)_2$ (0.334 g, 1 mmol, 1 equiv), titanium powder (0.056 g, 1.0 mmol, 1.0 equiv), and dioxane (0.5 mL). The solution was stirred for 1 h over which solids form, and then 1 mL dioxane was added to the solution and stirring was continued for an additional 1 h. 4-Bromoisoxazole (1c, 0.148 g, 1 mmol) and 1-(1,2-di(4-tolyl)vinyl)pyrrolidine (2e, 1 g, 4 mmol, 4 equiv) were added to the solution in dioxane (1 mL). The pressure tube was sealed and transferred from the glovebox to a preheated 100 °C aluminum block. The reaction was heated with stirring for 12 h. After heating, the pressure tube was cooled to room temperature over 10 min. Then, 2 mL of 20% aqueous K₂CO₃ was added, and the mixture was stirred for 5 min. After stirring, solids were removed by vacuum filtration and were washed with CH₂Cl₂ (~10 mL). The filtrate was dried with Na₂SO₄ and filtered through a piece of cotton. The solvent was removed under reduced pressure. The product was purified by a silica gel auto-column chromatography, eluted with hexane and dichloromethane (9:1 to 4:6) to get white solid (285 mg, 84%). m.p. = 93-95 °C. ¹H NMR (CDCl₃, 500 MHz): δ 8.69 (s, 1H), δ 7.83 (s, 1H), 7.22 (d, J = 7.5 Hz, 2H), 7.09 (t, J = 8.0 Hz, 2H), 7.07-7.02 (m, 5H), 2.34 (s, 3H), 2.31 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 126 MHz): δ 155.763, 148.995, 140.830, 138.069, 137.671, 137.523, 136.477, 135.949, 129.731, 129.366, 129.353, 128.871, 118.815, 21.417, 21.345. MS (EI): m/z 337 (M⁺).

Spectral Data for Pyridine Derivatives

 ^1H NMR and $^{13}\text{C}\{1\text{H}\}$ NMR of 5,6,7,8-tetrahydroquinoline





$^1\mathrm{H}$ NMR and $^{13}\mathrm{C}\{1\mathrm{H}\}$ NMR of 3-(4-tolyl)-5,6,7,8-tetrahydroquinoline







¹H NMR and ¹³C{1H} NMR of 2-(N-acetylamino)-5,6,7,8-tetrahydroquinoline



 $^{1}\mathrm{H}$ NMR and $^{13}\mathrm{C}\{1\mathrm{H}\}$ NMR of 2-methyl-5,6,7,8-tetrahydroquinoline



¹H NMR and ¹³C{1H} NMR of *3-ethyl-2-(thiopheny-2-yl)-5,6,7,8-tetrahydroquinoline*



$^1\mathrm{H}$ NMR and $^{13}\mathrm{C}\{1\mathrm{H}\}$ NMR of 3-methyl-2-(4-tolyl)-5,6,7,8-tetrahydroquinoline





1H NMR and $^{13}C\{1H\}$ NMR of 3-phenylpyridine



1H NMR and $^{13}C\{1H\}$ NMR of 3-bromo-5-phenylpyridine





¹H NMR and ¹³C{1H} NMR of *3-(4-tolyl)-5-phenylpyridine*



^1H NMR and $^{13}\text{C}\{1\text{H}\}$ NMR of 3-methyl-2-phenylpyridine







 $^{1}\mathrm{H}$ NMR and $^{13}\mathrm{C}\{1\mathrm{H}\}$ NMR of 3-methyl-2-phenyl-5-(4-tolyl)pyridine



$^{1}\mathrm{H}$ NMR and $^{13}\mathrm{C}\{1\mathrm{H}\}$ NMR of 2-(N-acetoamino)-5-methyl-6-phenylpyridine

 $^1\mathrm{H}$ NMR and $^{13}\mathrm{C}\{1\mathrm{H}\}$ NMR of 2,3-diphenylpyridine



 ^1H NMR and $^{13}\text{C}\{1\text{H}\}$ NMR of 3-bromo-5,6-diphenylpyridine




$^1\mathrm{H}$ NMR and $^{13}\mathrm{C}\{1\mathrm{H}\}$ NMR of 2,3-di-(4-tolyl)pyridine



^1H NMR and $^{13}\text{C}\{1\text{H}\}$ NMR of 3-bromo-5,6-di-4-tolylpyridine



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Chapter 3. Investigation of Asymmetric Ancillary Ligand Effect for Titanium-Catalyzed Hydroamination

3.1 Introduction

Catalysis affects all fields of chemical synthesis, such as food production, transportation, pharmaceuticals, etc.¹ Although attention to organocatalysis has been rapidly growing,² transition metal catalysis has been the major pillar of the field of catalysis. Numerous innovative chemical reactions have been developed with transition metal catalysis, such as coupling reactions³, olefin metathesis⁴, and C–H activation⁵, and these chemistries are currently being used widely in various fields. In the field of transition metal catalysis, understanding ancillary ligand effects is one of the most critical aspects to study and design catalysts. To understand ligand effects in depth, methods for quantification of ligand properties, such as electronic and steric effects, are needed. Moreover, high valent transition metals, such as titanium(IV), play a critical role in chemical industry. For example, polyolefins are produced on a massive scale from Zeigler-Natta polymerization.⁶ Polyolefins are widely used materials, accounting for more than 50% in weight of the produced polymers. In 2015, approximately 178 million tons of polyolefins were produced.^{7,8} Consequently, parameterization methods of ligand properties for high valent transition metals are necessary and are drawing interests from researchers. Optimization and design of new catalysts with high valent transition metals would be more rational if the relationship between ligand properties and reaction outcomes, such as yields, rates, and selectivity, is unveiled using these parameterization methods.

3.1.1 Electronic Parameterization for Low Valent Transition Metals

Phosphine ligands are widely used in palladium and other low valent transition metal catalysts, such as Suzuki-Miyaura coupling or Buchwald-Hartwig coupling reactions. Especially, Suzuki-Miyaura coupling and other palladium-catalyzed cross coupling reactions are frequently used reactions in the area of medicinal chemistry.⁹ Naturally, phosphines became the most important ligands for late transition metal catalysts. Parameterization tools for phosphine ligands were developed by Chadwick Tolman in 1970s to measure the electronic donation from phosphine ligands to low valent, late transition metals.¹⁰ Electronic effects of phosphines were experimentally measured using Ni(CO)₃(PR₃) complexes with various phosphines (PR₃), and the CO stretching frequencies in the nickel complexes were used as parameters for the donor properties of phosphines. A more electron-donating phosphine ligand results in a weaker CO bond due to a higher electron occupation in the antibonding orbital of CO ligands, giving a lower CO stretching frequency.

Therefore, the donating effect of various phosphine ligands can be directly compared by measuring CO stretching frequencies of Ni(CO)₃(PR₃) complexes.

Cone Angle, O

Ni(CO) ₄ $\frac{+ PR_3}{- CO}$	B PR ₃ I OC ^{Ni} , (CO CO	B B P 2.28 Å Ni(CO) ₃
Phosphine ligands	CO <i>v</i> , cm ⁻¹	Cone angle, deg
P(o-Tol)3	2066.6	194 <u>±</u> 6
PMe ₃	2064.1	118±4
PEt ₃	2061.7	132±4
P(ⁱ Pr) ₃	2059.2	160±10
P('Bu) ₃	2056.1	182±2

Table 3.1 CO Stretching Frequencies (v, cm⁻¹).¹¹

Tolman's cone angle was introduced to explain steric effect of phosphine ligands.¹¹ The cone angle is the apex angle of a cylindrical cone, centered at 2.28 Å from the ligand center P atom, and this was used as steric parameter.

$$Z = a + b(v) + c(\theta)$$
 (Eq 3.1)

These steric and electronic parameters can be used together in an equation (Eq 3.1), where a, b, and c are coefficients and Z can be an experimental outcome being investigated, such as reaction rate. However, these methods were not applicable for high oxidation state transition metal catalysts with various types of ligands. For example, titanium(IV) has many common ancillary ligands, such as halide, pyrrolide, indolide, and alkoxide. But it is very difficult to rank these ligands by electron donating ability. In addition, the use of early transition metal catalysis is a recent trend due to the potential benefits from studying catalysts with the earth abundant metals, such as global accessibility and biocompatibility.¹² Various catalysts with earth abundant metals have been investigated in parallel with the better known precious metal catalysis in organic

synthesis.¹² As a result, electronic parameterization methods for high valent transition metal catalysts are needed to understand the donor abilities of these ligands.

3.1.2 Electronic Parameterization for High Valent Transition Metals

Although Tolman successfully described the ligand donation to low valent metal centers, electronic parametrization methods are not available for high valent transition metals with a very different group of ancillary ligands in high oxidation state metal catalysts. pKa values or Hammett parameters are often considered as quantification methods for the electronic donation from organic ligands. However, these methods do not measure accurate electronic interactions between high oxidation metals and ligands. For example, π -donation is not considered when comparing pKa values.



Figure 3.1 Chromium system for the measurement of LDP of ligand X.¹³

In 2012, the Odom group developed an experimentally-defined parameter for the electron donation of ancillary ligands towards a high valent metal center to provide a better approach to investigate electronic effects of anionic ligands.¹⁴ A chromium(VI) complex, NCr(NⁱPr₂)₂X, with various mono-anionic ligands, X, was synthesized for measuring electronic donation from X to a high valent metal center (**Figure 3.1**). In this system, the electron donation competition between the amido ligand and the X ligand is utilized to study the donating effect of X ligands. The electron donation competition between the amide lone pair and the X ligand affects the Cr-NⁱPr₂ bond's single or double bond character.



Figure 3.2 Ligand Donor Parameters (kcal/mol) for various ligands measured with $NCr(N^{i}Pr_{2})_{2}X$.¹⁵

If X is a good donor ligand, the amide ligand lone pair donates less electron density to the metal center, and the Cr-N bond will have more single bond character. If X is a poor donor ligand, more electron donation comes from the amide ligand lone pair to the metal center, and the Cr-N bond will have more double bond character. In short, the rotation barrier of the Cr-N bond can be utilized as a parameter for the donor ability of the X ligand towards the metal center. Using ¹H NMR spectroscopy the rotation rate of the Cr-N bond can be measured, and these rate values are inserted into the Eyring equation to obtain the free energy for rotation. With an assumption that $\Delta S^{\ddagger} = -9$ cal/mol•K for a temperature independent measurement (This value was obtained from experiments using NCr(NⁱPr₂)₂I over a wide range of temperatures), the enthalpic barrier (Ligand Donor Paramter, LDP) can be obtained. A poor donor ligand will give high LDP values. Using LDP, the donor ability of various ligands toward high valent transition metal center can be directly compared. LDP values from some of the ligands we have explored are shown in **Figure 3.2**.¹⁵

3.1.3 Percent Buried Volume (%V_{bur})

For a metric of ligand steric effects, a structurally-based system (Percent Buried Volume, $\%V_{bur}$) developed by Cavallo and coworkers¹⁶ is used instead of cone angle from Tolman's work. In this system, the coordination sphere occupied by the ligand within 3.5 Å radius from the metal center can be measured from crystal structure data of chromium(VI) complexes with X ligands. This system demonstrates a strong correlation with Tolman's cone angle. Using this tool, the steric effect is considered by using this measured volume (percent buried volume or $\%V_{bur}$). The $\%V_{bur}$ and LDP can be used together in a simple model (Eq. 3.1). For our study, the sterics ($\%V_{bur}$) and electronics (LDP) were measured with chromium complexes, NCr(N'Pr₂)₂X, with mono-anionic ligands X. These data sets have a potential use for other high valent metal catalysts.



Figure 3.3 Percent Buried Volume (%Vbur) is defined as the percent of the coordination sphere occupied by X ligand within 3.5 Å radius (R) from the metal center. The bond length between metal and ligand (d) is determined from the X-ray crystallography.¹⁶

3.1.4 Investigation of Symmetric Ligand Effects in Titanium Catalysis

The Odom group has been interested in C-N and C-C bond forming reactions. Titaniumcatalyzed hydroamination and iminoamination have been incorporated into various nitrogencontaining heterocycles but also biologically-active compounds.¹⁷ For example, the exploration of NRF2 inhibitors was started from titanium-catalyzed iminoamination.¹⁸ The LDP and %V_{bur} system are employed to understand ligand effects in titanium catalysis. In the previous study, the Odom group designed a model to correlate the electronic and steric parameters of the symmetrical bidentate ligands with reaction rate of titanium-catalyzed hydroamination (**Eq. 3.2**).¹³ This model not only allows the prediction of catalyst performance but also guides future catalytic studies.

Reaction rate = $a + LDP(electronic parameter) + %V_{bur}(steric parameter)$ (Eq 3.2)

As mentioned above, LDP and V_{bur} of the ligands were measured on the same chromium complex. Only one half of the bidentate ligand can be measured for the LDP system, and the linkers between the fragments are ignored due to a small influence on catalysis.



With a set of ligands (**Figure 3.4**), LDP and %V_{bur} were measured, and the reaction rates of titanium-catalyzed hydroamination were obtained using the catalysts with various bidentate ligands. For the kinetic study of titanium-catalyzed intermolecular hydroamination, *pseudo*-first order kinetics was measured using 10-fold of aniline to give *pseudo*-first order kinetics. (**Eq 3.3**). The concentration of alkyne was monitored over time and fit into an exponential decay. **Eq. 3.4** was obtained from modeling the rate constant with the electronic and steric parameters of the ligands with scaled coefficients.¹³ Based on the model, electron-deficient and small ligands provide faster reaction rates than those with electron-rich and sterically bulky ligands.

$$k_{obs}(\times 10^4) = 1.34 + 1.61(LDP) - 2.25(\% V_{bur})$$
 (Eq. 3.4)



Figure 3.4 Titanium-catalyzed hydroamination reaction and a set of catalysts with symmetric bidentate ligands used for studying ligand effects.¹³

Catalysts with various ligands fit the model very well, and a prediction of reaction rates can be made prior to the catalyst synthesis using this model. However, this study only considered symmetric ligands, and it has been shown that unsymmetrical ligands can perform faster catalysis than symmetrical ligands in the preliminary studies. In this chapter, the investigation of bidentate ligands in titanium-catalyzed hydroamination reactions is expanded to unsymmetrical ligands using a 5-parameter model. In addition, 3-unsubstituted indoles as a part of the ligand are proposed to go through a unique hydroamination mechanism where the indole fragments are involved in proton transfer resulting in faster catalysis.

3.1.5 Asymmetrical Ligand Environments

The ancillary ligand effect toward a high-valent metal was studied by Schrock and coworkers for olefin metathesis using d⁰ molybdenum catalysts (Mo(=NR)(=CHR')(X)(Y), X and Y are mono-anionic ligands, such as pyrrolide, alkoxide). From these studies, Schrock and coworkers discovered that the reactivity increases when the Lewis acidity of their d⁰ molybdenum catalysts increased when X and Y are same or very similar.¹⁹ However, the reactivity can be even higher when X and Y are very different ligands, in particular a weak σ -donor, such as an alkoxide or siloxide, and a strong σ -donor, such as alkyl or pyrrolide.²⁰



Figure 3.5 Examples of the molybdenum catalysts used for ring closing metathesis.²⁰

Theoretical studies from Eisenstein and Copéret also supported the results.^{21,22} Based on the proposed mechanism, the strong σ -donor ligand would minimize the unfavorable *trans*-effect, and olefin approaches more readily to the vacant site. In addition, the metal center is Lewis acidic enough due to the weak σ -donor ligand so that the olefin can coordinate to the metal center easily. Lastly, the donor ligand is trans to the new olefin after cycloreversion, and this leads to the disassociation of the new olefin. In short, electronic dissymmetry from two different ligands can facilitate olefin coordination and metallacyclobutane collapse.



Figure 3.6 Proposed mechanism of molybdenum-catalyzed ring closing metathesis. D is a strong σ -donor and A is a weak σ -donor.²⁰

The protonolysis from a five-coordinated titanium complex is believed to be the rate determining step for the titanium-catalyzed hydroamination of alkynes shown below in **Figure 3.7**. Two scenarios can be considered for a five-coordinated titanium complex. A bidentate ligand is on the same plane with Ti-C bond (**A** in **Figure 3.7**), and asymmetric ligands are not making a significant difference in the reaction rate since effects from both sides would be averaged out. However, electronic dissymmetry from asymmetric ligands can be effective since each side of the ligands can be in a different environment (**B**).



Figure 3.7 Proposed mechanism of titanium-catalyzed hydroamination of alkynes. A and B are possible geometries for five-coordinated titanium complex in the catalytic cycle.

3.1.6 Model Considerations

In the new model for asymmetric ligands, LDP and V_{bur} are measured separately for each side of the chelating ligand, using the chromium(VI) system. For example, ligand A has pyrrole and indole as each side of the chelate (**Figure 3.8**). With this strategy, we can utilize each LDP and V_{bur} for various combination of two mono-anionic ligands.

$$k_{obs}(\times 10^4) = a + b(LDP1) + c(LDP2) + d(\% V_{bur}1) + e(\% V_{bur}2)$$
 (Eq. 3.5)



Figure 3.8 An example of titanium catalyst with an asymmetric ligand and chromium(VI) system with pyrrolide and indolide ligands, respectively, for LDP and %V_{bur} measurement.

To evaluate various combinations of ligands, a 5-parameter model (**Eq. 3.5**) was used. Five parameters are two LDP and two %V_{bur} values for each side of the ligand, as well as a fitting constant. The *1* and *2* refer to ligand 1 and 2, respectively. The linker in between each side of the ligand is ignored. In the equation (**Eq 3.5**), LDP and %V_{bur} values of each side of ligands are weighted differently. To make a consistent data analysis, ligand 1 and 2 should be assigned based on LDP or %V_{bur} values. For example, a side of the ligand with a higher LDP value than the other side can be assigned to 1 (assignment based on electronics), or the side of ligands with higher %V_{bur} values than the other side can be assigned to 1 (assignment based on sterics). Models with both cases were tried, but the assignment based on LDP results in a better modelled. Therefore, the fragments with a higher LDP value were assigned to side 1.

3.2 Investigation of Symmetric Ligand Effects in Titanium Catalysis

This project was undertaken in close collaboration with Dr. Zhilin Hou, Dr. Tanner McDaniel, Rashmi Jena, and Hannah Barr. Zhilin, Rashmi and Tanner also participated in the syntheses of ligands and catalysts. Hannah Barr contributed to chromium complex syntheses and LDP measurement.

In the previous studies, pyrroles, indoles, and phenols are effective ligands for titaniumcatalyzed hydroamination.¹³ Therefore, asymmetric di-anionic ligands from pairing two different mono-anionic ligands via a linker are expected to be effective for titanium-catalyzed hydroamination. To synthesize a new set of ligands, two different strategies for the unsymmetrical bidentate ligands were developed: Mono-functionalization of symmetrical ligands, such as DPM, or pairing two different monodentate ligands into a bidentate framework (**Figure 3.5**).

(a) Strategy 1: Functionalization



Figure 3.9 Two different synthetic strategies for asymmetric ligands. L1 and L2 can be substituted pyrroles, indoles, and phenols.

3.2.1 Synthesis of Asymmetric Ligands and Titanium Catalysis

Previous work from the Odom group has discovered that 5,5'-dimethyldipyrromethane is one of the fastest symmetric ligands for hydroamination of alkynes.¹³ Therefore, this study was started with syntheses of asymmetric dipyrrolylmethane derivatives by mono-functionalization. In this strategy, the reactive 5-position of dipyrrolylmethane was utilized, and iridium-catalyzed C-H borylation and the Vilsmeier-Haack reaction were used to generate mono-functionalization in the 5-position of H₂dpm. First, H₂dpm was formylated via Vilsmeier-Haack reaction, followed by reduction of aldehyde using hydrazine hydrate and potassium hydroxide.



Figure 3.10 Asymmetric ligand synthesis via Strategy 1 (Vilsmeier-Haack reaction followed by reduction).

The mono-borylated H₂dpm was used for Suzuki-Miyaura coupling with aryl bromide to replace the boronic ester with an aryl group. 3,5-Bis(trifluoromethyl)bromobenzene, and 5-bromo-

m-xylene, and bromobenzene were used for the coupling reactions to compare the electronic effects from the aryl group.



Figure 3.11 Asymmetric ligand synthesis using Strategy 1 (C-H borylation followed by Suzuki-Miyaura coupling).

The second strategy is substitution of a leaving group with a mono-anionic ligand. With this strategy, a diverse library of ligands with two different mono-anionic ligands was achieved. Dr. Tanner McDaniel found that a hydroxyl group can be replaced by another mono-anionic ligands in the presence of a Lewis acid, InCl₃.³¹ However, Dr. Zhilin Hou successfully replaced a hydroxyl group with pyrrole and indole using catalytic amount of BF₃•OEt₂ under milder condition with a shorter reaction time.²⁴ Therefore, this synthetic method was used for all syntheses in Strategy 2.



Figure 3.12 Asymmetric ligand synthesis using Strategy 2 (Substitution of a hydroxyl group of N-tosyl-pyrrole-2-methanol in the presence of catalytic amount of BF₃•OEt₂).

The first synthesis in this strategy is substitution of a hydroxyl group of *N*-tosyl-pyrrole-2methanol, which was prepared from the reduction of *N*-tosyl-pyrrole-2-carboxaldehyde. The protecting group was installed to prevent a nucleophilic attack from the 2-position of pyrrole. In addition, 3-methylindole was used to generate the desired product only since the 3-position of indole is the most nucleophilic site of an unsubstituted indole. After substitution, the product was deprotected to generate the desired ligand.



Figure 3.13 Asymmetric ligand synthesis using Strategy 2 (Substitution of a hydroxyl group of 2- (1*H*-indol-2-yl)propan-2-ol in the presence of catalytic amount of BF₃•OEt₂).

Another synthetic route in the substitution strategy is using 2-(1*H*-indol-2-yl)propan-2-ol, and replace the hydroxy group with substituted pyrroles. In this strategy, the indole is not protected but an excess of substituted pyrroles was used to prevent the nucleophilic attack from the 3-position of the indole. Pyrrole derivatives used for the substitution reaction were synthesized from *N*-Boc-2-Bpin-pyrrole using Suzuki-Miyaura coupling.



Figure 3.14 An example of titanium catalyst synthesis from Ti(NMe₂)₄ and one of asymmetric ligands.

Titanium catalysts were synthesized using commercially available Ti(NMe₂)₄ with ligands prepared using the methods above (**Scheme 3.8**). The catalysts were purified by recrystallization and characterized by NMR and single-crystal XRD.

3.2.2 Modeling Reaction Rate with Asymmetric Ligands

The synthesized catalysts were used for building a model for titanium-catalyzed hydroamination reactions of alkyne for studying asymmetric ligand effects using NMR techniques. An excess of aniline (ten-fold) was used to produce *pseudo*-first order kinetics of alkyne. The concentration of alkyne was monitored by ¹H NMR over time and was fit into an exponential decay. The rate constant of the catalyst was calculated from the fit.



Figure 3.15 An example of a kinetic data. The concentration of alkyne was monitored by ¹H NMR using ferrocene as an internal standard.

Catalysts	Chromium complexes for LDP and %V _{bur}	LDP (kcal/mol)	%V _{bur}	Rate constant (× 10 ⁻⁴)
N Ti NMe2 NMe2 3a	N N N Pr Pr	13.46	23.7	3.1
	N Crown Pr N Pr Pr	13.64	20.4	
N N N N Me ₂ 3b	N Crown Pr N Pr Pr	13.09	23.1	1.9
		13.46	23.7	
Sc	N CrN ^{∠Pr} N [→] Pr Pr	13.64	20.4	6.6
	$ = \sum_{\substack{P_r \\ P_r \\ P_r}} \sum_{\substack{P_r \\ P_r} \sum_{\substack{P_r \\ P_r}} \sum_{\substack{P_r}} \sum_{\substack{P_r}} \sum_{\substack{P_r \\ P_r} \sum_{\substack{P_r}} \sum_{\substack{P_r} \sum_{\substack{P_r}} \sum_{\substack{P_r} \sum_{\substack{P_r}} \sum_{\substack{P_r}} \sum_{\substack{P_r}} \sum_{\substack{P_r}} \sum_{\substack{P_r}} \sum_{\substack{P_r} \sum_{\substack{P_r}} \sum_{\substack{P_r}} \sum_{\substack{P_r}} \sum_{\substack{P_r}} \sum_{\substack{P_r} \sum_{\substack{P_r}} \sum_{\substack{P_r} \sum} \sum_{\substack{P_r} \sum_{P_r$	12.99	22.3	
NMe ₂ 3c	$\sum_{\mathbf{p}_r}^{\mathbf{N}} \sum_{\mathbf{p}_r}^{\mathbf{p}_r} \sum_{\mathbf{p}_r}^{\mathbf{p}_r}$	14.03	27.1	3.97
		13.64	20.4	
N TI NMe2 NMe2 3d	$\sum_{r=1}^{N} \sum_{\substack{n < r \\ n < p_r \\ p_r}} \sum_{r=1}^{N} \sum_{r=1}^{n}$	13.91	26.7	3.46
		13.64	20.4	
CF ₃ CF ₃ CF ₃ CF ₃ MMe ₂ 3e	F ₃ C CF ₃ N Cr _N N ^{/Pr} N T ^{Pr} Pr	14.32	27.9	5.5
		13.64	20.4	

Table 3.2 A library of titanium catalysts with rate constants and LDP and $%V_{bur}$ of the ligands.

Table 3.2 (cont'd)

Catalysts	Chromium complexes for LDP and %V _{bur}	LDP (kcal/mol)	%V _{bur}	Rate constant (× 10 ⁻⁴)
TI NMe2 NMe2 3f	N N C N Pr Pr	13.46	23.7	11.5
		12.99	22.3	
N N N N N N N Me ₂ 3g	N Crown Pr N Pr Pr	13.64	20.4	3.64
	N ^{Pr} N ^{CC} ^N Pr Pr	12.49	22.6	
N N N N N N N N N N N N N N N N N N N	N Crown Pr N Pr Pr	13.64	20.4	4.4
	N Crown Pr N Pr Pr	12.22	23.3	
Si		13.91	26.7	6.9
	Cr,Pr Pr Pr Pr	12.99	22.3	
CF3 CF3 CF3 CF3 CF3 CF3 CF3 CF3 CF3 CF3	$F_{3}C \underbrace{\bigvee}_{N} CF_{3} \underbrace{\bigvee}_{Pr} Pr}_{Pr}$	14.32	27.9	15.2
	CrV Pr Pr Pr	12.99	22.3	
NMe2 3k	$\sum_{\substack{\mathbf{N}_{r} \in \mathcal{N}_{r} \\ \mathbf{N}_{r} \neq \mathbf{P}_{r} \\ \mathbf{P}_{r}' \neq \mathbf{P}_{r}}} N_{r} \neq \mathbf{N}_{r} \neq \mathbf{N}_{r}$	14.03	27.1	9.8
	$\sum_{\substack{\mathbf{p}_r \\ \mathbf{p}_r }}^{N} \sum_{\substack{\mathbf{p}_r \\ \mathbf{p}_r \\ \mathbf{p}$	12.99	22.3	

Table 3.2 (cont'd)

Catalysts	Chromium complexes for LDP and %V _{bur}	LDP (kcal/mol)	%V _{bur}	Rate constant (× 10 ⁻⁴)
CF3 CF3 CF3 CF3 CF3 CF3 CF3 CF3 CF3 CF3	$F_{3}C$ $F_{3}C$ V	12.99	22.3	Unstable
	N − CrN − Pr Pr Pr Pr	12.99	22.3	
^{'Bu} O N ^{TI} ····NMe ₂		11.98	^{Bu} ^{'Bu} 21.6	0.46
3m	N N N N Pr Pr	13.64	20.4	
^{(Bu} ^{(Bu} ^(D)		11.98	^N ^{Bu} ^{Bu} ^{Pr} ^{Pr} ^{Pr} ^{Pr} ^{Pr} ^{Pr} ^{Pr} ^{Pr}	0.67
3n	$\sum_{\substack{n \in \mathcal{N}_{r}, \dots, n \in \mathcal{P}_{r} \\ p_{r} \neq p_{r}}} \sum_{\substack{n \in \mathcal{P}_{r} \\ p_{r} \neq p_{r}}}^{N} \sum_{\substack{n \in \mathcal{P}_{r} \\ p_{r} \neq p_{r}}}^{p_{r}}$	12.49	22.6	
^{'Bu} O NMe ₂		11.98	^N ¹ Bu ¹ Bu 21.6	0.67
1 F 30	F Crown Pr N Crown Pr Pr	12.66	22.6	

Most of the catalysts fit the model well except for precatalysts with ligands containing 3unsubstituted indoles, which show significantly higher rate constants. However, precatalysts with 3-methylindole did fit well into the model. Therefore, precatalysts with ligands containing 3unsubstituted indoles are not include in the regression analysis (**Figure 3.10**). The model without catalysts containing 3-unsubstituted indoles showed a linear relationship between the experimental and calculated rate constants. The model parameters are obtained from the regression analysis using natural parameters (Eq. 3.6).

$$k (\times 10^4) = -9.60 + (2.0 \pm 0.3)(LDP1) + (0.1 \pm 0.3)(LDP2) - (0.15 \pm 0.05)(\% V_{bur}1) - (0.56 \pm 0.05)(\% V_{bur}2) (Eq. 3.6)$$

Using these parameters, rate constants of a catalyst that was not explored in this study can be predicted. As mentioned above, LDP1 and $%V_{bur}1$ are from the side of ligand with higher LDP, and LDP2 and $%V_{bur}2$ are from the side of ligand with lower LDP. Based on the parameters in **Eq 3.6**, the donor ability from ligand 1 is makes a large contribution to the rate than ligand 2. In contrast, the sterics of ligand 2 is weighed more than ligand 1. In addition, a faster catalyst must consist of an electron-deficient ligand (**ligand 1**) and a smaller ligand (**ligand 2**).



Figure 3.16 the regression analysis using the experimental and calculated rate constants. The fit is shown as a red line. Black dots represents rate constants of titanium precatalysts, except for precatalysts with ligands containing 3-unsubstituted indoles (blue squares).



Figure 3.17 A proposed mechanism of titanium-catalyzed hydroamination of alkyne with a 5coordinated titanium complex in the transition state before the Ti–C protonolysis.

Faster reaction rates from asymmetric ligands suggests that two sides of ligands reside in different environments. The small ligand with lower LDP (ligand 2) is expected be in an axial position experiencing larger steric interaction, and electron deficient ligand might be preferred for another position (ligand 1) because of the acidity increase of the titanium amido complexes after the first protonolysis.

3.2.3 Indolyl Effect

The precatalysts with ligands containing 3-unsubstituted indoles showed outstanding rate constants unlike 3-substituted indoles fitting in the model above. The significant change in the reaction rate suggests that the mechanism can be different with 3-unsubstituted indoles as ligand. The 3-position of the indoles can be a proton shuttle during the catalysis as proposed in other catalytic reactions.²³ Proton transfer through through the 3-position of the indole may lower the energy barrier to the protonolysis.



Figure 3.18 H/D exchange experiments between the 3-position of the indole and aniline- d_8 .²⁴

The labelling experiments conducted by Dr. Zhilin Hou showed that the treatment of catalyst 3c with 5 equivalents of aniline-d₈ results in deuteration of the 3-position of the indole fragment as well as 3-, 4-, and 5-position of the pyrrole fragment.²⁴

3.3 Conclusion

Titanium-catalyzed hydroamination reactions of alkynes with asymmetric ligands were successfully modeled with the electronic (LDP) and steric ($%V_{bur}$) properties of the ligands. The kinetic study with asymmetric ligands resulted in a model with five parameters from multivariate analysis. The model showed an excellent linear relationship between reaction rates and calculated reaction rates with a high R² (0.98). Based on the model, a fast catalyst has an electron-deficient side and a smaller side. In addition, the reaction rate of titanium catalysts with symmetrical or unsymmetrical ligands can be predicted using this model. Lastly, catalysts with 3-unsubstituted indole fragments were outliers with higher reaction rates, suggesting that there is a unique hydroamination mechanism with 3-unsubstituted indole fragments. In this mechanism, the 3-position of the indoles can be a proton shuttle during the catalysis. The labelling experiment using NMR showed the H/D exchange between aniline and the ligands of titanium catalysts.

3.4 Experimental Details

General Considerations

All syntheses and handling of materials were carried out under an inert nitrogen atmosphere, either in a MBraun glovebox or by standard Schlenk techniques, except as noted and for column chromatography and preparation of GC samples. The ¹H and ¹³C{¹H} NMR spectra were recorded on Agilent DDR2 500 MHz NMR spectrometer equipped with a 5 mm PFG OneProbe operating at 499.84 MHz (¹H) and 125.73 MHz (¹³C), respectively. The chemical shifts (δ) for ¹H and ¹³C NMR spectra are given in ppm relative to residual protio signals of the solvent (CDCl₃: $\delta_{\rm H} = 7.26$ ppm ¹H NMR, $\delta_{\rm C} = 77.16$ ppm ¹³C NMR and C₆D₆: $\delta_{\rm H} = 7.16$ ppm ¹H NMR, $\delta_{\rm C} = 128.06$ ppm ¹³C NMR). GCMS data was collected on an Agilent 5973 MSD with a 6890N series GC. Toluene was sparged with dinitrogen and passed over an activated alumina column prior to use. n-Hexane was dried over sodium-benzophenone radical, refluxed, and distilled under dinitrogen prior to use. All deuterated NMR solvents were purchased from Cambridge Isotope Laboratories. Benzene-d6 was dried over CaH₂ and distilled under dinitrogen. CDCl₃ was dried over P₂O₅ and distilled under dinitrogen. $Ti(NMe_2)_4$ was purchased from Gelest and used as received. Tetrakis(triphenylphosphine)palladium(0) was purchased from Strem and used as received. 1phenyl-1-propyne was purchased from Combi-blocks and distilled from barium oxide prior to use. Aniline was purchased from Sigma-Aldrich and distilled from KOH and passed through dry alumina prior to use. [Ir(COD)OMe]₂, *H2dpm*, 3-(3,5-bis(trifluoromethyl)phenyl)-1*H*-pyrrole were prepared according to the literature procedures.^{25,26,27}

Synthesis of Asymmetric Ligands and Intermediates

Synthesis of *H*₂*dpm*^{2-Me}



A 100 mL Schlenk flask equipped with a stir bar was purged with dinitrogen and charged with DMF (3.6 mL), and the flask was cooled in an ice bath for 10 min. POCl₃ (0.54 mL, 5.8 mmol) was added dropwise, and the solution was stirred at 0 °C for 10 min. Then, a solution of H₂dpm (1.0 g, 5.5 mmol) in DMF (10 mL) was added. The resulting mixture was stirred in an ice bath for 2 h, and then added to a cold mixture of an aqueous NaOH solution (2 M, 300 mL) and DCM (200 mL). After stirring for 20 min, the organic layer was separated, washed with saturated aqueous NH₄Cl solution and then water, and then dried over Na₂SO₄. The mixture was dried in *vacuo*, and was purified by column chromatography on silica gel (hexanes : ethyl acetate = 9 : 1) to give a yellow solid (0.59 g, 53%). ¹H NMR (CDCl3, 500 MHz, 25 °C): δ 9.97 (s, 1H), 7.80 (d, J = 8.4 Hz, 2H), 7.62 (dd, J = 3.1, 1.8 Hz, 1H), 7.33 (d, 2H, 8.4 Hz), 7.15 (dd, J = 3.8, 1.8 Hz, 1H), 6.40 (t, J = 3.4 Hz, 1H), 2.42 (s, 3H). LRMS (EI): calc'd: 202; found: 202. ¹H NMR spectrum was consistent with those previously reported.²⁸ The yellow solid (0.50 g, 2.47 mmol), potassium hydroxide (0.99 g, 25.3 mmol), and hydrazine hydrate (1.067 g, 21.31 mmol) were dissolved in ethylene glycol (13 mL) in a 100 mL Schlenk flask. The reaction mixture was degassed with nitrogen and stirred at 70 °C for 1 h. After 1 hour, the reaction was refluxed for 2 h. Then, the mixture was cooled down to room temperature and diluted with water (50 mL) and DCM (50 mL). The aqueous layer was extracted with DCM (3 x 50 mL). The organic layers were combined, dried with Na₂SO₄, and filtered. The crude product was purified using column chromatography on silica gel (hexanes : ethyl acetate = 9 : 1) to yield the product as an off white solid. (0.25 g, 52% yield). ¹H NMR (CDCl₃, 500 MHz): $\delta = 7.82$ (s br, 1H), 7.45 (s br, 1H), 6.65-6.62 (m, 1H), 6.83 (dd, J =

3.3 Hz, 2.7 Hz, 1H), 5.95 (t, J = 3.0 Hz, 1H), 5.78-5.75 (m, 1H), 2.17 (s, 3H), 1.62 (s, 6H). LRMS (EI): calc'd: 188; found: 188.

Synthesis of (1-tosyl-1H-pyrrol-2-yl)methanol



The synthesis was adapted from a literature procedure.²⁸ In a N₂ glove box, a 250 mL Schlenk flask equipped with a stir bar was purged with dinitrogen and charged with pyrrole-2carboxaldehyde (2.0 g, 21 mmol, 1.0 equiv) and THF (50 mL). The mixture was cooled down in the freezer (-35 °C) for 30 min. After 30 min, sodium hydride (0.6 g, 23.1 mmol, 1.1 equiv) was added in portions over 30 min. The mixture was warmed up and stirred at room temperature until no gas was released. Then, a solution of para-toluenesulphonyl chloride (4.4 g, 23.1 mmol, 1.1 equiv) in THF (15 ML) was added dropwise to the reaction, and the mixture was stirred at room temperature for 12 h. The reaction was quenched with 50 mL of water. The crude product was extracted with ethyl acetate and washed with brine. Removal of the solvent afforded the crude product as a brown solid (5.2 g). ¹H NMR and ¹³C NMR spectra were consistent with those previously reported.²⁹ ¹H NMR (CDCl₃, 500 MHz, 25 °C): δ 9.97 (s, 1H), 7.80 (d, J = 8.4 Hz, 2H), 7.62 (dd, J = 3.1, 1.8 Hz, 1H), 7.33 (d, 2H, 8.4 Hz), 7.15 (dd, J = 3.8, 1.8 Hz, 1H), 6.40 (t, J = 3.4 Hz, 1H), 2.42 (s, 3H). The brown solid was dissolved in 30 mL of MeOH. Sodium borohydride (1.6 g, 2.0 equiv) was added in 3 portions over 10 min, and the resulting mixture was stirred for 2 h. To the reaction was added 20 mL of water and then 20 mL of ethyl acetate. The organic layer was separated, dried over Na₂SO₄, and evaporated to afford a brown solid. The crude product was purified by recrystallization in DCM/hexanes (white solid, 5.14 g, 97%). ¹H NMR (CDCl₃, 500 MHz, 25 °C): δ 7.71 (d, J = 8.6 Hz, 2H), 7.31 (d, J = 8.7 Hz, 2H), 7.28-7.25 (m, 1H), 6.25 (dd, J = 3.4, 1.9 Hz, 1H), 6.23 (t, J = 3.3 Hz, 1H), 4.60 (d, J = 5.7 Hz, 2H), 2.41 (s, 3H). LRMS (EI): calc'd: 251; found: 251. The ¹H NMR spectrum was consistent with that previously reported.²⁹



A 50 mL Schlenk flask was loaded with 5-methoxy-1*H*-indole-3-carbaldehyde (1.05 g, 1.0 equiv, 6 mmol), and THF (30 mL), and a stir bar. The solution was cooled in an ice bath for 20 min. To the solution, lithium aluminum hydride (455 mg, 2.0 equiv, 12 mmol) was added in portions. After the addition was complete, the mixture was warmed up to room temperature and stirred for 12 h. The reaction was cooled down in an ice bath for 10 min, and 3 mL of water was added dropwise. After stirring for 15 min, ethyl acetate (50 mL) was added, and the organic layer was separated and dried over MgSO4. The product was purified by chromatography on silica gel (hexanes). ¹H NMR (CDCl₃, 500 MHz, 25 °C): δ 7.84 (s br, 1H), 7.24 (d, J = 8.7 Hz, 1H), 7.07 (s, 1H), 6.96 (s, 1H), 6.9 (d, J = 8.7 Hz, 1H), 3.92 (s, 3H), 2.35 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 500 MHz, 25 °C): δ 153.89, 131.50, 128.66, 122.65, 112.11, 111.83, 111.40, 100.71, 56.03, 9.83. LRMS (EI): calc'd: 161; found: 161. ¹H NMR and ¹³C NMR spectra were consistent with those previously reported.³⁰ Synthesis of 2-((1H-pyrrol-2-yl)methyl)-3-methyl-5-methoxyindole



A 50 mL Schlenk flask was loaded with (1-tosyl-pyrrol-2-yl)methanol (502 mg, 1.0 equiv, 2 mmol), 3-methyl-5-methoxyindole (322 mg, 1.0 equiv, 2.0 equiv), DCM (5 mL), and a stir bar. Then, boron trifluoride etherate (0.1 ml, 40 mol %) was added to the mixture dropwise via syringe. The reaction was stirred for one hour at room temperature. The production of the intermediate and the consumption of the starting material were confirmed by GC/MS. After the removal of solvent, the product was dissolved in a mixture of methanol (20 mL) and THF (20 mL). KOH (450 mg, 8.0 equiv) was added to the mixture, and the mixture was refluxed for 4 h. The organic layer was washed with brine, then, separated, and dried over Na₂SO₄. After the removal of solvent, the product was purified by chromatography on silica gel (10% ethyl acetate in hexanes) to obtain light yellow oil (290 mg, 40%). ¹H NMR (CDCl₃, 500 MHz, 25 °C): δ 7.74 (s br, 1H), 7.45 (s br, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.99 (d, J = 2.6 Hz, 1H), 6.80 (dd, J = 7.4 Hz, 2.6 Hz, 1H), 6.62 (m, 1H), 6.19 (m, 1H), 6.08 (m, 1H), 4.05 (s, 2H), 3.88 (s, 3H), 2.28 (s, 3H). ¹³C{¹H} NMR (CDCl₃,

500 MHz, 25 °C): δ 154.01,132.58, 130.52, 129.66, 128.40, 117.51, 111.41, 111.30, 108.64, 107.74, 106.67, 100.66, 56.08, 24.88, 8.67. LRMS (EI): calc'd: 240; found: 240. Synthesis of *2-(1H-indol-2-yl)propan-2-ol*

A 250 mL Schlenk flask equipped with a stir bar was purged with dinitrogen and charged with ethyl indole-2-carboxylate (1.89 g, 10 mmol, 1.0 equiv) and dry THF (30 mL). The solution was cooled to -78 °C in a dry ice/acetone bath for 15 min. Methyllithium (3.1 M in DME, 16.1 mL, 5.0 equiv) was added dropwise over 15 min. The reaction was stirred at -78 °C for 3 h. Then, water (5 mL) was added dropwise to quench the reaction. The reaction mixture was allowed to warm to room temperature. Ethyl acetate (50 mL) was added to extract the product. The organic layer was washed with brine (50 mL) and separated from the aqueous layer. The organic layer was separated, dried over Na₂SO₄, and evaporated to afford the product as a light yellow oil (1.44 g, 82%). ¹H NMR (CDCl₃, 500 MHz, 25 °C): δ 8.70 (s, 1H), 7.85 (s, 1H), 7.45-7.35 (m, 2H), 6.38 (s, 1H), 1.96 (s, 1H), 1.70 (s, 6H). LRMS (EI): calc'd: 175; found: 175. ¹H NMR spectrum was consistent with those previously reported.³⁰

Synthesis of 2-(2-(4-(3,5-bis(trifluoromethyl)phenyl)-1H-pyrrol-2-yl)propan-2-yl)-1H-indole



A 50 mL Schlenk flask was loaded with 2-(1*H*-indol-2-yl)propan-2-ol (525 mg, 2 mmol), 3-(3,5bis(trifluoromethyl)phenyl)-1*H*-pyrrole (921 mg, 2.2 mmol, 1.1 equiv), DCM (5 mL), and a stir bar. Then, boron trifluoride etherate (0.15 ml, 40 mol %) was added to the mixture dropwise via syringe. The reaction was stirred for an hour at room temperature. The production of the intermediate and the consumption of the starting material was confirmed by GC/MS. Saturated aqueous Na₂CO₃ solution (10 mL) was added to the mixture, and the mixture was stirred for 20 min. Ethyl acetate (20 mL) was added, and the organic layer was separated. The product was purified by a silica gel auto-column chromatography, eluted with hexane and ethyl acetate (8:2) to get a purple oil (98 mg, 14%). ¹H NMR (CDCl₃, 500 MHz, 25 °C): δ 7.97 (s br, 1H), 7.91 (s, 2H), 7.83 (s br, 1H), 7.66 (s, 1H), 7.61 (d, J = 7.5 Hz, 2H), 7.26 (d, J = 7.5 Hz, 2H), 7.19-7.08 (m, 2H), 7.19-7.08 (m, 2H), 7.02 (s, 1H), 6.52 (s, 1H), 6.49 (s, 1H), 1.81 (s, 6H). $^{13}C{^{1}H}$ NMR (CDCl₃, 126 MHz, 25 °C): δ 145.02, 140.67, 138.08, 136.31, 132.07, 131.80, 128.48, 128.23, 124.79, 122.24, 122.11, 120.45, 120.11, 115.50, 110.84, 102.45, 98.91, 36.11, 28.91. ^{19}F NMR (470 MHz, C₆C₆, 25 °C) δ –62.82. LRMS (EI): calc'd: 436; found: 436.

Synthesis of 2-phenyl-1*H*-pyrrole



In a N₂ glovebox, Pd(PPh₃)₄ (0.117 g, 0.01 mmol) was loaded into a 35 mL pressure tube. Bromobenzene (0.330 g, 2.10 mmol, 1.05 equiv) and 5 mL DME were added, and the solution was stirred for 10 min. To the solution 2-(pinacolboryl)-N-BOC-pyrrole (0.586 g, 2 mmol) in DME (2 mL) was added. Finally, K₃PO₄ (0.400 g, 3.0 mmol, 1.5 equiv) was added. The tube was capped, taken out of the glovebox, and heated at 100 °C in an oil bath for 24 h. When the reaction was complete as judged by GC-FID, the solution was transferred to a separatory funnel. The tube was rinsed with diethyl ether (30 mL) and water (30 mL). The solution was extracted with diethyl ether (2 × 30 mL). The combined organic layers were dried over MgSO₄. Volatiles were removed in *vacuo* to yield a viscous oil, which was placed under a continuous flow of N₂ and heated in an oil bath at 170 °C and left to stir for ~20 min. The product was purified by chromatography on silica gel (10% ethyl acetate in hexanes), and a white solid was obtained. (0.209 g, 73%). ¹H NMR (CDCl₃, 500 MHz): 8.45 (br s, 1H), 7.48 (d, J = 7.1 Hz, 2H), 7.37 (t, J = 7.45 Hz, 2H), 7.21 (t, J = 7.45 Hz, 1H), 6.87 (m, 1H), 6.53 (m, 1H), 6.31 (m, 1H). ¹³C{¹ H} NMR (CDCl₃, 500 MHz): 132.90, 132.20, 129.03, 126.35, 123.99, 118.95, 110.26, 106.08. LRMS (EI): calc'd: 143; found: 143. Synthesis of 2-(*p*-tolyl)-1*H*-pyrrole



In a N₂ glovebox, Pd(PPh₃)₄ (0.117 g, 0.01 mmol) was loaded into a 35 mL pressure tube. To the pressure tube, 4-iodotoluene (0.458 g, 2.10 mmol, 1.05 equiv) and DME (5 mL) were added, and

the solution was stirred for 10 min. To the solution 2-(pinacolboryl)-N-BOC-pyrrole (0.586 g, 2 mmol) in DME (2 mL) were added. Finally, K₃PO₄ (0.400 g, 3.0 mmol, 1.5 equiv) was added. The tube was capped, taken out the dry box, and heated at 100 °C in an oil bath for 24 h. When the reaction was complete as judged by GC-FID, the solution was transferred to a separatory funnel. The tube was rinsed with diethyl ether (30 mL) and water (30 mL). The solution was extracted with diethyl ether (2 X 30 mL). The combined organic layers were dried over MgSO₄. Volatiles were removed in *vacuo* to yield a viscous oil, which was placed under a continuous flow of N₂ and heated in an oil bath at 170 °C and left to stir for ~20 min. The product was purified by chromatography on silica gel (10% ethyl acetate in hexanes). A white solid (0.245 g, 78%). ¹H NMR (CDCl₃, 500 MHz): 8.40 (br s, 1H), 7.38 (d, J = 7.7 Hz, 2H), 7.18 (d, J = 7.7 Hz, 2H), 6.85 (m, 1H), 6.48 (m, 1H), 6.29 (m, 1H), 2.35 (s, 3H). ¹³C {¹ H} NMR (CDCl₃, 500 MHz): 136.07, 129.69, 123.98, 118.53, 110.13, 105.51, 21.26. LRMS (EI): calc'd: 157; found: 157. ¹H NMR and ¹³C NMR spectra were consistent with those previously reported.³²

Synthesis of 2-(2-(5-phenyl-1H-pyrrol-2-yl)propan-2-yl)-1H-indole



A 50 mL Schlenk flask was loaded with 2-(1*H*-indol-2-yl)propan-2-ol (525 mg, 2 mmol), 2-phenyl-1*H*-pyrrole (315 mg, 2.2 mmol, 1.1 equiv), DCM (5 mL), and a stir bar. Then, boron trifluoride etherate (0.15 ml, 40 mol %) was added to the mixture dropwise via syringe. The reaction was stirred for one hour at room temperature. The production of the intermediate and the consumption of the starting material were confirmed by GC/MS. Saturated aqueous Na₂CO₃ solution (10 mL) was added to the mixture, and the mixture was stirred for 20 min. Ethyl acetate (20 mL) was added, and the organic layer was separated. The product was purified by a silica gel auto-column chromatography, eluted with hexane and ethyl acetate (8:2) to obtain a purple oil (98 mg, 14%). ¹H NMR (CDCl₃, 500 MHz): 8.06 (br s, 1H), 7.91 (br s, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.36 (d, J = 7.3 Hz, 1H), 7.30 (t, J = 7.3 Hz, 1H), 7.19-7.07 (m, 2H), 1.80 (s, 6H). ¹³C{¹ H} NMR (C₆D₆, 500 MHz): 145.50, 139.49, 136.65, 133.14, 132.27, 129.14, 128.89, 126.11, 123.90, 122.04, 120.70, 120.29, 111.24, 106.87, 106.37, 99.16, 36.20, 29.32. LRMS (EI): calc'd: 300; found: 300.

Synthesis of 2-(2-(5-(p-tolyl)-1H-pyrrol-2-yl)propan-2-yl)-1H-indole



A 50 mL Schlenk flask was loaded with 2-(1*H*-indol-2-yl)propan-2-ol (525 mg, 2 mmol), 2phenyl-1*H*-pyrrole (346 mg, 2.2 mmol, 1.1 equiv), dichloromethane (5 mL), and a stir bar. Then, boron trifluoride etherate (0.15 ml, 40 mol %) was added to the mixture dropwise via syringe. The reaction was stirred for one hour at room temperature. The production of the intermediate and the consumption of the starting material were confirmed by GC/MS. Saturated aqueous Na₂CO₃ solution (10 mL) was added to the mixture, and the mixture was stirred for 20 min. Ethyl acetate (20 mL) was added, and the organic layer was separated. The product was purified by a silica gel auto-column chromatography, eluted with hexane and ethyl acetate (8:2) to obtain a purple oil (98 mg, 14%). ¹H NMR (CDCl₃, 500 MHz): 7.97 (br s, 1H), 7.87 (br s, 1H), 7.61 (d, J = 7.7 Hz, 1H), 7.38 (d, J = 7.7 Hz, 1H), 7.25 (d, J = 6.5 Hz, 1H), 7.17-7.07 (m, 4H), 2.06 (s, 3H), 1.80 (s, 6H). ¹³C{¹ H} NMR (CDCl₃, 500 MHz): 145.98, 139.97, 136.17, 135.98, 129.66, 129.58, 128.37, 123.96, 123.74, 121.77, 120.29, 119.87, 110.84, 106.15, 105.06, 98.34, 36.13, 29.13, 21.15. LRMS (EI): calc'd: 314; found: 314. Synthesis of *H₂dpm^{2-Bpin}*



In a N₂ glovebox, $[Ir(COD)OMe]_2$ (14 mg, 0.01 equiv) and 4,4'-di-tert-butyl-2,2'-bipyridine (5.4 mg, 0.02 equiv) were dissolved in THF (2 mL) in a 35 mL pressure tube, and the mixture was stirred for 5 min. B₂pin₂ (127 mg, 0.5 equiv) was added to the pressure tube, and mixture was stirred for another 5 min. Then, H₂dpm (174 g, 1.0 equiv) was added as a solution in THF (3 mL). The pressure tube was sealed, removed from the glovebox, and heated in oil bath at 80 °C for 24

h. The mixture was allowed to cool to room temperature, and THF was removed by rotary evaporation. The crude product was diluted with a mixture of hexane (30 mL) and ethyl acetate (30 mL) and flushed through a silica plug. Removal of the solvent afforded crude product as a light brown oil (290 mg, 96%). The product was used in the next step without further purification. ¹H NMR (CDCl₃, 500 MHz, 25 °C) δ 8.29 (s br, 1H), 7.77 (s br, 1H), 6.77 (t, J = 3.0 Hz, 1H), 6.64 (s, 1H), 6.16-6.13 (m, 2H), 6.09 (s, 1H), 6.11-6.07 (m, 1H), 1.66 (s, 6H), 1.29 (s, 12H). LRMS (EI): calc'd: 300, found: 300. The NMR shows a compound with modest purity, that was used without further purification in the next step.

Synthesis of 2-(2-(1H-pyrrol-2-yl)propan-2-yl)-5-phenyl-1H-pyrrole



In a N₂ glovebox, Pd(PPh₃)₄ (0.117 g, 0.01 mmol) was loaded into a 35 mL pressure tube. Bromobenzene (0.165 g, 1.05 mmol, 1.05 equiv) and 1 mL DME were added, and the solution was stirred for 10 min. To the solution of H_2dpm^{2-Bpin} (0.300 g, 1 mmol) in DME (2 mL). Finally, K₃PO₄ (0.200 g, 1.5 mmol, 1.5 equiv) was added. The tube was capped, taken out of the glovebox, and heated at 100 °C in an oil bath for 24 h. When the reaction was complete as judged by GC-FID, the solution was transferred to a separatory funnel. The tube was rinsed with diethyl ether (30 mL) and water (30 mL). The solution was extracted with diethyl ether (2 X 30 mL). The combined organic layers were dried over MgSO₄. The product was purified by chromatography on silica gel (2% ethyl acetate in hexanes), and a colorless solid was obtained. (0.0775 g, 31%).

¹H NMR (CDCl₃, 500 MHz, 25 °C): δ 7.97 (s br, 1H), 7.87 (s br, 1H), 7.38 (d, J = 7.2 Hz, 1H), 7.33 (d, J = 7.2 Hz, 1H), 7.18 (d, J = 7.2 Hz, 1H), 6.68-6.65 (m, 1H), 6.45 (dd, J = 3.5 Hz, 2.7 Hz, 1H), 6.20-6.14 (m, 2H), 1.70 (s, 6H). LRMS (EI): calc'd: 250; found: 250.

Synthesis of 2-(2-(1H-pyrrol-2-yl)propan-2-yl)-5-(3,5-dimethylphenyl)-1H-pyrrole



In a N₂ glovebox, Pd(PPh₃)₄ (0.117 g, 0.01 mmol) was loaded into a 35 mL pressure tube. 5-Bromo-m-xylene (0.195 g, 1.05 mmol, 1.05 equiv) and 1 mL DME were added, and the solution was stirred for 10 min. To the solution of H_2dpm^{2-Bpin} (0.300 g, 1 mmol) in DME (2 mL). Finally, K₃PO₄ (0.200 g, 1.5 mmol, 1.5 equiv) was added. The tube was capped, taken out of the glovebox, and heated at 100 °C in an oil bath for 24 h. When the reaction was complete as judged by GC-FID, the solution was transferred to a separatory funnel. The tube was rinsed with diethyl ether (30 mL) and water (30 mL). The solution was extracted with diethyl ether (2 X 30 mL). The combined organic layers were dried over MgSO₄. The product was purified by chromatography on silica gel (2% ethyl acetate in hexanes), and a colorless solid was obtained. (0.117 g, 42%). ¹H NMR (CDCl₃, 500 MHz, 25 °C): δ 7.93 (s br, 1H), 7.85 (s br, 1H), 6.98 (s, 1H), 6.81 (s, 1H), 6.39-6.36 (m, 1H), 6.18-6.15 (m, 1H), 6.15-6.12 (m, 2H), 2.30 (s, 6H), 1.69 (s, 6H). ¹³C {¹ H} NMR (CDCl₃, 500 MHz): 138.36, 127.99, 127.85, 121.82, 121.58, 121.55, 118.49, 109.97, 105.75, 105.72, 105.39, 102.83, 35.19, 29.11, 21.42. LRMS (EI): calc'd: 278; found: 278.

Synthesis of 2-(2-(1H-pyrrol-2-yl)propan-2-yl)-5-(3,5-dimethylphenyl)-1H-pyrrole



In a N₂ glovebox, Pd(PPh₃)₄ (0.117 g, 0.01 mmol) was loaded into a 35 mL pressure tube. 5-Bromo-m-xylene (0.308 g, 1.05 mmol, 1.05 equiv) and 1 mL DME were added, and the solution was stirred for 10 min. To the solution of H_2dpm^{2-Bpin} (0.300 g, 1 mmol) in DME (2 mL). Finally, K₃PO₄ (0.200 g, 1.5 mmol, 1.5 equiv) was added. The tube was capped, taken out of the glovebox, and heated at 100 °C in an oil bath for 24 h. When the reaction was complete as judged by GC-FID, the solution was transferred to a separatory funnel. The tube was rinsed with diethyl ether (30 mL) and water (30 mL). The solution was extracted with diethyl ether (2 X 30 mL). The combined organic layers were dried over MgSO₄. The product was purified by chromatography on silica gel (2% ethyl acetate in hexanes), and a colorless solid was obtained. (0.140 g, 36%). ¹H NMR (CDCl₃, 500 MHz, 25 °C): δ 8.07 (s br, 1H), 7.87 (s br, 1H), 7.73 (s, 2H), 7.61 (s, 1H), 6.72-6.70 (m, 1H), 6.58 (dd, J = 3.7, 2.7 Hz, 1H), 6.23-6.21 (m, 1H), 6.21-6.18 (m, 1H), 6.18-6.16 (m, 1H), 1.72 (s, 6H). ¹³C{¹ H} NMR (CDCl₃, 500 MHz): 141.61, 138.43, 134.61, 132.04, 129.16, 129.01, 123.34, 120.88, 111.01, 108.67, 108.58, 107.11, 102.81, 35.17, 29.09. LRMS (EI): calc'd: 386; found: 386. ¹H NMR spectrum was consistent with those previously reported.²⁸
Spectral Data for Asymmetric Ligands and Intermediates

¹H NMR of *1-tosyl-1H-pyrrole-2-carbaldehyde*



 1H NMR and $^{13}C\{^1H\}$ NMR of (1-tosyl-1H-pyrrol-2-yl)methanol





1H NMR and $^{13}C\{^1H\}$ NMR of 3-methyl-5-methoxyindole



 $^{1}\mathrm{H}$ NMR and $^{13}\mathrm{C}\{^{1}\mathrm{H}\}$ NMR of 2-((1H-pyrrol-2-yl)methyl)-3-methyl-5-methoxyindole



 1H NMR and $^{13}C\{^1H\}$ NMR of 2-(1H-indol-2-yl)propan-2-ol

 $^{1}\mathrm{H}\ \mathrm{NMR}\ \mathrm{of}\ 2-(2-(4-(3,5-bis(trifluoromethyl)phenyl)-1H-pyrrol-2-yl)propan-2-yl)-1H-indole$



¹³C{¹H} NMR and ¹⁹F NMR of 2-(2-(4-(3,5-bis(trifluoromethyl)phenyl)-1H-pyrrol-2-yl)propan-2-yl)-1H-indole





 1H NMR and $^{13}C\{^1H\}$ NMR of 2-(phenyl)-1H-pyrrole



¹H NMR and ¹³C{¹H} NMR of 2-(p-tolyl)-1H-pyrrole



 ^1H NMR and $^{13}\text{C}\{^1\text{H}\}$ NMR of 2-(2-(5-phenyl-1H-pyrrol-2-yl)propan-2-yl)-1H-indole



 $^1\mathrm{H}$ NMR and $^{13}\mathrm{C}\{^1\mathrm{H}\}$ NMR of 2-(2-(5-(p-tolyl)-1H-pyrrol-2-yl)propan-2-yl)-1H-indole

¹H NMR of $H_2 dpm$



¹H NMR of $H_2 dpm^{2-Bpin}$



¹H NMR of $H_2 dpm^{2-CHO}$



¹H NMR of $H_2 dpm^{2-Me}$





¹H NMR and ¹³C{¹H} NMR of *2-(2-(1H-pyrrol-2-yl)propan-2-yl)-5-(3,5-dimethylphenyl)-1H-pyrrole*



 ${}^{l}HNMR of 2-(2-(1H-pyrrol-2-yl)propan-2-yl)-5-(3,5-bis(trifluoromethyl)phenyl)-1H-pyrrole$



¹H NMR of 2-(2-(1H-pyrrol-2-yl)propan-2-yl)-5-(phenyl)-1H-pyrrole

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APPENDIX: COMPUTATIONAL DETAILS IN CHAPTER 2: TITANIUM-MEDIATED PYRIDINE SYNTHESES FROM ISOXAZOLE VIA INVERSE ELECTRON-DEMAND *HETERO*-DIELS-ALDER REACTION

Computational method

All calculations were performed with the Gaussian 16 B.01. Density functional theory (DFT) calculations using the aug-cc-PVDZ basis set and the B3LYP-D3 functional were employed to optimize geometry and to find transition states. The reported energies in this work are Gibbs free energy (Δ G) and enthalpies (Δ H), all in the gas phase at 298 K. The solvent effect with several solvents was estimated with SMD solvation model. To simplify the calculations, ethenamine was employed for enamines. All figures of structures were prepared by using GaussView6.

Computational Modeling of the Gas Phase Mechanistic Pathway

Both Path A and B share an initial [4 + 2]-cycloaddition (Scheme 2.5), which is where our investigations into the mechanism began. The cycloaddition step gives us four possible isomers: endo and exo of I1-1 and I1-2. Calculation of the energy barrier for the cycloaddition step (Figure 2.6) gave us clarity about the relative stability of these species.

The energy of isomers **I1-1** both exo/endo is ~1-2 kcal/mol lower than **I1-2** (**Figure 4.1**). However, the activation energy for the formation of **I1-1** is approximately 14 kcal/mol lower than **I1-2**; therefore, **I1-1** would be the more favored regioisomer over **I1-2**. The energy barrier for the formation of endo isomers is always slightly lower than exo isomers; whereas, thermodynamically **I1-1** exo is slightly more stable than **I1-1** endo. We can say that **I1-1** exo is the thermodynamic product, and **I1-1** endo is slightly favored kinetically. In all likelihood, both endo and exo **I1-1** are generated; however, both lead to the same observed final product after amine elimination.

According to the NBO calculations, for **I1-1**, the lone pair present on N1 donates its electron density into the C2-N3 antibonding orbital (**Figure 4.1**). Furthermore, there is donation from N1 to the antibonding orbital of the C-H bond at C2. With another regioisomer **I1-2**, there are no such secondary interactions possible.

The cycloaddition step follows a concerted mechanism in the gas phase. The transition states for the cycloaddition step are symmetrical, i.e., 2 bonds are being made to the electron-rich olefin, and asynchronous, i.e., the asymmetric dienophile leads to a different amount of bond making in the two new bonds. All the transition states were asynchronous, but the symmetry changes when incorporating solvent models into our calculations (vide infra).



Figure 4.1 (Top) Free energy profile for cycloaddition (CA) reaction, (bottom) **I1-1** endo. Since **TS1-1** endo/exo is far lower in energy than **TS1-2** endo/exo, we only consider this pathway going forward. We proposed two possible mechanisms to access the pyridine N-oxide from **I1-1**. Path A is amine loss followed by ring-opening, and Path B ring opening followed by amine loss (**Scheme 2.5**).

To quantify the trend in the symmetry of the transition state (TS), we used bond length ratios τ (Eq 4.1). This ratio τ can be used to discern the nature of the TS. Subjectively, when $\tau < \sim 0.7$, the transition state looks asymmetric, and, when $\tau > 0.7$, the transition state looks symmetric.

$$\tau = \frac{(C-C \text{ bond length in } TS)/(C-C \text{ bond length in Product})}{(C-N \text{ bond length in } TS)/(C-N \text{ bond length in Product})}$$
(Eq 4.1)

	No solvent	Heptane	1,4- Dioxane	THF	DCM	EtOH	H ₂ O
k	0	1.92	2.21	7.52	8.93	24.6	78.5
TS1-1-endo	0.693	0.678	0.676	0.682	0.684	0.692	0.695
TS1-1-exo	0.745	0.708	0.699	0.649	0.649	0.591	0.588
TS1-2-endo	0.909	0.896	0.893	0.882	0.878	0.885	0.845
TS1-2-exo	0.873	0.865	0.864	0.857	0.854	0.844	0.823

Table 4.1 The τ value for cycloaddition in different solvents with their dielectric constant (k). See Figure 4.1 for structures.

After the cycloaddition step, this reaction mechanism divaricates into two pathways. In **Path A**, **I1** (cycloaddition products, *endo* and *exo*) eliminates ammonia and forms a double bond within the pyridine ring to make **I2_\alpha** (**Figure 4.2**). Then, C–O bond cleavage of norbornadiene-like **I2_\alpha** leads to pyridine-N-oxide (**I3**). In **Path B**, C–O bond cleavage in **I1** leads to dihydropyridine-*N*-oxide **I2_\beta**, and, losing ammonia, the pyridine ring aromatizes to give pyridine-*N*-oxide (**I3**).

In **Path A**, norbornadiene-like I2_ α (plus ammonia) is roughly 26 kcal/mol higher in energy than the initial cycloaddition products (I1), and the transition state energy is 61.5 kcal/mol (TS2_ α). The activation energy for the formation of the pyridine-*N*-oxide (TS3_ α) is 60 kcal/mol, and this is an exergonic by 100 kcal/mol.



Figure 4.2 Energy diagram for two pathway mechanism for exo (right) and endo (left). Energy values for **I1** in each energy diagram are set to 0; however, **I1-1** endo is ~1.5 kcal/mol higher in energy than **I1-1** exo.

In **Path B**, cyclohexadiene-like $I2_{\beta}$ is 21.7 kcal/mol lower in energy than the initial cycloaddition product I1, and the activation energy is 38.7 kcal/mol. Elimination of the amine to make the pyridine-N-oxide (Step 2 in Path B) is also exergonic with an activation barrier of 29.3 kcal/mol.

Effects on Solvent on the Mechanistic Pathway

To get more realistic data we added a solvent model and reoptimized the pathway. It was noticed that **TS1-1** (**Figure 4.1**), both exo and endo, are asymmetric when a solvent model is used; whereas, **TS1-2** endo/exo were both symmetric. The asymmetric transition states for **TS1-1** endo/exo show more C–N bond formation than C–C bond. While the nature of the transition state is different with the inclusion of the solvent model, the energy of the transition state is similar to the gas phase calculation.



Figure 4.3 Correlation between τ (Eq. 4.1) and dielectric constant (κ) of different solvents. The dielectric constants for the solvents are (left to right) represented by the vertical lines: gas phase (0), heptane, dioxane, THF, dichloromethane, EtOH, and water.

To investigate the effect of solvent polarity on the energies and structures, the compounds and transition states were reoptimized in different solvents using the SMD model. The energies were recalculated in heptane, dioxane, THF, DCM, ethanol (EtOH), and H₂O. Figure 4 shows variation of τ value (**Eq. 4.1**) in different solvents. The only transition state structure showing structural changes (by this metric) as a function of solvent polarity is **TS1-1** exo, which gets more asymmetric as the polarity is increased. The other isomers of the transition state showed little energy change with solvent polarity. It was observed that **I1-1** endo/exo are energetically favored products irrespective of the solvent polarity (**Figure 4.4**). In low polarity solvents, **I1-1** exo is slightly less kinetically favored than *endo* isomer but in high polarity solvents, **I1-1** exo is both kinetically and thermodynamically favored product.



$\Delta \mathbf{G}^{\ddagger}$							
(kcal/mol)	Gas Phase	Heptane	Dioxane	THF	DCM	EtOH	H2O
Reactants	0.00	0.00	0.00	0.00	0.00	0.00	0.00
TS1-1-endo	41.93	40.69	39.51	39.42	39.52	37.13	36.17
TS1-1-exo	42.89	42.12	40.90	40.64	40.83	36.56	35.22
TS1-2-endo	54.46	54.97	54.10	55.45	55.81	54.50	54.02
TS1-2-exo	55.25	55.92	55.13	56.67	56.94	55.67	54.86
I1-1-endo	31.27	30.70	29.70	31.10	31.24	29.01	26.94
I1-1-exo	27.94	27.66	26.70	28.36	28.55	26.57	24.57
I1-2-endo	34.44	34.23	33.18	34.40	34.59	32.45	30.35
I1-2-exo	32.86	32.82	31.84	33.28	33.46	31.31	28.95

Figure 4.4 Energy barrier ΔG^{\ddagger} (kcal/mol) of cycloaddition transition states in different solvents (top), free energy for cycloaddition products ΔG_{rxn} (kcal/mol) (middle), and the table of the transition state energy barrier (ΔG^{\ddagger}) and free energy of cycloaddition products (ΔG_{rxn}) in different solvents. See **Figure 4.1** for structures.

Input Files for Calculated Structures

Gas phase

Enamine

Zero-point correction= 0.068536 (Hartree/Particle)
Thermal correction to Energy= 0.072490
Thermal correction to Enthalpy= 0.073434
Thermal correction to Gibbs Free Energy= 0.043867
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Sum of electronic and thermal Energies= -133.900095
Sum of electronic and thermal Enthalpies= -133.899151
Sum of electronic and thermal Free Energies= -133.928718

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geom=connectivity empirical dispersion=gd3

Title Card Required

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- Н -0.92722554 -0.00229978 -0.57737189
- N -1.11429162 -0.06923289 2.17241399
- Н -1.00796633 0.32196915 3.10013323
- Н -2.00660723 0.15987070 1.74775490

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2 3 1.0 6 1.0

Isoxazole

Zero-point correction= 0.057503 (Hartree/Particle) Thermal correction to Energy= 0.061104 Thermal correction to Enthalpy= 0.062049 Thermal correction to Gibbs Free Energy= 0.031287 Sum of electronic and zero-point Energies= -246.014287 Sum of electronic and thermal Energies= -246.010685 Sum of electronic and thermal Enthalpies= -246.009741 Sum of electronic and thermal Free Energies= -246.040503 %chk=isoxazole.chk # opt=calcall freq b3lyp/aug-cc-pvdz scf=(qc,maxcycle=600) geom=connectivity empirical dispersion=gd3

Title Card Required

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- N -1.26839185 0.0000000 0.34354479
- Н 0.26067470 -0.00000000 -1.05610309
- Н 1.94848522 0.00000000 1.15545321
- Н 0.13761140 0.00000000 3.26453969

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3 7 1.0
4 5 1.0
5
6
7
8
```

TS1-1-endo

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Thermal correction to Gibbs Free Energy= 0.098057
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Sum of electronic and thermal Energies= -379.864971
Sum of electronic and thermal Enthalpies= -379.864027
Sum of electronic and thermal Free Energies= -379.902395

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geom=connectivity empirical dispersion=gd3
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Н	0.06282010 -2.21548468 2.19974948
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Η	0.40549714 0.41210285 3.17781246
Ν	-1.54551196 -2.33695332 0.15399493
Н	-1.32130528 -3.23099568 0.58066030
Η	-2.40900181 -2.45390652 -0.37037842
Н	-1.18490639 -1.53794048 3.28573349

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13 14 1.0 15 1.0
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14					
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TS1-1-exo

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Η
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Η
      -2.49677996 -0.45189818 8.14903546
Η
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Η
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Η
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Н	2.29854309 -0.44775776 0.36482588
Н	0.56421000 2.57374417 0.04548253

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3 11 1.0
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Title Card Required

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Н	0.29292099 3.38240760 -0.19699660

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16				

TS1-2-endo

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Sum of electronic and therma	l Energies=	-379.844690
Sum of electronic and therma	l Enthalpies=	-379.843746
Sum of electronic and therma	l Free Energies=	-379.882435

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С	-0.88414629 -0.32520325 0.00000000
С	-0.88414629 -0.32520325 2.17083335
С	-0.02205738 -0.32520325 1.12772671
С	-0.75999840 -0.24530169 8.16657357

С	-0.05115491 -0.25808196 9.30152225
0	-2.14471958 -0.32520325 1.73185535
N	-2.14086210 -0.32520325 0.35042799
Η	-0.62961145 -0.32520325 -1.05053484
Η	1.05474702 -0.32520325 1.15088209
Η	-0.75267467 -0.32520325 3.24213866
Η	1.03530283 -0.25755915 9.26378999
Η	-0.25270063 -0.24333238 7.20992462
Η	-1.84650500 -0.24864615 8.16912213
Ν	-0.56008067 -0.33640941 10.58495977
Η	-1.53646857 -0.10045330 10.69447635
Н	0.02122401 0.04705656 11.31452716

```
1 3 1.0 7 2.0 8 1.0
```

```
2 3 2.0 6 1.0 10 1.0
```

```
391.0
```

```
4 5 2.0 13 1.0 12 1.0
```

```
5 11 1.0 14 1.0
```

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671.0
```

```
7
8
9
10
11
12
13
14 16 1.0 15 1.0
15
```

С	-1.63019696 0.68927789 0.00000000
С	-0.40308053 0.82517287 1.87779991
С	-0.95519878 1.60659441 0.69813412
С	-0.14538786 -1.09507136 0.50100458
С	0.72167729 -0.12097967 1.34927757
0	-1.45647374 -0.14427631 2.08809974
N	-1.56761874 -0.60171704 0.69319836
Н	-2.12110331 0.73748644 -0.96850074
Н	-0.75920679 2.64348381 0.44424786
Н	-0.18677583 1.36246632 2.80546961
Н	1.12866334 -0.66199714 2.21751639
Н	-0.09297319 -2.12270732 0.87367392
Н	0.10515156 -1.07475018 -0.56582340
N	1.75455748 0.56831093 0.57045212
Н	2.34145744 1.12507853 1.19104997
Н	2.37673479 -0.11637795 0.14392389

```
1 3 2.0 7 1.0 8 1.0
2 3 1.0 5 1.0 6 1.0 10 1.0
3 9 1.0
4 5 1.0 7 1.0 12 1.0 13 1.0
```

5 11 1.0 14 1.0

```
671.0
```

7 8 9

- 11
- 12
13 14 15 1.0 16 1.0 15 16

Title Card Required

0	1
~	_

С	-2.94310726 -0.33916849 0.00000000
С	-1.71599083 -0.20327351 1.87779991
С	-2.26810908 0.57814804 0.69813412
С	-1.12803148 -2.23808317 0.45637385
С	-0.36938814 -1.33604319 1.24503293
0	-2.76938404 -1.17272269 2.08809974
N	-2.88052904 -1.63016341 0.69319836
Н	-3.43401361 -0.29095993 -0.96850074
Н	-2.07211709 1.61503743 0.44424786
Н	-1.49968613 0.33401994 2.80546961
Н	0.03759792 -1.87706065 2.11327175
Н	-1.07561680 -3.26571912 0.82904318
Н	-0.87749206 -2.21776198 -0.61045413
Ν	0.66349205 -0.64675258 0.46620748
Н	1.25039201 -0.08998499 1.08680533
Н	1.28566936 -1.33144146 0.03967925

1 3 1.5 7 1.5 8 1.0 2 3 1.5 5 0.5 6 1.0 10 1.0 3 9 1.0 4 5 1.5 7 0.5 12 1.0 13 1.0 5 11 1.0 14 1.0 6 7 1.0

7
8
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10
11
12
13
14 15 1.0 16 1.0
15
16

TS1-2-exo

Zero-point correction=	0.128257 (Hartree/Particle)
Thermal correction to Energy	= 0.135190
Thermal correction to Enthalp	oy= 0.136134
Thermal correction to Gibbs H	Free Energy= 0.097515
Sum of electronic and zero-po	oint Energies= -379.850431
Sum of electronic and therma	l Energies= -379.843498
Sum of electronic and therma	l Enthalpies= -379.842553
Sum of electronic and thermat	l Free Energies= -379.881172

%chk=TS4.chk

```
# opt=(calcall,qst3) freq b3lyp/aug-cc-pvdz scf=(qc,maxcycle=600)
geom=connectivity empirical dispersion=gd3
```

Title Card Required

01	
С	-0.57926826 -0.32520325 0.00000000
С	-0.57926826 -0.32520325 2.17083335
С	0.28282065 -0.32520325 1.12772671

C -0.45512037 -0.24530169 8.16657357

- C 0.25372312 -0.25808196 9.30152225
- O -1.83984155 -0.32520325 1.73185535
- N -1.83598407 -0.32520325 0.35042799
- Н -0.32473342 -0.32520325 -1.05053484
- Н 1.35962505 -0.32520325 1.15088209
- Н -0.44779664 -0.32520325 3.24213866
- Н 1.34018086 -0.25755915 9.26378999
- Н 0.05217740 -0.24333238 7.20992462
- Н -1.54162697 -0.24864615 8.16912213
- N -0.25520264 -0.33640941 10.58495977
- Н -1.23159054 -0.10045330 10.69447635
- Н 0.32610204 0.04705656 11.31452716

```
1 3 1.0 7 2.0 8 1.0
```

```
2 3 2.0 6 1.0 10 1.0
```

391.0

```
4 5 2.0 13 1.0 12 1.0
```

- 5 11 1.0 14 1.0
- 671.0
- 7
- 8
- 9
- 10
- 11
 - 12
- 13

14 16 1.0 15 1.0

15

16

01

С	-2.17724292 -0.18599562 0.00000000
С	-3.97323550 -1.39692251 0.61253180
С	-2.65162670 -1.42679591 -0.13777443
С	-4.30500935 0.85668057 -0.04968782
С	-4.97584218 -0.55246442 -0.22060038
0	-3.66049867 -0.45912457 1.67759310
Ν	-3.10116106 0.60242098 0.82971730
Н	-1.30739374 0.30685105 -0.42623111
Н	-2.24817746 -2.25164485 -0.71794040
Н	-4.36892272 -2.32865994 1.02436892
Н	-4.99766727 -0.87557991 -1.26704418
Н	-4.97812988 1.53748420 0.48305472
Н	-3.97794301 1.32162675 -0.98611972
Ν	-6.32988799 -0.67689614 0.32547044
Н	-6.34217976 -0.34117478 1.28866742
Н	-6.96985420 -0.07516021 -0.19070513

1 3 2.0 7 1.0 8 1.0

```
2 3 1.0 5 1.0 6 1.0 10 1.0
3 9 1.0
4 5 1.0 7 1.0 12 1.0 13 1.0
5 11 1.0 14 1.0
6 7 1.0
7
8
9
10
11
12
```

13 14 15 1.0 16 1.0 15 16

Title Card Required

С	-2.78993439	0.40481400 0.00000000
С	-4.58592698	-0.80611289 0.61253180
С	-3.26431818	-0.83598629 -0.13777443
С	-5.20237830	1.50761568 -0.25764329
С	-5.79302919	0.21058413 -0.39052923
0	-4.27319015	0.13168505 1.67759310
N	-3.71385253	1.19323060 0.82971730
Н	-1.92008522	0.89766067 -0.42623111
Н	-2.86086893	-1.66083523 -0.71794040
Н	-4.98161419	-1.73785033 1.02436892
Н	-5.81485428	-0.11253136 -1.43697303
Н	-5.87549883	2.18841931 0.27509926
Н	-4.87531196	1.97256187 -1.19407518
N	-7.14707499	0.08615241 0.15554159
Н	-7.15936676	0.42187377 1.11873857
Н	-7.78704120	0.68788834 -0.36063398

1 3 1.5 7 1.5 8 1.0 2 3 1.5 5 0.5 6 1.0 10 1.0 3 9 1.0 4 5 1.5 7 0.5 12 1.0 13 1.0 5 11 1.0 14 1.0 6 7 1.0

I1-1 endo

Zero-point correction= ().132540 (Hartree/Particle)
Thermal correction to Energy=	0.138743
Thermal correction to Enthalpy	= 0.139687
Thermal correction to Gibbs Fre	ee Energy= 0.102681
Sum of electronic and zero-poir	nt Energies= -379.892455
Sum of electronic and thermal H	Energies= -379.886253
Sum of electronic and thermal H	Enthalpies= -379.885309
Sum of electronic and thermal H	Free Energies= -379.922314

%chk=I1N.chk

opt=(calcall,tight,maxcycle=500) freq b3lyp/aug-cc-pvdz

geom=connectivity empirical dispersion=gd3

Title Card Required

- C -0.17544496 -1.27014475 -0.63381447
- C -1.06900567 -0.42073047 0.31597016
- C 0.44198878 1.41836854 -0.08311413
- C 1.26486459 0.72403180 -0.87641270

- С 1.22195026 -0.68130375 -0.29319254
- Η -1.43226714 -1.02748483 1.15052695
- Η -0.44964201 -1.15071188 -1.68826158
- Η 0.10115958 2.44782549 -0.13928463
- Η 1.78726156 1.04982393 -1.77129236
- Η -0.22746992 -2.33281058 -0.37317295
- Ν -0.06014925 0.55052329 0.98224831
- 1.05468826 -0.38559222 1.11387635 0
- Ν -2.19232531 0.20104180 -0.32879690
- Η -1.91102817 0.77953972 -1.11606194
- Η -2.73209797 0.76832119 0.31942214
- Η 2.08778190 -1.33204911 -0.44366422

```
1 2 1.0 5 1.0 7 1.0 10 1.0
```

- 261.0111.0131.0
- 3 4 2.0 8 1.0 11 1.0
- 4 5 1.0 9 1.0
- 5 12 1.0 16 1.0
- 6

```
7
```

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8
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9
10
```

```
11 12 1.0
12
13 14 1.0 15 1.0
```

14 15

16

I1-1 exo

Zero-point correction=

```
0.132491 (Hartree/Particle)
```

Thermal correction to Energy=	0.138703
Thermal correction to Enthalpy=	0.139647
Thermal correction to Gibbs Free Er	nergy= 0.102598
Sum of electronic and zero-point En	ergies= -379.894804
Sum of electronic and thermal Energ	gies= -379.888592
Sum of electronic and thermal Entha	lpies= -379.887647
Sum of electronic and thermal Free I	Energies= -379.924697

%chk=I1X.chk

opt=(calcall,tight,maxcycle=500) freq b3lyp/aug-cc-pvdz

geom=connectivity empirical dispersion=gd3

Title Card Required

С	0.99183102 -0.21223765 -0.54478675
С	0.32162386 1.19287018 -0.63269700
С	-0.89185609 0.98256591 0.31086586
С	-1.84864286 0.02386368 -0.39169185
С	-1.20788537 -1.14701772 -0.34025413
Ν	0.04904560 -0.98910691 0.39444583
0	-0.30656627 0.10707191 1.30001022
Н	-1.30666766 1.87242526 0.79271075
Н	-2.78513631 0.27043804 -0.88282256
Н	-1.44542083 -2.11430553 -0.77388607
Н	0.99909880 -0.74687074 -1.50196088
Н	0.03640908 1.47403932 -1.65195968
Н	1.00016488 1.95449979 -0.23267147
Ν	2.33782539 -0.13247161 -0.04005880
Н	2.33432659 0.31100371 0.87701952
Н	2.72123535 -1.06702183 0.08416262

1 2 1.0 6 1.0 11 1.0 14 1.0
2 3 1.0 12 1.0 13 1.0
3 4 1.0 7 1.0 8 1.0
4 5 2.0 9 1.0
5 6 1.0 10 1.0
6 7 1.0
7
8
9
10
11
12
13
14 15 1.0 16 1.0
15
16

Ι2_α

Zero-point correction=	0.126331 (Hartree/Particle)
Thermal correction to Energy=	0.135225
Thermal correction to Enthalpy=	0.136169
Thermal correction to Gibbs Free Ener	gy= 0.091625
Sum of electronic and zero-point Energy	gies= -379.846568
Sum of electronic and thermal Energies	s= -379.837674
Sum of electronic and thermal Enthalp	ies= -379.836730
Sum of electronic and thermal Free En	ergies= -379.881273

%chk=I2-1_NH3.chk

opt=(calcall,tight,maxcycle=500) freq b3lyp/aug-cc-pvdz

geom=connectivity empirical dispersion=gd3

01

С	-2.02660273 -0.18781117 -0.32158089
С	0.01225212 -0.75247566 0.48761132
С	-1.50101750 -1.06957762 0.52858847
Н	-3.04753819 0.03233497 -0.61512705
Н	-1.99282417 -1.82188505 1.13632153
С	-0.39578158 1.46082558 0.22721327
Н	-0.57740048 2.53031741 0.21511404
С	0.20453974 0.65470939 1.10168925
Н	0.70293877 0.88823363 2.03608712
Н	0.72982580 -1.52668843 0.76504397
0	0.12934760 -0.40609691 -0.91120099
Ν	-0.92128145 0.63334887 -0.90472042
Ν	3.15725008 -0.26460810 -0.12062838
Н	2.38801188 -0.14900195 -0.78069973
Н	3.96450333 -0.58746236 -0.65012043
Н	3.38558148 0.66771850 0.21930153

1 3 2.0 4 1.0 12 1.0

```
2 3 1.0 8 1.0 10 1.0 11 1.0
3 5 1.0
4
5
6 7 1.0 8 2.0 12 1.0
7
8 9 1.0
9
10
11 12 1.0 14 0.5
12
```

13 14 1.0 15 1.0 16 1.0 14 15 16

I2_β endo

Zero-point correction= 0.131584 (Hartree/Particle) Thermal correction to Energy= 0.138804 Thermal correction to Enthalpy= 0.139748 Thermal correction to Gibbs Free Energy= 0.100161 Sum of electronic and zero-point Energies= -379.921427 Sum of electronic and thermal Energies= -379.914207 Sum of electronic and thermal Enthalpies= -379.913263 Sum of electronic and thermal Free Energies= -379.952850

%chk=I2-2N.chk

opt=(calcall,tight) freq b3lyp/aug-cc-pvdz geom=connectivity
empiricaldispersion=gd3

- C -0.58789118 -0.65054582 0.35647587
- C 0.59945383 -1.42989753 -0.20948513
- C 1.90469365 -0.72065960 0.01959088
- C 1.90846092 0.62728527 0.05140207
- $C \qquad 0.68541651 \ 1.39115819 \ \text{-}0.08022122$
- N -0.50025212 0.82621494 0.00618942
- O -1.60394996 1.46074412 -0.05325409
- Н 2.83132088 -1.29047744 0.08245895
- H 2.83531337 1.19254688 0.15014129
- Н 0.67537405 2.46979246 -0.21781782
- Н 0.42799744 -1.57401938 -1.29065230

Н 0.59586177 -2.43056920 0.24415444

Н -0.53379024 -0.63629895 1.46333416

N -1.84053948 -1.15410635 -0.16836815

Н -2.12075610 -1.98799485 0.34034028

Н -2.55498262 -0.43773562 -0.03725001

```
1 2 1.0 6 1.0 13 1.0 14 1.0
2 3 1.0 11 1.0 12 1.0
3 4 2.0 8 1.0
4 5 1.0 9 1.0
5 6 2.0 10 1.0
671.0
7
8
9
10
11
12
13
14 15 1.0 16 1.0
15
16
```

$I2_\beta$ exo

Zero-point correction=	0.132350 (Hartree/Particle)
Thermal correction to Energy=	0.139362
Thermal correction to Enthalpy	v= 0.140306
Thermal correction to Gibbs Fr	ree Energy= 0.101391
Sum of electronic and zero-poi	nt Energies= -379.926003
Sum of electronic and thermal	Energies= -379.918992
Sum of electronic and thermal	Enthalpies= -379.918048
Sum of electronic and thermal	Free Energies= -379.956962

%chk=I2-2X.chk

opt=(calcall,tight,maxcycle=500) freq b3lyp/aug-cc-pvdz
geom=connectivity empirical dispersion=gd3

Title Card Required

~ -

С	0.39182318 0.92498171 -0.30534961
С	-1.06649386 0.95351854 -0.76808140
С	-1.91281117 -0.05119911 -0.03307431
С	-1.34309165 -1.19939004 0.38814619
С	0.06789577 -1.46516302 0.19564312
Ν	0.89602553 -0.51563850 -0.19078883
0	2.15054838 -0.66306470 -0.35478030
Н	-2.97876514 0.13225575 0.09638443
Н	-1.93183114 -1.97997097 0.87038857
Н	0.51709496 -2.43868648 0.37985773
Н	1.06043815 1.35522339 -1.05669583
Н	-1.10630977 0.73336278 -1.84892831
Н	-1.43746860 1.97792065 -0.63593162
Ν	0.57797998 1.62224698 0.94103923
Н	-0.01624830 1.23911759 1.67320059
Н	1.54673057 1.56254703 1.24451018

1 2 1.0 6 1.0 11 1.0 14 1.0 2 3 1.0 12 1.0 13 1.0 3 4 2.0 8 1.0 4 5 1.0 9 1.0 5 6 2.0 10 1.0 6 7 1.0 7

8					
9					
10					
11					
12					
13					
14	15	1.0	16	1.0	
15					
16					

I3

Zero-point correction= 0.129145 (Hartree/Particle) Thermal correction to Energy= 0.138027 Thermal correction to Enthalpy= 0.138971 Thermal correction to Gibbs Free Energy= 0.094571 Sum of electronic and zero-point Energies= -379.952773 Sum of electronic and thermal Energies= -379.943891 Sum of electronic and thermal Enthalpies= -379.942947 Sum of electronic and thermal Free Energies= -379.987346 %chk=I3 NH3.chk

opt=(calcall,tight,maxcycle=500) freq b3lyp/aug-cc-pvdz

geom=connectivity empirical dispersion=gd3

Title Card Required

С	-1.14897497 -1.23136829 -0.00000000
С	-2.30146874 -0.46065540 0.00000001
С	-2.21698402 0.93451520 0.00000000
С	-0.94281412 1.50901391 -0.00000000

- С 0.19469473 0.71489612 -0.00000002
- Ν 0.09247187 -0.65267506 -0.00000002

Н -3.11352814	1.55196830	0.0000002
---------------	------------	-----------

Н -1.12994742 -2.31729095 -0.00000000

Н -3.26487398 -0.96936850 0.00000002

Н -0.81224314 2.59061595 0.00000000

Н 1.21633189 1.09200139 -0.00000003

O 1.14653989 -1.39491133 -0.00000003

N 3.51153736 0.59039990 -0.00000006

Н 2.95919126 -0.27150414 -0.00000005

H 4.11898369 0.56019245 0.81634820

H 4.11898490 0.56019300 -0.81634744

I2-1 (without NH3)

Zero-point correction=0.090279 (Hartree/Particle)Thermal correction to Energy=0.095032Thermal correction to Enthalpy=0.095976

Thermal correction to Gibbs Free Energy=	0.062247
Sum of electronic and zero-point Energies=	-323.304118
Sum of electronic and thermal Energies=	-323.299365
Sum of electronic and thermal Enthalpies=	-323.298421
Sum of electronic and thermal Free Energies	-323.332151

%chk=I2-1.chk

opt=(calcall,tight,maxcycle=500) freq b3lyp/aug-cc-pvdz
geom=connectivity empirical dispersion=gd3

Title Card Required

С	-0.48448483 -0.67888251 1.19056230
С	0.33783302 1.06105591 -0.00000000
С	-0.48448483 0.65239965 1.24744321
Н	-0.95587102 -1.44078893 1.80241687
Н	-0.95797396 1.31584415 1.96365615
С	-0.48448483 -0.67888251 -1.19056230
Н	-0.95587102 -1.44078893 -1.80241687
С	-0.48448483 0.65239965 -1.24744321
Н	-0.95797396 1.31584415 -1.96365615
Н	0.82736026 2.03860915 -0.00000000
0	1.30130728 -0.01032896 -0.00000000
Ν	0.31292990 -1.10780415 0.00000000

```
1 3 2.0 4 1.0 12 1.0
2 3 1.0 8 1.0 10 1.0 11 1.0
3 5 1.0
4
5
6 7 1.0 8 2.0 12 1.0
```

I3 (without NH₃)

Zero-point correction= 0.092635 (Hartree/Particle)
Thermal correction to Energy= 0.097707
Thermal correction to Enthalpy= 0.098651
Thermal correction to Gibbs Free Energy= 0.064572
Sum of electronic and zero-point Energies= -323.407838
Sum of electronic and thermal Energies= -323.402765
Sum of electronic and thermal Enthalpies= -323.401821
Sum of electronic and thermal Free Energies= -323.435900

%chk=I3.chk

opt=(calcall,tight,maxcycle=500) freq b3lyp/aug-cc-pvdz

geom=connectivity empirical dispersion=gd3

Title Card Required

- C -0.00000000 -1.18114406 0.28568423
- C -0.00000000 -1.19627916 -1.10057461
- C -0.00000000 0.00000000 -1.82412224
- C 0.00000000 1.19627916 -1.10057461
- C 0.00000000 1.18114406 0.28568423
- N 0.0000000 0.0000000 0.98512743
- Н -0.00000000 -0.00000000 -2.91248950
- Н -0.00000000 -2.06580882 0.91575002
- Н -0.00000000 -2.16134098 -1.60642677

Н 0.0000	0000 2.1613	4098 -1.60	642677
Н 0.0000	0000 2.1613	4098 -1.60	642677

- Н 0.00000000 2.06580882 0.91575002
- O 0.00000000 -0.00000000 2.26517112

```
1 2 1.5 6 1.5 8 1.0
2 3 1.5 9 1.0
3 4 1.5 7 1.0
4 5 1.5 10 1.0
5 6 1.5 11 1.0
6 12 1.0
7
8
9
10
11
12
```

Biradical

Zero-point correction= 0.087296 (Hartree/Particle) Thermal correction to Energy= 0.092978 Thermal correction to Enthalpy= 0.093922 Thermal correction to Gibbs Free Energy= 0.056845 Sum of electronic and zero-point Energies= -323.332751 Sum of electronic and thermal Energies= -323.327069 Sum of electronic and thermal Enthalpies= -323.326125 Sum of electronic and thermal Free Energies= -323.363202

%chk=BR.chk

opt=(calcall,tight,maxcycle=500) freq ub3lyp/aug-cc-pvdz
geom=connectivity empiricaldispersion=gd3

03

С	1.12186144 -1.16171475 0.05130517
С	-1.05535375 0.00000106 -0.32246401
С	-0.22836885 -1.24564691 -0.17890003
Н	1.70823354 -2.07535483 0.17375176
Η	-0.74016426 -2.20670851 -0.22655216
С	1.12186295 1.16171386 0.05130555
Η	1.70823617 2.07535299 0.17375349
С	-0.22836712 1.24564750 -0.17890039
Η	-0.74016102 2.20670996 -0.22655212
Η	-1.52505980 0.00000007 -1.35029000
0	-2.19557473 0.00000032 0.47230680
Ν	1.82338646 -0.00000098 0.16333670

TS2_α_exo (amine loss from I1-1 Exo)

Zero-point correction=0.128601 (Hartree/Particle)Thermal correction to Energy=0.135067Thermal correction to Enthalpy=0.136011Thermal correction to Gibbs Free Energy=0.098481

Sum of electronic and zero-point Energies=	-379.794247
Sum of electronic and thermal Energies=	-379.787782
Sum of electronic and thermal Enthalpies=	-379.786838
Sum of electronic and thermal Free Energies	-379.824367

%mem=4GB %Nprocs=1 %chk=TS1X.chk # opt=(calcall,tight,qst3,noeigentest,maxcycle=500) freq b3lyp/aug-cc-pvdz geom=connectivity empiricaldispersion=gd3

Title Card Required

С	0.00000000 0.00000000 0.00000000
С	0.00000000 0.00000000 1.55924133
С	1.52620463 0.00000000 1.83811661
С	2.06017478 -1.36835255 1.42504870
С	1.98750898 -1.34008105 0.09159477
Ν	1.50087697 -0.03060650 -0.34779198
0	1.99333162 0.81694265 0.74182411
Н	1.85715601 0.42226036 2.79114337
Н	2.34794956 -2.18722934 2.07747078
Н	2.17772355 -2.10736005 -0.65352713
Η	-0.44512933 -0.90455313 -0.43094197
Η	-0.52132014 -0.86003451 1.99267615
Н	-0.46513994 0.91960919 1.93137246
Ν	-0.67136281 1.15573737 -0.53512294
Н	-0.22656476 2.00294710 -0.18568704
Н	-0.58535715 1.17248963 -1.54909559

1 2 1.0 6 1.0 11 1.0 14 1.0
2 3 1.0 12 1.0 13 1.0
3 4 1.0 7 1.0 8 1.0
4 5 2.0 9 1.0
5 6 1.0 10 1.0
671.0
7
8
9
10
11
12
13
14 15 1.0 16 1.0
15
16

0	1

С	$0.00000000 \ 0.0000000 \ 0.00000000$
С	0.00000000 0.00000000 1.33226020
С	1.50445488 0.00000000 1.69399426
С	2.08909620 -1.35496647 1.23087643
С	1.99793623 -1.29518150 -0.09752692
Ν	1.41836051 0.02942814 -0.47909202
0	1.99493286 0.83319428 0.61901328
Η	$1.78948967 \ 0.40194519 \ 2.66789442$
Η	2.45548288 -2.15676797 1.86337534
Η	2.23129758 -2.00568341 -0.88344829
Н	-0.79501056 -0.04334300 -0.73690174

-0.83101661 -0.01364103 2.02886615 Η

Η 1.08472007 3.98659347 2.62825746

Ν 0.72065798 3.05979286 2.41670622

Η 1.18460311 2.73835041 1.56687326

Η -0.26207046 3.18007018 2.17859146

```
1 11 1.0 2 2.0 6 1.0
2 3 1.0 12 1.0
3 4 1.0 8 1.0 7 1.0
4 5 2.0 9 1.0
```

5 10 1.0 6 1.0

- 671.0
- 7 15 0.5
- 8
- 9
- 10

- 11 12
- 13 14 1.0
- 14 15 1.0 16 1.0

15

16

01	
С	0.82177355 -0.09009585 -0.72034797
С	0.26621281 1.23539663 -0.65019319
С	-0.83905803 1.00069895 0.39754924
С	-1.89578427 0.09356631 -0.25035232
С	-1.30311097 -1.10568361 -0.34725241

Ν	0.03876803 -1.00684670 0.22959162
0	-0.20178619 0.01884389 1.26741729
Н	-1.19328611 1.84528197 0.99630696
Н	-2.86864374 0.39582054 -0.62918036
Н	-1.59820691 -2.02958427 -0.83420011
Н	1.05425714 -0.58337035 -1.67061585
Η	-0.01325016 1.71082786 -1.59114403
Н	2.89010347 0.56945379 -0.33856397
Ν	2.28652037 -0.13556432 0.08351758
Η	2.02069127 0.18814942 1.01971496
Η	2.74540714 -1.05374754 0.14015955

1 2 1.5 6 1.0 11 1.0 14 0.5 2 3 1.0 12 1.0 13 0.5

```
3 4 1.0 7 1.0 8 1.0
```

- 4 5 2.0 9 1.0
- 5 6 1.0 10 1.0
- 671.0

7 13 0.5 15 0.5

15 16

TS3_α (ring opening from I2-2)

Zero-point correction= 0.129228 (Hartree/Particle)

Thermal correction to Energy= 0.135722
Thermal correction to Enthalpy= 0.136666
Thermal correction to Gibbs Free Energy= 0.098972
Sum of electronic and zero-point Energies= -379.833384
Sum of electronic and thermal Energies= -379.826890
Sum of electronic and thermal Enthalpies= -379.825946
Sum of electronic and thermal Free Energies= -379.863640

%mem=4GB

%Nprocs=4

%chk=TS3.chk

opt=(calcall,tight,qst3) freq b3lyp/aug-cc-pvdz geom=connectivity empiricaldispersion=gd3

Title Card Required

С	0.0000000 0.0000000 0.0000000
С	0.0000000 0.0000000 1.33200977
С	1.50631533 0.00000000 1.69340004
С	2.08948054 -1.35908818 1.23349720
С	1.99866229 -1.29795388 -0.09432913
Ν	1.42345053 0.02990814 -0.47045308
0	1.99869839 0.83280604 0.62372576
Н	1.80598906 0.38774641 2.67058924
Η	2.44787029 -2.16393754 1.86672210
Н	2.22041540 -2.01092067 -0.88116212
Н	-0.77882040 -0.04742856 -0.75384631
Н	-0.83540647 -0.02601213 2.02377754
Н	0.80576048 0.54418068 -2.62970601
N	0.00473195 0.52697760 -3.26359083
Н	0.34822833 0.24282384 -4.17883647

```
1 11 1.0 2 2.0 6 1.0
2 3 1.0 12 1.0
3 4 1.0 8 1.0 7 1.0
4 5 2.0 9 1.0
5 10 1.0 6 1.0
671.0
7 13 0.5
8
9
10
11
12
13 14 1.0
14 16 1.0 15 1.0
15
16
```

Title Card Required

С	0.0000000 0.0000000 0.0000000
С	0.00000000 0.00000000 1.38644869
С	1.20670795 0.00000000 2.09178147
С	2.39256150 0.00000000 1.35197828
С	2.36477607 0.00000000 -0.03502465
N	1.17114986 0.00000000 -0.71027026
0	1.14010734 -0.00000000 -1.99907211
Η	1.22158965 0.00000000 3.18027495
Н	3.36423262 0.00000000 1.84469201

- Н 3.24616479 0.00000000 -0.67463753
- Н -0.89210235 0.00000000 -0.61947017
- Н -0.95841796 0.00000000 1.90449648
- H 3.08158069 0.00000000 -2.88135851
- N 4.10508708 0.0000000 -2.86137572
- H 4.41765135 0.81634732 -3.38311177
- Н 4.41765021 -0.81634821 -3.38311106

1 2 1.5 6 1.5 11 1.0

Title Card Required

- C 1.24814029 -1.18630544 -0.52132968
- C 2.12089546 -0.35279221 0.07646749
- C 1.45926861 0.82482064 0.63915938

С	0.55555788 1.50276758 -0.28465633
С	-0.30407420 0.64616026 -0.87429960
Ν	-0.11584018 -0.71167496 -0.39619887
0	-0.29406076 -0.60305446 0.97617161
Н	1.87085280 1.34044183 1.50626779
Η	0.48182195 2.58548877 -0.35490712
Η	-1.22317999 0.87810762 -1.40306824
Η	1.42199540 -2.20213347 -0.86389012
Η	3.17361148 -0.57380722 0.23779456
Η	-3.53271280 -0.93269765 -0.26833083
Ν	-3.28066854 -0.00880880 0.07830559
Η	-2.48229328 -0.14609588 0.70103041
Н	-4.06077675 0.31061287 0.64893605

1 2 2.0 6 1.0 11 1.0

2 3 1.0 12 1.0

3 4 1.0 7 0.5 8 1.0

12 13 14 1.0 14 15 1.0 16 1.0 15

TS3_β_endo (ring opening from I1-1 endo)

Zero-point correction= 0.129370 (Hartree/Particle) Thermal correction to Energy= 0.135841 Thermal correction to Enthalpy= 0.136785 Thermal correction to Gibbs Free Energy= 0.099147 Sum of electronic and zero-point Energies= -379.833455 Sum of electronic and thermal Energies= -379.826984 Sum of electronic and thermal Enthalpies= -379.826040 Sum of electronic and thermal Free Energies= -379.863678

%mem=4GB

%Nprocs=4

%chk=TS2N.chk

opt=(calcall,qst3) freq b3lyp/aug-cc-pvdz geom=connectivity
empiricaldispersion=gd3

Title Card Required

- C 0.0000000 0.0000000 0.0000000
- C 0.00000000 0.00000000 1.55629234
- C 1.53000171 0.00000000 1.82935800
- C 2.04918838 -1.37769929 1.44290625
- C 1.97983124 -1.37600992 0.10734000
- N 1.50735077 -0.07178616 -0.35747976
- O 2.00350188 0.79074382 0.71321005
- H 1.86834128 0.43580033 2.77348718
- Н 2.33320177 -2.18554650 2.11116355
- Н 2.18132363 -2.16046275 -0.61594118

- Н -0.31047778 0.97500808 -0.38672650
- Н -0.46826433 0.90978031 1.94735169
- Н -0.51433586 -0.87155700 1.97718875
- N -0.82475875 -1.01728225 -0.59083152
- Н -0.77393716 -1.00081551 -1.60596413
- Н -0.57869007 -1.94819603 -0.26460499

```
1 2 1.0 11 1.0 6 1.0 14 1.0
```

```
2 3 1.0 13 1.0 12 1.0
```

3 4 1.0 7 1.0 8 1.0

- 4 5 2.0 9 1.0
- 5 10 1.0 6 1.0
- 671.0
- 7
- ,
- 8
- 9

10

11

- -

12

-

13 14 16 1.0 15 1.0

15

16

Title Card Required

C 0.0000000 0.0000000 0.0000000
 C 0.0000000 0.0000000 1.52888511
 C 1.39186542 0.00000000 2.09620954
 C 2.37116786 -0.61202886 1.40024341

- C 2.11781380 -1.21795110 0.10976481
- N 1.00326171 -0.99830658 -0.55504052
- O 0.75402649 -1.46724688 -1.71361184
- H 1.57858815 0.42262571 3.08302522
- Н 3.38357682 -0.69715511 1.79534744
- Н 2.84189990 -1.85155470 -0.39692190
- Н 0.39302350 0.96601510 -0.37497925
- Н -0.57693941 0.87127003 1.86825845
- Н -0.55097122 -0.89417834 1.86942420
- N -1.30496255 -0.35057793 -0.52185480
- Н -1.91665765 0.46068320 -0.50289977
- Н -1.19350302 -0.65124963 -1.49035179

1 2 1.0 6 1.0 11 1.0 14 1.0

- 2 3 1.0 13 1.0 12 1.0
- 3 4 2.0 8 1.0
- 4 5 1.0 9 1.0
- 5 6 2.0 10 1.0
- 671.0
- 7
- 8
- 9
- 10
- 11
- **
- 12
- 13
- 14 15 1.0 16 1.0

15

16

01

С	1.08633558 0.03717126 0.39558703
С	0.31024060 1.42046110 0.36110345
С	-1.09672612 1.16898801 -0.01488234
С	-1.33671180 0.18912278 -1.03195442
С	-0.73707334 -1.02102778 -0.81410256
N	0.05487933 -1.01301253 0.37462562
0	-0.77605336 -0.81091170 1.39722861
Η	-1.88514906 1.86073180 0.27797545
Η	-2.14259601 0.28589285 -1.75909377
Η	-1.07269679 -1.96806855 -1.22804262
Η	1.56754536 -0.06063712 1.37496699
Η	0.39696197 1.98031773 1.29891870
Η	0.81455111 1.99851468 -0.42942053
N	2.07856258 -0.05111932 -0.64934591
Η	2.58683556 -0.93017568 -0.59217866
Н	1.65249188 0.00134864 -1.57241928

13 14 15 1.0 16 1.0 15 16

TS3_ β _exo (Ring opening from I1-1 exo)

Zero-point correction=	0.129228 (Hartree/Particle)	
Thermal correction to Energy=	0.135722	
Thermal correction to Enthalpy=	0.136666	
Thermal correction to Gibbs Free Ener	rgy= 0.098972	
Sum of electronic and zero-point Ener	gies= -379.833384	
Sum of electronic and thermal Energie	es= -379.826890	
Sum of electronic and thermal Enthalp	oies= -379.825946	
Sum of electronic and thermal Free Er	nergies= -379.863640	

%mem=4GB

%Nprocs=4

%chk=TS2X.chk

opt=(calcall,qst3) freq b3lyp/aug-cc-pvdz geom=connectivity

empiricaldispersion=gd3

Title Card Required

$0\ 1$

- C 0.0000000 0.0000000 0.0000000
- C 0.0000000 0.0000000 1.55924133
- C 1.52620463 0.0000000 1.83811661
- C 2.06017478 -1.36835255 1.42504870
- C 1.98750898 -1.34008105 0.09159477
- N 1.50087697 -0.03060650 -0.34779198
- O 1.99333162 0.81694265 0.74182411

- H 1.85715601 0.42226036 2.79114337
- Н 2.34794956 -2.18722934 2.07747078
- Н 2.17772355 -2.10736005 -0.65352713
- Н -0.44512933 -0.90455313 -0.43094197
- Н -0.52132014 -0.86003451 1.99267615
- Н -0.46513994 0.91960919 1.93137246
- N -0.67136281 1.15573737 -0.53512294
- Н -0.58535715 1.17248963 -1.54909559
- Н -0.22656476 2.00294710 -0.18568704

Title Card Required

01

C 0.0000000 0.0000000 0.0000000

С	0.00000000 0.00000000 1.53010891
С	1.39143916 0.00000000 2.10039877
С	2.38629713 -0.59293416 1.41030685
С	2.14258596 -1.20097416 0.11605766
N	1.02056572 -1.00384919 -0.53343854
0	0.74972935 -1.50350074 -1.69302237
Н	1.56604508 0.43008306 3.08589732
Η	3.39763783 -0.66506280 1.80869035
Η	2.87921568 -1.83217830 -0.37728053
Η	-0.94804655 -0.37486185 -0.39553219
Н	-0.53400449 -0.89363680 1.89430647
Н	-0.57602384 0.87105852 1.86604874
N	0.25100415 1.31238923 -0.54301603
Н	0.28324850 1.28570635 -1.55919916
Н	1.13473468 1.69078292 -0.20717727

1 2 1.0 6 1.0 11 1.0 14 1.0 2 3 1.0 12 1.0 13 1.0 3 4 2.0 8 1.0 4 5 1.0 9 1.0 5 6 2.0 10 1.0 6 7 1.0

- 7 8 9 10
- 11 12
- 13 14 16 1.0 15 1.0

16

Title Card Required

01	
С	0.93973558 0.08934461 -0.58175770
С	0.28528108 1.41444414 -0.02993143
С	-1.09200947 1.12528545 0.41719588
С	-1.86053307 0.19506882 -0.35776468
С	-1.23346576 -0.99806614 -0.58412083
Ν	0.09848009 -1.02135636 -0.07459242
0	-0.00116984 -0.90124216 1.25822839
Н	-1.58369133 1.76147525 1.15251240
Н	-2.93832296 0.29031583 -0.48542912
Н	-1.74151921 -1.93914088 -0.77972665
Н	0.89344983 0.04864835 -1.67687746
Н	0.26505879 2.10518913 -0.88975747
Н	0.89209155 1.87771050 0.75579397
Ν	2.31412904 0.02140897 -0.15704698
Н	2.76363415 -0.79803491 -0.55869295
Н	2.33634386 -0.09305554 0.85609854

```
10
11
12
13
14 15 1.0 16 1.0
15
16
```

$TS2_\beta$ _endo (amine loss from $I2_\beta$ endo)

```
0.129256 (Hartree/Particle)
Zero-point correction=
Thermal correction to Energy=
                                   0.135918
Thermal correction to Enthalpy=
                                    0.136862
Thermal correction to Gibbs Free Energy=
                                           0.098915
Sum of electronic and zero-point Energies=
                                             -379.845307
Sum of electronic and thermal Energies=
                                           -379.838645
Sum of electronic and thermal Enthalpies=
                                            -379.837701
Sum of electronic and thermal Free Energies=
                                              -379.875648
```

%mem=4GB

%Nprocs=1

%chk=TS4N_TS.chk

opt=(calcall,tight,ts,verytight,noeigentest,maxcycle=500) freq

b3lyp/aug-cc-pvdz geom=connectivity empiricaldispersion=gd3

01		
С	0.00000000 0.00000000 0.	00000000
С	0.00000000 0.00000000 1.	45442619
С	1.31312532 0.00000000 1.	99392573
С	2.43373664 0.23575411 1.	18512099
С	2.23079243 0.77278621 -0	.10892224
- N 1.01260091 0.76146819 -0.67411958
- O 0.70702202 1.30633044 -1.82399504
- Н 1.44516407 -0.06348227 3.07637914
- Н 3.44532458 0.21343849 1.58622530
- Н 3.00961647 1.24982870 -0.69691177
- Н -0.93906693 0.10630263 -0.53990988
- Н -0.64671895 0.65661773 2.04108449
- Н 1.52546215 -1.51785156 0.00028303
- N 0.58915124 -1.59591631 -0.42257213
- Н 0.65703039 -1.71665291 -1.43216400
- Н 0.05099333 -2.33632602 0.02338804

TS2_ β _exo (amine loss from I2_ β _exo)

Zero-point correction= 0.129256 (Hartree/Particle) Thermal correction to Energy= 0.135917 Thermal correction to Enthalpy= 0.136862 Thermal correction to Gibbs Free Energy= 0.098915 Sum of electronic and zero-point Energies= -379.845307 Sum of electronic and thermal Energies= -379.838645 -379.837701 Sum of electronic and thermal Enthalpies= Sum of electronic and thermal Free Energies= -379.875648

%mem=4GB

%Nprocs=4

%chk=TS4X.chk

opt=(calcall,tight,qst3,noeigentest,maxcycle=500) freq b3lyp/aug-cc-pvdz

geom=connectivity empirical dispersion=gd3

Title Card Required

- C 0.0000000 0.0000000 0.0000000
- C 0.00000000 0.00000000 1.53023647
- C 1.39502894 0.00000000 2.09578067
- C 2.37869871 -0.61176277 1.40405129
- C 2.13622792 -1.22170308 0.11263388
- N 1.01176171 -1.01256635 -0.54201330
- O 0.73615095 -1.48894184 -1.69073449
- Н 1.58044566 0.43776773 3.07590983
- Н 3.38969543 -0.68801694 1.80473750
- Н 2.86540534 -1.85401004 -0.38931342

- Н -0.94840116 -0.36828461 -0.40196604
- Н -0.53297725 -0.89673293 1.89091530
- Н -0.57797215 0.87164007 1.86291843
- N 0.26102181 1.30888387 -0.54130302
- Н 1.14628712 1.68061261 -0.20354765
- Н 0.28812843 1.27821779 -1.55740402

```
1 2 1.0 6 1.0 11 1.0 14 1.0
```

```
2 3 1.0 12 1.0 13 1.0
3 4 2.0 8 1.0
4 5 1.0 9 1.0
5 6 2.0 10 1.0
6 7 1.0
```

01			
С	0.00000000	0.00000000	0.00000000
С	0.00000000	0.00000000	1.38728131
С	1.20043305	0.00000000	2.10318505
С	2.39277213	0.00000000	1.37382493

С 2.36500338 0.00000000 -0.01234575 Ν 1.17986258 0.00000000 -0.69901698 0 1.18508586 0.00000000 -1.98818213 Η 1.20735543 0.0000000 3.19175833 Η 3.36137373 -0.00000000 1.87257298 Η 3.24451967 0.00000000 -0.64955935 Η -0.89402259 -0.00000000 -0.62183156 Η -0.96160787 0.00000000 1.89935754 Η -0.77366922 0.00000000 -2.83140645 Ν -1.79657014 0.00000000 -2.79092817 Η -2.11952028 0.81634826 -3.30629865 Η -2.11952144 -0.81634738 -3.30629934

1 2 1.5 6 1.5 11 1.0

- 2 3 1.5 12 1.0
- 3 4 1.5 8 1.0
- 4 5 1.5 9 1.0
- 5 6 1.5 10 1.0
- 671.0
- 7 13 0.5
- 8
- 9
- 10
- 11
- 12
- 13 14 1.0
- 14 15 1.0 16 1.0
- 15

16

01

С	0.08475011 -1.00929196 0.38954841
С	-1.03334505 -0.39755404 1.11786218
С	-1.50282233 0.78163624 0.56991502
С	-0.78451914 1.39611823 -0.49819111
С	0.55780489 1.03731588 -0.68656572
Ν	1.09947327 -0.06074571 -0.07056262
0	2.22552684 0.17316458 0.59692908
Н	-2.39375548 1.26802277 0.96856885
Η	-1.18092115 2.26997372 -1.01172136
Н	1.29849218 1.70421075 -1.12202320
Η	0.56751730 -1.88715923 0.82335053
Н	-1.38084264 -0.81403875 2.06018509
Н	-1.00216117 -0.49731520 -1.31629757
Ν	-0.58863569 -1.43046866 -1.05156803
Η	0.10117255 -1.71131578 -1.75201932
Н	-1.32079027 -2.12854031 -0.92597377

1 2 1.5 6 1.0 11 1.0 13 0.5 14 0.5 2 3 1.0 12 1.0 13 0.5

- 3 4 2.0 8 1.0
- 4 5 1.0 9 1.0
- 5 6 2.0 10 1.0
- 671.0
- 7 13 0.5
- 8
- 9
- 10
- 11
- 12

```
13 14 0.5
14 15 1.0 16 1.0
15
16
```

TS3_α (ring opening from I2-2, without NH₃)

Zero-point correction= 0.087360 (Hartree/Particle)
Thermal correction to Energy= 0.092346
Thermal correction to Enthalpy= 0.093290
Thermal correction to Gibbs Free Energy= 0.059064
Sum of electronic and zero-point Energies= -323.248926
Sum of electronic and thermal Energies= -323.243940
Sum of electronic and thermal Enthalpies= -323.242996
Sum of electronic and thermal Free Energies= -323.277223

%mem=4GB

%Nprocs=4

%chk=TS3_wo_NH3.chk

opt=(calcall,tight,qst3) freq b3lyp/aug-cc-pvdz geom=connectivity

empirical dispersion=gd3

Title Card Required

- C 0.0000000 0.0000000 0.0000000
- C 0.0000000 0.0000000 1.33249554
- C 1.50771074 0.00000000 1.68753518
- C 2.08931749 -1.35940299 1.22601466
- C 1.99406791 -1.29742983 -0.10162649
- N 1.41654044 0.02960666 -0.47933886
- O 1.99486766 0.83257371 0.61712942
- H 1.80964668 0.38755450 2.66420691

Н 2.45465935 -2.16192498 1.85830925

Н 2.22217588 -2.00818076 -0.88894383

- Н -0.79673413 -0.04394323 -0.73508651
- Н -0.83425505 -0.02201169 2.02592678

```
1 11 1.0 2 2.0 6 1.0
2 3 1.0 12 1.0
3 4 1.0 8 1.0 7 1.0
4 5 2.0 9 1.0
5 10 1.0 6 1.0
6 7 1.0
7
8
9
10
11
```

12

Title Card Required

С	0.00000000	0.0000000 0.0000000
С	0.00000000	0.00000000 1.38634146
С	1.20410705	0.00000000 2.09678585
С	2.39241573	0.00000000 1.36022120
С	2.36214735	0.0000000 -0.02578979
Ν	1.17343765	0.00000000 -0.71229641
0	1.15946304	-0.00000000 -1.99226382
Н	1.21598907	0.00000000 3.18508825
Н	3.36294258	0.00000000 1.85550735
Н	3.23988077	0.00000000 -0.66547617

- Н -0.89149064 0.0000000 -0.62037009
- Н -0.95948178 0.0000000 1.90269933

```
1 2 1.5 6 1.5 11 1.0
2 3 1.5 12 1.0
3 4 1.5 8 1.0
4 5 1.5 9 1.0
5 6 1.5 10 1.0
6 7 1.0
7
8
9
10
11
12
```

Title Card Required

С	-0.45409171 -0.59515511 -1.21375208
С	-0.45409171 0.75262425 -1.22661036
С	0.10524498 1.32011474 0.00000000
С	-0.45409171 0.75262425 1.22661036
С	-0.45409171 -0.59515511 1.21375208
Ν	0.15407509 -1.10902668 0.00000000
0	1.41382126 -0.56402896 0.00000000
Н	0.58402487 2.29864788 0.00000000
Н	-0.71901960 1.35744118 2.09110446
Н	-0.63417508 -1.27421497 2.04171916
Н	-0.63417508 -1.27421497 -2.04171916
Н	-0.71901960 1.35744118 -2.09110446

1 2 2.0 6 1.0 11 1.0
2 3 1.0 12 1.0
3 4 1.0 7 0.5 8 1.0
4 5 2.0 9 1.0
5 6 1.0 10 1.0
671.0
7
8
9
10
11
12

TS_Biradical (N-O cleavage from I2_α)

```
Zero-point correction=
                             0.087093 (Hartree/Particle)
Thermal correction to Energy=
                                   0.092091
Thermal correction to Enthalpy=
                                    0.093035
Thermal correction to Gibbs Free Energy=
                                           0.058755
Sum of electronic and zero-point Energies=
                                             -323.260597
Sum of electronic and thermal Energies=
                                           -323.255599
Sum of electronic and thermal Enthalpies=
                                            -323.254655
Sum of electronic and thermal Free Energies=
                                              -323.288935
```

%mem=4GB

%Nprocs=4

%chk=TSR.chk

opt=(calcall,qst3) freq b3lyp/aug-cc-pvdz geom=connectivity
empiricaldispersion=gd3

01	
С	0.0000000 0.0000000 0.0000000
С	0.00000000 0.00000000 2.26295050
С	0.88780008 0.0000000 0.99365998
Н	0.10435710 -0.04397503 -1.07900258
Н	1.97192271 -0.02204696 0.95491092
С	-1.55462742 -1.29751131 1.25273125
Н	-2.24921502 -2.00829547 0.81752470
С	-0.74108519 -1.35948782 2.30622879
Н	-0.59216372 -2.16206527 3.02107233
Н	0.42552905 0.38756596 3.19244783
0	-1.07643582 0.83245900 1.78932004
Ν	-1.37571255 0.02960157 0.58636418

Title Card Required

01

C 0.0000000 0.0000000 0.0000000

- C 0.0000000 0.0000000 2.49591517 C 0.71181387 0.0000000 1.17323294
- Н 0.53005411 0.02028883 -0.95508841
- Н 1.80104347 0.03720666 1.17949228
- C -2.05640389 0.00457851 1.08142824
- Н -3.14362640 0.02846971 0.97683775
- C -1.49316148 0.00490930 2.33279221
- Н -2.10515600 0.04590268 3.23369572
- Н 0.29430176 -0.93424965 3.05949621
- O 0.46264714 0.97509246 3.37152891
- N -1.35885761 -0.00526795 -0.08801713

```
1 3 2.0 4 1.0 12 1.0
```

- 2 3 1.0 8 1.0 10 1.0 11 1.0
- 3 5 1.0
- 4
- 5
- 671.082.0121.0
- 7
- 891.0
- 0 / 110
- 9
- 10
- 11
- 12

Title Card Required

- C -1.19630840 -0.86892763 -0.07591932
- C -0.07096172 1.12166026 -0.15368977
- C -1.35143899 0.38490956 -0.50328835

Н	-1.90212930 -1.69712202 -0.13891124
Н	-2.22448608 0.80438220 -0.99577589
С	1.14099205 -0.91060231 -0.27575134
Н	2.02422185 -1.54525039 -0.20504869
С	1.13816570 0.38518483 -0.73551604
Н	2.01665839 0.89550901 -1.12731975
Η	-0.10208588 2.19881349 -0.38690538
0	0.22445779 0.88468503 1.20457321
Ν	0.06135242 -1.20102298 0.52605203

```
1 3 2.0 4 1.0 12 1.0
2 3 1.0 8 1.0 10 1.0 11 1.0
3 5 1.0
4
5
6 7 1.0 8 2.0 12 1.0
7
8 9 1.0
9
10
11 12 0.5
12
```

In 1,4-dioxane

Enamine

Zero-point correction=	0.068466 (Hartree/Particle)
Thermal correction to Energy=	= 0.072411
Thermal correction to Enthalp	y= 0.073355
Thermal correction to Gibbs F	ree Energy= 0.043812
Sum of electronic and zero-po	int Energies= -133.905785

Sum of electronic and thermal Energies=	-133.901841
Sum of electronic and thermal Enthalpies=	-133.900896
Sum of electronic and thermal Free Energies	-133.930439

%chk=eneamine.chk

opt=calcall freq b3lyp/aug-cc-pvdz scrf=(smd,solvent=1,4-dioxane)
scf=(qc,maxcycle=600) geom=connectivity empirical dispersion=gd3
Title Card Required

~ 1

С	-1.25611076 -0.19663277 0.01314654
С	-0.06575363 0.43013315 0.00049825
Н	-0.02436375 1.52229660 -0.00536861
Н	-2.17873080 0.38018942 0.00678221
Н	-1.33712187 -1.28560215 0.01436371
N	1.18442722 -0.17223587 -0.07946532
Н	1.95741765 0.34791818 0.31466431
Н	1.22299457 -1.16015320 0.14394687

```
1 2 2.0 4 1.0 5 1.0
2 3 1.0 6 1.0
3
4
5
6 7 1.0 8 1.0
7
8
```

Isoxazole

Zero-point correction= 0.057630 (Hartree/Particle) Thermal correction to Energy= 0.061228

Thermal correction to Enthalpy= 0.062	172
Thermal correction to Gibbs Free Energy=	0.031415
Sum of electronic and zero-point Energies=	-246.017103
Sum of electronic and thermal Energies=	-246.013506
Sum of electronic and thermal Enthalpies=	-246.012561
Sum of electronic and thermal Free Energies	-246.043318

%chk=isoxazole.chk

opt=calcall freq b3lyp/aug-cc-pvdz scrf=(smd,solvent=1,4-dioxane)
scf=(qc,maxcycle=600) geom=connectivity empirical dispersion=gd3

Title Card Required

01	
С	0.61819600 -0.96588700 0.00000000
С	$0.00000000 \ 1.13010200 \ 0.00000000$
С	1.12822700 0.36593600 0.00000000
0	-1.09589200 0.34942900 0.00000000
Ν	-0.69473100 -0.99523300 0.00000000
Н	1.16481300 -1.90602500 0.00000000
Н	2.16098400 0.69439800 0.00000000
Н	$-0.17408900 \ 2.20192000 \ 0.00000000$

TS1-I-endo

Zero-point correction= 0.128697 (Hartree/Particle)
Thermal correction to Energy= 0.135453
Thermal correction to Enthalpy= 0.136397
Thermal correction to Gibbs Free Energy= 0.098170
Sum of electronic and zero-point Energies= -379.880260
Sum of electronic and thermal Energies= -379.873504
Sum of electronic and thermal Enthalpies= -379.872560
Sum of electronic and thermal Free Energies= -379.910787

%chk=TS1.chk

opt=(calcall,qst3) freq b3lyp/aug-cc-pvdz scrf=(smd,solvent=1,4-dioxane)
scf=(qc,maxcycle=600) geom=connectivity empirical dispersion=gd3

Title Card Required

С	0.0000000 0.0000000 0.0000000
С	0.00000000 0.00000000 2.18525469
С	0.86596214 0.00000000 1.13313420
С	-7.57957227 -0.00049825 3.27682996
С	-8.89861311 -0.01314654 3.01241200
0	-1.27197387 0.00000000 1.74649261
Ν	-1.26759683 0.0000000 0.34327262
Н	-7.23090629 0.00536861 4.31267075
Н	-9.28437825 -0.01436371 1.99084341
Η	0.25832848 0.00000000 -1.05636953
Η	1.94945173 0.00000000 1.15601841
Η	0.13623331 0.00000000 3.26253828
N	-6.55086670 0.07946532 2.34539801

Н	-6.79335098	-0.14394687	1.38692555
Н	-5.66230347	-0.31466431	2.62562974
Н	-9.62036541	-0.00678221	3.82667558
1 3 1.0	7 2.0 10 1.0		
2 3 2.0	6 1.0 12 1.0		
3 11 1.	0		
4 5 2.0	8 1.0 13 1.0		
5 16 1.	091.0		
671.0	671.0		
7			
8			
9			
10			
11			
12			
13 15 1.0 14 1.0			
14			
15			
16			

Title Card Required

С	0.00000000 0.0000000 0.00000000
С	0.0000000 0.0000000 2.24779242
С	0.87703471 0.00000000 1.00780718
С	-1.67499509 -1.28990241 1.15103613
С	-0.66470981 -1.40495607 2.32807991
0	-1.11792567 0.80141511 1.78817359
N	-1.35961742 0.08103159 0.53719980

Η -2.69478086 -1.17492089 1.53963222 Η 0.05882252 -2.21773918 2.19218908 Η 0.14188693 -0.09427391 -1.07132598 Η 1.95905643 -0.08717643 0.96965668 Η 0.40537368 0.41026923 3.17674791 Ν -1.54527989 -2.32508906 0.14586634 Η -1.37304913 -3.23187155 0.56823007 -2.38552174 -2.40004623 -0.42145507 Η Η -1.18657263 -1.54041536 3.28215798

Title Card Required

01

C 0.0000000 0.0000000 0.0000000

С	0.00000000 0.00000000 2.24779242
С	0.87703471 0.00000000 1.00780718
С	-1.74222093 -1.58213043 1.28188136
С	-0.79525782 -1.68088734 2.34384826
0	-1.11792567 0.80141511 1.78817359
N	-1.35961742 0.08103159 0.53719980
Η	-2.76200670 -1.46714891 1.67047746
Η	-0.07172549 -2.49367045 2.20795742
Η	0.14188693 -0.09427391 -1.07132598
Η	1.95905643 -0.08717643 0.96965668
Η	0.40537368 0.41026923 3.17674791
N	-1.61250573 -2.61731708 0.27671158
Η	-1.44027497 -3.52409958 0.69907530
Η	-2.45274758 -2.69227426 -0.29060983
Η	-1.31712064 -1.81634663 3.29792633

TS1-I-exo

Zero-point correction= 0	.128283 (Hartree/Particle)	
Thermal correction to Energy=	0.135358	
Thermal correction to Enthalpy=	0.136302	
Thermal correction to Gibbs Free	e Energy= 0.097179	
Sum of electronic and zero-point	Energies= -379.877479	
Sum of electronic and thermal Energies= -379.870404		
Sum of electronic and thermal En	nthalpies= -379.869460	
Sum of electronic and thermal Fr	ree Energies= -379.908583	

%chk=TS2BCDIOCARTESIAN.chk

opt=(calcall,qst3) freq b3lyp/aug-cc-pvdz scrf=(smd,solvent=1,4-dioxane)
scf=(qc,maxcycle=600) geom=connectivity empirical dispersion=gd3

n	1
υ	т

С	0.00000000 0.0000000 0.00000000
С	0.00000000 0.00000000 2.18525469
С	0.86596214 0.00000000 1.13313420
С	-7.57957227 -0.00049825 3.27682996
С	-8.89861311 -0.01314654 3.01241200
0	-1.27197387 0.00000000 1.74649261
N	-1.26759683 0.0000000 0.34327262
Н	-7.23090629 0.00536861 4.31267075
Н	-9.28437825 -0.01436371 1.99084341
Н	0.25832848 0.00000000 -1.05636953

Н 0.13623331 0.00000000 3.26253828

N -6.55086670 0.07946532 2.34539801

Н -6.79335098 -0.14394687 1.38692555

Н -5.66230347 -0.31466431 2.62562974

Н -9.62036541 -0.00678221 3.82667558

```
1 \ 3 \ 1.0 \ 7 \ 2.0 \ 10 \ 1.0
```

2 3 2.0 6 1.0 12 1.0

3 11 1.0

4 5 2.0 8 1.0 13 1.0

5 16 1.0 9 1.0

671.0

7

8

9

·

10

11

12

_

13 15 1.0 14 1.0

14

15

16

Λ	1
υ	1

С	0.00000000 0.00000000 0.00000000
С	0.00000000 0.00000000 2.25011467
С	0.87952098 0.00000000 1.00538892
С	-1.63567114 -1.33909314 1.13291768

С	-0.65882313 -1.39946626 2.34623038
0	-1.12344683 0.78779498 1.78883988
N	-1.36064838 0.05635140 0.53816868
Н	-1.39877773 -2.06647861 0.34883812
Н	0.06154014 -2.22177550 2.28271130
Н	0.13692335 -0.08347660 -1.07474634
Н	1.96264691 -0.07123315 0.96696557
Н	0.40465467 0.42235879 3.17410919
N	-3.00687227 -1.50705730 1.53926665
Н	-3.25293061 -0.80344713 2.23364966
Н	-3.63015479 -1.37272761 0.74553911
Н	-1.22650156 -1.49815024 3.27849326

01	
С	0.0000000 0.0000000 0.0000000
С	0.00000000 0.00000000 2.22589609
С	0.89370120 0.00000000 1.04292516
С	-1.38773444 -2.05032810 1.58674941
С	-0.54472644 -1.77140942 2.66072335
0	-1.17573323 0.63046051 1.76239591
Ν	-1.29260430 0.18359733 0.38343723
Н	-1.02041679 -2.47568229 0.65719254
Н	0.37095838 -2.36508427 2.73448231
Н	0.19199420 -0.18454220 -1.05735123
Н	1.95118798 -0.24272124 1.02585931
Н	0.33899999 0.47034416 3.15489571
Ν	-2.68337789 -2.21864404 1.84647802
Н	-3.08581727 -1.85416089 2.70213459
Н	-3.32911715 -2.46396682 1.10665084
Н	-1.04009733 -1.71679656 3.63807449

13 14 1.0 15 1.0 14 15 16

I1-I-endo

Zero-point correction= 0.132481 (Hartree/Particle) Thermal correction to Energy= 0.138695 Thermal correction to Enthalpy= 0.139639 Thermal correction to Gibbs Free Energy= 0.102613 Sum of electronic and zero-point Energies= -379.899341 Sum of electronic and thermal Energies= -379.893127 Sum of electronic and thermal Enthalpies= -379.892183 Sum of electronic and thermal Free Energies= -379.929210

%chk=I1N.chk # opt=(calcall,maxcycle=500) freq b3lyp/aug-cc-pvdz scrf=(smd,solvent=1,4-dioxane) geom=connectivity empiricaldispersion=gd3

0	1
~	-

- C -1.06961543 -0.42827312 0.31710169
- C 0.43466408 1.42004686 -0.08021721
- C 1.25841316 0.72937170 -0.87548373
- C 1.22371006 -0.67641019 -0.29762587
- Н -1.43259597 -1.03596244 1.15022377

- Н -0.44539213 -1.15040440 -1.68783897
- Н 0.08498076 2.44666588 -0.13595152
- Н 1.77546356 1.05689869 -1.77297817
- Н -0.21559597 -2.33392935 -0.37545686
- N -0.06255131 0.54763258 0.98365065
- O 1.05958973 -0.38421764 1.11385312
- N -2.18939329 0.19813415 -0.32878370
- Н -1.90430679 0.77332289 -1.11759492
- Н -2.72440074 0.77327079 0.31743045
- Н 2.09130364 -1.32310730 -0.45372726

```
1 2 1.0 5 1.0 7 1.0 10 1.0
2 6 1.0 11 1.0 13 1.0
3 4 2.0 8 1.0 11 1.0
4 5 1.0 9 1.0
5 12 1.0 16 1.0
6
7
8
9
10
11 12 1.0
12
13 14 1.0 15 1.0
14
15
16
```

I1-I-exo

Zero-point correction=0.132466 (Hartree/Particle)Thermal correction to Energy=0.138681Thermal correction to Enthalpy=0.139625

Thermal correction to Gibbs Free Energy=	0.102574
Sum of electronic and zero-point Energies=	-379.901311
Sum of electronic and thermal Energies=	-379.895096
Sum of electronic and thermal Enthalpies=	-379.894152
Sum of electronic and thermal Free Energies	-379.931204

%chk=I1X.chk

```
# opt=(calcall,maxcycle=500) freq b3lyp/aug-cc-pvdz
scrf=(smd,solvent=1,4-dioxane) geom=connectivity empirical dispersion=gd3
```

Title Card Required

01

С	0.99221062 -0.21248454 -0.54589937
С	0.32022071 1.19139044 -0.63288225
С	-0.89457839 0.98330579 0.30667737
С	-1.84648830 0.02057327 -0.39325196
С	-1.20547675 -1.15005281 -0.33762513
N	0.05060262 -0.98742572 0.39723966
0	-0.30959438 0.11072809 1.30265709
Н	-1.31202623 1.87494388 0.78271210
Н	-2.78086766 0.26610976 -0.88959368
Н	-1.43859403 -2.11849707 -0.77186860
Н	0.99470783 -0.75190817 -1.49931715
Н	0.03534363 1.47359650 -1.65188058
Н	0.99594120 1.95472570 -0.23060669
Ν	2.33834865 -0.13253788 -0.04086391
Н	2.34214814 0.32454365 0.86954408
Н	2.72211591 -1.06598657 0.09301163

1 2 1.0 6 1.0 11 1.0 14 1.0

```
2 3 1.0 12 1.0 13 1.0
3 4 1.0 7 1.0 8 1.0
4 5 2.0 9 1.0
5 6 1.0 10 1.0
6 7 1.0
7
8
9
10
11
12
13
14 15 1.0 16 1.0
15
16
```

Ι2_α

Zero-point correction= 0.125939 (Hartree/Particle)
Thermal correction to Energy= 0.135039
Thermal correction to Enthalpy= 0.135983
Thermal correction to Gibbs Free Energy= 0.090137
Sum of electronic and zero-point Energies= -379.850682
Sum of electronic and thermal Energies= -379.841583
Sum of electronic and thermal Enthalpies= -379.840639
Sum of electronic and thermal Free Energies= -379.886485

%chk=I2-2_NH3.chk

```
# opt=(calcall,maxcycle=500) freq b3lyp/aug-cc-pvdz
scrf=(smd,solvent=1,4-dioxane) geom=connectivity empiricaldispersion=gd3
```

С	1.66719518 -0.99051379 0.21237444
С	0.76203196 0.90124588 -0.64088476
С	2.07914877 0.15277931 -0.33474379
Η	2.19658509 -1.83455616 0.64257813
Η	3.08737933 0.51461301 -0.50902963
С	-0.22554518 0.05545987 1.21439430
Н	-0.68210155 -0.25446105 2.14795066
С	0.10044960 1.24630619 0.71369097
Η	-0.02765841 2.23610981 1.13972664
Η	0.76946432 1.66442432 -1.42312452
0	-0.05901872 -0.23094731 -1.01333716
N	0.17377790 -1.00051559 0.23204472
N	-3.24860808 -0.22456935 -0.15116105
Н	-2.33978741 -0.36555770 -0.59196616
Η	-3.35197602 0.78155988 -0.02814120
Н	-3.95562628 -0.51062374 -0.82646929

```
1 3 2.0 4 1.0 12 1.0
2 3 1.0 8 1.0 10 1.0 11 1.0
3 5 1.0
4
5
6 7 1.0 8 2.0 12 1.0
7
8 9 1.0
9
10
11 12 1.0 14 0.5
12
```

```
13 14 1.0 15 1.0 16 1.0
14
15
16
```

$I2_\beta_endo$

Zero-point correction=	0.131697 (Hartree/Particle)
Thermal correction to Energy=	= 0.138888
Thermal correction to Enthalp	y= 0.139832
Thermal correction to Gibbs F	Free Energy= 0.100384
Sum of electronic and zero-po	oint Energies= -379.928812
Sum of electronic and thermal	Energies= -379.921622
Sum of electronic and thermal	Enthalpies= -379.920677
Sum of electronic and thermal	Free Energies= -379.960126

%chk=I2-1N_1.chk

opt=(calcall,maxcycle=500) freq b3lyp/aug-cc-pvdz

scrf=(smd,solvent=1,4-dioxane) geom=connectivity empiricaldispersion=gd3

Title Card Required

- C -0.59561068 -0.64095887 0.36004656
- C 0.59327031 -1.43447604 -0.18339784
- C 1.89940864 -0.72299396 0.02166009
- C 1.91016426 0.62475157 0.03817776
- C 0.68811141 1.39127157 -0.08746741
- N -0.49691480 0.83127999 0.00632246
- O -1.60267743 1.47487864 -0.04381468
- Н 2.82433877 -1.29665606 0.07884658
- H 2.83975530 1.18828991 0.11991844

- Н 0.68592609 2.47010173 -0.22686124
- Н -0.56354222 -0.62217560 1.46641484
- Н 0.59291495 -2.42191418 0.29796429
- Н 0.42785345 -1.60834420 -1.26150136
- N -1.83625518 -1.14685851 -0.18928684
- Н -2.02310386 -2.07339431 0.18652949
- Н -2.60259677 -0.53145233 0.07584211

```
1 2 1.0 6 1.0 11 1.0 14 1.0
```

```
2 3 1.0 12 1.0 13 1.0

3 4 2.0 8 1.0

4 5 1.0 9 1.0

5 6 2.0 10 1.0

6 7 1.0

7

8

9

10

11

12

13

14 15 1.0 16 1.0

15

16
```

$I2_\beta_{exo}$

Zero-point correction= 0.132294 (Hartree/Particle) Thermal correction to Energy= 0.139302 Thermal correction to Enthalpy= 0.140247 Thermal correction to Gibbs Free Energy= 0.101354 Sum of electronic and zero-point Energies= -379.933814

Sum of electronic and thermal Energies=	-379.926805
Sum of electronic and thermal Enthalpies=	-379.925861
Sum of electronic and thermal Free Energies	-379.964753

%chk=I2-1X.chk # opt=(calcall,maxcycle=500) freq b3lyp/aug-cc-pvdz scrf=(smd,solvent=1,4-dioxane) geom=connectivity empiricaldispersion=gd3

Title Card Required

01

С	0.39024790 0.92841555 -0.30623075
С	-1.06839518 0.95034567 -0.76805658
С	-1.91150562 -0.05793632 -0.03730583
С	-1.34047768 -1.20271188 0.38981692
С	0.07242438 -1.46054086 0.19865049
Ν	0.89534893 -0.51084120 -0.18893036
0	2.15612742 -0.66244607 -0.35835110
Η	-2.97921699 0.12182787 0.08573956
Η	-1.92554184 -1.98668507 0.87100560
Η	0.52065902 -2.43512745 0.38207004
Η	1.05656479 1.36120856 -1.05701566
Η	-1.11003080 0.73334911 -1.84926650
Η	-1.44669180 1.97179987 -0.63382926
Ν	0.57086691 1.62280637 0.94334723
Η	-0.02090484 1.23267146 1.67438639
Н	1.53886942 1.57133505 1.25155503

1 2 1.0 6 1.0 11 1.0 14 1.0

2 3 1.0 12 1.0 13 1.0

3 4 2.0 8 1.0

I3

Zero-point correction= 0.128942 (Hartree/Particle)
Thermal correction to Energy= 0.137918
Thermal correction to Enthalpy= 0.138862
Thermal correction to Gibbs Free Energy= 0.093830
Sum of electronic and zero-point Energies= -379.958684
Sum of electronic and thermal Energies= -379.949707
Sum of electronic and thermal Enthalpies= -379.948763
Sum of electronic and thermal Free Energies= -379.993795

%chk=I3 NH3.chk

opt=(calcall,maxcycle=500) freq b3lyp/aug-cc-pvdz scrf=(smd,solvent=1,4-dioxane) geom=connectivity empiricaldispersion=gd3

Title Card Required

-1.13139946 -1.23830180 0.00001455
-2.30209479 -0.49537926 0.00003896
-2.24984242 0.90093798 0.00002146
-0.99096730 1.50690851 -0.00002117
0.16307814 0.73728500 -0.00004463
0.09245537 -0.62917504 -0.00002638
-3.16108601 1.49684771 0.00004037
-1.09195831 -2.32387177 0.00002719
-3.25283424 -1.02731723 0.00007104
-0.88520619 2.59111950 -0.00003598
1.17275708 1.14180311 -0.00007332
1.17162772 -1.34755811 -0.00004534
3.56981602 0.58285335 0.00005740
2.93301551 -0.21945571 0.00004171
4.17192854 0.48838908 0.81629033
4.17181713 0.48849950 -0.81627081

```
1 2 1.5 6 1.5 8 1.0
2 3 1.5 9 1.0
3 4 1.5 7 1.0
4 5 1.5 10 1.0
5 6 1.5 11 1.0
6 12 1.0
7
8
9
10
11
12 14 0.5
13 14 1.0 15 1.0 16 1.0
14
```

I2_ α (without NH3)

0.090351 (Hartree/Particle) Zero-point correction= Thermal correction to Energy= 0.095100 Thermal correction to Enthalpy= 0.096045 Thermal correction to Gibbs Free Energy= 0.062320 Sum of electronic and zero-point Energies= -323.309924 Sum of electronic and thermal Energies= -323.305175 Sum of electronic and thermal Enthalpies= -323.304231 Sum of electronic and thermal Free Energies= -323.337955

%chk=I2-2.chk

opt=(calcall,maxcycle=500) freq b3lyp/aug-cc-pvdz scrf=(smd,solvent=1,4-dioxane) geom=connectivity empiricaldispersion=gd3

Λ	1
υ	1
-	

С	-0.48399108 -0.67951871 1.19081180
С	0.33558496 1.06268953 -0.00000000
С	-0.48399108 0.65181256 1.24561710
Н	-0.95695339 -1.44215622 1.80099327
Н	-0.95898070 1.31683624 1.95963765
С	$-0.48399108 \ -0.67951871 \ -1.19081180$
Н	-0.95695339 -1.44215622 -1.80099327
С	-0.48399108 0.65181256 -1.24561710
Н	-0.95898070 1.31683624 -1.95963765
Н	0.82156632 2.04161253 -0.00000000
0	1.30384581 -0.00967854 -0.00000000

N 0.31168737 -1.10817252 0.00000000

```
1 3 2.0 4 1.0 12 1.0
2 3 1.0 8 1.0 10 1.0 11 1.0
3 5 1.0
4
5
6 7 1.0 8 2.0 12 1.0
7
8 9 1.0
9
10
11 12 1.0
12
```

Biradical

Zero-point correction= 0.087274 (Hartree/Particle) Thermal correction to Energy= 0.092966 Thermal correction to Enthalpy= 0.093911 Thermal correction to Gibbs Free Energy= 0.056795 Sum of electronic and zero-point Energies= -323.339605 Sum of electronic and thermal Energies= -323.333913 -323.332969 Sum of electronic and thermal Enthalpies= Sum of electronic and thermal Free Energies= -323.370084

%chk=Biradical_Triplet.chk # opt=(calcall,maxcycle=500) freq ub3lyp/aug-cc-pvdz scrf=(smd,solvent=1,4-dioxane) geom=connectivity empiricaldispersion=gd3

0	3
0	3

С	-1.12081734 -1.16285298 -0.05124530
С	1.05545353 -0.00015193 0.32091301
С	0.22900078 -1.24612771 0.17968015
Н	-1.70672539 -2.07694054 -0.17209259
Н	0.73847430 -2.20824847 0.23309194
С	-1.12058428 1.16298167 -0.05122245
Н	-1.70633263 2.07718621 -0.17196680
С	0.22925512 1.24605541 0.17967984
Н	0.73887632 2.20809784 0.23316291
Н	1.52139537 -0.00008786 1.35149535
0	2.19017509 -0.00005018 -0.47363658
N	-1.82013365 0.00013821 -0.16448995

I3 (without NH₃)

Zero-point correction=0.092713 (Hartree/Particle)Thermal correction to Energy=0.097778Thermal correction to Enthalpy=0.098722

Thermal correction to Gibbs Free Energy=	0.064001
Sum of electronic and zero-point Energies=	-323.415284
Sum of electronic and thermal Energies=	-323.410219
Sum of electronic and thermal Enthalpies=	-323.409275
Sum of electronic and thermal Free Energies	-323.443996

%chk=I3.chk

opt=(calcall,maxcycle=500) freq b3lyp/aug-cc-pvdz
scrf=(smd,solvent=1,4-dioxane) geom=connectivity empirical dispersion=gd3

Title Card Required

01

С	-0.00000000 0.28552634 1.18001547
С	0.00000000 -1.10080685 1.19648629
С	0.00000000 -1.82278125 0.00000000
С	0.00000000 -1.10080685 -1.19648629
С	-0.0000000 0.28552634 -1.18001547
N	-0.0000000 0.98068260 0.00000000
Н	0.00000010 -2.91136714 0.00000000
Н	-0.0000000 0.91178829 2.06748546
Н	-0.00000003 -1.60610689 2.16161217
Н	-0.00000003 -1.60610689 -2.16161217
Н	$-0.0000000 \ \ 0.91178829 \ \ -2.06748546$
0	-0.0000000 2.26940998 -0.00000000

1 2 1.5 6 1.5 8 1.0

- 2 3 1.5 9 1.0
- 3 4 1.5 7 1.0
- 4 5 1.5 10 1.0
- 5 6 1.5 11 1.0
| 6 1 2 | 1.0 | |
|-------|-----|--|
| 7 | | |
| 8 | | |
| 9 | | |
| 10 | | |
| 11 | | |
| 12 | | |

TS2_ α _endo

Zero-point correction= 0.128708 (Hartree/Particle) 0.135259 Thermal correction to Energy= Thermal correction to Enthalpy= 0.136204 Thermal correction to Gibbs Free Energy= 0.098488 Sum of electronic and zero-point Energies= -379.797289 Sum of electronic and thermal Energies= -379.790737 Sum of electronic and thermal Enthalpies= -379.789792 Sum of electronic and thermal Free Energies= -379.827508

%chk=TS1N_TS.chk

opt=(calcall,tight,ts,verytight,noeigentest,maxcycle=500) freq b3lyp/aug-cc-pvdz scrf=(smd,solvent=1,4-dioxane) geom=connectivity empiricaldispersion=gd3

Title Card Required

0 1	
C -0.83328103 -0.72638177 0.31774671	
C -0.03081477 -1.27535350 -0.73788146	
C 1.26811193 -0.52453820 -0.50968356	
C 1.04892535 0.94342752 -0.87213036	

C 0.25319485 1.41455571 0.09158878

Ν	0.00078019 0.32499650 1.06495714
0	1.28194904 -0.36349027 0.98924219
Н	2.19694123 -0.99510023 -0.84270075
Н	1.40352292 1.44601749 -1.76820529
Н	-0.21978407 2.38188687 0.23538355
Н	-1.36968358 -1.37053733 1.01799489
Н	0.04112015 -2.36378200 -0.76826756
Н	-2.86867285 -0.47272456 -0.56119980
Ν	-2.17520007 0.20723751 -0.25256103
Н	-2.60646483 0.84715905 0.42258455
Н	-1.84845015 0.71910615 -1.07414051

1 2 1.5 6 1.0 11 1.0 14 0.5 2 3 1.0 12 1.0 13 0.5

```
3 4 1.0 7 1.0 8 1.0
```

```
4 5 2.0 9 1.0
```

5 6 1.0 10 1.0

671.0

7 13 0.3

8
9
10
11
12
13 14 0.5
14 15 1.0 16 1.0
15

16

TS2_α_exo

Zero-point correction=

0.128351 (Hartree/Particle)

Thermal correction to Energy=	0.134973
Thermal correction to Enthalpy=	0.135918
Thermal correction to Gibbs Free En	nergy= 0.098043
Sum of electronic and zero-point End	ergies= -379.805584
Sum of electronic and thermal Energ	gies= -379.798962
Sum of electronic and thermal Entha	lpies= -379.798017
Sum of electronic and thermal Free I	Energies= -379.835892

%chk=TS1X_TS.chk

opt=(calcall,tight,ts,verytight,noeigentest,maxcycle=500) freq b3lyp/aug-cc-pvdz scrf=(smd,solvent=1,4-dioxane) geom=connectivity empiricaldispersion=gd3

Title Card Required

С	0.79919263 -0.06048530 -0.73236172
С	0.22266683 1.23431147 -0.65381274
С	-0.87793321 0.99188291 0.39472313
С	-1.92272874 0.05706997 -0.24066376
С	-1.29627364 -1.12269216 -0.34389336
Ν	0.05242235 -0.98466391 0.22233501
0	-0.21721064 0.02946666 1.26493944
Н	-1.24899551 1.83365872 0.98787050
Н	-2.91176424 0.33097697 -0.59967515
Н	-1.57047818 -2.05801742 -0.82221391
Н	1.07183912 -0.55015797 -1.67025905
Н	-0.02247003 1.75380868 -1.58023316
Н	2.99025600 0.53141024 -0.36211883
Ν	2.36641660 -0.13411026 0.09202333
Н	2.14560634 0.21248401 1.02717667

Н 2.80227579 -1.05899865 0.15547971

```
1 2 1.5 6 1.0 11 1.0 14 0.5
2 3 1.0 12 1.0 13 0.5
3 4 1.0 7 1.0 8 1.0
4 5 2.0 9 1.0
5 6 1.0 10 1.0
671.0
7 13 0.2 15 0.3
8
9
10
11
12
13 14 0.5
14 15 1.0 16 1.0
15
16
```

TS3_α

Zero-point correction=	0.123688 (Hartree/Particle)
Thermal correction to Energy=	0.132610
Thermal correction to Enthalpy=	0.133554
Thermal correction to Gibbs Free Ener	gy= 0.089312
Sum of electronic and zero-point Energy	gies= -379.792294
Sum of electronic and thermal Energie	s= -379.783373
Sum of electronic and thermal Enthalp	ies= -379.782429
Sum of electronic and thermal Free En	ergies= -379.826671

%mem=4GB %Nprocs=4 %chk=TS3.chk

opt=(calcall,qst3,maxcycle=500) freq b3lyp/aug-cc-pvdz

scrf=(smd,solvent=1,4-dioxane) geom=connectivity empiricaldispersion=gd3

01	
С	0.0000000 0.0000000 0.0000000
С	0.00000000 0.00000000 1.33232546
С	1.50339939 0.00000000 1.69484882
С	2.09030710 -1.35315681 1.23308390
С	1.99877440 -1.29476068 -0.09521375
Ν	1.41820921 0.02735817 -0.47695663
0	1.99624562 0.83708833 0.62195934
Н	1.80049606 0.38701675 2.67277881
Н	2.45470462 -2.15381258 1.86868807
Н	2.22751105 -2.00661951 -0.88177132
Н	-0.79258524 -0.02963267 -0.73956240
Н	$-0.83458180 \ -0.02275882 \ 2.02556737$
Н	0.84557932 2.67377652 -0.21477367
Ν	0.07929809 3.29369866 -0.47678763
Н	-0.50756202 3.38598287 0.35097654
Н	0.48445372 4.21185307 -0.65167128
1 11 1	.0 2 2.0 6 1.0
231.0	0 12 1.0

- 3 4 1.0 8 1.0 7 1.0
- 4 5 2.0 9 1.0
- 5 10 1.0 6 1.0
- 671.0
- 7 13 0.5

Title Card Required

С	0.00000000 0.0000000 0.00000000
С	0.00000000 0.00000000 1.38713418
С	1.20260710 0.00000000 2.09826216
С	2.39328369 0.00000000 1.36701569
С	2.36183160 -0.00000000 -0.01915610
Ν	1.17602892 -0.00000000 -0.69939730
0	1.17494056 -0.00000000 -1.99581004
Н	1.21241695 0.00000000 3.18701238
Н	3.36333550 -0.00000000 1.86286142
Н	3.24310339 -0.00000000 -0.65427638
Н	-0.89674450 0.00000454 -0.61557760
Н	-0.96070374 0.00000000 1.90069743
Н	-0.74087042 0.00014938 -2.83531600
Ν	-1.76167848 0.00019299 -2.91996593
Н	-2.01713632 0.81644068 -3.47330144
Н	-2.01720903 -0.81612046 -3.47317133

1 2 1.5 6 1.5 11 1.0

2 3 1.5 12 1.0
3 4 1.5 8 1.0
4 5 1.5 9 1.0
5 6 1.5 10 1.0
671.0
7 13 0.5
8
9
10
11
12
13 14 1.0
14 15 1.0 16 1.0
15
16

0	1

С	-0.25676844 0.69927474 0.87719299
С	0.62971008 1.50901797 0.26397519
С	1.49216222 0.77806367 -0.65729073
С	2.10608742 -0.41900175 -0.08969181
С	1.20213733 -1.20351668 0.52910885
N	-0.14192315 -0.67423354 0.42605532
0	$\textbf{-0.33610412} \hspace{0.1in} \textbf{-0.57699314} \hspace{0.1in} \textbf{-0.95900712}$
Н	1.90510428 1.25708062 -1.54478399
Н	3.14242323 -0.69528943 -0.27223823
Н	1.33624951 -2.22464560 0.87577155
Н	-1.14311522 0.98545993 1.43514832
Н	0.61101315 2.59513757 0.32107574

Н -2.47574234 -0.09811814 -0.67008450

N -3.31158344 0.01166390 -0.09194558

- Н -4.10145356 0.13654028 -0.72274341
- Н -3.45107172 -0.88526037 0.37137628

```
1 2 2.0 6 1.0 11 1.0
2 3 1.0 12 1.0
3 4 1.0 7 0.5 8 1.0
4 5 2.0 9 1.0
5 6 1.0 10 1.0
671.0
7 13 0.5
8
9
10
11
12
13 14 1.0
14 15 1.0 16 1.0
15
16
```

```
$END
```

TS3_β_endo

Zero-point correction=	0.129192 (Ha	0.129192 (Hartree/Particle)	
Thermal correction to Energy	y= 0.1356	80	
Thermal correction to Enthal	py= 0.136	624	
Thermal correction to Gibbs	Free Energy=	0.098960	
Sum of electronic and zero-p	oint Energies=	-379.841689	
Sum of electronic and therma	al Energies=	-379.835201	

Sum of electronic and thermal Enthalpies= -379.834257 Sum of electronic and thermal Free Energies= -379.871921

%mem=4GB %Nprocs=4 %chk=TS2N.chk # opt=(calcall,qst3,maxcycle=500) freq b3lyp/aug-cc-pvdz scrf=(smd,solvent=1,4-dioxane) geom=connectivity empiricaldispersion=gd3

Title Card Required

01

С	$0.00000000 \ 0.00000000 \ 0.00000000$
С	0.00000000 0.00000000 1.55579174
С	1.52736733 0.00000000 1.83465332
С	2.04933331 -1.37426567 1.44697805
С	1.98451146 -1.37343227 0.11137293
Ν	1.51023026 -0.07003704 -0.35377527
0	2.00527026 0.79493974 0.71918726
Η	1.86095638 0.43366479 2.78120317
Η	2.32908215 -2.18245071 2.11682046
Н	2.18424147 -2.15822647 -0.61218588
Н	-0.31327816 0.97210287 -0.38987995
Η	-0.46915863 0.90889415 1.94789985
Н	-0.51272183 -0.87244354 1.97658138
Ν	-0.81305056 -1.02612442 -0.59116322
Н	-0.75043258 -1.01904924 -1.60636605
Η	-0.56384044 -1.95334716 -0.25576520

 $1\ 2\ 1.0\ 11\ 1.0\ 6\ 1.0\ 14\ 1.0$

 $2\;3\;1.0\;13\;1.0\;12\;1.0$

3 4 1.0 7 1.0 8 1.0
4 5 2.0 9 1.0
5 10 1.0 6 1.0
671.0
7
8
9
10
11
12
13
14 16 1.0 15 1.0
15
16

Title Card Required

С	0.0000000 0.0000000 0.0000000
С	0.0000000 0.0000000 1.52675812
С	1.38808481 0.00000000 2.10137937
С	2.38680565 -0.59047234 1.41518502
С	2.15880157 -1.20975933 0.12503729
Ν	1.04089967 -1.02244374 -0.53819998
0	0.78252796 -1.53239418 -1.68051185
Н	1.55797035 0.42723775 3.08958784
Н	3.39646682 -0.65368886 1.82183264
Н	2.90032939 -1.84365575 -0.35786156
Н	0.38988664 0.95231430 -0.38794890
Н	-0.57605518 0.87149142 1.86168127
Н	-0.54654735 -0.89223040 1.88747947

N	-1.30410528	-0.23010923	-0.52746039
Н	-1.26774170	-0.31593029	-1.54034669
Н	-1.69588580	-1.09855979	-0.16734145

```
1 2 1.0 6 1.0 11 1.0 14 1.0
2 3 1.0 12 1.0 13 1.0
3 4 2.0 8 1.0
4 5 1.0 9 1.0
5 6 2.0 10 1.0
671.0
7
8
9
10
11
12
13
14 15 1.0 16 1.0
15
16
```

Title Card Required

С	-1.08523753 -0.03809327 0.40009728
С	-0.30554232 -1.41845948 0.36973314
С	1.09780199 -1.16600005 -0.00975776
С	1.33320417 -0.19525087 -1.03564333
С	0.73127518 1.01306809 -0.82085459
N	-0.06173254 1.01947857 0.36661240
0	0.78378124 0.82349169 1.39320124

- Н 1.89165463 -1.84664086 0.29553166
- Н 2.13772261 -0.29559537 -1.76406954
- Н 1.05335044 1.95611589 -1.25562819
- Н -1.56294908 0.06154715 1.38043107
- Н -0.39045393 -1.97837315 1.30740736
- Н -0.80129717 -2.00237244 -0.42234116
- N -2.07996105 0.04386712 -0.64379909
- Н -2.57740289 0.93060083 -0.60035292
- Н -1.65802814 -0.02822188 -1.56772986

\$END

TS3_β_exo

Zero-point correction=

0.129312 (Hartree/Particle)

Thermal correction to Energy=	0.135783
Thermal correction to Enthalpy=	0.136727
Thermal correction to Gibbs Free En	nergy= 0.099095
Sum of electronic and zero-point End	ergies= -379.841325
Sum of electronic and thermal Energ	gies= -379.834854
Sum of electronic and thermal Entha	lpies= -379.833909
Sum of electronic and thermal Free I	Energies= -379.871541

%mem=4GB

%Nprocs=4

%chk=TS2X.chk

opt=(calcall,qst3,maxcycle=500) freq b3lyp/aug-cc-pvdz scrf=(smd,solvent=1,4-dioxane) geom=connectivity empiricaldispersion=gd3

С	0.0000000 0.0000000 0.0000000
С	0.0000000 0.0000000 1.55884618
С	1.52356036 0.00000000 1.84269864
С	2.06021476 -1.36399623 1.42508182
С	1.99177152 -1.33294203 0.09140018
Ν	1.50245045 -0.02349091 -0.34461796
0	1.99425409 0.82346765 0.74911636
Н	1.85001208 0.41790060 2.79908695
Н	2.34421096 -2.18524568 2.07669792
Н	2.18137692 -2.09856099 -0.65604397
Н	-0.43548086 -0.90679281 -0.43367359
Н	-0.52062504 -0.86017806 1.99266189
Н	-0.46458288 0.91956889 1.93255773
Ν	-0.67285265 1.15455677 -0.53647725

- Н -0.24379535 2.00582861 -0.17727427
- Н -0.57996454 1.17910280 -1.55003323

```
1 2 1.0 6 1.0 11 1.0 14 1.0
2 3 1.0 12 1.0 13 1.0
3 4 1.0 7 1.0 8 1.0
4 5 2.0 9 1.0
5 6 1.0 10 1.0
671.0
7
8
9
10
11
12
13
14 15 1.0 16 1.0
15
16
```

Title Card Required

С	0.0000000 0.0000000 0.0000000
С	0.00000000 0.00000000 1.53016459
С	1.39213642 0.00000000 2.09886543
С	2.38136795 -0.60399775 1.40920932
С	2.14021869 -1.21200509 0.11634943
Ν	1.01766423 -1.00785701 -0.53752228
0	0.74594425 -1.49598449 -1.69040980
Η	1.57149307 0.43419302 3.08211032

- Н 3.39217141 -0.67969226 1.81046145
- Н 2.87376987 -1.84418957 -0.38026059
- Н -0.94672005 -0.36984305 -0.40237204
- Н -0.53341168 -0.89532582 1.89306896
- Н -0.57699052 0.87150647 1.86490683
- N 0.26394261 1.30983438 -0.53936550
- Н 1.15060033 1.67928134 -0.20148335
- Н 0.29201553 1.28581964 -1.55588181

1 2 1.0 6 1.0 11 1.0 14 1.0

2 3 1.0 12 1.0 13 1.0 3 4 2.0 8 1.0 4 5 1.0 9 1.0 5 6 2.0 10 1.0 6 7 1.0

- 7 8
- 9 10
- 11
- 12

13

14 15 1.0 16 1.0 15

16

Title Card Required

- C 0.93805394 0.09067171 -0.58278232
- C 0.28553980 1.41205538 -0.02624424

С	-1.09184304 1.12384715 0.41475217
С	-1.85977480 0.19616078 -0.36196033
С	-1.23001825 -0.99576416 -0.58336439
Ν	0.10274663 -1.02524941 -0.07713928
0	-0.00684546 -0.90161265 1.26550934
Н	-1.58320643 1.75529407 1.15494678
Н	-2.93757316 0.29157521 -0.49052647
Н	-1.73785118 -1.93481450 -0.79239554
Н	0.88793468 0.05120347 -1.67697408
Н	0.26004202 2.10912238 -0.88106334
Н	0.88822290 1.87433988 0.76328407
Ν	2.31451499 0.02295000 -0.16089715
Η	2.34448243 -0.07483999 0.85372447
Н	2.76013512 -0.80470866 -0.55122089

1 2 1.0 6 1.0 11 1.0 14 1.0

\$END

TS2_β_endo

Zero-point correction= 0.130416 (Hartree/Particle) Thermal correction to Energy= 0.137238 Thermal correction to Enthalpy= 0.138182 Thermal correction to Gibbs Free Energy= 0.099880 Sum of electronic and zero-point Energies= -379.886008 Sum of electronic and thermal Energies= -379.879187 Sum of electronic and thermal Enthalpies= -379.878243 Sum of electronic and thermal Free Energies= -379.916545

%mem=4GB

%Nprocs=1

%chk=TS4N_1.chk

opt=(calcall,qst3,verytight,maxcycle=500) freq b3lyp/aug-cc-pvdz

scrf=(smd,solvent=1,4-dioxane) geom=connectivity empiricaldispersion=gd3
scf=xqc

Title Card Required

- C 0.0000000 0.0000000 0.0000000
- C 0.0000000 0.0000000 1.52919565
- C 1.38761368 0.0000000 2.10259003
- C 2.37918129 -0.58989346 1.40572138
- C 2.14184987 -1.17479332 0.10252580
- N 1.02753579 -0.96499226 -0.56152382
- O 0.79516957 -1.41539725 -1.73735766
- Н 1.56079221 0.40614479 3.09903866

- Н 3.38941550 -0.67253675 1.80696124
- Н 2.88391224 -1.78350608 -0.40945288
- Н 0.35950915 0.97637320 -0.37799539
- Н -0.57642705 0.87072387 1.87024625
- Н -0.54663257 -0.89567731 1.87394927
- N -1.29894725 -0.39087532 -0.50680660
- Н -1.24847943 -0.51312616 -1.51616546
- Н -1.97781492 0.33917074 -0.30484034

1 2 1.0 6 1.0 11 1.0 14 1.0 2 3 1.0 12 1.0 13 1.0

- 3 4 2.0 8 1.0
- 4 5 1.0 9 1.0
- $5\ 6\ 2.0\ 10\ 1.0$
- 671.0
- 7
- 8
- 9
- 10
- 11
- 12
- 13
- 14 16 1.0 15 1.0
- 15
- 16

Title Card Required

- C 0.0000000 0.0000000 0.0000000
- C 0.00000000 0.00000000 1.38713418

С	1.20260710 0.00000000 2.09826216
С	2.39328369 0.00000000 1.36701569
С	2.36183160 -0.00000000 -0.01915610
Ν	1.17602892 -0.00000000 -0.69939730
0	1.17494056 -0.00000000 -1.99581004
Н	1.21241695 0.00000000 3.18701238
Η	3.36333550 -0.00000000 1.86286142
Η	3.24310339 -0.00000000 -0.65427638
Η	-0.89674450 0.00000454 -0.61557760
Η	-0.96070374 0.00000000 1.90069743
Η	-2.01720904 -0.81612047 -3.47317133
Ν	-1.76167848 0.00019299 -2.91996593
Η	-2.01713632 0.81644068 -3.47330144
Н	-0.74087042 0.00014938 -2.83531600

1 2 1.5 6 1.5 11 1.0 2 3 1.5 12 1.0 3 4 1.5 8 1.0 4 5 1.5 9 1.0

Title Card Required

01 С -0.29475911 0.87507724 -0.42105897 С 1.05545198 0.69105575 -0.96820739 С 1.80335991 -0.31668535 -0.37383692 С 1.18235970 -1.22853528 0.50903810 С -0.22266241 -1.31465939 0.48869543 Ν -0.96740555 -0.36381626 -0.09921720 0 -2.21596389 -0.53935448 -0.51707251 Η 2.85112831 -0.45930301 -0.64574084 Η 1.75166536 -1.98194811 1.04941789 Η -0.77657361 -2.18591490 0.83243981 Η -0.98299309 1.51281262 -0.97495939 Η 1.33553421 1.16475919 -1.90661616 Η 0.51889749 0.99301859 1.53882524 Ν -0.10634241 1.61656681 1.01400793 Η 0.37258122 2.50986688 0.88312588 Η -0.96879347 1.75477290 1.54877099

1 2 1.5 6 1.0 11 1.0 13 0.5 14 0.5

2 3 1.0 12 1.0 13 0.5

\$END

TS2_β_exo

Zero-point correction=	0.130213 (Hartree/Particle)
Thermal correction to Energy=	0.137110
Thermal correction to Enthalpy	= 0.138055
Thermal correction to Gibbs Fr	ee Energy= 0.099557
Sum of electronic and zero-poin	nt Energies= -379.885931
Sum of electronic and thermal	Energies= -379.879034
Sum of electronic and thermal	Enthalpies= -379.878090
Sum of electronic and thermal l	Free Energies= -379.916588

%mem=4GB %Nprocs=1 %chk=TS4X_2.chk # opt=(calcall,qst3,maxcycle=500) freq b3lyp/aug-cc-pvdz scrf=(smd,solvent=1,4-dioxane) geom=connectivity empiricaldispersion=gd3

Title Card Required

- C 0.0000000 0.0000000 0.0000000
- C 0.0000000 0.0000000 1.53016459
- C 1.39213642 0.0000000 2.09886543

С	2.38136795 -0.60399775 1.40920932
С	2.14021869 -1.21200509 0.11634943
Ν	1.01766423 -1.00785701 -0.53752228
0	$0.74594425 \ -1.49598449 \ -1.69040980$
Η	1.57149307 0.43419302 3.08211032
Н	3.39217141 -0.67969226 1.81046145
Н	2.87376987 -1.84418957 -0.38026059
Н	-0.94672005 -0.36984305 -0.40237204
Н	$-0.53341168 \ -0.89532582 \ 1.89306896$
Н	-0.57699052 0.87150647 1.86490683
Ν	0.26394261 1.30983438 -0.53936550
Н	1.15060033 1.67928134 -0.20148335
Н	0.29201553 1.28581964 -1.55588181

1 2 1.0 6 1.0 11 1.0 14 1.0

Title Card Required

01

С	0.00000000 0.00000000 0.00000000
С	0.00000000 0.00000000 1.38713418
С	1.20260710 0.00000000 2.09826216
С	2.39328369 0.00000000 1.36701569
С	2.36183160 -0.00000000 -0.01915610
Ν	1.17602892 -0.00000000 -0.69939730
0	1.17494056 -0.00000000 -1.99581004
Η	1.21241695 0.00000000 3.18701238
Η	3.36333550 -0.00000000 1.86286142
Η	3.24310339 -0.00000000 -0.65427638
Η	-0.89674450 0.00000454 -0.61557760
Η	$-0.96070374 \ 0.00000000 \ 1.90069743$
Η	-2.01713632 0.81644068 -3.47330144
Ν	-1.76167848 0.00019299 -2.91996593
Η	-0.74087042 0.00014938 -2.83531600
Н	-2.01720903 -0.81612046 -3.47317133

1 2 1.5 6 1.5 11 1.0

- 2 3 1.5 12 1.0 3 4 1.5 8 1.0 4 5 1.5 9 1.0 5 6 1.5 10 1.0 6 7 1.0 7 15 0.5 8 9 10
- 11

Title Card Required

01

С	0.29559837 0.87136522 -0.43021896
С	-1.05103923 0.67864067 -0.97815448
С	-1.79952739 -0.32504785 -0.37870319
С	-1.18035814 -1.22794646 0.51430257
С	0.22457122 -1.30823919 0.50249516
Ν	0.96815787 -0.36142294 -0.09564354
0	2.21545004 -0.54341990 -0.51743360
Н	-2.84520623 -0.47343145 -0.65540416
Н	-1.74981729 -1.97639848 1.06143361
Н	0.78103285 -2.17202959 0.86055305
Н	0.98559300 1.50772189 -0.98314788
Н	-1.33432223 1.15271301 -1.91551113
Н	-0.40618769 0.94581874 1.59033751
Ν	0.09853757 1.63013108 1.01327175
Н	0.95893969 1.91112408 1.49040481
Н	-0.51596948 2.43824960 0.88907896

1 2 1.5 6 1.0 11 1.0 13 0.5 14 0.5

2 3 1.0 12 1.0 13 0.5

3 4 2.0 8 1.0

4 5 1.0 9 1.0

5 6 2.0 10 1.0

\$END

TS3_ α (without NH₃)

Zero-point correction= 0.087392 (Hartree/Particle)
Thermal correction to Energy= 0.092390
Thermal correction to Enthalpy= 0.093335
Thermal correction to Gibbs Free Energy= 0.059082
Sum of electronic and zero-point Energies= -323.256273
Sum of electronic and thermal Energies= -323.251275
Sum of electronic and thermal Enthalpies= -323.250331
Sum of electronic and thermal Free Energies= -323.284584

%mem=4GB

%Nprocs=1

%chk=TS3_wo_NH3.chk

opt=(calcall,tight,qst3,maxcycle=500) freq b3lyp/aug-cc-pvdz

scrf=(smd,solvent=1,4-dioxane) geom=connectivity empiricaldispersion=gd3

01	
С	$0.00000000 \ 0.00000000 \ 0.00000000$
С	0.00000000 0.00000000 1.33245884
С	1.50432484 0.00000000 1.69175469
С	2.08727514 -1.35610873 1.22999200
С	1.99543813 -1.29644196 -0.09795846
Ν	1.41643063 0.02860668 -0.47727030
Н	1.80285761 0.38558690 2.66984929
Н	-0.79521921 -0.04736275 -0.73689479
Н	-0.83408406 -0.02452976 2.02628810
Н	2.44967219 -2.15799575 1.86508456
Н	2.22269736 -2.00811192 -0.88504794
0	1.99485944 0.83597270 0.62029410

Title Card Required

С $0.0000000 \ 0.0000000 \ 0.0000000$ С 0.0000000 0.0000000 1.38643103 С 1.20497892 0.0000000 2.09414021 С 2.39280371 0.00000000 1.35800248 С 2.35986439 0.00000000 -0.02803720 Ν 1.17167373 0.00000000 -0.70912580 Η 1.21791134 0.0000000 3.18264927 Η -0.89484737 0.00000000 -0.61567460 Η -0.95905480 0.00000000 1.90316112 Η 3.36386446 0.00000000 1.85180115 Η 3.23983176 0.00000000 -0.66479811 0 1.15636363 0.00000000 -1.99776224

1 2 1.5 6 1.5 8 1.0

- 2 3 1.5 9 1.0
- 3 4 1.5 7 1.0
- 4 5 1.5 10 1.0
- 5 6 1.5 11 1.0
- 6 12 1.0
- 7 8 9
- . .
- 10
- 11
- 12

Title Card Required

- C -0.45413252 -0.59244330 -1.21169369
- C -0.45413252 0.75528443 -1.22649645

- C 0.10301631 1.31963632 0.00000000
- C -0.45413252 0.75528443 1.22649645
- C -0.45413252 -0.59244330 1.21169369
- N 0.14456339 -1.11657663 0.00000000
- Н 0.59931236 2.28966917 0.00000000
- Н -0.63418117 -1.26853146 -2.04299117
- Н -0.71047197 1.36146904 -2.09295689
- Н -0.71047197 1.36146904 2.09295689
- Н -0.63418117 -1.26853146 2.04299117
- O 1.41989160 -0.56642742 0.00000000

\$END

TS_Biradical (N-O bond cleavage)

Zero-point correction= 0.083679 (Hartree/Particle)

Thermal correction to Energy= 0.089330

Thermal correction to Enthalpy= 0.090274

Thermal correction to Gibbs Free Energy=	0.053863
Sum of electronic and zero-point Energies=	-323.228569
Sum of electronic and thermal Energies=	-323.222918
Sum of electronic and thermal Enthalpies=	-323.221974
Sum of electronic and thermal Free Energies	-323.258385

%mem=4GB %Nprocs=4 %chk=TS_Triplet_tight.chk # opt=(calcall,tight,qst3,maxcycle=500) freq b3lyp/aug-cc-pvdz scrf=(smd,solvent=1,4-dioxane) geom=connectivity empiricaldispersion=gd3

Title Card Required

0	3

С	0.00000000 0.00000000 0.00000000
С	0.00000000 0.00000000 2.26385229
С	0.88541595 0.00000000 0.99573347
Н	0.10459459 -0.04736275 -1.07909569
Н	1.96976683 -0.02452976 0.95997829
С	-1.55626460 -1.29644196 1.25276083
Н	-2.24911242 -2.00811193 0.81558980
С	-0.74247336 -1.35610873 2.30615072
Н	-0.59127153 -2.15799575 3.02156123
Н	0.42685107 0.38558690 3.19314719
0	-1.07855491 0.83597270 1.78911942
Ν	-1.37562983 0.02860667 0.58455560

1 3 2.0 4 1.0 12 1.0

2 3 1.0 8 1.0 10 1.0 11 1.0

3 5 1.0

Title Card Required

С	0.0000000 0.0000000 0.0000000
С	0.0000000 0.0000000 2.49530166
С	0.71177590 0.00000000 1.17287906
Н	0.53019650 0.02042814 -0.95494646
Н	1.80125402 0.03337534 1.17687504
С	-2.05780787 -0.00025861 1.08394351
Н	-3.14521709 0.01987853 0.98105555
С	-1.49321045 -0.00025188 2.33434877
Н	-2.10617356 0.03285028 3.23505977
Н	0.29501441 -0.93725722 3.05540626
0	0.45853923 0.97451118 3.36649154
Ν	-1.35910551 -0.00643468 -0.08489379

```
1 3 2.0 4 1.0 12 1.0
```

2 3 1.0 8 1.0 10 1.0 11 1.0

- 3 5 1.0
- 4

Title Card Required

03

С	0.78867248 1.07835322 0.39651059
С	-1.12628970 -0.00000263 -0.28043453
С	-0.61056669 1.06402309 0.64855498
Н	1.55703755 1.76468157 0.73889480
Н	-1.17222025 1.62675705 1.38792936
С	0.78867755 -1.07834941 0.39651125
Н	1.55704553 -1.76467559 0.73889342
С	-0.61056195 -1.06402519 0.64855592
Н	-1.17221296 -1.62676083 1.38793101
Н	-2.17457132 -0.00000534 -0.58428307
0	$-0.23144223 \ -0.00000096 \ -1.39435188$
N	1.12526702 0.00000234 -0.48181997
1 2 2 0	4 1 0 10 1 0

1 3 2.0 4 1.0 12 1.0 2 3 1.0 8 1.0 10 1.0 11 1.0 3 5 1.0 4 5 6 7 1.0 8 2.0 12 1.0 7

\$END

With TiCl4 in 1,4-dioxane

SM

Zero-point correction= 0.135120 (Hartree/Particle)
Thermal correction to Energy= 0.153040
Thermal correction to Enthalpy= 0.153984
Thermal correction to Gibbs Free Energy= 0.085761
Sum of electronic and zero-point Energies= -3070.620773
Sum of electronic and thermal Energies= -3070.602853
Sum of electronic and thermal Enthalpies= -3070.601909
Sum of electronic and thermal Free Energies= -3070.670132

%chk=CAR_TiCl4.chk

opt=(calcall,tight,maxcycle=500) freq b3lyp/aug-cc-pvdz scrf=(smd,solvent=1,4-dioxane) geom=connectivity empiricaldispersion=gd3

01			
С	1.59557709	0.97189487	-1.31371403
С	2.71092069	1.76621794	-0.96237094
С	2.51421677	2.02613990	0.36454098
0	1.37492898	1.46680547	0.79122371

Н	1.33452797 0.53341361 -2.26971316
Н	3.53465276 2.07891264 -1.59191137
Ν	0.80723987 0.78136651 -0.27424235
Н	3.07831072 2.57614612 1.11057016
С	3.82332869 -0.99215444 1.10840806
Н	3.74324093 -0.70631283 2.15490508
Н	4.76216582 -0.78156417 0.59260810
С	2.79992486 -1.62083168 0.50055616
Н	1.87775619 -1.81809232 1.04852214
Ν	2.78947306 -2.11380735 -0.79448770
Н	1.88505303 -2.20350187 -1.23823384
Н	3.52184489 -1.79719340 -1.41770876
Ti	-1.30180986 -0.04206899 0.02282558
Cl	-0.59642544 -0.64098572 2.03424965
Cl	-1.88954868 2.08958943 -0.23087979
Cl	-3.37434974 -0.86755704 0.18705184
Cl	-0.72426239 -1.30288476 -1.75068063

```
1 2 1.0 5 1.0 7 2.0
2 3 2.0 6 1.0
3 4 1.0 8 1.0 10 0.5
4 7 1.0 10 0.5
5
6
7 17 0.5
8
9 10 1.0 11 1.0 12 2.0
10
11
12 13 1.0 14 1.0
13
```

```
14 15 1.0 16 1.0
15
16
17 18 1.0 19 1.0 20 1.0 21 1.0
18
19
20
21
```

I1A_M_endo

Zero-point correction= 0.138517 (Hartree/Particle)
Thermal correction to Energy= 0.154247
Thermal correction to Enthalpy= 0.155191
Thermal correction to Gibbs Free Energy= 0.094347
Sum of electronic and zero-point Energies= -3070.600144
Sum of electronic and thermal Energies= -3070.584414
Sum of electronic and thermal Enthalpies= -3070.583470
Sum of electronic and thermal Free Energies= -3070.644315

%chk=CAIN_TiCl4.chk

opt=(calcall,tight,maxcycle=500) freq b3lyp/aug-cc-pvdz scrf=(smd,solvent=1,4-dioxane) geom=connectivity empiricaldispersion=gd3

01	
С	2.40230243 -0.94563332 0.97596667
С	3.28541075 0.22161324 1.00593100
С	2.77371458 1.31369960 -0.08601274
С	2.80473744 0.76111258 -1.46862348

С 1.57286474 0.22307472 -1.64953398 Ν 0.74761280 0.48449157 -0.57764892 Ο 1.39106973 1.53664624 0.15364387 3.32051109 2.24113573 0.10900984 Η Η 3.66054022 0.71727603 -2.13292330 Η 1.19474499 -0.38438525 -2.46370107 Η 1.49309198 -0.97120924 1.57191581 Η 3.23615632 0.71248130 1.98274811 Η 4.32311442 -0.02989247 0.75484946 Ν 2.63685406 -1.98216306 0.21736443 Η 3.44595096 -2.01564440 -0.39398376 Η 1.91884628 -2.69007215 0.08407031 Ti -1.16291025 0.03823426 -0.02312059 Cl -1.63011491 2.23217286 -0.35401693 Cl -3.33783488 -0.58029785 -0.34118273 Cl -0.90138637 -0.15094975 2.18422979 Cl -0.53436597 -2.06995548 -0.92296287

```
1 2 1.0 11 1.0 14 2.0
2 3 1.0 12 1.0 13 1.0
3 4 1.0 7 1.0 8 1.0
4 5 2.0 9 1.0
5 6 1.0 10 1.0
6 7 1.0 17 0.5
7
8
9
10
11
12
13
```

```
14 15 1.0 16 1.0
15
16
17 18 1.0 19 1.0 20 1.0 21 1.0
18
19
20
21
```

I1A_M_exo

Zero-point correction=	0.138385 (Hartree/Particle)
Thermal correction to Energy=	= 0.154343
Thermal correction to Enthalp	y= 0.155287
Thermal correction to Gibbs F	Free Energy= 0.092845
Sum of electronic and zero-po	oint Energies= -3070.597165
Sum of electronic and thermal	Energies= -3070.581207
Sum of electronic and thermal	Enthalpies= -3070.580263
Sum of electronic and thermal	Free Energies= -3070.642705

%chk=CAIX_TiCl4.chk

opt=(calcall,tight,maxcycle=500) freq b3lyp/aug-cc-pvdz scrf=(smd,solvent=1,4-dioxane) geom=connectivity empiricaldispersion=gd3

01	
С	1.47687997 -1.44685823 1.10866310
С	2.71832527 -1.76154040 0.67428429
С	2.88036239 -1.00291013 -0.60251257
0	1.54028808 -0.77028828 -1.02179750
Η	0.99164705 -1.69244988 2.04630963
----	-------------------------------------
Н	3.48127686 -2.33717889 1.18622821
Ν	0.79168720 -0.66531913 0.19684323
Н	3.41644841 -1.49828667 -1.41914044
С	3.57059149 0.42669415 -0.37681183
Н	4.53615561 0.23453279 0.10913898
Н	3.73292793 0.89870702 -1.35402753
С	2.73664198 1.27515962 0.48383127
Η	2.55673501 1.00450602 1.52289896
Ν	2.20425809 2.38662742 0.06744181
Н	1.54640783 2.90137013 0.64402497
Η	2.29185606 2.68429772 -0.89942223
Ti	-1.16247066 -0.04274200 -0.01043023
Cl	-1.51861951 -1.90719453 -1.22762714
Cl	-1.04569840 0.13635403 2.27827460
Cl	-0.54084119 1.72439531 -1.27169060
Cl	-3.39894844 0.51201601 0.04416748

```
1 2 2.0 5 1.0 7 1.0
2 3 1.0 6 1.0
3 4 1.0 8 1.0 9 1.0
4 7 1.0
5
6
7 17 0.5
8
9 10 1.0 11 1.0 12 1.0
10
11
12 13 1.0 14 2.0
13
```

```
14 15 1.0 16 1.0
15
16
17 18 1.0 19 1.0 20 1.0 21 1.0
18
19
20
21
```

I1_M_endo

Zero-point correction=	0.140085 (Hartree/Particle)
Thermal correction to Energy=	0.155035
Thermal correction to Enthalpy	= 0.155980
Thermal correction to Gibbs Fr	ee Energy= 0.096807
Sum of electronic and zero-point	nt Energies= -3070.599313
Sum of electronic and thermal	Energies= -3070.584362
Sum of electronic and thermal	Enthalpies= -3070.583418
Sum of electronic and thermal	Free Energies= -3070.642590

%chk=I1N_N_TiCl4_2.chk

opt=(calcall,tight,maxcycle=500) freq b3lyp/aug-cc-pvdz scrf=(smd,solvent=1,4-dioxane) geom=connectivity empiricaldispersion=gd3

 C 2.03212536 -1.11128662 0.4827346 C 3.33995999 -0.35625333 0.8192802 C 2.97722701 1.10097230 0.44330829 C 2.85203359 1.16408712 -1.0668625 	01	
C3.33995999-0.356253330.8192802C2.977227011.100972300.44330829C2.852033591.16408712-1.0668625	С	2.03212536 -1.11128662 0.48273468
C 2.97722701 1.10097230 0.44330829 C 2.85203359 1.16408712 -1.0668625	С	3.33995999 -0.35625333 0.81928027
C 2.85203359 1.16408712 -1.0668625	С	2.97722701 1.10097230 0.44330829
	С	2.85203359 1.16408712 -1.06686250

С	1.71017592 0.53023988 -1.33653488
Ν	1.10394793 0.11164053 -0.06282110
0	1.58225764 1.14024414 0.83772118
Н	3.52608810 1.89639473 0.95217792
Н	3.58177453 1.56033827 -1.76615284
Н	1.23167583 0.25539823 -2.26857518
Н	1.48947763 -1.41798390 1.37649334
Н	3.56210393 -0.43268503 1.88851576
Н	4.19104500 -0.74387729 0.24911501
Ν	2.19921021 -2.20430489 -0.39558819
Н	2.69573650 -1.97378232 -1.25082831
Н	1.33700439 -2.69255396 -0.61111721
Ti	-1.21205052 0.02895029 0.02789219
Cl	-1.08821968 2.12380481 -0.68455302
Cl	-3.45430158 -0.10397850 0.09039640
Cl	-0.88564414 -0.41401719 2.18423558
Cl	-0.93648719 -1.57804523 -1.51523873

```
1 2 1.0 6 1.0 11 1.0 14 1.0
2 3 1.0 12 1.0 13 1.0
3 4 1.0 7 1.0 8 1.0
4 5 2.0 9 1.0
5 6 1.0 10 1.0
6 7 1.0 17 0.5
7
8
9
10
11
12
13
```

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14 15 1.0 16 1.0
15
16
17 18 1.0 19 1.0 20 1.0 21 1.0
18
19
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21
```

I1_M_exo

Zero-point correction= 0.140576 (Hartree/Particle)	
Thermal correction to Energy= 0.155312	
Thermal correction to Enthalpy= 0.156257	
Thermal correction to Gibbs Free Energy= 0.097721	
Sum of electronic and zero-point Energies= -3070.598870	
Sum of electronic and thermal Energies= -3070.584134	
Sum of electronic and thermal Enthalpies= -3070.583189	
Sum of electronic and thermal Free Energies= -3070.64172	5

%chk=I1X_N_TiCl4.chk

opt=(calcall,tight,maxcycle=500) freq b3lyp/aug-cc-pvdz scrf=(smd,solvent=1,4-dioxane) geom=connectivity empiricaldispersion=gd3

01	
С	-2.05815499 -1.09967682 0.55139662
С	-3.41231400 -0.68760453 -0.07941188
С	-3.09194738 0.70548331 -0.66425543
С	-2.83447634 1.64416123 0.50303910

С	-1.64907602 1.26655696 0.97709347
Ν	-1.14119633 0.16455754 0.13400116
0	-1.74197607 0.48429250 -1.14530576
Н	-3.72164748 1.05494542 -1.48573342
Н	-3.51755877 2.38382485 0.90833643
Н	-1.08184168 1.56360848 1.85113106
Н	-2.04975384 -1.07959500 1.64268845
Н	-4.22436329 -0.67048167 0.65430828
Н	-3.67183062 -1.38653242 -0.88171514
Ν	-1.59481006 -2.35191396 0.08801730
Н	-1.52855375 -2.40105253 -0.92402806
Н	-0.70736865 -2.62331818 0.49964564
Ti	1.17946685 0.04854087 -0.02474363
Cl	1.06198529 2.23013888 -0.38685251
Cl	0.88217126 -0.76237407 2.05990265
Cl	3.41797631 -0.10537015 0.03938656
Cl	0.86835613 -1.21213960 -1.82062070

```
1 2 1.0 6 1.0 11 1.0 14 1.0
2 3 1.0 12 1.0 13 1.0
3 4 1.0 7 1.0 8 1.0
4 5 2.0 9 1.0
5 6 1.0 10 1.0
6 7 1.0 17 0.5
7
8
9
10
11
12
13
```

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14 15 1.0 16 1.0
15
16
17 18 1.0 19 1.0 20 1.0 21 1.0
18
19
20
21
```

I2_M_ α

Zero-point correction= 0.137768 (Hartree/Particle)
Thermal correction to Energy= 0.153394
Thermal correction to Enthalpy= 0.154338
Thermal correction to Gibbs Free Energy= 0.094571
Sum of electronic and zero-point Energies= -3070.569049
Sum of electronic and thermal Energies= -3070.553423
Sum of electronic and thermal Enthalpies= -3070.552479
Sum of electronic and thermal Free Energies= -3070.612246

%chk=I2-2_TiCl4_NH3.chk

opt=(calcall,tight,maxcycle=500) freq b3lyp/aug-cc-pvdz scrf=(smd,solvent=1,4-dioxane) geom=connectivity empiricaldispersion=gd3

-2.02590892 -0.89689588 1.02112376
-3.39449852 0.64706708 0.07466280
-3.27558569 -0.46335874 1.13883548
-1.45077101 -1.68546695 1.48599169

Н	-4.06260089 -0.82046226 1.79415604
С	-2.04237484 -0.48410081 -1.35071054
Н	-1.50577628 -1.12105741 -2.04064122
С	-3.29306955 -0.03579774 -1.30360556
Н	-4.09320037 -0.17266031 -2.02330471
Н	-4.14362648 1.42841403 0.21756628
0	-2.05600747 1.19455901 0.15781056
N	-1.36206154 -0.07534061 -0.06563302
N	0.80994132 0.38411982 -2.20509835
Н	-0.07436411 0.81878342 -2.46872606
Н	0.92791226 -0.46206377 -2.76153565
Н	1.54357877 1.03555089 -2.48301755
Ti	$1.02053077 \ \ 0.02384030 \ \ 0.02966862$
Cl	0.77985394 2.29332667 0.04892852
Cl	0.91744997 -0.25375285 2.25900294
Cl	3.24409441 -0.05292222 -0.30721649
Cl	0.64146625 -2.21400067 -0.54320904

```
1 3 2.0 4 1.0 12 1.0
2 3 1.0 8 1.0 10 1.0 11 1.0
3 5 1.0
4
5
6 7 1.0 8 2.0 12 1.0
7
8 9 1.0
9
10
11 12 1.0
12 17 0.5
13 14 1.0 15 1.0 16 1.0 17 0.5
```

14									
15									
16									
17	18	1.0	19	1.0	20	1.0	21	1.0	
18									
19									
20									
21									

I2_M_ β _endo

Zero-point correction= 0.139609 (Hartree/Particle)
Thermal correction to Energy= 0.155428
Thermal correction to Enthalpy= 0.156372
Thermal correction to Gibbs Free Energy= 0.094102
Sum of electronic and zero-point Energies= -3070.639981
Sum of electronic and thermal Energies= -3070.624162
Sum of electronic and thermal Enthalpies= -3070.623218
Sum of electronic and thermal Free Energies= -3070.685488

%chk=I2-1N_O_TiCl4.chk

```
# opt=(calcall,maxcycle=500) freq b3lyp/aug-cc-pvdz
scrf=(smd,solvent=1,4-dioxane) geom=connectivity empirical dispersion=gd3
```

- C 3.70209378 -0.66903103 -0.57380122
- C 4.19284059 0.72962473 -0.34738314
- C 3.39317957 1.66127758 0.20845678

С 2.03266523 1.32252496 0.57074302 Ν $1.64460220 \ \ 0.08652986 \ \ 0.61317526$ Ο 0.41811886 -0.26574134 0.95542173 5.18943218 0.99677136 -0.70046570 Η Η 3.70382691 2.69652697 0.33575224 Η 1.28453294 2.07875320 0.80383971 Η 3.03908465 -1.23379887 1.42481063 Η 4.52314760 -1.39234342 -0.50576221 Η 3.30955436 -0.74082895 -1.60414927 Ν 1.96749084 -2.28708934 0.00611038 Η 1.27322725 -2.59916488 0.67852604 Η 1.51308939 -2.17871120 -0.89795525 Ti -1.34960246 0.02738163 0.02769112 C1 -0.12138578 -0.01125942 -1.89797067 Cl -1.54175833 2.04775408 0.98651758 C1 -2.01413786 -1.74299600 1.24160374 Cl -3.28921276 0.15551874 -1.14043700

```
14 15 1.0 16 1.0
15
16
17 18 1.0 19 1.0 20 1.0 21 1.0
18
19
20
21
```

I2_M_*β*_exo

Zero-point correction= 0.139814 (Hartree/Particle)
Thermal correction to Energy= 0.155602
Thermal correction to Enthalpy= 0.156546
Thermal correction to Gibbs Free Energy= 0.094578
Sum of electronic and zero-point Energies= -3070.640028
Sum of electronic and thermal Energies= -3070.624240
Sum of electronic and thermal Enthalpies= -3070.623296
Sum of electronic and thermal Free Energies= -3070.685263

%chk=I2-1X_O_TiCl4.chk

```
# opt=(calcall,maxcycle=500) freq b3lyp/aug-cc-pvdz
scrf=(smd,solvent=1,4-dioxane) geom=connectivity empirical dispersion=gd3
```

Title Card Required

01	
С	-2.67876663 1.12716710 -0.32010476
С	-4.06868556 0.54654494 -0.59887953
С	-4.28086977 -0.80054008 0.02262919
С	-3.23843101 -1.62673847 0.24361349

С	-1.89361385 -1.21221044 -0.09074507
Ν	-1.64212937 0.01743081 -0.43454294
0	-0.43368680 0.47186514 -0.71787319
Н	-5.29949795 -1.12281789 0.23951784
Н	-3.36467085 -2.63140711 0.64220668
Н	$-1.05546677 \ -1.90327306 \ -0.06563280$
Н	-2.37908460 1.83609903 -1.09570700
Н	-4.22004085 0.44918466 -1.68713753
Н	-4.81018240 1.27204098 -0.24204943
Ν	-2.59370816 1.75755696 0.96185993
Н	-2.81573144 1.12011391 1.72342721
Н	-1.67325702 2.15500044 1.13115567
Cl	3.47408938 -0.37995950 0.81645528
Cl	0.42740072 -0.15919613 1.97795497
Ti	1.42368828 0.03178987 -0.06310201
Cl	2.00698457 1.97674943 -1.00479388
Cl	1.40795754 -1.80697567 -1.36284282

```
14 15 1.0 16 1.0
15
16
17 19 1.0
18 19 1.0
19 20 1.0 21 1.0
20
21
```

I3_M

Zero-point correction= 0.139406 (Hartree/Particle)
Thermal correction to Energy= 0.155678
Thermal correction to Enthalpy= 0.156622
Thermal correction to Gibbs Free Energy= 0.094200
Sum of electronic and zero-point Energies= -3070.686696
Sum of electronic and thermal Energies= -3070.670423
Sum of electronic and thermal Enthalpies= -3070.669479
Sum of electronic and thermal Free Energies= -3070.73190

%chk=I3_NH3_TiCl4.chk

opt=(calcall,tight,maxcycle=500) freq b3lyp/aug-cc-pvdz scrf=(smd,solvent=1,4-dioxane) geom=connectivity empiricaldispersion=gd3

01

С	2.41641319	-1.26140355	0.07185339
С	3.72391567	-1.19510782	-0.38370483

- C 4.44055020 -0.00252597 -0.25869876
- C 3.82222972 1.10034920 0.33328655

С	2.51165106 0.99767298 0.77583673
N	1.84511210 -0.17079825 0.63403076
0	0.59683620 -0.27085021 1.09732912
Н	5.46759539 0.06469738 -0.61482370
Н	4.34236817 2.04837906 0.45474901
Н	1.94980651 1.80054902 1.23876271
Н	1.78128024 -2.13884160 0.01713102
Н	4.16599571 -2.08156320 -0.83414348
Ti	-1.12694661 -0.00393722 -0.01461512
C1	-0.33393472 -1.26623228 -1.73505521
C1	-0.13317896 2.01129279 -0.74415478
C1	-1.96660291 -1.72215694 1.29473134
C1	-3.15357672 0.56600061 -0.88371994
Ν	-1.68506579 1.23306265 1.78808493
Н	-1.02421152 1.05889458 2.54481366
Н	-2.61392212 0.98946606 2.12917127
Н	-1.67567389 2.23070845 1.58036686

$TS1A_M_endo$

Zero-point correction= 0.136165 (Hartree/Particle)
Thermal correction to Energy= 0.152	2273
Thermal correction to Enthalpy= 0.15	53217
Thermal correction to Gibbs Free Energy=	= 0.089738
Sum of electronic and zero-point Energies	-3070.597550
Sum of electronic and thermal Energies=	-3070.581442
Sum of electronic and thermal Enthalpies=	-3070.580498
Sum of electronic and thermal Free Energ	ies= -3070.643977

%mem=4GB %Nprocs=4 %chk=TSCA1N_TiCl4.chk # opt=(calcall,tight,qst3,maxcycle=500) freq b3lyp/aug-cc-pvdz scrf=(smd,solvent=1,4-dioxane) geom=connectivity empiricaldispersion=gd3

Title Card Required

- C 0.0000000 0.0000000 0.0000000
- C 0.00000000 0.00000000 1.41364132
- C 1.32820809 0.0000000 1.73428166

0	2.08101064 -0.02127551 0.62715644
Н	-0.83565367 0.00075089 -0.68994851
Н	-0.85126506 0.01477073 2.08279242
N	1.23155236 -0.00000648 -0.47069764
Н	1.87079180 0.01272012 2.67380798
С	1.40225003 3.33813872 1.25613310
Н	2.42916575 3.30986576 1.61379262
Н	0.61260026 3.52324019 1.98688891
С	1.14037052 3.18766165 -0.05567887
Н	1.95537998 3.00775088 -0.75779357
Ν	-0.10168101 3.28135853 -0.66296870
Н	-0.21745749 2.78619644 -1.53723491
Н	-0.91593221 3.24761141 -0.06224089
Ti	2.17509420 -0.33142551 -2.52356837
Cl	3.78912411 1.00226388 -1.80365282
C1	2.26382474 -2.45171808 -1.85256115
C1	2.98141136 -0.67398337 -4.58180212

Cl 0.23848372 0.58350149 -3.21711624

0	1

С	0.0000000 0.0000000 0.0000000
С	0.0000000 0.0000000 1.35360026
С	1.43705374 0.00000000 1.74791907
0	2.10250403 -0.51174350 0.59777682
Н	-0.82504326 0.10098707 -0.69551596
Н	-0.85383712 0.06454603 2.01908823
Ν	1.28074477 -0.10820509 -0.50539051
Н	1.72011425 -0.61302147 2.60978997
С	2.00073667 1.49030232 2.03901065
Н	3.04628187 1.37942050 2.34193211
Н	1.40573078 1.90808424 2.86090586
С	1.90286565 2.28847216 0.81501689
Н	2.69880835 2.27153194 0.07105422
Ν	0.84235170 2.97629438 0.51114845
Н	0.72536796 3.34072717 -0.43453897
Н	0.03692758 3.00488466 1.12906562
Ti	2.08731877 0.19204273 -2.29321350
Cl	3.72514401 1.77206162 -2.36451794

Cl 1.25005280 -0.79108189 -4.14047339 C1 3.56821756 -1.48815612 -1.87703285 Cl 0.40893269 1.91815501 -2.53015352 1 2 2.0 5 1.0 7 1.0 2 3 1.0 6 1.0 3 4 1.0 8 1.0 9 1.0 471.0 5 6 7 17 0.5 8 9 11 1.0 10 1.0 12 1.0 10 11 12 13 1.0 14 2.0 13 14 15 1.0 16 1.0 15 16 17 19 1.0 21 1.0 20 1.0 18 1.0 18 19 20 21

Title Card Required

С	-1.56068986	-0.41664602	-1.55361634
С	-2.77633891	-1.01776356	-1.32042825

С	-2.71824683 -1.40057851 0.06161079
0	-1.39714089 -1.36734281 0.43638921
Η	-1.21200954 0.10514862 -2.43665484
Н	-3.62851656 -1.08074752 -1.98611160
Ν	-0.74304431 -0.50303347 -0.48266572
Н	-3.25492460 -2.24187252 0.49843314
С	-3.55013926 -0.00680850 1.13259172
Η	-3.40607530 -0.42274451 2.12922938
Н	-4.57512029 -0.06262986 0.75830454
С	-2.81715977 1.15702597 0.84869328
Н	-1.90693894 1.38809445 1.39953871
Ν	-3.08839624 1.95520439 -0.18165922
Н	-2.44782244 2.68802268 -0.45626632
Н	-3.90900642 1.81443759 -0.75652388
Ti	1.26299334 0.00503499 0.00074951
Cl	0.60589467 0.49433624 2.09107805
C1	3.43120503 0.63755397 0.30615553
C1	1.75319148 -2.15895659 -0.31819991
Cl	0.97954525 1.53198939 -1.66846805

```
12 13 1.0 14 1.5
13
14 15 1.0 16 1.0
15
16
17 18 1.0 19 1.0 20 1.0 21 1.0
18
19
20
21
$END
```

TS1A_M_exo

Zero-point correction= 0.136296 (Hartree/Particle)
Thermal correction to Energy= 0.152371
Thermal correction to Enthalpy= 0.153315
Thermal correction to Gibbs Free Energy= 0.090657
Sum of electronic and zero-point Energies= -3070.594139
Sum of electronic and thermal Energies= -3070.578064
Sum of electronic and thermal Enthalpies= -3070.577120
Sum of electronic and thermal Free Energies= -3070.639778

%mem=4GB %Nprocs=4 %chk=TSCA1X_TiCl4.chk # opt=(calcall,tight,qst3,maxcycle=500) freq b3lyp/aug-cc-pvdz scrf=(smd,solvent=1,4-dioxane) geom=connectivity empiricaldispersion=gd3

01	
С	$0.00000000 \ 0.00000000 \ 0.00000000$
С	0.00000000 0.00000000 1.41172325
С	1.31975392 0.00000000 1.73616980
0	2.07684079 -0.00276001 0.62985397
Н	-0.83276626 0.00886339 -0.68322591
Н	-0.84931611 0.00806009 2.07184349
Ν	1.22834756 -0.00803815 -0.46717500
Н	1.86014311 0.00446907 2.66894333
С	0.35409351 3.40690756 0.07023131
Н	1.25111496 2.85138149 0.30429845
Н	-0.25454744 3.76206708 0.89563480
С	0.03579263 3.65602568 -1.20747613
Н	0.67455875 3.28133826 -2.00149417
Ν	-1.02005847 4.42781997 -1.66929801
Н	-1.37274730 4.18234523 -2.58264492
Н	-1.76169439 4.60745663 -1.00604945
Ti	2.27047699 -0.01327902 -2.47964372
Cl	3.19357088 1.86816994 -1.76241962
Cl	3.16342605 -1.92205518 -1.74959399
Cl	3.25911651 -0.02644722 -4.50608769
Cl	0.17797785 0.16649766 -3.24751194

Title Card Required

С	0.00000000 0.00000000 0.00000000
С	0.0000000 0.0000000 1.34241083
С	1.42952972 0.00000000 1.76826169
0	2.13834566 -0.34640085 0.57525590
Н	-0.83394854 0.06997895 -0.67793530
Н	-0.85017274 0.06513217 2.00120256
Ν	1.27243975 -0.08363540 -0.53374716
Н	1.69397333 -0.72850566 2.53650706
С	1.94942137 1.40540769 2.29794795
Н	1.30854101 1.68236805 3.13955475
Н	2.97793402 1.29488720 2.64279224
С	1.84110604 2.42543733 1.24988819
Н	0.86451775 2.72120851 0.88074720

- N 2.86055245 2.96468761 0.68225222
- Н 2.75788794 3.60793058 -0.09504000
- H 3.81000839 2.71572665 0.94183523
- Ti 2.15656119 -0.24606450 -2.32019258
- Cl 2.83168787 -2.34432776 -1.78833603
- Cl 0.10225628 0.38242858 -3.15459370
- Cl 3.81781924 1.18714710 -1.73049201
- Cl 2.97027972 -0.43956851 -4.54390678

01	
С	1.36184068 -1.64145690 0.88793038
С	2.57015346 -1.99196093 0.34455669
С	2.76419053 -1.06226095 -0.73630996
0	1.55405065 -0.46030317 -0.97240208
Н	0.86999144 -2.02945817 1.77229713
Н	3.28751407 -2.71115597 0.72088414
Ν	0.74357370 -0.66724818 0.17851990
Н	3.29501512 -1.29505413 -1.65929275
С	3.98238758 0.35033506 -0.17394078
Н	4.74702924 -0.24733024 0.32031756
Н	4.28422119 0.76093612 -1.14084906
С	3.22689866 1.20126861 0.65105863
Н	3.06195491 0.95286792 1.69975007
Ν	2.58193858 2.27332142 0.21275855
Н	1.86977417 2.71973281 0.77538574
Н	2.61916690 2.54262881 -0.76299492
Ti	-1.25944409 0.00886510 -0.00070970
Cl	-1.46245088 -1.49484945 -1.65963180
Cl	-1.35207622 -0.50509022 2.20985369
Cl	-0.50733598 2.02564530 -0.65276832
Cl	-3.47053184 0.58700991 -0.04506456

1 2 1.5 5 1.0 7 1.5 2 3 1.5 6 1.0 3 4 1.0 8 1.0 9 0.5 10 0.5 4 7 1.0 10 0.5 5

\$END

TS1B_M_endo

Zero-point correction= 0.138167 (Hartree/Particle) Thermal correction to Energy= 0.153197 Thermal correction to Enthalpy= 0.154141 Thermal correction to Gibbs Free Energy= 0.093916 Sum of electronic and zero-point Energies= -3070.597091 Sum of electronic and thermal Energies= -3070.582061 Sum of electronic and thermal Enthalpies= -3070.581117 Sum of electronic and thermal Free Energies= -3070.641342 %mem=4GB

%Nprocs=4

%chk=TSCA2N_TiCl4.chk

opt=(calcall,tight,qst3,noeigentest,maxcycle=500) freq b3lyp/aug-cc-pvdz scrf=(smd,solvent=1,4-dioxane) geom=connectivity empiricaldispersion=gd3

Title Card Required

С	$0.00000000 \ 0.00000000 \ 0.00000000$
С	0.00000000 0.00000000 1.46398179
С	1.53477539 0.00000000 2.00369583
С	2.27322098 -1.21242491 1.55352784
С	2.84326523 -0.84867460 0.37774769
Ν	2.63585520 0.48690498 0.11030542
0	2.21294573 1.06519233 1.35231457
Н	1.49621962 0.20911482 3.07698166
Н	2.26486376 -2.19059067 2.02122026
Н	3.37272877 -1.45112674 -0.35134077
Η	0.05668454 0.93241582 -0.55665139
Η	-0.46348186 0.91491679 1.84563731
Η	$-0.49409839 \ -0.88450006 \ 1.88428216$
Ν	-0.02970606 -1.10151641 -0.70047476
Η	-0.04617341 -2.01132975 -0.25161632
Н	0.15254435 -1.07539438 -1.70074482
Ti	3.08716230 1.79544412 -1.38662238
Cl	4.52582626 2.76389495 0.07402412
Cl	4.23552720 2.57856030 -3.19825968
Cl	1.27657371 3.09760990 -1.33452384
Cl	2.48194591 -0.08609230 -2.70676701

1 2 1.0 11 1.0 14 2.0
2 3 1.0 12 1.0 13 1.0
3 4 1.0 7 1.0 8 1.0
4 5 2.0 9 1.0
5 6 1.0 10 1.0
6 7 1.0 17 0.5
7
8
9
10
11
12
13
14 15 1.0 16 1.0
15
16
17 18 1.0 19 1.0 20 1.0 21 1.0
18
19
20
21

01	
С	$0.0000000 \ 0.0000000 \ 0.0000000$
С	0.00000000 0.00000000 1.54837528
С	1.52062342 0.00000000 1.85553659
С	2.06368987 -1.35658163 1.45228294
С	2.04356718 -1.34408843 0.12009376
Ν	1.56259466 -0.02057838 -0.31772685

0	2.00746149 0.82715312 0.76959244
Н	1.83212173 0.42513617 2.81215755
Н	2.30845296 -2.18334905 2.11153410
Н	2.24538662 -2.10597407 -0.62153171
Н	-0.30229373 0.97027824 -0.39974861
Н	-0.47283286 0.90878619 1.93482587
Н	-0.50721622 -0.87778232 1.96533002
Ν	-0.65841123 -1.11453039 -0.59797428
Н	-1.34074878 -1.55614443 0.00417907
Н	-1.05810768 -0.92052877 -1.50787405
Ti	2.41829419 0.82285527 -2.32124507
Cl	4.37937968 0.37204019 -1.38672868
Cl	3.23228077 1.63086058 -4.25462986
Cl	1.29332550 2.66206314 -1.75684391
Cl	1.30665674 -0.89204811 -3.21285923

17 18 1.0 19 1.0 20 1.0 21 1.0

Title Card Required

С	2.19128531 -1.18346434 0.58831223
С	3.32450429 -0.23826008 0.87015847
С	2.89883627 1.18570546 0.34696348
С	2.81225967 1.14345831 -1.15538150
С	1.62780196 0.55735496 -1.39660112
Ν	0.95928793 0.30236063 -0.16904587
0	1.52215047 1.27233309 0.72819191
Н	3.46080390 2.00007411 0.81101461
Н	3.58517288 1.42369059 -1.86314848
Η	1.18103606 0.21845888 -2.32423216
Η	1.47165366 -1.37679084 1.37834906
Η	3.48011598 -0.17293387 1.95254795
Η	4.25387582 -0.56809993 0.39142197
Ν	2.37917919 -2.18744912 -0.28348041
Н	3.05629994 -2.07250253 -1.02802190
Η	1.60315887 -2.80409216 -0.49087761
Ti	-1.18431698 0.02748401 0.02308521
Cl	-1.34680714 2.13049800 -0.70549586
Cl	-3.42388320 -0.35733400 0.06108517
Cl	-0.84487354 -0.26772152 2.20979675
Cl	-0.77924449 -1.68334033 -1.41912070

TS2_M_ α _endo

Zero-point correction=0.136494 (Hartree/Particle)Thermal correction to Energy=0.151615Thermal correction to Enthalpy=0.152559Thermal correction to Gibbs Free Energy=0.093175

Sum of electronic and zero-point Energies= -3070.500495 Sum of electronic and thermal Energies= -3070.485374 Sum of electronic and thermal Enthalpies= -3070.484430 Sum of electronic and thermal Free Energies= -3070.543814 %chk=PathA_1N_TS.chk # opt=(calcall,tight,ts,verytight,noeigentest,maxcycle=500) freq b3lyp/aug-cc-pvdz scrf=(smd,solvent=1,4-dioxane) geom=connectivity empiricaldispersion=gd3

Title Card Required

С	-2.02538849 0.79253838 0.84043547
С	-3.23364755 0.08558855 1.04490892
С	-2.99961034 -1.18215474 0.26347671
С	-2.92372437 -0.84542777 -1.22369263
С	-1.77445650 -0.19102055 -1.38511799
N	-1.11513308 -0.13393534 -0.04347466
0	-1.52456714 -1.40998599 0.49335305
Н	-3.55268991 -2.07738378 0.55410740
Н	-3.69840381 -1.02919348 -1.96217018
Н	-1.30585867 0.30364451 -2.22654124
Н	-1.45862779 1.24429939 1.65226495
Н	-3.61345843 0.00413021 2.06125879
Н	-2.91461636 2.00553505 -0.88163930
Ν	-2.21289720 2.22868957 -0.17494454
Н	-1.36621584 2.60722422 -0.61060758
Н	-2.60965793 2.92271468 0.45669724
Ti	1.18998134 -0.05150255 0.03164518
Cl	1.09851267 -1.83843848 -1.26743103
Cl	3.43155927 0.11350867 0.11466150

```
Cl
       0.88858988 -0.21487461 2.22806616
Cl
       0.90920005 1.92871915 -1.03985644
1 2 1.5 6 1.0 11 1.0 14 0.5
2 3 1.0 12 1.0 13 0.5
3 4 1.0 7 1.0 8 1.0
4 5 2.0 9 1.0
5 6 1.0 10 1.0
671.0170.5
7
8
9
10
11
12
13 14 0.5
14 15 1.0 16 1.0 17 0.3
15
16
17 18 1.0 19 1.0 20 1.0 21 1.0
18
19
20
21
```

TS2_M_ a_exo

Zero-point correction=0.136305 (Hartree/Particle)Thermal correction to Energy=0.151471Thermal correction to Enthalpy=0.152415Thermal correction to Gibbs Free Energy=0.092685

Sum of electronic and zero-point Energies=	-3070.501130
Sum of electronic and thermal Energies=	-3070.485964
Sum of electronic and thermal Enthalpies=	-3070.485020
Sum of electronic and thermal Free Energies	-3070.544749

%chk=PathA_1X_TS.chk

opt=(calcall,tight,ts,verytight,noeigentest,maxcycle=500) freq b3lyp/aug-cc-pvdz scrf=(smd,solvent=1,4-dioxane) geom=connectivity empirical dispersion=gd3

01	
С	-2.16477139 -0.96631168 0.63386387
С	-3.43763593 -0.66271067 0.10027893
С	-3.16086876 0.63371589 -0.66661200
С	-2.84322306 1.71116403 0.38224144
С	-1.65883590 1.36410358 0.88683732
Ν	-1.20564893 0.14421432 0.15279271
0	-1.80631943 0.38015529 -1.15243289
Н	-3.80038151 0.91571064 -1.50754363
Н	-3.49701358 2.51402283 0.71110038
Н	-1.06967015 1.71788480 1.72288306
Н	-1.97600790 -1.24477626 1.67051251
Н	-4.30564863 -0.72119879 0.75533404
Н	-1.48935590 -2.20878618 -1.14460802
Ν	-1.46450400 -2.40109782 -0.14246000
Н	-2.14560279 -3.13179338 0.05756645
Н	-0.52771827 -2.71074851 0.13344644
Ti	1.17528140 0.07667113 -0.00569187
Cl	0.90589735 -1.15457532 -1.83737635

- Cl 1.07018264 2.24375671 -0.39360009
- Cl 3.40668080 -0.10736957 0.10851402
- Cl 0.83423004 -0.77827680 2.05505106

```
1 2 1.5 6 1.0 11 1.0 14 0.5
2 3 1.0 12 1.0 13 0.5
3 4 1.0 7 1.0 8 1.0
4 5 2.0 9 1.0
5 6 1.0 10 1.0
671.0170.5
7
8
9
10
11
12
13 14 0.5
14 15 1.0 16 1.0 17 0.3
15
16
17 18 1.0 19 1.0 20 1.0 21 1.0
18
19
20
21
```

$TS3_M_\alpha_endo$

Zero-point correction=0.133665 (Hartree/Particle)Thermal correction to Energy=0.150077Thermal correction to Enthalpy=0.151021

Thermal correction to Gibbs Free Energy=	0.088695
Sum of electronic and zero-point Energies=	-3070.531927
Sum of electronic and thermal Energies=	-3070.515515
Sum of electronic and thermal Enthalpies=	-3070.514571
Sum of electronic and thermal Free Energies	-3070.576897

%chk=PathA_2_TS.chk

opt=(calcall,tight,ts,verytight,noeigentest,maxcycle=500) freq b3lyp/aug-cc-pvdz scrf=(smd,solvent=1,4-dioxane) geom=connectivity empirical dispersion=gd3

~ -	0	1
-----	---	---

С	-2.36852656 -1.26367176 0.69756181
С	-2.73402031 -0.16676650 1.39305042
С	-2.71911842 1.01220239 0.54818072
С	-3.42083322 0.88618429 -0.72666298
С	-3.05882638 -0.23614400 -1.37157332
Ν	-2.03173823 -1.00618513 -0.69100954
0	-1.03639558 0.08575310 -0.50539660
Η	-2.41161858 1.98359010 0.93619965
Η	-4.04386546 1.68054204 -1.13084838
Н	-3.30817397 -0.52102733 -2.39024823
Η	-2.08298698 -2.22827889 1.10732386
Η	-2.80822813 -0.11570983 2.47565515
Ti	0.95347565 0.01465249 -0.00904371
Cl	0.57118458 -0.21737631 2.22610277
Cl	0.57569773 2.33415708 -0.08836526
Cl	0.87984802 -2.23368965 -0.53393770
Cl	3.23517899 0.17915335 0.06186079

- N 1.24239344 0.26615707 -2.24000060
- Н 0.34157712 0.24155014 -2.71557452
- Н 1.82322052 -0.47575743 -2.62761591
- Н 1.68568023 1.15792529 -2.45525658

```
1 2 2.0 6 1.0 11 1.0
2 3 1.0 12 1.0
3 4 1.5 7 0.5 8 1.0
4 5 1.5 9 1.0
5 6 1.5 10 1.0
671.0130.3
7 13 0.3
8
9
10
11
12
13 14 1.0 15 1.0 16 1.0 17 1.0 18 0.5
14
15
16
17
18 19 1.0 20 1.0 21 1.0
19
20
21
```

TS3_M_β_endo

Zero-point correction= 0.136324 (Hartree/Particle)

Thermal correction to Energy= 0.151727

Thermal correction to Enthalpy=0.152672Thermal correction to Gibbs Free Energy=0.090921Sum of electronic and zero-point Energies=-3070.553699Sum of electronic and thermal Energies=-3070.538296Sum of electronic and thermal Enthalpies=-3070.537352Sum of electronic and thermal Free Energies=-3070.599102

%chk=PathB_1N_TS.chk

opt=(calcall,tight,ts,noeigentest,maxcycle=500) freq b3lyp/aug-cc-pvdz
scrf=(smd,solvent=1,4-dioxane) geom=connectivity empiricaldispersion=gd3

С	2.54499835 0.90978691 -0.55626679
С	2.99366118 -0.41481963 -1.29552682
С	2.61558063 -1.56839012 -0.47165981
С	2.81218923 -1.46576847 0.94093781
С	2.24862706 -0.35081324 1.48279854
Ν	1.62323191 0.53137654 0.53987309
0	0.69038202 -0.32432547 -0.09986487
Н	2.32972419 -2.51984745 -0.92178517
Н	3.11086122 -2.31403842 1.55540452
Н	2.04615345 -0.21477287 2.54262714
Н	1.91495010 1.47040215 -1.25380588
Н	2.60588881 -0.48684628 -2.31527526
Н	4.09540666 -0.39031778 -1.34222469
Ν	3.65696526 1.71932630 -0.13983251
Н	3.34286660 2.60075624 0.25875331
Н	4.25256602 1.25143489 0.53908618
Ti	-1.27429379 0.00685217 -0.02078907
Cl -3.54825802 0.16564218 -0.08895001

Cl -1.16664005 -0.08965243 2.22966140

Cl -0.93138634 2.05454878 -0.89242638

Cl -1.26187609 -1.85805659 -1.31937226

```
1 2 1.0 6 1.0 11 1.0 14 1.0
2 3 1.0 12 1.0 13 1.0
3 4 1.5 7 0.5 8 1.0
4 5 1.5 9 1.0
5 6 1.5 10 1.0
671.0170.3
7 17 0.3
8
9
10
11
12
13
14 15 1.0 16 1.0
15
16
17 18 1.0 19 1.0 20 1.0 21 1.0
18
19
20
21
```

TS3_M_β_exo

Zero-point correction= 0.137014 (Hartree/Particle)

Thermal correction to Energy= 0.152008

Thermal correction to Enthalpy= 0.152	953
Thermal correction to Gibbs Free Energy=	0.093783
Sum of electronic and zero-point Energies=	-3070.550126
Sum of electronic and thermal Energies=	-3070.535132
Sum of electronic and thermal Enthalpies=	-3070.534187
Sum of electronic and thermal Free Energies	s= -3070.593357

%chk=PathB_1X_TS.chk

opt=(calcall,tight,ts,noeigentest,maxcycle=500) freq b3lyp/aug-cc-pvdz
scrf=(smd,solvent=1,4-dioxane) geom=connectivity empiricaldispersion=gd3

Title Card Required

~ -

С	-2.41541502 -0.92162261 0.57227359
С	-3.17612466 -0.51862512 -0.71829355
С	-2.77688716 0.85828656 -1.12516812
С	-2.57697350 1.81902434 -0.07956260
С	-1.74977420 1.36059638 0.89142962
Ν	-1.19949778 0.04645299 0.57210843
0	-0.82691062 0.10348486 -0.81427705
Н	-2.92000102 1.17484314 -2.16072602
Н	-2.91322950 2.85088579 -0.15615678
Н	-1.46798375 1.82888557 1.82825535
Н	-2.96551659 -0.66593867 1.48419765
Н	$-4.26358055 \ -0.49847904 \ -0.53341902$
Н	-2.99578889 -1.23555376 -1.52529757
Ν	-2.10280744 -2.30242941 0.57236067
Н	-1.52232655 -2.56218935 -0.22213378
Н	-1.60606449 -2.57592072 1.41616075
Ti	0.98378004 -0.01651334 -0.06935692

- Cl 1.87445395 -0.35612910 1.98796881
- Cl 0.82528633 2.33559749 0.37511507
- Cl 0.99379797 -2.29992051 -0.51919528
- Cl 2.47786169 0.40426149 -1.68778091

```
1 2 1.0 6 1.0 11 1.0 14 1.0
2 3 1.0 12 1.0 13 1.0
3 4 1.5 7 0.5 8 1.0
4 5 1.5 9 1.0
5 6 1.5 10 1.0
671.0170.3
7 17 0.3
8
9
10
11
12
13
14 15 1.0 16 1.0
15
16
17 18 1.0 19 1.0 20 1.0 21 1.0
18
19
20
21
```

I1_M_endo (with pyrrolidine)

Zero-point correction=	0.231786 (Hartree/Particle)
Thermal correction to Energy=	0.250714
Thermal correction to Enthalpy=	0.251658
Thermal correction to Gibbs Free Energy	gy= 0.180932
Sum of electronic and zero-point Energ	gies= -3226.551358
Sum of electronic and thermal Energies	-3226.532429
Sum of electronic and thermal Enthalpi	es= -3226.531485
Sum of electronic and thermal Free End	ergies= -3226.602211

%chk=I1_M_endo.chk

opt=(calcall,maxcycle=500) freq b3lyp/aug-cc-pvdz
scrf=(smd,solvent=1,4-dioxane) geom=connectivity empiricaldispersion=gd3

Title Card Required

01			
С	-1.93456022	0.23221586	-0.55042571
С	-1.65492295	1.69040358	-1.02910806
С	-0.43072309	2.05141835	-0.15500803
С	-0.90689560	2.18969569	1.27459818
С	-1.23191040	0.94977791	1.64534356
Ν	-0.91758679	0.01036258	0.57010286
0	0.19949765	0.71836730	-0.07822399
Н	0.28001973	2.77596762	-0.55006529
Н	-1.02248301	3.11783185	1.82455768
Н	-1.68258542	0.56572079	2.55341307
Н	-1.63635238	-0.48828006	-1.33193023
Н	-1.39874442	1.71003556	-2.09297074
Н	-2.49152025	2.36850949	-0.83936016
Ti	2.18463428	-0.24419775	-0.05867590
Cl	2.02817466	-0.19998824	2.15486247

4.22998935	-1.13601806	-0.16447546
2.72636362	1.63736128	-1.15246635
1.13748827	-1.89463930	-1.12102294
-4.32203408	0.17911328	-1.05265825
-3.46651338	-1.39381994	0.43217592
-5.56297467	-0.44333206	-0.38919012
-4.07655313	-0.35751859	-1.99239037
-4.44717484	1.24128847	-1.29250998
-4.98996209	-1.48581543	0.61198902
-2.90293739	-1.56890486	1.35565493
-3.11318508	-2.12688591	-0.32091128
-6.13925139	0.32626486	0.13889800
-6.22412846	-0.89809989	-1.13676491
-5.26910231	-1.22754350	1.64088754
-5.35263195	-2.50197140	0.41556881
-3.26135558	-0.01652149	-0.05138511
	4.22998935 2.72636362 1.13748827 -4.32203408 -3.46651338 -5.56297467 -4.07655313 -4.44717484 -4.98996209 -2.90293739 -3.11318508 -6.13925139 -6.22412846 -5.26910231 -5.35263195 -3.26135558	4.22998935-1.136018062.726363621.637361281.13748827-1.89463930-4.322034080.17911328-3.46651338-1.39381994-5.56297467-0.44333206-4.07655313-0.35751859-4.447174841.24128847-4.98996209-1.48581543-2.90293739-1.56890486-3.11318508-2.12688591-6.139251390.32626486-6.22412846-0.89809989-5.26910231-1.22754350-5.35263195-2.50197140-3.26135558-0.01652149

TS3_M_β_endo (with pyrrolidine)

Zero-point correction=	0.228554 (Hartree/Particle)
Thermal correction to Energy=	0.247681
Thermal correction to Enthalpy=	0.248625
Thermal correction to Gibbs Free Ene	rgy= 0.177734
Sum of electronic and zero-point Ener	gies= -3226.517823
Sum of electronic and thermal Energie	es= -3226.498695
Sum of electronic and thermal Enthalp	oies= -3226.497751
Sum of electronic and thermal Free Er	nergies= -3226.568643

%chk= TS3_M_beta_endo.chk

opt=(calcall,ts,noeigentest,maxcycle=500) freq b3lyp/aug-cc-pvdz scrf=(smd,solvent=1,4-dioxane) geom=connectivity empiricaldispersion=gd3

Title Card Required

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С	0.00000000	0.00000000	0.00000000
С	0.00000000	0.00000000	1.58494837
С	1.38948506	0.00000000	2.05453270
С	2.30790100	-0.86339612	1.38110784
С	2.29792145	-0.70920337	0.03122402
Ν	1.36608591	0.26692192	-0.46082480
0	1.71889576	1.43527033	0.26184788
Η	1.68024680	0.51889340	2.96860406
Н	3.11364927	-1.38272096	1.89744110
Η	3.06112485	-1.08608216	-0.64446686
Н	-0.57430093	0.89043461	-0.31536748
Η	-0.58794885	0.81744909	2.00987597
Н	-0.43180507	-0.96025311	1.90792759
С	-0.44334838	-1.23744698	-2.06110831
С	-1.90037580	-1.51525709	-0.26971483
С	-1.28370957	-2.46709504	-2.43618115
Н	0.59026412	-1.28587783	-2.41779535
Н	-0.89475916	-0.31150678	-2.46681393
С	-2.26954436	-2.64319354	-1.24856940
Н	-2.52856932	-0.62030792	-0.45544401
Н	-2.02941893	-1.80566634	0.77988326
Н	-1.79849589	-2.31725094	-3.39262913
Н	-0.64176895	-3.35055081	-2.54005262
Н	-3.31905046	-2.56644642	-1.55701874
Н	-2.13494672	-3.62189586	-0.77197913
Ν	-0.48877602	-1.22842351	-0.58253676
Ti	2.42849226	3.03515331	-0.68573137

Cl	4.09051235	1.76237474	-1.53053762
Cl	0.55655930	3.09778903	-1.93285935
Cl	2.45111215	3.82293572	1.44633279
Cl	3.26464799	4.98968770	-1.52166394

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3 4 1.5 7 0.5 8 1.0
4 5 1.5 9 1.0
5 6 1.5 10 1.0
671.0270.3
7 27 0.3
8
9
10
11
12
13
14 16 1.0 17 1.0 18 1.0 26 1.0
15 19 1.0 20 1.0 21 1.0 26 1.0
16 19 1.0 22 1.0 23 1.0
17
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19 24 1.0 25 1.0
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23
24
25
26
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27 28 1.0 29 1.0 30 1.0 31 1.0