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**Development of 1,2,3-Triazole-Borane Complex
as Effective Reagent for Aldehyde/Ketone
Reductive Amination**

Wenyan Liao

**Thesis
Submitted to the Eberly College of Arts and Sciences
At
West Virginia University
In partial fulfillment of the requirements for the degree of
Master of Science
In Organic Chemistry**

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Morgantown, West Virginia
2009**

**Keyword: Lewis Base Catalysis, Isoxazoline-N-oxide, Triazole-Borane,
Reductive Amination**

Abstract

Synthesis of Isoxazoline-*N*-oxide through [3+2] Cycloaddition

Wenyan Liao

A catalytic cascade synthesis of Isoxazoline *N*-oxide was developed through proline-catalyzed nitroalkene activation. A large variety of nitroalkenes and vinyl esters were suitable for this transformation, giving only trans isomer with good to excellent yields. Mechanistic studies revealed intramolecular cycloaddition as the rate-determining step. This strategy provided not only a new approach for the construction of substituted isoxazoline derivatives but further evidence of secondary amine nucleophilic activation of nitroalkene, an alternative path of proline catalysis.

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Air, moisture and thermally stable 1,2,3-triazole-boranes were successfully prepared and applied as reductants in aldehyde/ketone reductive amination with high efficiency and excellent substrate diversity. Detailed studies regarding to the reaction mechanism and application of this new reagent for other important transformations are currently under investigation in our group.

DEDICATED TO

My parents and my family

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Part I

Synthesis of Isoxazoline *N*-oxide through [3+2] Cycloaddition

1. Introduction

1.1 Cascade reaction in organic synthesis

In modern organic synthesis, efficiency in constructing complex frameworks became more and more important in both academic and industrial research. As one of the most popular techniques to date, multi-component organo catalytic cascade reaction has been widely used to synthesize the backbones of natural compounds due to its high atomic economy and possibility to obtain good stereo selectivity.

1.2 Lewis base catalysis

In year 2000, the term “organocatalysis” was brought forward by David Macmillan. Since then, the area became more and more important as an useful methodology. Two main advantages of organocatalysis are: 1 There is no need for metal-based catalysis thus making a contribution to green chemistry. 2 When the organocatalyst is chiral, an avenue is opened to asymmetric catalysis. Common organocatalysts are based on nitrogen such as pyridine used in the Doebner modification of the Aldol condensation, DMAP used in esterifications, DABCO used in the Baylis-Hillman reaction. In the 1970s, a pioneering asymmetric organocatalysed reaction was developed by Hoffmann-La Roche^{1,2}, Schering AG³ and Hajos-Parrish. Among the most reported small organic catalysts, proline analogues are popular due to good accessibility and high efficiency. In the reaction, carbonyl group was activated by proline to form corresponding enamin or iminium cation (Scheme 1). Many reactions can be carried out by this strategy, such as Aldol reaction, Mannich reaction, Michael addition, Friedel-Crafts alkylation, epoxidation and Diel-Alder reaction.

Scheme 1A. Enamine Asymmetric Organocatalysis

Scheme 1B. Iminium Asymmetric Organocatalysis

Meanwhile, with the presence of nitrogen lone-pair electrons, amines can also serve as Lewis base catalyst. Lewis base catalysis is the process which an electron-pair donor increases the rate of a given chemical reaction by interacting with an acceptor atom in one of the substrates or the reagents. The binding event may enhance either the electrophilic or nucleophilic character of the bound species so that the reaction can happen (Scheme 2)⁴. Further more, the Lewis base should not be consumed or altered during the course of the reaction. Although Lewis base activation is quite common, it is less widely employed compared to Lewis acids in organic synthesis. Reasons for this include the lack of target Lewis acidic sites as well as the limited number of opportunities for valence expansion at carbon centers.

Scheme 2. Parallels between the Catalyzed (right) and Uncatalyzed Reactions (left) of Unsaturated Functional Groups

1.3 Literature reported synthesis of isoxazoline *N*-oxide and its applications

Isoxazoline *N*-oxides and their derivatives are frequently used as intermediates in the synthesis of complex molecules in chemical⁵ and biological field⁶. In the year 1964, the fact that nitronic esters undergo 1,3-dipolar cycloaddition to olefins to afford isoxazolidine was discovered and developed by Tartakovskii and co-workers⁷ (Scheme 3).

Scheme 3. Synthesis of Isoxazolidine

Later on, they developed a strategy by using trinitromethane silver salt react with trimethylsilylchloride to form silylnitronate, followed by [3+2] cycloaddition and elimination to give isoxazoline *N*-oxide as product⁸. One synthesis was done recently by using the similar pathway in Tartakovskii's group⁹ (Scheme 4).

Scheme 4. Synthesis of Isoxazoline-*N*-oxide by Tartakovskii

In 1976, Holy reported that dimethylsulfoxonium methylide could react with nitroalkene to afford isoxazoline *N*-oxides in the presence of copper(I)¹⁰ (Scheme 5).

Scheme 5. Synthesis of Isoxazoline *N*-oxide by Holy

After the pioneer work, different alkyl nitronate was developed for O-alkylation to synthesis isoxazoline *N*-oxide. It is known that reactions at C atom of nitro compound can happen with different electrophiles, such as aldehydes and epoxides. Thus the incorporation of the nitro moiety and the cycloaddition can be combined into a tandem sequence. Examples are shown in Scheme 6.

Scheme 6. Synthesis of Isoxazoline *N*-oxide via O-alkylation

Overall, among the developed protocols, two types of strategies are highly appreciated. One path is the intramolecular O-alkylation of aliphatic nitro compounds. However, no general method for the synthesis of such starting nitro compounds is available, each particular substrate requires special approach. The other way is the highly efficient hetero cycloaddition between nitronates and alkenes (known as [3+2]). Elimination from cyclic nitronic ester to isoxazoline *N*-oxide remains a challenge for this methodology.

The stereoselective synthesis of isoxazoline *N*-oxide is an important task in the context of synthetic strategies toward the preparation of biological target molecules such as polyhydroxylated amino acids, aminopolyols and amino sugars¹¹. Within one step reduction, isoxazoline can be obtained from isoxazoline *N*-oxide. N-O bond cleavage of isoxazoline followed by hydrolytic workup provides β -hydroxyketone, hence provides an alternate route to an aldol product. The dehydrogenation of intermediate iminoalcohol arising from N-O bond cleavage affords β -hydroxy nitriles. Complete reduction of the isoxazoline ring delivers γ -aminoalcohols. Base-mediated ring opening would provide α , β -unsaturated oximes (Scheme 7). All the hydroxyl compounds can be easily dehydrated or the other functional group can be transformed further to obtain synthetically useful molecules.

Scheme 7. Ring Opening Application

The dipolar character of these cyclic nitronates can be exploited for further 1,3-dipolar cycloaddition with olefins to afford multicyclic structure moiety in total synthesis. The placement of the tether at the C3 position of the nitronate provides access to the spiro mode cycloadditions. This class has been evaluated for the preparation of five- and six-membered spiro ring systems¹² (Scheme 8).

Scheme 8. Spiro Mode Intramolecular Cycloadditions

Rosini's group reported the first example of a silicon-tethered intramolecular 1,3-dipolar cycloaddition¹³. The tricyclic compound was converted to the corresponding bicyclic diol by an oxidative removal of the temporary silicon linker. The unstable diol was protected immediately as the diacetate. Reductive ring opening of the nitroso acetal moiety was performed with hydrogen and a catalytic amount of Raney Ni, to afford the polyhydroxylated aminolactone derivative (Scheme 9).

Scheme 9. Transformation of Isoxazoline N-oxide

2. Research Objective

2.1 Lewis-base catalyzed cascade cross conjugated addition

Recently, our group reported a catalytic cascade intermolecular double Michael addition between β -alkyl nitroalkenes and enones¹⁴ (Scheme 10). Experimental and computational studies suggested that L-proline served as an effective Lewis base catalyst for activation of nitroalkene to form nitronate as intermediate. This result initiated our interest in other functional group transformation studies based on our proline catalysis system.

Scheme 10. Lewis Base Catalyzed Cascade Conjugated Addition

2.2 Design of isoxazoline *N*-oxide synthesis

The 1,3-dipolarophile can be generated by addition of Lewis base to β -alkyl nitroalkene. We envisioned that followed by [3+2] cycloaddition with alkene, isoxazoline *N*-oxide will be obtained in high atomic efficiency. To evaluate this design, the one pot cascade reaction of β -alkyl nitroalkene and vinyl ethyl ether was first applied.

3. Results and Discussion

3.1 Reaction condition screening

The reaction result of β -methyl, phenyl nitroalkene **1a** and vinyl ethyl ether **2** are shown in Scheme 11.

Scheme 11. Cycloaddition of Nitroalkene and Vinyl Ether

Entry	Additive	Yield
1	None	0%
2	1 eq. NaOAc	5%
3	1 eq. BF ₃ -THF, 1 eq. NaOAc	56%
4	1 eq. BF ₃ -THF	0%

With only proline as catalyst, no cyclization product was observed, even at 70°C. The addition of one equivalent NaOAc help to give isoxazoline *N*-oxide as single trans isomer product in trace yield. NaOAc might perform as buffer tuning reagent for this transformation. Since OEt group was eliminated during the process, we then test the condition with the presence of one equivalent BF₃-THF and NaOAc along with 20% of L-proline at 70°C. Within 10 hours, the yield of isoxazoline *N*-oxide was increased to 56%. Meanwhile with only BF₃-THF and L-proline, the reaction would not happen. It is expected that the nitronate formed from Lewis base addition to the nitro alkene is crucial for the sequential [3+2] cycloaddition. BF₃-THF was used as a Lewis acid to bind with oxygen, made OEt a better leaving group for the following elimination.

With the leaving group hypothesis in mind, we then postulated a better leaving group on alkene as acetate. The reaction between nitroalkene **1a** and vinyl ether **4a** was tested. The results are given in Table 1.

Table 1. Screening of the Reaction Conditions

Entry	cat.	base	solvent	temp	time(h)	conv(%)	yield(%)
1	none	none	DMSO	70°C	8	0	0
2	none	NaOAc	DMSO	rt	8	90	0
3	none	NaOAc	DMSO	70°C	8	95	5
4	cat.-1	none	DMSO	rt	24	37	19
5	cat.-1	NaOAc	DMSO	rt	8	99	88
6	PPh ₃	NaOAc	DMSO	rt	8	95	8
7	NMI	NaOAc	DMSO	rt	8	87	9
8	DMAP	NaOAc	DMSO	rt	8	85	7
9	cat.-2	NaOAc	DMSO	rt	8	81	20
10	cat.-2	NaOAc/ HOAc(20%)	DMSO	rt	8	88	29
11	Glycine	NaOAc	DMSO	rt	8	90	54
12	cat.-3	NaOAc	DMSO	rt	8	99	45
13	cat.-1	CS ₂ CO ₃	DMSO	rt	8	99	46
14	cat.-1	NaOtBu	DMSO	rt	8	99	43
15	cat.-1	Et ₃ N	DMSO	rt	10	95	40
16	cat.-1	NaOAc	MeOH	rt	8	98	22
17	cat.-1	NaOAc	THF	rt	24	15	5
18	cat.-1	NaOAc	CH ₃ CN	rt	24	10	trace

Reactions were carried out with **1a:4a:cat.** = 1:2:0.2. Concentration is 0.2 M of **1a**. Conversion was based on the consumption of **1a** by NMR. Yield was determined by

NMR. Cat.-1: R = COOH; cat-2: R = H; cat-3: R = CH₂NHC(S)NHAr. (Ar = 2,3-di-CF₃-Ph).

As shown in Table 1, without L-proline as Lewis base, the thermo [4+2] cycloaddition was not observed even at higher temperature (Entry 1). This is probably due to the steric hindrance of the 2,2-disubstituted nitroalkene **1a**. The combination of proline as catalyst and NaOAc as additive was critical for good yield (Entry 2-5). With only NaOAc's presence, significant polymerization of **1a** was observed and very small amount of **3a** was produced at high temperature (Entry 3). This result suggested that rather than the base deprotonation of the methyl group in nitroalkene, nucleophilic addition by a Lewis base was the key step to form product **3a**. Phosphorus nucleophilic catalyst and tertiary amines resulted in significant amount of polymerization. Only secondary and primary amines were found as the effective catalysts for this reaction. Interestingly, glycine gave better yield than pyrrolidine (Entry 9 and 11), even when 20% of acetic acid was added to mimic the basicity of the proline/NaOAc condition (Entry 10). This effect was further emphasized when thiourea modified proline was applied (Entry 12). Both cases got reasonable good yields. The results strongly imply the formation of an intramolecular H-bond of the amino acid activated nitronate intermediate, which may lead to future enantioselective reactions. Other bases and solvents have also been investigated. NaOAc as an additive in DMSO was identified as the best condition.

3.2 Substrate scope

Various nitroalkenes and vinyl esters were applied to investigate the substrate scope. The results are shown in Table 2. **1** (1.0 equiv), **4** (2.0 equiv), L-Proline (20%), and NaOAc (1.0 equiv) were dissolved in DMSO (0.2M) and stirred at room temperature for 10 hours. Yields were isolated yields.

Table 2. Isoxazoline-*N*-oxide Synthesis Substrate Scope

Entry	Nitroalkene	Vinyl Ester	Product	Yield
1				88%
2				76%

10				61%
11				75%
12				87%
13				80%
14				74%
15				70%
16				72%
17				65%
18				55%

The substrates include aryl-alkyl and dialkyl (both cyclic and acyclic) nitroalkenes. A severe polymerization was observed when using monoalkyl or monoaryl nitroalkenes as the starting material, giving only trace amount of desired isoxazoline product. Different β -substituted vinyl esters were also tested for this transformation, giving easy access to the C-4 position of product. Notably, all cases give trans diastereomer as the only product.

3.3 Deuterium-labeling study

To further elucidate the reaction mechanism, especially the stereoselectivity, deuterium exchange study have been performed. When recharging product **3a** into the reaction condition under the presence of D_2O , no deuterium exchange was observed from NMR, which implied that no epimerization of the C-5 stereogenic center occurred after **3a** was formed. Therefore, the cyclization should be the key step that account for the formation of the single trans isomer. A reaction between **1a** and **2a** was then performed in the presence of D_2O . As expected, deuterium exchange was observed on the C-5 position along with the C-4 methyl groups and two alkene groups (Scheme 12). Notably, no deuterium exchange was obtained on the C-4 hydrogen. Therefore, a mechanism is proposed.

Scheme 12. Deuterium Labeling Study

3.4 Proposed mechanism

As illustrated in Scheme 13, the reaction between **1a** and proline produced nitro carbanion intermediate **B**. It is likely that **B** underwent a [3+2] dipolar cycloaddition with vinyl ester, forming five-membered heterocyclic intermediate **C**. However, the transformation from **B** and vinyl ester to **F** can went through different mechanisms, where the cycloaddition and retro-electro cycloaddition is just one possible pathway. And the formation of diene **F** is confirmed during our further study. The second nucleophilic addition of nitronate **B** to diene **F** underwent a Mukaiyama-type transition state, gave the corresponding intermediate **G**. After the fast epimerization of the C-5 proton, the cyclization of **H** gave the trans isomer as the only product. The fact that no proton exchange occurred on the C-4 position was consistent with the proposed mechanism.

Scheme 13. Proposed Mechanism for the Formation of Isoxazoline-*N*-oxide

If the reaction is carried out under deuterium environment, D-H exchange could happen in each equilibrium, such as in the intermediate **B** and **F**. However the C-4 H derived from starting material vinyl ester will stay the same, since it was not deprotonated during the whole process.

Scheme 14. Explanation of Deuterium Study

3.5 Further functional group transformation

As a very useful synthon, the isoxazoline *N*-oxide can be readily converted into other synthetically attractive building blocks. It can be oxidized to isoxazolidine or reduced to β -hydroxy amine through easy steps as shown in scheme 15.

Scheme 15. Synthetic Application of Isoxazoline-*N*-oxide

4. Conclusions

In conclusion, a catalytic cascade one-step synthesis of isoxazoline *N*-oxide was developed. A large variety of nitroalkenes and vinyl esters were suitable for this transformation, giving only trans isomer with good to excellent yields. Mechanistic studies revealed intramolecular nitronate cycloaddition as the rate-determining step. This strategy provided not only a new approach for the construction of substituted isoxazoline derivatives but also further evidence of secondary amine nucleophilic activation of nitroalkene, an alternative path of proline catalysis. Other secondary/primary amine-promoted nitroalkene cascade reactions are currently under investigation in our group.

Part II

Development of 1,2,3-Triazole-Borane Complex as Effective Reagent for Aldehyde/Ketone Reductive Amination

1. Introduction

1.1 Borane complexes and their reactivity

The application of boron reagents in organic synthesis led to Herbert C. Brown being awarded the Nobel Prize in Chemistry in 1979¹⁵. Since then, this relatively rare element has remained on the cutting-edge of modern synthetic chemistry.

Borane is well known for the hydroboration of alkenes and alkynes. It's an avid electron-pair acceptor, having only six valence electrons on boron. Borane complexes can be described as Lewis acid-base adducts of acidic BH_3 with different bases, include ethers, sulfides, phosphines and amines (Scheme 16).

Scheme 16. Typical Borane Complexes

Borane-tetrahydrofuran (BTHF) and borane-dimethyl sulfide (BMS) are often used as a borane source. Both reagents are in solution, and are therefore easier to handle than gaseous diborane. BTHF and BMS are widely used in hydroboration. They also offer interesting applications in the reduction of various functional groups, such as the direct reduction of amides to amines (BTHF) and carboxylic acids to alcohols (BMS). An example of BTHF is in the hydroboration of an alkene followed by oxidation, regioselectively gave the desired anti-Markovnikov alcohol¹⁶ (Scheme 17).

Scheme 17. Hydroboration of Alkenes by Borane-THF

EPIX Medical has used BTHF for the reduction of an amide in the synthesis of an injectable vascular contrast agent. They optimized conditions to minimize reduction of the Boc protecting group¹⁷ (Scheme 18).

Scheme 18. Reduction of Amide by Borane-THF

Compare with BTHF, the distinct advantage of borane-dimethylsulfide is its stability, allowing the production of BMS in high concentrations (~10M). Oxidation after the reaction effectively removes the dimethylsulfide component. A nitrile reduction¹⁸ is shown in Scheme 19.

Scheme 19. Nitrile Reduction by Borane-Dimethylsulfide

Further applications were developed in the recent years: In 2008, Attlesey in BASF synthesized a new kind of borane complexes with substituted THF ethers and applied them as reagents for asymmetric reduction of acetophenone¹⁹. In 2004, Santhosh's group developed recyclable fluoros borane-sulfide compounds to overcome the extremely volatile and environmentally unacceptable Me₂S associate with BMS²⁰. In addition to their usefulness as a regio- and chemoselective reducing agent, BTHF and BMS are often used with chiral oxazaborolidine catalysts for asymmetric ketone reduction. The most famous example is CBS catalyst^{21,22} (Scheme 20).

Scheme 20. Asymmetric Reduction of Ketones by Chiral CBS and BTHF/BMS

Phosphine-borane complexes were first reported by Burg and Wagner²³ in 1953. In 2004, Zhou and Manulty reported a simple, general, economical synthesis of phosphine-borane complexes using sodium borohydride as the borane source²⁴ (Scheme 21). These phosphine-borane complexes can be used in the synthesis of soluble hindered phosphine ligands and polymer-linked hindered phosphines.

Scheme 21. Synthesis of Phosphine-Borane Complexes

Posphine-borane can also be used in the synthesis of biologically active phosphorus heterocycles using a ring closure enyne metathesis methodology²⁵ (Scheme 22).

Scheme 22. Ring Closure Metathesis of Phosphine-Borane Complexes

Another application of phosphine-borane is the synthesis of P-chirogenic phosphines²⁶. The oxazaphospholidine boranes were prepared by heating bis(dimethylamino)-phosphine in toluene with ephedrine followed by addition of BMS(or BTHF). A regio- and stereoselective ring-opening of the heterocycle leading to an aninophosphine borane. Finally, the complex was easily transformed into the desired product by subsequent highly stereoselective reactions involving electrophilic or nucleophilic strategies (Scheme 23).

Scheme 23. Synthesis of P-Chirogenic Phosphorus via Phosphine-Borane

The first amine-borane complex (Scheme 24) was reported in 1937 and was prepared by the direct reaction of diborane with trimethylamine²⁷. Since then different types of amines have been used to prepare amine-boranes.

Scheme 24. First Synthesis of Amine-Borane Complex

Triethylamine borane can be used in the reduction of carboxylic acid, ketone and aldehyde groups at 80°C without solvent. In addition, triethylamine-borane has been effectively used in the reductive amination²⁸ (Scheme 25).

Scheme 25. Reductive Amination by Triethylamine Borane

Aldhydes can be selectively reduced in the presence of ketones by using tert-butylamine borane as the reducing agent. Tert-butylamine borane is also effective for reductive aminations, and for the reduction of enones at room temperature to give allylic alcohols. The following reaction shows tert-butylamine borane in a reductive ring closure for the synthesis of a benzazepine drug intermediate²⁹.

Scheme 26. Reductive Ring Closure by tert-Butylamine Borane

N,N-diethylaniline borane is a moderately reactive amine borane as a neat liquid. It is moisture sensitive and must be used in aprotic solvents. When combined with CBS catalyst, N,N-diethylaniline borane is an excellent borane source for the enantioselective reduction of ketones³⁰. For example, in the scale-up of a key intermediate of formoterol, a bronchodilator, N,N-diethylaniline borane was used as the borane source in the enantioselective ketone reduction³¹ (Scheme 27).

Scheme 27. Asymmetric Reduction of Ketones by Diethylaniline Borane

Pyridine borane (PYB) can be used to reduce oximes to the corresponding hydroxyl amines³² (Scheme 28). Reductions of oximes take place in the presence of other functional groups such as esters, nitriles, amides, and alkyl halides. Pyridine borane can also be used for reductive aminations.

Scheme 28. Reduction of Oximes by Pyridine Borane

Reduction of β -keto sulfones with pyridine borane in the presence of TiCl_4 resulted in ketone reduction primarily via a titanium chelated intermediate yielding erythro- β -hydroxy sulfones³³.

Scheme 29. Reduction of Ketones by PYB and TiCl_4

2-picoline borane is a valuable reagent for reductive aminations. The imine group is reduced by 2-picoline borane to an amine, while leaving cyano and chloro functionalities unaffected. Aromatic ketones can be aminated quite easily with 2-picoline borane³⁴ (Scheme 30). The reduction proceeds rapidly when conducted in methanol, water or even without solvent to give secondary amines in excellent yields.

Scheme 30. Reductive Amination by 2-Picoline Borane

Besides synthetic applications, amine-borane complexes are widely used in industry. For example, amine-boranes can perform as stabilizers and purifiers, fuel additives, photographic reagents, polymerization catalysts, and chemical plating agents³⁵. In pharmaceutical areas, borane complexes of α -amino acids, aromatic, aliphatic and heterocyclic amines, nucleosides possess a wide range biological activities including antineoplastic, antiviral, hypolipidemic, anti-inflammatory activities, anti-osteoporotic and dopamine receptor antagonist activities³⁶.

After the year 1995, two new kinds of borane complexes—metal borane complex and *N*-heterocyclic carbene borane complex, have raised unceasing interests in the research field. The first reports on the existence of metal-boron bonds were published in the 1960s³⁷, however, the identity wasn't confirmed until recently. In the metal borane complexes, borane forms a fourfold coordination with transition metal. The first structurally authenticated borane complexes, namely the metallaboratrane derivatives $[\text{M}\{\text{B}(\text{mt})_3(\text{CO})(\text{PPh}_3)\}]$ (1: $\text{M} = \text{Ru}$, 2: $\text{M} = \text{Os}$; $\text{mt} = 2$ -sulfanyl-1-methylimidazole) was prepared by $[\text{M}(\text{R})\text{Cl}(\text{CO})-(\text{PPh}_3)_2]$ with $\text{Na}[\text{HB}(\text{mt})_3]$ (Scheme 31)³⁸. Different metal-

boryl complexes were prepared as well include dihaloboryl³⁹, asymmetric haloboryl⁴⁰, and iminoboryl complexes⁴¹ (Scheme 32). Further experimental and theoretical studies of the bonding descriptions are going on. Their potential application in stoichiometric or catalytic reactions is likely to emerge shortly.

Scheme 31. Synthesis of zero-valent metallaboratranes

Scheme 32. Examples of Dihaloboryl, Asymmetric Haloboryl, and Iminoboryl Complexes

The search for simple, non-toxic, non-explosive compounds to mediate free-radical synthesis has led to a great deal of interests in organic chemistry. Recently, a new direction was developed from the research groups of Fensterbank, Lacote, Malacria, and Curran, who described a marriage of organoborane chemistry with *N*-heterocyclic carbenes. A large variety of scaffolds, including imidazolium, triazolium, and thiazolium derivatives can be used as NHC ligands⁴² (Scheme 33). The heteroatom donor groups remove the degeneracy of the carbene orbitals and thus enhance the nucleophilicity of the carbon atom. Study shows that the NHC-borane complexes have weakened B-H bonds so that they are better H donors than amine-boranes or phosphine-boranes. The reactivity was tested as radical reducing reagents with a series of secondary and benzylic xanthates. With AIBN as initiator, reduced products were isolated in reasonable yields⁴³ (Scheme 34). Development of practical stereoselective radical reduction protocols by NHC-Borane reagents is under investigation.

Scheme 33. *N*-Heterocyclic Carbene-Borane Complexes

Scheme 34. Reduction of a Secondary Hexenyl Xanthate with NHC-Borane

1.2 Reductive amination by different boranes

One-pot reductive amination is one of the most useful and versatile methods for the preparation of amines in chemistry and biology⁴⁴. The reaction involves the initial formation of addition product as an aminol intermediate or carbinol amine, which under the suitable reaction conditions dehydrates to form an imine. The imine on protonation forms an iminium ion that subsequently reduced to the respective alkylated amine by a hydride reagent⁴⁵ (Scheme 35). The amines, thus obtained are very useful in industry that have found wide-spread applications as intermediates for pharmaceuticals, dyes, resins, fine chemicals, solvents, textile additives, disinfectants, rubber stabilizers, corrosion inhibitors, and in the manufacture of detergents and plastics. The reductive amination possess several advantages in organic synthesis, such as one pot reaction, mild reaction conditions, wide commercial availability of substrates, use of economy-friendly reagents and so on. However, the reductive amination sometimes is associated with limitations in terms of functional group tolerance, side reactions and reaction conditions. Catalytic reduction is incompatible with compounds having other reducible functional groups such as multiple bonds including cyano, nitro groups. As a result, the choice of the reducing agents is very critical to avoid side reactions and toxicity of the reaction condition.

Scheme 35. Mechanism of Reductive Amination

Reductive amination is widely used as the synthetic strategy to synthesize biologically active molecules and synthetic intermediates. Some applications are shown below.

Pyrrolizidinone amino acids are rigid dipeptide surrogates in which the peptide backbone is constrained within a fused 5,5-bicyclic structure. Enantio pure (3*S*, 5*R*, 8*S*)-3-[*N*-(Boc) amino]-1-aza-bicyclo [3.3.0] octan-2-one 8-carboxylic acid was synthesized via multi-step process involving reductive amination as a key step. In the reductive

amination, hydrogenation of diamino substrate with Pd-C as catalyst in 9:1 EtOH/AcOH proceeded by cleavage of the phenylfluorenyl groups, intramolecular imine formation, protonation, and hydrogen addition to the iminium ion intermediate (Scheme 36)⁴⁶.

Scheme 36. Synthesis of Pyrrolizidinone Amino Acid via Reductive Amination

Large alkyl substituents in proteins can be introduced by reductive amination to enhance the hydrophobicity. The free aldehyde form of reducing sugar has been coupled to protein by reductive amination⁴⁷. The reactions of hemoglobin with glucose and glyceraldehydes have been studied in detail in order to understand its nonenzymatic glycosylation. Without the presence of reducing agent, slow Amadori rearrangement happens to give ketoamine as product (Scheme 37).

Scheme 37. Reductive Amination of Sugar and Protein

In history, different boranes and borohydrides are used for reductive amination. Decaborane, a mild hydride reagent, has successfully been used by Yoon⁴⁸ in reductive amination of carbonyl compounds to respective amines in moderate yields (Scheme 38).

Scheme 38. Reductive Amination by Decaborane

Sodium Borohydride (NaBH_4) is known to reduce imines in the same manner as it reduces carbonyl group in aldehydes and ketones⁴⁹. However, its application is limited, as it reduces other reducible functionalities present in the same molecule. In order to eliminate the possibility of any other carbonyl group in being reduced to alcohol, it is necessary to convert the carbonyl group completely to imine first, which refers as an indirect reductive amination. Weak electrophilic carbonyl groups, poor nucleophilic amines and sterically hindered reactive centre do not favor the completion of imine formation. In those cases, NaBH_4 by itself won't give good results. Different NaBH_4 salts are developed to solve the problems.

a. Zinc salt: ZnCl_2 and $\text{Zn}(\text{CF}_3\text{COO})_2$ in an inert solvent such as THF yielded the amines from aldehydes in high yields via the in-situ formation of $\text{Zn}(\text{BH}_4)_2$ ⁵⁰.

b. Titanium salt: TiCl_4 and $\text{Ti}(\text{O}^i\text{-Pr})_4$ can be used to promote abstraction of water during imine formation⁵¹. $\text{Ti}(\text{O}^i\text{-Pr})_4\text{-NaBH}_4$ has been used by Bhattacharya in such reactions⁵² (Scheme 39).

Scheme 39. Reductive Amination by Ti(IV) Isopropoxide- NaBH_4

c. Nickel salt: Nickel boride($\text{NiCl}_2\text{-NaBH}_4$) was generated in situ from nickel chloride hexahydrate and sodium borohydride in Sarma's group. It was used for reductive amination of aldehydes and ketones. Unlike other borane reagents, nickel boride is also well suited to α , β -unsaturated ketones⁵³.

d. $\text{NaBH}_4\text{-H}_3\text{PW}_{12}\text{O}_{40}$ ⁵⁴, NaBH_4 -guanidine hydrochloride⁵⁵, NaBH_4 wet clay-microwave⁵⁶, NaBH_4 in micellar media⁵⁷, borohydride exchange resin⁵⁸ were also introduced for the efficient and selective reductive amination.

Sodium cyanoborohydride (NaBH_3CN) has been extensively used in reductive amination with remarkable selectivity⁵⁹. The advantages of NaBH_3CN include its stability in relatively strong acidic conditions ($\text{pH} = 3$), its solubility in hydroxylic solvents, and its different selectivity at different pH values. Those unique functions allow a convenient direct reductive amination by sodium cyanoborohydride for many substrates. Similar cyanoborohydride reagents were also developed, such as LiBH_3CN ⁶⁰, $(n\text{-Bu})_4\text{NBH}_3\text{CN}$ ⁶¹, $\text{ZnCl}_2\text{-NaBH}_3\text{CN}$ ⁶², $\text{Ti}(\text{O}^i\text{-Pr})_4\text{-NaBH}_3\text{CN}$ ⁶³, $\text{Mg}(\text{ClO}_4)_2\text{-NaBH}_3\text{CN}$ ⁶⁴ and so on.

In 1996, Abdel-Magid reported the comprehensive study of direct and indirect reductive amination by sodium triacetoxyborohydride ($\text{NaBH}(\text{OAc})_3$) as a mild reducing agent⁶⁵. Aliphatic acyclic and cyclic ketones, aliphatic and aromatic aldehydes, primary and secondary amines including a variety of weakly basic and nonbasic amines are the effective substrates during reductions with $\text{NaBH}(\text{OAc})_3$. Limitations include reaction with aromatic and unsaturated ketones and some sterically hindered ketones and amines. Acetic acid has been used as co-catalyst in ketone reactions. The procedure can be carried out in the presence of acid sensitive functional groups such as acetals and ketals, it can also be carried out in the presence of reducible functional groups such as C-C multiple bonds, cyano and nitro groups. In comparison with other reductive amination reagents such as NaBH_3CN , pyridine-borane, and catalytic hydrogenation, $\text{NaBH}(\text{OAc})_3$ gave better yields and less side products.

Spirocyclic bis-azetidines, an interesting system has been synthesized by the reductive amination of chloro aldehyde with amines through initial formation of aryl amine with $\text{NaBH}(\text{OAc})_3$ followed by cyclization⁶⁶ (Scheme 40).

Scheme 40. Reductive Amination by $\text{NaBH}(\text{OAc})_3$

Zinc borohydride ($\text{Zn}(\text{BH}_4)_2$)⁶⁷, $\text{Zn}(\text{BH}_4)_2\text{-ZnCl}_2$ ⁶⁸, and $\text{Zn}(\text{BH}_4)_2$ -silica gel⁶⁹ were also utilized for reductive amination of aldehydes and ketones. Recently, Alinezhad's group have reported thermally stable $\text{Zn}(\text{BH}_4)_2$ -N-methylpiperidine for efficient and chemoselective reductive amination under neutral conditions by adding 10% of hydrochloric acid in methanol⁷⁰.

Firouzabadi has used dichloro-bis(1,4-diazabicyclo[2.2.2] octane) tetrahydroborato zirconium ($\text{Zr}[(\text{BH}_4)_2\text{Cl}_2(\text{dabco})_2]$) for the successful reduction of imines, enamines, reductive amination of aldehydes and ketones, and reductive methylation of amines⁷¹. This compound is stable under mild aqueous acidic conditions (pH 4-6) and survives in water for several days without losing its reducing ability.

Bhanage developed a direct reductive amination protocol for aldehydes/ketones using bis(triphenylphosphine) copper(I) tetrahydroborate as a novel reducing agent in the presence of sulfamic acid. The reagent chemoselectively reduces the imine moiety without affecting other reducible functionalities such as chloro, nitro, cyano and methoxy⁷².

Besides borane metal salts, amine-borane complexes were also used as the reductant in reductive amination. Seo developed a reductive amination of terminal aldehyde carbohydrate with thiol amine by using the reductive coupling reagent dimethylamine borane. Later on the thiol amine was oriented immobilized onto a gold surface⁷³ (Scheme

41). This application was useful for the studies of carbohydrates-biomolecule interactions and carbohydrate sensor or array development for diagnosis and screening.

Scheme 41. Reductive Amination by Dimethylamine Borane

In 1995, DiMare reported in situ reductive amination with different amines and carbonyl compounds using methanolic pyridine-borane (PYB) and molecular sieves⁷⁴. Usually pyridine-borane of commercial origin is utilized without further purification. Due to its instability to heat and violent decompositions, its industrial application is not recommended.

In 2004, Kikugawa reported one-port reductive amination of aldehydes and ketones with amines using 2-picoline-borane (PICB), a cheap and commercially available reducing agent. It is an alternative to NaBH_3CN and pyridine-borane but superior because of its commercial availability, crystalline nature and relatively better stability. $\text{MeOH}/\text{H}_2\text{O}$ has been used as solvent for the reactions and neat conditions also works. The reaction in water offers a great opportunity for green chemistry.

Very recently, Coleridge reported 5-ethyl-2-methylpyridine borane (PEMB) complex as a useful reagent for reductive aminations in methanol or neat conditions⁷⁵. Two of the three hydrides on PEMB are effectively utilized maximizing the economy of the reductant.

Tributyl tin hydride and silicone hydride derivatives, such as Bu_3SnH , $n\text{-Bu}_2\text{SnClH}$ -HMPA, Et_3SiH -TFA, $\text{Ti}(\text{O}^i\text{-Pr})_4$ -polymethylhydrosiloxane, PhSiH_3 - Bu_2SnCl_2 , also promote effective reductive amination in chemo- and stereoselective manner⁷⁶⁻⁷⁸. Hantzsch dihydropyridine with 2% scandium triflate can perform as organo catalyst in reductive amination⁷⁹. The reduction is completely chemoselective for aldehyde-derived imines over ketone-derived ones (Scheme 42). MacMillan reported the first organocatalytic reductive amination, a biomimetic reaction that allows the asymmetric coupling of complex with chiral hydrogen-bonding catalysts and Hantzsch esters⁸⁰ (Scheme 43). They proposed that exposure of ketone and amine to a chiral hydrogen-bonding catalyst⁸¹ results in an iminium species formation in presence of a suitable Hantzsch dihydropyridine in asymmetric manner⁸².

Scheme 42. Reductive Amination by Hantzsch Dihydropyridine

Scheme 43. Asymmetric Reductive Amination by Hantzsch Dihydropyridine (HDHP)

1.3 Limitation and challenges of reducing agents

Although different reducing agents for reductive amination were well developed during the recent decades, most of them suffered some limitations. The industrial use of sodium cyano-borohydride is unattractive due to the toxicity and large excess needed. Sodium triacetoxyborohydride, although quite selective for reductive amination, has only one hydride per molecule so that sometimes more than five-fold excess is required for the transformation. Catalytic hydrogenation has limited use with compounds containing multiple C-C bonds or hydrogen sensitive functionalities in the substrates. Metal boranes are environmental unfriendly or even high toxic. Some amine-boranes works well, but the poor thermal stability or sensitivity toward moisture are the major drawbacks.

2. Research Objective

2.1 1,2,3-triazole overall view, structures and properties

2.1.1 Synthesis of 4,5-disubstituted 1,2,3-(NH)-triazole

During the past 5 years, the 1,2,3-triazole compounds have been received considerable attention from different research fields such as material science⁸³, chemical biology⁸⁴, and medicinal chemistry⁸⁵. This is due to the successful development of 1,2,3-triazole synthesis by Cu-catalyzed azide alkyne 1,3-dipolar cycloaddition system (referred as “click chemistry”) (Scheme 44)⁸⁶. However, one limitation of the methodology is the deficient reactivity with unsubstituted azides, which makes the preparation of 1,2,3-(NH)-triazole a challenge.

Scheme 44. Preparation of 1,2,3-Triazoles via "Click Chemistry"

In 2008, our group developed a Lewis base-catalyzed three-component cascade reaction for the synthesis of 4,5-disubstituted-1,2,3-(NH)-triazoles⁸⁷. This strategy was based on the previous study of the nitronate formation with Lewis base addition to nitroalkene. Henry reaction of nitroalkene and aryl aldehyde catalyzed by L-proline can give 1,3-diene as the key intermediate. With the presence of NaN₃, diene was quenched to form 1,2,3-(NH)-triazole product through cycloaddition (Scheme 45). A large number of aryl aldehydes and β -alkyl nitroalkenes were suitable for this transformation. Various 4,5-disubstituted NH-triazoles can be efficiently synthesized in good yields from this mild cascade process. The modifications of the side chain can easily be carried out and used for further study (Scheme 46).

Scheme 45. One Step Formation of 1,2,3-(NH)-Triazole

Scheme 46. Side Chain Modification of 1,2,3-(NH)-Triazoles

2.1.2 Synthesis of metal-triazole complex

Triazoles are considered as potential good ligands in coordination with transition metals due to its better σ -donating nitrogen and π -receiving aromatic ring system. Recently, our group further confirmed the theory by having our 1,2,3-(NH)-triazoles to react with rhodium and gold cations to form complexes.

4,5-disubstituted *NH*-1,2,3-triazoles were used to coordinate with Rh(I) to form a new class of triazole-bridged [Rh(COD)(triazole)]₂ complexes (Scheme 47)⁸⁸. The crystal structures were studied by X-ray crystallography. These new complexes showed improved stability toward air and moisture. The reactivity was tested by typical Pauson-

Khand reactions (Scheme 48). Interestingly, bonding sites can be switched to different nitrogens when C-4 substituted group varies.

Scheme 47. Preparation of [Rh(COD)(Triazole)]₂ Complex

Scheme 48. Triazole-Rh(I) Complex Catalyzed Pauson-Khand Reactions

A series of 1,2,3-triazole-Au(I) complexes were synthesized via similar method⁸⁹. Structures were confirmed by X-ray crystallography. As we expected, they possessed better thermal and moist stability than literature reported Au catalysts. As a result, the challenging intermolecular internal alkyne hydroaminations were successfully achieved at a higher reaction temperature, giving excellent yields with low catalyst loading (Scheme 49).

Scheme 49. Triazole-Au(I) Catalyzed Intermolecular Hydroamination

2.2 Design of triazole-borane synthesis

Our interest in developing 1,2,3-triazole-coordinated complexes was initiated by our recent success with a metal-free 1,2,3-NH-triazole synthesis and post-triazole regioselective derivatization. Comparing with other *N*-heterocyclic aromatic compounds, 1,2,3-triazoles possess unique functions include: high polarity and electron density on the nitrogen (more nucleophilic and less basic) allowing them to coordinate well with Lewis acids, while a lower LUMO in the aromatic ring enhancing back bonding, giving stable triazole-metal binding. Triazole-Rh(I) and triazole-Au(I) complexes were prepared,

provided much better stability toward air, moisture and heat. Therefore, we wondered whether 1,2,3-triazoles could interact with Lewis acid borane to form effective triazole-borane complex for further reduction application.

3. Results and Discussion

3.1 Synthesis of triazole-borane complex

The reaction results of different triazoles with $\text{BH}_3\text{-THF}$ is shown in Table 3.

Table 3. Preparation of Triazole-Borane Complexes

6 7		
Triazoles	Reaction Results	Yield (%)
6a	complex mixtures	n.d.
6b	stable white solid	7a , >99%
6c	no reaction	-
6d	stable white solid	7b , >99%
6e	no reaction	-
6f	complex mixtures	n.d.
6g	complex mixtures	n.d.
6h	no reaction	-

The reactions between *NH*-triazoles (**6a** and **6f**) and BH₃-THF gave complex mixtures, whose structure cannot be identified at this moment. This was probably due to the multiple nitrogen binding sites on the triazoles and possible formation of B-H-B 3c2e bond. The N-2 substituted benzyl triazoles (**6c**, **6e** and **6h**) indicated no complex formation even when treated at a higher temperature (50 °C). This lack of coordination was likely caused by the steric hindrance of the N-2 substituted groups. The 1,4-disubstituted triazole **6g** is the popular triazole derivative product prepared from “click-chemistry”⁸³. Unfortunately, the reaction between **6g** and BH₃-THF gave multiple complexes with low reaction rate (more than 12 hours at room temperature) and the complexes decomposed during attempt of isolation (Table 3).

In order to decrease the steric hindrance on the N-2 position, we examined the N-1 substituted benzotriazoles **6b** and **6d** react with BH₃-THF. To our great pleasure, the triazole borane complexes **7a** and **7b** were formed as white solids in nearly quantitative yields. The structure of **7a** was confirmed by X-ray crystallography with BH₃ bond on the N-3 position as expected. Notably, the triazole-boranes were very stable toward air and moisture and can even be purified by column chromatography. The complexes were also thermally stable as high as 80 °C (no decomposition).

3.2 Reductive amination of aldehyde and condition screening

With these new triazole-boranes **7a** and **7b** in hand, we then explored their reactivity as reductants. The transformation that particularly interested us was the aldehyde and ketone reductive amination, a very important reaction in organic synthesis especially for biological related systems. As a very attractive approach for bio-elongation, the key concerns regarding “good” reductive amination reagents are: a) good chemoselectivity (selectively reduce imine rather than aldehydes and ketones); b) bio-compatibility (“green” reaction conditions), and c) stability in protic solvents. Among these factors, the hydride stability under acidic conditions is particularly challenging due to H₂ formation. As a result, reductive amination of ketones is one extremely difficult task, since acid activation of ketone is often required for the effective imine formation.

To evaluate the reactivity of triazole boranes, aldehyde **8a** and aniline **9a** were first applied as shown in Table 4.

Table 4. Condition Screening of Aldehyde Reductive Amination

Entry	Tri-Borane	Solvent	Temp	Time(h)	Yield(%)
1	7a (0.7 eq.)	CH ₂ Cl ₂	rt	5	99
2	7b (0.7 eq.)	CH ₂ Cl ₂	rt	3.5	99
3	7b (0.7 eq.)	DMSO	rt	0.5	95
4	7b (0.7 eq.)	DMF	rt	5	91
5	7b (0.7 eq.)	THF	rt	15 min	72
6	7b (0.7 eq.)	Toluene	rt	1.5	99
7	7b (0.7 eq.)	CH ₃ CN	rt	4	99
8	7b (0.7 eq.)	MeOH	rt	2	99
9	7b (0.7 eq.)	neat	rt	5 min	94
10	7b (0.4 eq.)	DCE	rt	3	99
11	7b (0.4 eq.)	DCE	60°C	0.5	99
12	7b (0.4 eq.)	MeOH	rt	1	48

Reactions were carried out by mixing **8a** (1.05 equiv), **9a** (1.0 equiv), and **7** together under different conditions. The triazole boranes showed excellent reactivity toward aldehyde reductive amination in various solvents, giving near quantitative yields in most of the cases. Although both **7a** and **7b** were stable triazole borane complexes, **7b** showed improved solubility in organic solvents. As a result, a slightly improved reaction rate was observed (entries 1 and 2). The reaction in THF gave lower yield, which was likely due to the solvent coordination with borane that led to side reactions. Notably, these new borane complexes indicated great stability in protic solvent MeOH or at a higher temperature (entries 8 and 11). Impressively, the reaction gave quantitative yield in DCE even with only 0.4 equiv of reductant (a slight increase of reductant was needed for protic solvent, entries 8 and 12). Considering that 1 equiv of water was produced in this process, the fact that only the theoretical limit amount (0.33 equiv) of borane was needed indicated the extremely high hydride transfer efficiency and superior stability of the triazole-borane reductants. Representative aldehydes and amines were applied as shown in Table 5.

Table 5. Reductive Amination of Aldehydes

Entry	Aldehyde	Amine	T (h)	Product	Yield (%)
1			3		99
2			3		99

3			3		99
4			3		99
5			6		99
6			4		95
7			4		96
8			3		82
9			4		91
10			4		95
11			3		99
12			3		99

13			2		99
14			3		99
15			3		99
16			3		93
17			3		95
18			3		96

The results demonstrated that this transformation is suitable for a large variety of aldehydes (aromatic, aliphatic, unsaturated and heteroaromatic) and amines (aromatic, aliphatic and secondary amines). Excellent yields were obtained for almost all cases. Meanwhile, the benzotriazole by-product could be recovered in nearly quantitative yield.

3.3 Reductive amination of ketone

Encouraged by this success, we extended the investigation to ketones. Since acids were often required for the imine formation, 30% of AcOH was added as the catalyst (no reaction was observed without acid catalyst at room temperature for 24 hrs). Again, effective reductive amination of ketone was achieved using triazole-boranes with a slightly higher loading of reductant (0.8-1.2 equiv). Moreover, this ketone reductive amination could also be achieved by increasing the reaction temperature without further addition of acid catalyst (condition B). Reaction substrates are shown in Scheme 50.

Scheme 50. Reductive Amination of Ketones

As shown in Scheme 50, this reaction was suitable for primary amine, secondary amine and aniline. Meanwhile, the two different reaction conditions provided orthogonal approaches for sensitive substrates. For examples, in the synthesis of 12f, the furanyl ketone decomposed under acidic conditions. Therefore, using condition **A** gave 12f in less than 50% yields along with ketone decomposition by-products. Application of condition **B** could help to avoid the decomposition of ketone, giving 12f in excellent yield. The enone substrate has also been investigated (cyclohexenone). A mixture of different reduction products (including the desired allylic amine) was observed. The lack of chemo-selectivity was likely caused by the harsher conditions. Benzophenone also didn't work well due to its large steric hindrance of the two phenyl groups. However, when compared with other reductants, triazole-borane showed much better stability and reactivity in different ketone examples.

Overall, to the best of our knowledge, the triazole-borane was by far one of the most efficient metal-free reagents for the challenging ketone reductive amination. With clear evidence for improved proton and thermal stability of TAB, we then applied this reagent to the unprotected amino acid reductive amination in water.

3.4 Reductive amination of unprotected amino acids

To increase the solubility of amino acid in water, 30% Na₂CO₃ was added (Scheme 51). This modification helped the further evaluation of the triazole-borane reductant under basic conditions. As anticipated, good yields were obtained. Notably, this reaction tolerated functional groups that may potentially coordinate with borane, such as imidazole and sulfur (14b and 14c), which further enhanced the synthetic utility of the reductant.

Scheme 51. Reductive Amination of Amino Acid

3.5 Possible future studies

In the future, several directions can be dug into for the novel triazole-borane complexes:

- 1) Reactions will be designed for the mechanistic study of the triazole-borane reductions;
- 2) Asymmetric reductive amination by chiral triazole-boranes;
- 3) Design and synthesis of water soluble triazole-boranes for biological applications.

4. Conclusion

In conclusion, the triazole-boranes were successfully prepared and applied as reductants in ketone/aldehyde reductive amination. Compared with literature reported systems, the triazole-boranes showed clear advantages regarding efficiency, proton and thermal stability, which made them new practical reagents for related chemical and biological research. Detailed studies regarding reaction mechanism (borane dissociation process) and application of this new reagent for other important transformations are currently under investigation in our group.

Part III

Experimental Section

General Methods and Materials:

Unless otherwise noted, all commercial reagents and solvents were obtained from the commercial provider and used without further purification. Air and/or moisture-sensitive reactions were carried out under an atmosphere of nitrogen using oven/flame-dried glassware and standard syringe/septa techniques. ^1H -NMR and ^{13}C -NMR spectra were recorded on Joel 270 MHz and Varian 600 MHz spectrometers. Chemical shifts were reported relative to internal tetramethylsilane (δ 0.00 ppm) or CDCl_3 (δ 7.26 ppm) for ^1H and CDCl_3 (δ 77.0 ppm) for ^{13}C or CD_3OD (δ 4.87, 3.31 ppm) for ^1H and CD_3OD (δ 49.1 ppm) for ^{13}C . Melting points were measured on a Mel-Temp 1001D apparatus and uncorrected. HRMS were recorded on LTQ-FTUHRA spectrometer. Flash column chromatography was performed on 230-430 mesh silica gel. Analytical thin layer chromatography was performed with precoated glass baked plates (250 μ) and visualized by fluorescence and by charring after treatment with potassium permanganate stain.

The nitroalkene starting materials **1a-1e** were prepared according to reported procedures: 1) Ohta, H.; Kobayashi, N.; Ozaki, K. *J. Org. Chem.* **1989**, *54*, 1802-1804. 2) Matin, N. J. A.; Ozores, L.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 8976-8977. Nitroalkene **1f-1h** were prepared according to reported procedure: 3) Jang, Y. J.; Lin, W. W.; Shih, Y. K.; Liu, J. T.; Hwang, M. H.; Yao, C. F. *Tetrahedron*, **2003**, *59*, 4979-4992. Vinyl esters **4b-4d** were prepared according to reported procedures: Bedoukian, P. Z. *J. Am. Chem. Soc.* **1944**, *66*, 1325-1327. Triazoles **6a-6h** were prepared according to the literature: Liu, Y.; Yan, W.; Chen, Y.; Petersen, J. L.; Shi, X. *Org. Lett.* **2008**, *10*, 5389-5392.

General Procedure for synthesis of Isoxazoline-N-Oxide :

To a 25 ml vial was added L-Proline (23mg, 0.2 mmol) and Sodium acetate (82 mg, 1 mmol) in 10 ml DMSO, then vinyl ester **4a** (172 mg, 2.0 mmol) and nitroalkene **1a** (163 mg, 1.0 mmol) were added sequent. The resulting reaction mixture was stirred at room temperature and monitored by TLC. After the reaction completed, the resulting brown solution was diluted with ethyl acetate, and washed with water (30 mlx3). The aqueous phase was extracted with ethyl acetate and the combined organic phase was washed with water and brine, then dried over Na_2SO_4 . After remove solvent by evaporator, the residue product was purified by flash silica gel chromatography gave the Isoxazoline-N-Oxide **3a** as colorless oil in 88% yield.

General Procedure for transformation Isoxazoline-N-oxide to Isoxazoline

The Isoxazoline-N-oxide **3a** (305 mg, 1 mmol) was dissolved in 8 ml trimethyl phosphite in a flask equipped with a condenser. The solution was well degassed and heated to reflux under N₂. After 12 h the TLC analysis (hexane / ethyl acetate = 7/1) revealed that the starting material was consumed. The reaction was cooled to 0 °C then diethyl ether was added and the solution was washed with 1 N HCl (3x10 ml), water (10 ml). The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by flash silica gel chromatography gave the Isoxazoline **5a** as colorless oil in 81% yield.

Compound **5b** was synthesized by the same procedure as above.

General Procedure for transformation Isoxazoline-N-oxide to Isoxazole

The starting material **3a** (100 mg, 0.34 mmol) was dissolved in 2 ml DMF. Then the sealed reaction tube was heated to 160 °C by microwave (150 W) for 15 min. After cooled to room temperature, the solution was diluted with ethyl acetate (30 ml) and washed with water and brine. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by flash silica gel chromatography gave the Isoxazole **5c** as colorless oil in 71% yield.

General Procedure for transformation 5b to 5d

LiAlH₄ (222 mg, 6 mmol) was suspended in 6 ml THF under N₂. Then Isoxazoline **5b** (245 mg, 1 mmol) in 5 ml THF was added dropwise at 0 °C. After 2 h the reaction was allowed to warm to room temperature and keep stirring for another 12 h. TLC analysis (hexane / ethyl acetate = 5/1) revealed that the starting material was consumed. Then 5.0 ml of 6*N* HCl was added dropwise at -5 °C and the mixture was extracted several times with ethyl acetate, the organic layer was washed with water and brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude product was used directly for the next step.

The previous product was dissolved in 5 ml Et₃N, then Ac₂O (0.5 ml, 5 mmol) was added dropwise at room temperature. After 12 h the reaction mixture was concentrated *in vacuo*, diluted with CH₂Cl₂ and washed with saturated NaHCO₃, the organic layer was washed with water and brine, dried over Na₂SO₄. After remove solvent by evaporator, the residue product was purified by flash silica gel chromatography gave the *N*-1,3-dicyclohexenyl-3-hydroxy-2-methylpropyl) acetamide **5d** as colorless oil in 65% yield

Procedure for deuterium study and ¹H NMR spectrum

To a 25 ml vial was added L-Proline (23mg, 0.2 mmol) and Sodium acetate (82 mg, 1 mmol) in the mixture of 7.5 ml DMSO and 2.5 ml D₂O, then vinyl ester **4a** (172 mg, 2.0 mmol) and nitroalkene **1a** (163 mg, 1.0 mmol) were added sequent. The resulting reaction mixture was stirred at room temperature and monitored by TLC. After the staring material consumed, the reaction was worked up using the same procedure described above for the synthesis of isoxazoline-*N*-oxide, gave the deuterated product in 35% yield.

The compared spectrums are listed blow.

Representative Procedure for synthesis of 1,2,3-Triazole-Borane complexes:

The N-1 methyl benzotriazole **6b** (1.331 g, 10 mmol, 1 equiv) was dissolved in dry THF (10 mL, 1.0 M) in a 50ml round bottom flask under N₂ atmosphere. To this solution was added BH₃-THF (11 mL, 1.0 M in THF, 1.1 equiv) drop wise by a syringe. The resulting solution was stirred at room temperature and checked by TLC. A white precipitate was formed in about 10 min. After the completion of the reaction, **7a** (1.470 g, 10 mmol, yield: 99%) was obtained by filtration as white solid.

The N-1 phenyl benzotriazole **6d** (1.952 g, 10 mmol, 1 equiv) was dissolved in dry THF (10 mL, 1.0 M) in a 50 mL round bottom flask under N₂ atmosphere. To this solution was added BH₃-THF (11ml, 1.0 M in THF, 1.1 equiv) drop wise by a syringe. The resulting solution was stirred at room temperature and checked by TLC. When the reaction was completed, the resulting solution was concentrated and then added dry hexanes (10 mL), A white precipitate was formed immediately. **7b** (2.090 g, 10 mmol, yield: 99%) was obtained by filtration as white solid.

Representative Procedure for Reductive Amination of Aldehydes

The 4-chlorobenzaldehyde **8a** (147.6 mg, 1.05 mmol, 1.05 equiv) and aniline **9a** (93.13 mg, 1 mmol, 1 equiv) were dissolved in DCE (4 mL, 0.25 M). To this solution was added **7b** (83.6 mg, 0.4 mmol, 0.4 equiv) at room temperature. The resulting mixture was then stirred and checked by TLC. After the completion of the reaction, the mixture was quenched with water (10 mL), concentrated and extracted with ethyl acetate (10 mL x 3). The combined organic layer was washed with brine and dried over with anhydrous Na₂SO₄. The solvent was removed under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to obtain **10a** (218.0 mg, 1 mmol, yield: 99%) as colorless oil.

Representative Procedure for Reductive Amination of Ketones

Condition A: The cyclohexanone **11b** (127.6 mg, 1.3 mmol, 1.3 equiv), *p*-toluidine (107.2 mg, 1 mmol, 1 equiv) and AcOH (18 mg, 0.3 mmol, 0.3 equiv) were dissolved in DCE (4 mL, 0.25 M). To this solution was added the **7a** (117.6 mg, 0.8 mmol, 0.8 equiv) at room temperature. The resulting mixture was then stirred and checked by TLC. After the completion of the reaction, the mixture was quenched with water (10 mL), concentrated and extracted with ethyl acetate (10 mL x 3). The combined organic layer was washed with brine and dried over with anhydrous Na₂SO₄. The solvent was removed under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to obtain **12b** (189.1 mg, 1 mmol, yield: 99%) as white solid.

Condition B: The cyclohexanone **11b** (127.6 mg, 1.3 mmol, 1.3 equiv), *p*-toluidine (107.2 mg, 1 mmol, 1 equiv) were dissolved in DCE (4 mL, 0.25 M). To this solution was added the **7a** (88.2 mg, 0.6 mmol, 0.6 equiv) at room temperature. The resulting mixture was then stirred at 60°C and checked by TLC. After the reaction was completed, the mixture was cooled down and quenched with water (10 mL), concentrated and extracted with ethyl acetate (10 mL x 3). The combined organic layer was washed with brine and dried over with anhydrous Na₂SO₄. The solvent was removed under reduced pressure to give a residue, the residue was purified by flash silica gel chromatography to obtain **12b** (189.1 mg, 1 mmol, yield: 99%) as white solid.

Representative Procedure for Reductive Amination of Amino Acid

The methionine **13c** (149.2 mg, 1 mmol, 1 equiv) and Na₂CO₃ (31.8 mg, 0.3 mmol, 0.3 equiv) were dissolved in water (3 mL). To this solution was added 4-chlorobenzaldehyde **8a** (210.8 mg, 1.5 mmol, 1.5 equiv), methanol (2 mL) and **7a** (220.5 mg, 1.5 mmol, 1.5 equiv) successively at room temperature. The resulting mixture was then stirred and checked by TLC. After the completion of the reaction, the resulting mixture was filtered to remove the indissoluble solid (**6b**). The solvent of the filtered solution was removed to get a residue. The residue was then diluted with CH₂Cl₂ (5 mL) and water (5 mL). 0.1 M HCl solution was added to the solution until pH = 7, then a white solid was obtained by filtration of the mixture. **14c** was purified by recrystallization (MeOH/H₂O = 3:1) from the white solid as white crystal (232 mg, 0.85 mmol, yield: 85%).

Compounds Characterization:

3a

4-Methyl-3, 5-bis(1-phenylvinyl)isoxazoline-N-oxide 3a

Purified by flash chromatography (hexane-EtOAc, v/v = 7/1) as colorless oil (yield: 88%); ^1H NMR (270 MHz, CDCl_3) δ 7.42-7.30 (m, 5H), 7.28-7.20 (m, 3H), 7.06-6.98 (m, 2H), 6.24 (s, 1H), 5.71 (s, 1H), 5.62 (s, 1H), 5.48 (s, 1H), 5.02 (d, J = 5.4 Hz, 1H), 3.21-3.12 (m, 1H), 1.03 (d, J = 6.7 Hz, 3H); ^{13}C NMR (67.5 MHz, CDCl_3): δ 144.9, 138.2, 137.8, 135.7, 128.8, 128.5, 128.4, 128.2, 127.5, 127.1, 121.8, 117.5, 115.4, 82.6, 45.4, 17.7; HRMS Calculated for $\text{C}_{20}\text{H}_{19}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 306.14940, Found: 306.14925.

3b

4-Ethyl-3, 5-bis(1-phenylvinyl)isoxazoline-N-oxide 3b

Purified by flash chromatography (hexane-EtOAc, v/v = 7/1) as colorless oil (yield: 76%); ^1H NMR (270 MHz, CDCl_3) δ 7.38-7.34 (m, 5H), 7.25-7.20 (m, 3H), 7.00-6.96 (m, 2H), 6.25 (d, J = 0.73 Hz, 1H), 5.72 (d, J = 0.76 Hz, 1H), 5.63 (s, 1H), 5.44 (s, 1H), 5.11 (d, J = 2.46 Hz, 1H), 3.04-2.99 (m, 1H), 1.46-1.35 (m, 2H), 0.75 (t, J = 7.43 Hz, 3H); ^{13}C NMR (67.5 MHz, CDCl_3): δ 145.8, 138.3, 137.9, 135.9, 128.8, 128.4, 128.1, 127.5, 127.3, 121.7, 116.3, 115.3, 80.0, 51.3, 24.9, 9.97; HRMS Calculated for $\text{C}_{21}\text{H}_{21}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 320.16503, Found: 320.16480.

3c

4-Propyl-3, 5-bis(1-phenylvinyl)isoxazoline-N-oxide 3c

Purified by flash chromatography (hexane-EtOAc, v/v = 7/1) as colorless oil (yield: 71%); ^1H NMR (270 MHz, CDCl_3) δ 7.41-7.28 (m, 5H), 7.27-7.18 (m, 3H), 6.99-6.95 (m, 2H), 6.27 (d, J = 0.76 Hz, 1H), 5.71 (d, J = 0.73 Hz, 1H), 5.63 (s, 1H), 5.43 (s, 1H), 5.09 (d, J = 2.48 Hz, 1H), 3.06-3.01 (m, 1H), 1.50-0.81 (m, 4H), 0.56 (t, J = 7.18 Hz, 3H); ^{13}C NMR (67.5 MHz, CDCl_3): δ 145.6, 138.1, 137.7, 135.7, 128.6, 128.2, 128.0, 127.3, 127.1, 121.5, 116.5, 115.1, 80.2, 49.5, 33.7, 18.6, 13.2; HRMS Calculated for $\text{C}_{22}\text{H}_{23}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 334.18070, Found: 334.18049.

3d

4-(Phenylethyl)-3, 5-bis(1-phenylvinyl)isoxazoline-N-oxide 3d

Purified by flash chromatography (hexane-EtOAc, v/v = 7/1) as colorless oil (yield: 65%); ^1H NMR (600 MHz, CDCl_3) δ 7.39-7.34 (m, 5H), 7.26-7.19 (m, 4H), 7.13-7.11 (m, 2H), 6.94-6.92 (m, 2H), 6.75-6.73 (m, 2H), 6.25 (s, 1H), 5.71 (s, 1H), 5.62 (s, 1H), 5.48 (s, 1H), 5.02(d, J = 5.4 Hz, 1H), 3.21-3.12 (m, 1H), 2.53-2.48 (m, 1H), 2.38-2.32 (m, 1H), 1.82-1.75 (m, 1H), 1.71-1.65 (m, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ 145.8, 140.0, 138.2, 137.9, 135.7, 128.8, 128.37, 128.35, 128.1, 128.0, 127.4, 127.3, 126.0, 121.7, 116.2, 115.6, 80.5, 49.3, 33.2, 31.6; HRMS Calculated for $\text{C}_{27}\text{H}_{25}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 396.19635, Found: 396.19625.

3e

4-Methyl-3, 5-bis(1-p-tolylvinyl)isoxazoline-N-oxide 3e

Purified by flash chromatography (hexane-EtOAc, v/v = 7/1) as colorless oil (yield: 83%); ^1H NMR (270 MHz, CDCl_3) δ 7.29-7.25 (m, 2H), 7.19-7.16 (m, 2H), 7.07-7.04 (m, 2H), 6.95-6.92 (m, 2H), 6.18 (d, J = 0.73 Hz, 1H), 5.69 (d, J = 0.76 Hz, 1H), 5.58 (s, 1H), 5.44 (s, 1H), 5.01(d, J = 3.7 Hz, 1H), 3.23-3.13 (m, 1H), 2.35 (s, 3H), 2.31 (s, 3H), 1.03 (d, J = 6.91 Hz, 3H); ^{13}C NMR (67.5 MHz, CDCl_3): δ 144.7, 138.3, 138.1, 135.5, 135.3, 134.8, 129.5, 129.2, 127.4, 126.9, 121.3, 117.8, 114.4, 82.4, 45.6, 21.2, 17.7; HRMS Calculated for $\text{C}_{22}\text{H}_{23}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 334.18016, Found: 334.17992.

3f

4-(Phenylethyl)-3, 5-bis(1-p-tolylvinyl)isoxazoline-N-oxide 3f

Purified by flash chromatography (hexane-EtOAc, v/v = 6/1) as colorless oil (yield: 66%); ^1H NMR (270 MHz, CDCl_3) δ 7.25-7.17 (m, 4H), 7.11-7.07 (m, 3H), 7.00-6.97 (m, 2H), 6.83-6.79 (m, 2H), 6.75-6.69 (m, 2H), 6.20 (d, J = 0.76 Hz, 1H), 5.67 (d, J = 0.73 Hz, 1H), 5.59 (s, 1H), 5.39 (s, 1H), 5.14 (d, J = 2.21 Hz, 1H), 3.11-3.07 (m, 1H), 2.55-2.45 (m, 1H), 2.36 (s, 3H), 2.31 (s, 3H), 1.82-1.59 (m, 2H); ^{13}C NMR (67.5 MHz, CDCl_3): δ 145.7, 140.2, 138.3, 138.0, 135.6,

135.4, 135.0, 129.5, 129.1, 128.4, 128.2, 127.4, 127.3, 125.9, 121.3, 116.5, 114.8, 80.5, 49.5, 33.3, 31.7, 21.3; HRMS Calculated for C₂₉H₂₉NO₂ [M+H]⁺: 424.22711, Found: 424.22673.

3g

4-Methyl-3, 5-bis(1-*p*-chlorophenylvinyl)isoxazoline-*N*-oxide 3g

Purified by flash chromatography (hexane-EtOAc, v/v = 6/1) as colorless oil (yield: 77%); ¹H NMR (270 MHz, CDCl₃) δ 7.38-7.30 (m, 3H), 7.25-7.22 (m, 3H), 6.97-6.93 (d, *J* = 8.7 Hz 2H), 6.15 (s, 1H), 5.69 (s, 1H), 5.61 (s, 1H), 5.46 (s, 1H), 4.98 (d, *J* = 4.13 Hz, 1H), 3.16-3.07 (m, 1H), 1.06 (d, *J* = 6.94 Hz, 3H); ¹³C NMR (67.5 MHz, CDCl₃): δ 143.7, 136.3, 136.0, 134.7, 134.5, 134.3, 129.1, 128.8, 128.7, 128.5, 122.3, 117.1, 116.4, 82.6, 45.3, 17.7; HRMS Calculated for C₂₀H₁₇Cl₂NO₂ [M+H]⁺: 374.07146 Found: 374.07137

3h

4-Ethyl-3, 5-bis(1-*p*-chlorophenylvinyl)isoxazoline-*N*-oxide 3h

Purified by flash chromatography (hexane-EtOAc, v/v = 6/1) as colorless oil (yield: 58%); ¹H NMR (600 MHz, CDCl₃) δ 7.36 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.17 (s, 1H), 5.69 (s, 1H), 5.61 (s, 1H), 5.42 (s, 1H), 5.07 (d, *J* = 3.0 Hz, 1H), 2.98-2.95 (m, 1H), 1.46-1.43 (m, 2H), 0.79 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃): δ 145.0, 136.7, 136.3, 135.1, 134.7, 134.5, 129.2, 128.87, 128.85, 128.8, 122.3, 116.4, 115.8, 81.5, 58.0, 25.2, 11.1; HRMS Calculated for C₂₁H₁₉Cl₂NO₂ [M+H]⁺: 388.08656, Found: 388.08666.

3i

4-Methyl-3, 5-bis(1-(2-naphthyl)vinyl)isoxazoline-*N*-oxide 3i

Purified by flash chromatography (hexane-EtOAc, v/v = 5/1) as colorless oil (yield: 75%); ^1H NMR (600 MHz, CDCl_3) δ 7.87-7.83 (m, 4H), 7.22 (d, $J = 7.8$ Hz, 1H), 7.61 (d, $J = 7.4$ Hz, 1H), 7.58 (dd, $J = 1.8$ Hz, $J = 7.4$ Hz, 1H), 7.52-7.48 (m, 3H), 7.43-7.36 (m, 3H), 7.10 (dd, $J = 1.8$ Hz, $J = 7.4$ Hz, 1H), 6.32 (s, 1H), 5.82 (s, 1H), 5.75 (s, 1H), 5.64 (s, 1H), 5.16 (d, $J = 3.6$ Hz, 1H), 3.30-3.28 (m, 1H), 1.07 (d, $J = 6.6$ Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ 144.9, 135.5, 135.4, 135.1, 133.2, 133.0, 132.9, 132.7, 128.5, 128.1, 128.0, 127.9, 127.6, 126.5, 126.44, 126.41, 126.3, 126.2, 125.9, 125.1, 124.9, 122.0, 117.5, 115.9, 82.6, 45.4, 17.6; HRMS Calculated for $\text{C}_{28}\text{H}_{23}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 406.18016, Found: 406.18031.

3i

4-(Phenylethyl)-3, 5-bis(1-(2-naphthyl)vinyl)isoxazoline-*N*-oxide 3j

Purified by flash chromatography (hexane-EtOAc, v/v = 5/1) as colorless oil (yield: 61%); ^1H NMR (600 MHz, CDCl_3) δ 7.87-7.81 (m, 3H), 7.73 (s, 1H), 7.70 (d, $J = 7.8$ Hz, 1H), 7.54-7.47 (m, 4H), 7.42-7.39 (m, 1H), 7.37-7.33 (m, 2H), 7.21 (s, 1H), 6.92 (dd, $J = 1.8$ Hz, $J = 7.4$ Hz, 1H), 6.82 (t, $J = 7.8$ Hz, 1H), 6.70 (t, $J = 7.8$ Hz, 1H), 6.45 (d, $J = 7.2$ Hz, 1H), 6.37 (s, 1H), 5.77 (s, 1H), 5.73 (s, 1H), 5.55 (s, 1H), 5.26 (d, $J = 3.0$ Hz, 1H), 3.14-3.11 (m, 1H), 2.51-2.46 (m, 1H), 2.31-2.26 (m, 1H), 1.84-1.76 (m, 1H), 1.69-1.63 (m, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ 145.8, 139.3, 135.5, 135.4, 135.3, 133.2, 133.0, 132.8, 133.7, 128.5, 128.1, 128.0, 127.6, 127.4, 126.6, 126.5, 126.4, 126.2, 125.7, 125.18, 125.16, 122.06, 116.37, 80.7, 48.9, 32.9, 31.3; HRMS Calculated for $\text{C}_{35}\text{H}_{29}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 496.22711, Found: 496.22691.

3j

4-Methyl-3, 5-bis((*E*)-1-phenylprop-1-enyl)isoxazoline-*N*-oxide 3k

Purified by flash chromatography (hexane-EtOAc, v/v = 7/1) as colorless oil (yield: 75%), colorless solid formed several days later. m.p. 152-154 °C; ^1H NMR (600 MHz, CDCl_3) δ 7.40-7.37 (m, 2H), 7.34-7.31 (m, 1H), 7.25-7.22 (m, 3H), 7.20-7.18 (m, 2H), 6.99 (q, $J = 7.2$ Hz, 1H), 6.72-6.71 (m, 2H), 5.95-5.91 (q, $J = 6.6$ Hz), 4.63 (d, $J = 3.6$ Hz, 1H), 2.83-2.81 (m, 1H), 1.63 (t, $J = 7.2$ Hz, 3H), 1.57 (t, $J = 7.2$ Hz, 3H), 0.89 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3): δ 138.3, 136.3, 136.2, 132.4, 129.59, 129.56, 128.9, 128.7, 128.4, 127.8, 127.6, 127.5, 118.9, 85.9, 44.7, 18.0, 15.4, 14.6; HRMS Calculated for $\text{C}_{22}\text{H}_{23}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 334.18016, Found: 334.18013.

4-Methyl-3, 5-dicyclohexenylisoxazoline-*N*-oxide 3l

Purified by flash chromatography (hexane-EtOAc, v/v 7/1) as pale yellow solid (yield 87%), m.p. 126-128 °C; ¹H NMR (600 MHz, CDCl₃): δ 6.43-6.41 (m, 1H), 5.75 (s, 1H), 4.66 (d, *J* = 3.6 Hz, 1H), 3.28-3.26 (m, 1H), 2.54-2.50 (m, 1H), 2.28-2.19 (m, 3H), 2.10-2.02 (m, 3H), 1.92-1.88 (m, 1H), 1.75-1.52 (m, 8H), 1.31 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃): δ 134.4, 131.7, 125.8, 125.1, 120.1, 85.5, 43.3, 25.8, 25.5, 24.8, 22.8, 22.3, 22.12, 22.1, 21.4, 18.2; HRMS Calculated for C₁₆H₂₃NO₂ [M+H]⁺: 262.18070, Found: 262.18030.

4-Ethyl-3, 5-dicyclohexenylisoxazoline-*N*-oxide 3m

Purified by flash chromatography (hexane-EtOAc, v/v 7/1) as pale yellow solid (yield 80%), m.p. 115-117 °C; ¹H NMR (270 MHz, CDCl₃): δ 6.41-6.40 (m, 1H), 5.75 (s, 1H), 4.45 (d, *J* = 2.5 Hz, 1H), 3.07-3.05 (m, 1H), 2.51-2.44 (m, 1H), 2.27-2.15 (m, 3H), 2.08-1.95 (m, 3H), 1.91-1.77 (m, 1H), 1.71-1.48 (m, 10H), 0.95 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (67.5 MHz, CDCl₃): δ 135.4, 131.7, 125.2, 125.0, 124.9, 119.0, 82.6, 50.0, 26.0, 25.6, 25.1, 24.8, 22.8, 22.2, 21.5, 10.4; HRMS Calculated for C₁₇H₂₅NO₂ [M+H]⁺: 276.19635, Found: 276.19597.

4-Propyl-3, 5-dicyclohexenylisoxazoline-*N*-oxide 3n

Purified by flash chromatography (hexane-EtOAc, v/v 7/1) as pale yellow solid (yield 74%), m.p. 119-121 °C; ¹H NMR (600 MHz, CDCl₃): δ 6.44-6.42 (m, 1H), 5.77 (s, 1H), 4.46 (s, 1H), 3.13-3.10 (m, 1H), 2.54-2.46 (m, 1H), 2.28-2.16 (m, 3H), 2.08-1.95 (m, 3H), 1.90-1.84 (m, 1H), 1.74-1.50 (m, 10H), 1.48-1.32 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (67.5 MHz, CDCl₃): δ 135.4, 131.8, 125.2, 124.9, 119.2, 83.1, 48.5, 34.2, 26.0, 25.6, 24.8, 22.8, 22.4, 22.2, 21.5, 19.4, 13.9; HRMS Calculated for C₁₈H₂₇NO₂ [M+H]⁺: 290.21200, Found: 290.21166.

4--(Phenylethyl)-3, 5-dicyclohexenylisoxazoline-*N*-oxide **3o**

Purified by flash chromatography (hexane-EtOAc, v/v 7/1) as pale yellow solid (yield 70%), m.p. 123-125 °C; ^1H NMR (270 MHz, CDCl_3): δ 7.35-7.10 (m, 5H), 6.27 (s, 1H), 5.78 (s, 1H), 4.56 (s, 1H), 3.17-3.10 (m, 1H), 2.84-2.56 (m, 2H), 2.51-2.38 (m, 1H), 2.24-1.80 (m, 9H), 1.72-1.48 (m, 8H); ^{13}C NMR (67.5 MHz, CDCl_3): δ 140.6, 135.2, 131.9, 128.6, 128.4, 126.3, 125.6, 125.1, 119.0, 83.1, 77.5, 77.1, 76.6, 47.8, 32.2, 26.0, 25.5, 24.9, 22.8, 22.4, 22.2; HRMS Calculated for $\text{C}_{23}\text{H}_{29}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 352.22765, Found: 352.22747

4-Methyl-3, 5-dicyclopentenylisoxazoline-*N*-oxide **3P**

Purified by flash chromatography (hexane-EtOAc, v/v 7/1) as pale yellow solid (yield 72%), m.p. 48-50 °C; ^1H NMR (270 MHz, CDCl_3): δ 6.44 (s, 1H), 5.75 (s, 1H), 4.66 (d, $J = 3.7$ Hz, 1H), 3.28-3.15 (m, 1H), 2.84-2.67 (m, 1H), 2.66-2.52 (m, 1H), 2.45-2.42 (m, 2H), 2.35-2.20 (m, 4H), 1.98-1.79 (m, 4H), 1.32 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (67.5 MHz, CDCl_3): δ 140.5, 134.7, 134.6, 129.9, 129.3, 117.6, 81.1, 43.7, 33.3, 32.7, 32.2, 30.6, 23.2, 17.8; HRMS Calculated for $\text{C}_{14}\text{H}_{19}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 234.14940, Found: 234.14951.

4-Ethyl-3, 5-dicyclopentenylisoxazoline-*N*-oxide **3q**

Purified by flash chromatography (hexane-EtOAc, v/v 7/1) as colorless oil (yield 65%); ^1H NMR (270 MHz, CDCl_3): δ 6.48-6.44 (m, 1H), 5.77 (s, 1H), 4.82 (s, 1H), 3.07-3.05 (m, 1H), 2.83-2.58 (m, 1H), 2.53-2.45 (m, 2H), 2.39-2.28 (m, 4H), 1.99-1.87 (m, 5H), 1.78-1.68 (m, 2H), 0.99 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (67.5 MHz, CDCl_3): δ 141.5, 134.5, 130.0, 128.5, 116.2, 79.0, 50.3, 33.3, 32.7, 32.2, 30.6, 24.6, 23.2, 10.5; HRMS Calculated for $\text{C}_{15}\text{H}_{21}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 248.16451, Found: 248.16442.

3r

4-Methyl-3, 5-di(prop-1-en-2-yl)isoxazoline-N-oxide **3r**

Purified by flash chromatography (hexane-EtOAc, v/v = 8/1) as colorless oil (yield: 55%); ^1H NMR (270 MHz, CDCl_3) δ 5.55 (s, 1H), 5.29 (s, 1H), 5.10 (s, 1H), 4.94 (s, 1H), 4.45 (d, J = 3.94 Hz, 1H), 3.33-3.22 (m, 1H), 2.09 (s, 3H), 1.77 (s, 3H), 1.36 (d, J = 6.94 Hz 3H); ^{13}C NMR (67.5 MHz, CDCl_3): δ 141.1, 131.0, 119.5, 118.9, 113.5, 84.2, 43.9, 20.5, 18.2, 16.9; HRMS Calculated for $\text{C}_{10}\text{H}_{15}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 182.11756, Found: 182.11743.

5a

4-Methyl-3, 5-bis(1-phenylvinyl)isoxazoline **5a**

Purified by flash chromatography (hexane-EtOAc, v/v = 10/1) as pale yellow oil (yield: 81%); ^1H NMR (270 MHz, CDCl_3) δ 7.44-7.29 (m, 10H), 5.56 (s, 1H), 5.51 (s, 1H), 5.46 (s, 1H), 5.41 (s, 1H), 5.21 (d, J = 4.97 Hz, 1H), 3.31-3.21 (m, 1H), 1.28 (d, J = 7.18 Hz, 3H); ^{13}C NMR (67.5 MHz, CDCl_3): δ 161.7, 145.7, 139.1, 138.3, 138.2, 128.7, 128.3, 128.2, 128.1, 127.1, 120.3, 114.2, 89.75, 48.5, 18.2; HRMS Calculated for $\text{C}_{20}\text{H}_{19}\text{NO}$ $[\text{M}+\text{H}]^+$: 290.15449, Found: 290.15430.

5b

4-Methyl-3, 5-dicyclohexenylisoxazoline **5b**

Purified by flash chromatography (hexane-EtOAc, v/v = 10/1) as pale yellow solid (yield: 90%), m.p. 74-76 °C; ^1H NMR (600 MHz, CDCl_3) δ 6.04-6.03 (m, 1H), 5.67 (s, 1H), 4.44 (d, J = 4.8 Hz, 1H), 3.21-3.18 (m, 1H), 2.45-2.41 (m, 1H), 2.28-2.16 (m, 3H), 2.03-1.96 (m, 3H), 1.80-1.77 (m, 1H), 1.69-1.49 (m, 8H), 1.25 (d, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3): δ 161.8, 136.0, 131.2, 128.7, 124.3, 92.7, 45.4, 25.8, 25.0, 24.9, 22.9, 22.28, 22.27, 22.1, 21.9, 19.3; HRMS Calculated for $\text{C}_{16}\text{H}_{23}\text{NO}$ $[\text{M}+\text{H}]^+$: 246.18524, Found: 246.18519.

5c

4-Methyl-3, 5-bis(1-phenylvinyl)isoxazole **5c**

Purified by flash chromatography (hexane-EtOAc, v/v = 10/1) as pale yellow oil (yield: 71%); ^1H NMR (270 MHz, CDCl_3) δ 7.45-7.23 (m, 10H), 5.86 (s, 1H), 5.78 (s, 1H), 5.76 (s, 1H), 5.66

(s, 1H), 1.46 (s, 3H); ^{13}C NMR (67.5 MHz, CDCl_3): δ 165.4, 164.1, 138.1, 137.8, 137.4, 128.63, 128.61, 128.5, 128.4, 127.6, 126.9, 119.8, 119.3, 111.6, 8.78; HRMS Calculated for $\text{C}_{20}\text{H}_{17}\text{NO}$ $[\text{M}+\text{H}]^+$: 288.13884, Found: 288.13865.

N-1, 3-dicyclohexenyl-3-hydroxy-2-methylpropyl)acetamide 5d

Purified by flash chromatography (hexane-EtOAc, v/v = 2/1) as colorless oil (yield: 65%); ^1H NMR (600 MHz, CDCl_3) δ 5.67 (s, 1H), 5.44 (d, J = 9.6 Hz, 1H), 3.91 (t, J = 9.6 Hz, 1H), 3.77 (d, J = 9.6 Hz, 1H), 2.10-1.97 (m, 2H), 1.83-1.74 (m, 1H), 1.65-1.41 (m, 11H), 1.25-1.11 (m, 2H), 0.91 (d, J = 6.6 Hz, 3H); ^{13}C NMR (67.5 MHz, CDCl_3): δ 170.0, 135.9, 126.0, 86.8, 80.4, 64.4, 42.4, 36.7, 33.3, 25.7, 25.3, 23.7, 23.0, 22.8, 22.7, 21.8, 14.1; HRMS Calculated for $\text{C}_{18}\text{H}_{29}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 292.22711, Found: 292.22695.

1-methyl benzotriazole borane (7a): m.p. 187.2-188.9 $^\circ\text{C}$. ^1H NMR (600 MHz, CDCl_3): δ 8.17-8.15 (m, 1H), 7.68-7.64 (m, 2H), 7.63-7.58 (m, 1H), 4.37 (s, 3H), 2.73-2.54 (br m, 3H). ^{13}C NMR (150 MHz, CDCl_3): δ 139.7, 134.1, 129.3, 127.3, 118.0, 110.2, 35.7. HRMS Calculated for $\text{C}_7\text{H}_{11}\text{BN}_3$ $[\text{M}+\text{H}]^+$: 147.10769, Found: 147.10763.

1-phenyl benzotriazole borane (7b): m.p. 91.9-92.6 $^\circ\text{C}$. ^1H NMR (600 MHz, CDCl_3): δ 8.31 (d, J = 8.4 Hz, 1H), 7.81-7.77 (m, 3H), 7.73-7.70 (m, 1H), 7.69-7.66 (m, 3H), 7.64-7.62 (m, 1H), 2.88-2.65 (br m, 3H). ^{13}C NMR (150 MHz, CDCl_3): δ 140.3, 135.3, 133.2, 130.5, 130.2, 127.6, 123.6, 118.9, 118.7, 111.3. HRMS Calculated for $\text{C}_{12}\text{H}_{13}\text{BN}_3$ $[\text{M}+\text{H}]^+$: 209.04728, Found: 209.04723.

N-(4-chlorobenzyl)benzenamine (10a). **10a** was purified by flash silica gel chromatography

(Hexane-EtOAc, v/v = 30:1) as colorless oil, yield: 99%. m.p. 110.1-112.3 °C. ^1H NMR (600 MHz, CDCl_3): δ 7.36-7.32 (m, 4H), 7.24-7.21 (m, 2H), 6.80-6.77 (m, 1H), 6.66-6.64 (m, 2H), 4.35 (s, 2H), 4.09 (br, 1H). ^{13}C NMR (150 MHz, CDCl_3): δ 147.8, 138.0, 132.8, 129.2, 128.7, 128.6, 117.7, 112.8, 47.5. HRMS Calculated for $\text{C}_{13}\text{H}_{13}\text{ClN}$ $[\text{M}+\text{H}]^+$: 218.07310, Found: 218.07318.

***N*-(4-methoxybenzyl)benzenamine (10b).** **10b** was purified by flash silica gel chromatography (Hexane-EtOAc, v/v = 30:1) as colorless oil, yield: 99%. m.p. 112.8-114.0 °C. ^1H NMR (600 MHz, CDCl_3): δ 7.33-7.31 (m, 2H), 7.22-7.20 (m, 2H), 6.93-6.91 (m, 2H), 6.77-6.74 (m, 1H), 6.68-6.66 (m, 2H), 4.28 (s, 2H), 4.03 (br, 1H), 3.83 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3): δ 158.8, 148.1, 131.3, 129.2, 128.8, 117.5, 114.0, 112.9, 55.2, 47.8. HRMS Calculated for $\text{C}_{14}\text{H}_{16}\text{NO}$ $[\text{M}+\text{H}]^+$: 214.12264, Found: 214.12278.

***N*-benzylbenzenamine (10c).** **10c** was purified by flash silica gel chromatography (Hexane-EtOAc, v/v = 50:1) as white solid, yield: 99%. m.p. 67.3-68.2 °C. ^1H NMR (600 MHz, CDCl_3): δ 7.43-7.39 (m, 4H), 7.35-7.32 (t, J = 7.2 Hz, 1H), 7.25-7.22 (m, 2H), 6.80-6.77 (m, 1H), 6.70-6.69 (m, 2H), 4.38 (s, 2H), 4.09 (br, 1H). ^{13}C NMR (150 MHz, CDCl_3): δ 148.1, 139.4, 129.2, 128.6, 127.5, 127.1, 117.6, 112.8, 48.3. HRMS Calculated for $\text{C}_{13}\text{H}_{14}\text{N}$ $[\text{M}+\text{H}]^+$: 184.11207, Found: 184.11220.

***N*-(4-chlorobenzyl)-4-methoxybenzenamine (10d).** **10d** was purified by flash silica gel chromatography (Hexane-EtOAc, v/v = 30:1) as white solid, yield: 99%. m.p. 156.1-157.8 °C. ^1H NMR (600 MHz, CDCl_3): δ 7.30 (s, 4H), 6.77-6.76 (m, 2H), 6.60-6.58 (m, 2H), 4.26 (s, 2H), 3.74 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3): δ 151.4, 141.0, 139.2, 136.5, 129.0, 128.9, 115.2, 114.6, 56.0, 48.9. HRMS Calculated for $\text{C}_{14}\text{H}_{15}\text{ClNO}$ $[\text{M}+\text{H}]^+$: 248.08367, Found: 248.08373.

***N*-(4-chlorobenzyl)-4-fluorobenzenamine (10e).** **10e** was purified by flash silica gel chromatography (Hexane-EtOAc, v/v = 30:1) as white solid, yield: 99%. m.p. 123.1-124.6 °C. ¹H NMR (600 MHz, CDCl₃): δ 7.32-7.28 (m, 4H), 6.90-6.87 (m, 2H), 6.56-6.54 (m, 2H), 4.27 (s, 2H), 4.10 (br, 1H). ¹³C NMR (150 MHz, CDCl₃): δ 156.8, 155.3, 144.0, 137.5, 133.0, 128.7, 115.7, 113.8, 48.3. HRMS Calculated for C₁₃H₁₂ClFN [M+H]⁺: 236.06368, Found: 236.06398.

***N*-(4-chlorobenzyl)(phenyl)methanamine (10f).** **10f** was purified by flash silica gel chromatography (Hexane-EtOAc, v/v = 5:1) as white solid, yield: 95%. m.p. 121.3-122.2 °C. ¹H NMR (600 MHz, CDCl₃): δ 7.35-7.26 (m, 8H), 3.80 (s, 2H), 3.78 (s, 2H), 1.76 (br, 1H). ¹³C NMR (150 MHz, CDCl₃): δ 140.0, 138.7, 132.6, 129.5, 128.5, 128.4, 128.1, 127.0, 53.0, 52.3. HRMS Calculated for C₁₄H₁₅ClN [M+H]⁺: 232.08875, Found: 232.08887.

***N*-(4-chlorobenzyl)(4-methoxyphenyl)methanamine (10g).** **10g** was purified by flash silica gel chromatography (Hexane-EtOAc, v/v = 6:1) as white solid, yield: 96%. m.p. 168.1-170.2 °C. ¹H NMR (600 MHz, CDCl₃): δ 7.28-7.25 (m, 4H), 7.24-7.22 (m, 2H), 6.86-6.85 (m, 2H), 3.79 (s, 3H), 3.76 (s, 2H), 3.75 (s, 2H), 1.52 (br, 1H). ¹³C NMR (150 MHz, CDCl₃): δ 158.6, 138.9, 132.5, 132.2, 129.4, 129.2, 128.4, 113.8, 55.2, 52.5, 52.2. HRMS Calculated for C₁₅H₁₇ClNO [M+H]⁺: 262.09932, Found: 262.09947.

***N*-(4-nitrobenzyl)(4-methoxyphenyl)methanamine (10h).** **10h** was purified by flash silica gel chromatography (Hexane-EtOAc, v/v = 8:1) as white solid, yield: 82%. m.p. 179.0-181.2 °C. ¹H NMR (600 MHz, CDCl₃): δ 8.18-8.17 (m, 2H), 7.53-7.51 (m, 2H), 7.26-7.24 (m, 2H), 6.88-6.87 (m, 2H), 3.89 (s, 2H), 3.80 (s, 3H), 3.75 (s, 2H), 1.64 (br, 1H). ¹³C NMR (150 MHz, CDCl₃): δ 158.8, 148.2, 147.0, 131.9, 129.3, 128.6, 123.6, 113.9, 55.3, 52.6, 52.2. HRMS Calculated for C₁₅H₁₇N₂O₃ [M+H]⁺: 273.12337, Found: 273.12350.

***N*-(4-chlorobenzyl)butan-1-amine (10i).** **10i** was purified by flash silica gel chromatography (Hexane-EtOAc, v/v = 3:1) as colorless oil, yield: 91%. ¹H NMR (600 MHz, CDCl₃): δ 7.30-7.26 (m, 4H), 3.76 (s, 2H), 2.61 (t, *J* = 7.2Hz, 2H), 1.81 (br, 1H), 1.53-1.48 (m, 2H), 1.37-1.33 (m, 2H), 0.91 (t, *J* = 7.2Hz, 3H). ¹³C NMR (150 MHz, CDCl₃): δ 148.4, 147.0, 128.6, 123.6, 53.2, 49.2, 32.2, 20.4, 13.9. HRMS Calculated for C₁₁H₁₇ClN [M+H]⁺: 198.10440, Found: 198.10446.

1-(4-chlorobenzyl)pyrrolidine (10j). **10j** was purified by flash silica gel chromatography (Hexane-EtOAc, v/v = 3:1) as yellow oil, yield: 95%. ¹H NMR (600 MHz, CDCl₃): δ 7.30-7.23 (m, 4H), 3.55 (s, 2H), 2.95 (br, 1H), 2.47-2.45 (m, 4H), 1.77-1.74 (m, 4H). ¹³C NMR (150 MHz, CDCl₃): δ 139.6, 137.7, 130.2, 128.3, 59.9, 54.0, 23.4. HRMS Calculated for C₁₁H₁₅ClN [M+H]⁺: 196.08875, Found: 196.08874.

***N*-(4-chlorobenzyl)-*N*-methylbenzenamine (10k).** **10k** was purified by flash silica gel chromatography (Hexane-EtOAc, v/v = 30:1) as yellow oil, yield: 99%. ¹H NMR (600 MHz, CDCl₃): 7.30-7.28 (m, 2H), 7.25-7.22 (m, 2H), 7.18-7.17 (m, 2H), 6.75-6.74 (m, 3H), 4.50 (s, 2H), 3.01 (s, 3H). ¹³C NMR (150 MHz, CDCl₃): δ 149.5, 137.5, 132.6, 129.2, 128.7, 128.1, 116.9, 112.5, 56.2, 38.5. HRMS Calculated for C₁₄H₁₅ClN [M+H]⁺: 232.08875, Found: 232.08880.

***N*-(3-phenylpropyl)benzenamine (10l).** **10l** was purified by flash silica gel chromatography (Hexane-EtOAc, v/v = 35:1) as yellow oil, yield: 99%. ¹H NMR (600 MHz, CDCl₃): δ 7.19-7.17 (m, 2H), 7.10-7.03 (m, 5H), 6.60-6.57 (m, 1H), 6.46-6.44 (m, 2H), 3.44 (b, 1H), 3.01 (t, *J* = 7.2 Hz, 2H), 2.60 (t, *J* = 7.8 Hz, 2H), 1.84-1.79 (m, 2H). ¹³C NMR (150 MHz, CDCl₃): δ 148.3, 141.6, 129.1, 128.4, 128.3, 125.9, 117.1, 112.7, 43.3, 33.3, 31.0. HRMS Calculated for C₁₅H₁₈N [M+H]⁺: 212.14338, Found: 212.14338.

***N*-((pyridin-4-yl)methyl)benzenamine (10m).** **10m** was purified by flash silica gel chromatography (Hexane-EtOAc, v/v = 1:1) as yellow solid, yield: 99%. m.p. 128.1-130.2 °C. ¹H NMR (600 MHz, CDCl₃): δ 8.63 (s, 1H), 8.53 (d, *J* = 4.8 Hz, 1H), 7.70-7.69 (m, 1H), 7.27-7.25 (m, 1H), 7.18-7.16 (m, 2H), 6.76-6.73 (m, 1H), 6.64-6.62 (m, 2H), 4.36 (s, 2H). ¹³C NMR (150 MHz, CDCl₃): δ 149.0, 148.6, 147.6, 129.3, 123.5, 118.0, 112.9, 45.80. HRMS Calculated for C₁₂H₁₃N₂ [M+H]⁺: 185.10732, Found: 185.10743.

***N*-((furan-2-yl)methyl)benzenamine (10n).** **10n** was purified by flash silica gel chromatography (Hexane-EtOAc, v/v=30:1) as yellow oil, yield: 99%. ¹H NMR (600 MHz, CDCl₃): δ 7.41 (t, *J* = 1.2 Hz, 1H), 7.25-7.22 (m, 2H), 6.81-6.78 (m, 1H), 6.73-6.71 (m, 2H), 6.37-6.36 (m, 1H), 6.28-6.27 (m, 1H), 4.35 (s, 2H), 4.02 (br, 1H). ¹³C NMR (150 MHz, CDCl₃): δ 152.7, 147.6, 141.8, 129.2, 118.0, 113.1, 110.3, 106.9, 41.4. HRMS Calculated for C₁₁H₁₂NO [M+H]⁺: 174.09134, Found: 174.09147.

***N*-((thiophen-2-yl)methyl)benzenamine (10o).** **10o** was purified by flash silica gel chromatography (Hexane-EtOAc, v/v = 30:1) as colorless oil, yield: 99%. ¹H NMR (600 MHz, CDCl₃): δ 7.24-7.21 (m, 3H), 7.05-7.04 (m, 1H), 7.00-6.99 (m, 1H), 6.80-6.77 (m, 1H), 6.71-6.70 (m, 2H), 4.53 (s, 2H), 4.14 (br, 1H). ¹³C NMR (150 MHz, CDCl₃): δ 147.5, 142.8, 129.2, 126.8, 125.0, 124.6, 118.1, 113.2, 43.5. HRMS Calculated for C₁₁H₁₂NS [M+H]⁺: 190.06850, Found: 190.06860.

***N*-((1H-imidazol-2-yl)methyl)benzenamine (10p).** **10p** was purified by flash silica gel chromatography (Hexane-EtOAc, v/v = 4:1) as white solid, yield: 93%. m.p. 195.0-197.2 °C ¹H NMR (600 MHz, CDCl₃): δ 7.13-7.11 (m, 2H), 6.97 (s, 2H), 6.74-6.71 (m, 1H), 6.54-6.52 (m, 2H), 4.35 (s, 2H). ¹³C NMR (150 MHz, CDCl₃): δ 147.5, 146.6, 129.3, 121.9, 118.4, 113.1,

42.3. HRMS Calculated for $C_{10}H_{12}N_3$ $[M+H]^+$: 174.10257, Found: 174.10256.

N-cinnamylbenzenamine (10q). **10q** was purified by flash silica gel chromatography (Hexane-EtOAc, v/v = 50:1) as yellow oil, yield: 95%. ^1H NMR (600 MHz, $CDCl_3$): δ 7.42-7.41 (m, 2H), 7.37-7.34 (m, 2H), 7.29-7.22 (m, 3H), 6.80-6.77 (m, 1H), 6.73-6.71 (m, 2H), 6.66 (d, J = 15.6 Hz, 1H), 6.37 (dt, J = 15.6 Hz; 6.0 Hz, 1H), 3.97 (dd, J = 6.0 Hz; 1.8 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 147.9, 136.8, 131.5, 129.2, 128.5, 127.5, 127.0, 126.3, 117.6, 113.1, 46.2. HRMS Calculated for $C_{15}H_{16}N$ $[M+H]^+$: 210.12773, Found: 210.12785.

(S)-N-(4-chlorobenzyl)-1-phenylethanamine (10r). **10r** was purified by flash silica gel chromatography (Hexane-EtOAc, v/v = 20:1) as colorless oil, yield: 95%. ^1H NMR (600 MHz, $CDCl_3$): δ 7.29-7.28 (m, 4H), 7.21-7.16 (m, 5H), 3.74 (q, J = 6.6 Hz, 1H), 3.57 (d, J = 13.2 Hz, 1H), 3.50 (d, J = 13.2 Hz, 1H), 1.33 (d, J = 6.6 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 132.9, 129.9, 129.7, 128.6, 128.5, 127.2, 126.8, 123.0, 57.5, 50.6, 24.1. HRMS Calculated for $C_{15}H_{17}ClN$ $[M+H]^+$: 246.10440, Found: 246.10456.

N-benzylcyclohexanamine (12a). **12a** was purified by flash silica gel chromatography (Hexane-EtOAc, v/v = 8:1) as yellow oil, yield: 95%. ^1H NMR (600 MHz, $CDCl_3$): δ 7.33-7.30 (m, 4H), 7.24-7.22 (m, 1H), 3.81 (s, 2H), 2.52-2.47 (m, 1H), 1.93-1.91 (m, 2H), 1.76-1.72 (m, 2H), 1.63-1.60 (m, 1H), 1.30-1.10 (m, 5H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 141.3, 128.6, 128.3, 127.0, 56.4, 33.8, 26.5, 25.2. HRMS Calculated for $C_{13}H_{20}N$ $[M+H]^+$: 190.15903, Found: 190.15904.

N-cyclohexyl-4-methylbenzenamine (12b). **12b** was purified by flash silica gel chromatography (Hexane-EtOAc, v/v = 50:1) as white solid, yield: 99%. m.p. 62.1-64.6 °C. ^1H NMR (600 MHz, $CDCl_3$): δ 6.99-6.98 (m, 2H), 6.55-6.53 (m, 2H), 3.37 (br, 1H), 3.26-3.22 (m, 1H), 2.25 (s, 3H), 2.08-2.06 (m, 2H), 1.79-1.76 (m, 2H), 1.68-1.65 (m, 1H), 1.41-1.35 (m, 2H),

1.27-1.21 (m, 1H), 1.18-1.12 (m, 2H). ^{13}C NMR (150 MHz, CDCl_3): δ 145.4, 130.0, 126.3, 113.7, 52.3, 33.8, 26.2, 25.3, 20.6. HRMS Calculated for $\text{C}_{13}\text{H}_{20}\text{N}$ $[\text{M}+\text{H}]^+$: 190.15903, Found: 190.15902.

***N*-(1-phenylethyl)benzenamine (12c).** **12c** was purified by flash silica gel chromatography (Hexane-EtOAc, v/v = 30:1) as colorless oil, yield: 99%. ^1H NMR (600 MHz, CDCl_3): δ 7.40-7.39 (m, 2H), 7.36-7.33 (m, 2H), 7.26-7.24 (m, 1H), 7.13-7.10 (m, 2H), 6.69-6.66 (m, 1H), 6.55-6.54 (m, 2H), 4.53-4.50 (m, 1H), 4.14 (br, 1H), 1.55 (d, J = 6.9 Hz, 3H). ^{13}C NMR (150 MHz, CDCl_3): δ 147.2, 145.1, 129.1, 128.6, 126.8, 125.8, 117.3, 113.4, 53.5, 24.9. HRMS Calculated for $\text{C}_{14}\text{H}_{16}\text{N}$ $[\text{M}+\text{H}]^+$: 198.12773, Found: 198.12788.

***N*-cyclohexyl-*N*-methylbenzenamine (12d).** **12d** was purified by flash silica gel chromatography (Hexane-EtOAc, v/v = 25:1) as colorless oil, yield: 99%. ^1H NMR (600 MHz, CDCl_3): δ 7.25-7.22 (m, 2H), 6.80-6.78 (m, 2H), 6.70-6.68 (m, 1H), 3.60-3.55 (m, 1H), 2.78 (s, 3H), 1.86-1.79 (m, 4H), 1.71-1.68 (m, 1H), 1.55 (br, 1H), 1.50-1.43 (m, 2H), 1.41-1.33 (m, 2H), 1.18-1.11 (m, 1H). ^{13}C NMR (150 MHz, CDCl_3): δ 150.0, 129.1, 116.2, 113.2, 58.2, 31.1, 30.0, 26.2, 25.9. HRMS Calculated for $\text{C}_{13}\text{H}_{20}\text{N}$ $[\text{M}+\text{H}]^+$: 190.15903, Found: 190.15902.

***N*-benzyl-1-phenylethanamine (12e).** **12e** was purified by flash silica gel chromatography (Hexane-EtOAc, v/v = 8:1) as colorless oil, yield: 87%. ^1H NMR (600 MHz, CDCl_3): δ 7.40-7.25 (m, 10H), 3.84 (q, J = 6.6 Hz, 1H), 3.79 (d, J = 13.2 Hz, 1H), 3.62 (d, J = 13.2 Hz, 1H), 1.73 (br, 1H), 1.40 (d, J = 6.6 Hz, 3H). ^{13}C NMR (150 MHz, CDCl_3): δ 145.5, 140.6, 128.4, 128.3, 128.1, 126.9, 126.8, 126.7, 57.5, 51.6, 24.4. HRMS Calculated for $\text{C}_{15}\text{H}_{18}\text{N}$ $[\text{M}+\text{H}]^+$: 212.14338, Found: 212.14339.

***N*-(1-(furan-2-yl)ethyl)benzenamine (12f).** **12f** was purified by flash silica gel

chromatography (Hexane-EtOAc, v/v = 25:1) as yellow oil, yield: 96%. ^1H NMR (600 MHz, CDCl_3): δ 7.31 (d, J = 1.2 Hz, 1H), 7.14 (m, 2H), 6.69 (t, J = 7.2 Hz, 1H), 6.61 (d, J = 7.8 Hz, 2H), 6.27-6.26 (m, 1H), 6.14 (d, J = 3.0 Hz, 1H), 4.62 (q, J = 6.6 Hz, 1H), 3.84 (br, 1H), 1.53 (d, J = 6.6 Hz, 3H). ^{13}C NMR (150 MHz, CDCl_3): δ 157.2, 147.0, 141.4, 129.1, 117.7, 113.4, 110.0, 105.0, 47.3, 20.8. HRMS Calculated for $\text{C}_{12}\text{H}_{14}\text{NO}$ $[\text{M}+\text{H}]^+$: 188.10699, Found: 188.10702.

2-((naphthalene-3-yl)methylamino)-4-methylpentanoic acid (14a). **14a** was purified by recrystallization as white solid, yield: 65%. ^1H NMR (600 MHz, CD_3OD): δ 8.33 (d, J = 8.4 Hz, 1H), 7.97 (dd, J = 16.2 Hz; 8.4 Hz, 2H), 7.70-7.65 (m, 2H), 7.60-7.53 (m, 2H), 4.76 (d, J = 13.2 Hz, 1H), 4.54 (d, J = 13.2 Hz, 1H), 3.66 (dd, J = 8.4 Hz; 6.0 Hz, 1H), 1.87-1.77 (m, 2H), 1.63-1.58 (m, 1H), 1.00 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H). ^{13}C NMR (150 MHz, CD_3OD): δ 135.4, 133.1, 131.4, 130.7, 129.9, 128.4, 127.5, 126.4, 124.4, 63.2, 41.2, 26.1, 23.2, 22.5. HRMS Calculated for $\text{C}_{17}\text{H}_{22}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 272.16451, Found: 272.16461.

(S)-2-(4-chlorobenzylamino)-3-(1H-imidazol-5-yl) propanoic acid (14b). **14b** was purified by recrystallization as white solid, yield: 65%. ^1H NMR (600 MHz, CD_3OD): δ 7.69 (d, J = 1.2 Hz, 1H), 7.48-7.46 (m, 2H), 7.44-7.42 (m, 2H), 6.98 (d, J = 1.2 Hz, 1H), 4.23 (d, J = 13.2 Hz, 1H), 4.16 (d, J = 13.2 Hz, 1H), 3.73 (dd, J = 7.8 Hz; 4.8 Hz, 1H), 3.23 (dd, J = 15.6, 4.8 Hz, 1H), 3.08 (dd, J = 15.6, 4.8 Hz, 1H). ^{13}C NMR (150 MHz, CD_3OD): δ 172.8, 136.4, 136.3, 135.5, 132.6, 132.3, 130.2, 116.7, 63.6, 50.6, 49.6, 28.3. HRMS Calculated for $\text{C}_{13}\text{H}_{15}\text{ClN}_3\text{O}_2$ $[\text{M}+\text{H}]^+$: 280.08473, Found: 280.08487.

2-(4-chlorobenzylamino)-4-(methylthio)butanoic acid (14c). **14c** was purified by recrystallization as white solid, yield: 65%. ^1H NMR (600 MHz, CDCl_3 with CF_3COOH): δ 7.43 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 4.40 (d, J = 12.6, 1H), 4.32 (d, J = 12.6, 1H), 4.27 (br, 1H), 2.70 (br, 2H), 2.36 (br, 3H), 2.12 (br, 2H). ^{13}C NMR (150 MHz, CDCl_3 with CF_3COOH): δ 137.6, 131.5, 130.3, 126.9, 59.2, 51.4, 30.0, 27.6, 15.1. HRMS Calculated for $\text{C}_{12}\text{H}_{17}\text{ClNO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 274.06630, Found: 274.06636.

2-(4-chlorobenzylamino)acetic acid (14d). **14d** was purified by recrystallization as white solid, yield: 55%. ^1H NMR (600 MHz, CD_3OD): δ 7.42-7.40 (m, 2H), 7.36-7.35 (m, 2H), 3.96 (s, 2H), 3.29 (s, 2H). ^{13}C NMR (150 MHz, CD_3OD): δ 136.2, 135.2, 132.5, 129.9, 58.4, 54.9. HRMS Calculated for $\text{C}_9\text{H}_{11}\text{ClNO}_2$ $[\text{M}+\text{H}]^+$: 200.04728, Found: 200.04723.

ORTEP Drawing of the Crystal Structures

Figure 1. Perspective view of the molecular structure of **3K** (C₂₂H₂₃NO₂) with the atom labeling scheme. The thermal ellipsoids are scaled to enclose 30% probability. CCDC number : 686861

Figure 2. Perspective view of the molecular structure of **3I** ($C_{16}H_{23}NO_2$) with the atom labeling scheme. Each cyclohexenyl ring suffers from a two-site conformational disorder. For purposes of clarity, only the major site is depicted. The thermal ellipsoids are scaled to enclose 30% probability. CCDC number: 687371

Figure 3. Perspective view of the molecular structures of the two independent molecules of **7a** with their respective atom labeling schemes. The thermal ellipsoids are scaled to enclose 30% probability. CCDC number: 741401.

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¹H-NMR and ¹³C-NMR Spectra

¹H NMR of **3a**

¹³C NMR of **3a**

^1H NMR of **3b**

^{13}C NMR of **3b**

^1H NMR of **3c**

¹³C NMR of **3c**

¹H NMR of **3d**

^{13}C NMR of **3d**

^1H NMR of **3e**

¹³C NMR of **3e**

^1H NMR of **3f**

¹³C NMR of **3f**

^1H NMR of **3g**

¹³C NMR of **3g**

^1H NMR of **3h**

^{13}C NMR of **3h**

^1H NMR of **3i**

^1H NMR of **3j**

¹³C NMR of **3j**

^1H NMR of **3k**

^{13}C NMR of **3k**

^1H NMR of **31**

^{13}C NMR of **31**

^1H NMR of **3m**

^1H NMR of **3n**

^{13}C NMR of **3n**

^1H NMR of **30**

^{13}C NMR of **30**

^1H NMR of **3p**

^{13}C NMR of **3p**

¹H NMR of **3q**

^{13}C NMR of **3q**

^1H NMR of **3r**

^{13}C NMR of **3r**

¹H NMR of **5a**

^{13}C NMR of **5a**

^1H NMR of **5b**

^{13}C NMR of **5b**

¹H NMR of **5c**

¹³C NMR of **5c**

^1H NMR of **5d**

^{13}C NMR of **5d**

10c

10c

10e

100