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Toward Expanded Reactivity and Understanding of Asymmetric Catalysis in Enantiopure
Supramolecular Hosts

by

Elizabeth Dawn Heafner

A dissertation submitted in partial satisfaction of the

requirements for the degree of

Doctor of Philosophy

in

Chemistry

in the

Graduate Division

of the

University of California, Berkeley

Committee in charge:

Professor F. Dean Toste, Co-Chair
Professor Kenneth N. Raymond, Co-Chair
Professor Markita del Carpio Landry

Summer 2024

Abstract

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by

Elizabeth Dawn Heafner

Doctor of Philosophy in Chemistry

University of California, Berkeley

Professor F. Dean Toste, Co-Chair

Professor Kenneth N. Raymond, Co-Chair

Chapter 1. An overview of enantioselective catalysis in supramolecular hosts is presented. A brief background of the main principles of supramolecular cage catalysis and types of hosts commonly utilized is given to provide context for an overview of the state of homogenous enantioselective supramolecular catalysis. This discussion outlines work towards catalysis approaches during the 21st century of thermally catalyzed reactions. The potential for supramolecular catalysts to complement existing state-of-the-art organocatalysts and transition metal catalysts for difficult synthetic transformations is noted and opportunities to advance the field toward this goal are highlighted.

Chapter 2. A brief description of the state of enantioselective reductions of oximes to hydroxylamines is presented. An introduction to oximes and hydroxylamines as relevant functional groups is given before state-of-the-art approaches towards enantioselective oxime reductions to hydroxylamines and outstanding challenges are discussed.

Chapter 3. The development and application of an enantiopure Ga₄L₆ host catalyst system for enantioselective oxime reductions is presented. Particular emphasis in this work is directed toward gaining insight into the interactions and features relevant for enantioinduction in the host with these substrates. Application of the supramolecular host system enabled an expanded range of reducible oximes. Reaction scope and mechanistic study informed resulting data science analysis of potential interactions in the catalytic system. In addition to steric effects, exhibited through a high degree of size and shape recognition, electronic effects were also found to be important for enantioinduction of some substrates. This work serves as proof-of-concept for supramolecular hosts' potential to complement existing catalytic scaffolds and helps lay the foundation for future study into the mechanism of enantioinduction in these hosts.

Chapter 4. Initial results towards an expanded reaction scope and improved understanding of enantioselective reductions in a supramolecular M₄L₆ system are presented. This work is designed to further build on the findings of Chapter 3. The ability to modulate and improve enantioselectivity of oximes by tuning host scaffold, namely host

metal identity and spacer group, is explored. The use of pyridine borane reductant to tune enantioselectivity is also discussed. These findings are used to inform ongoing work towards the enantioselective reductions of ketones and indoles, both poorly selective substrate classes under initial conditions. Enantiodivergent behavior of substrates based on both host and pyridine borane identity is revealed.

Toward Expanded Reactivity and Understanding of Asymmetric Catalysis in Enantiopure Supramolecular Hosts

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Chapter 1

An Introduction to Enantioselective Supramolecular Catalysis

1.1 A Brief Introduction to Supramolecular Catalysis and Common Supramolecular Scaffolds Used for Enantioselective Catalysis

Enzymes have repeatedly demonstrated themselves to possess exquisite reactivity and precise reaction control for selectivity, making them ideal catalysts in many ways. However, this is generally achieved through an ensemble of highly substrate-specific electrostatic and non-covalent interactions, which inhibits their more general synthetic application.¹⁻³ Synthetic chemists' long-standing goal of developing broadly tolerant catalysts which impart comparable levels of reactivity and selectivity has driven immense development of synthetic catalytic scaffolds, but still these generally fall short of enzymatic reactivity and selectivity. More recent synthetic efforts have attempted to take more direct inspiration from enzymes, and, among other things, led to the development of supramolecular catalysis.

Following the advent of the field of supramolecular chemistry through the pioneering discoveries of crown ethers, cryptands, carcerands, and hemicarcerands, supramolecules capable of binding ions and simple molecules, efforts were quickly devoted towards the development of increasingly complex scaffolds capable of binding and interacting with a range of guest molecules.⁴⁻⁶ These supramolecular assemblies are composed of smaller, repeating units which combine through self-assembly processes and are held together through covalent bonds or a series of non-covalent interactions, particularly hydrogen bonding or hydrophobic interactions.⁴ When applied to catalysis, these supramolecular hosts take much inspiration from enzymes and similarly seek to apply principles such as confinement-driven reactivity and selectivity. Like enzyme active sites, the cavities of supramolecular hosts often display solvent exclusion abilities and utilize electrostatic and non-covalent interactions to engage guest molecules.^{4,7} Furthermore, many hosts are soluble in aqueous solvents and utilize these principles to catalyze organic and organometallic reactions in water. Due to the inherent nature of catalysis within a confined space, these hosts also require size and shape complementarity for encapsulation.^{5,7,8} However, unlike enzymes, these hosts generally lack specific features which engage a particular substrate, making them more promiscuous. Increasing work in the field of supramolecular catalysis has enabled impressive, enzyme-like rate accelerations and differential chemo- and regioselectivities relative to bulk solution, but supramolecular hosts are still generally far from achieving the same degrees of selectivity and reactivity as observed in native enzymes.^{4,7} The unique microenvironment provided by supramolecular host cavities make these systems particularly promising for fundamental study but could have some practical applications.

In the quest to further explore the boundaries and potential of supramolecular hosts, attention has been directed towards the possibility of asymmetric catalysis. While there are some examples of enantioselective binding studies in supramolecular hosts, such work is beyond the scope of this dissertation and has been discussed in a recent review.⁹ The field of enantioselective supramolecular catalysis within the larger field of supramolecular catalysis is still a nascent and underexplored area. Seminal reports of enantioselective catalysis using naturally occurring supramolecular scaffolds began in the latter half of the 20th century, and examples in man-made synthetic scaffolds were first reported in the early 2000s. While some early examples of enantioselective supramolecular catalysis were reported to occur in the solid state, these have been

excluded to focus discussion solely on solution state catalysis. For the sake of brevity, this introduction will further be limited solely to thermally catalyzed reactions reported in the 21st century.

Covalent organic cages are a class of macrocyclic cages held together through discrete covalent bonds and can be natural or synthetic.^{4,10} Cyclodextrins (CDs), one of the initial supramolecular host types explored for asymmetric catalysis, are one such example (**Figure 1.1**). In contrast to many other synthetic cages reported for enantioselective catalysis, CDs, which are macrocyclic oligosaccharides composed of glucopyranose units linked by α -(1,4) glycosidic bonds, are naturally occurring supramolecular scaffolds.^{11,12} This oligomer gives rise to helical structures with a shape often described as a truncated cone due to its cylindrical structure which is narrower at one end than the other. They come in multiple sizes of n amylose groups which may be utilized for catalysis, often under aqueous conditions: for α -CD, $n=6$, for β -CD, $n=7$, and for γ -CD, $n=8$. Larger CDs have been reported but are generally not used in catalysis.^{13–15} These scaffolds are intrinsically chiral due to their sugar building blocks, making them a logical choice for enantioselective catalysis since no additional host design is required. There are also a small number of reports using cucurbiturils for enantioselective catalysis. Like CDs, cucurbiturils (Q[n]s) are organic macrocyclic hosts, but are entirely synthetic scaffolds prepared from glycoluril and formaldehyde.¹⁶ Their structures are compared to a flattened sphere or pumpkin with an opening at the top and bottom.^{16,17} A number of curubit[n]urils, composed of a range of glycoluril units from 5–8, 10, and 13–15, have been reported, but have been the subject of minimal study within the field of asymmetric catalysis to date. Calixarene- and resorcinarene-based hosts are another example of these synthetic covalently bound hosts.¹⁰ Resorcinarenes are a subtype within the broader category of calixarenes, which are comprised of phenoxy groups bridged by methyl or methenyl spacer groups. Classically, calixarenes are composed of *para-tert*-butyl-phenols and uses the nomenclature of calix[n]arene where n denotes the number of phenol units,¹² while resorcinarenes feature two phenoxy groups meta to one another.¹⁷ While these scaffolds can be derivatized with relative ease, they are more commonly used for enantiorecognition and enantioseparations than catalysis.^{12,17} Although generally robust, these covalent, macrocyclic scaffolds inherently limit the potential shapes, sizes, and charges the host can take on, which can pose challenges in applying them more broadly and in optimizing the scaffold for enantioselectivity.

Conversely, coordination cages are formed through self-assembly processes, which rely on the kinetic lability of individual components to successfully form a more stable cage.⁷ However, the resulting hosts are notably less stable than covalent cages.⁴ Beyond a somewhat limited range of stability, an inherent challenge to the application of these assemblies is the self-assembly process, which is poorly understood. Thus, beyond the challenges more broadly assumed in asymmetric catalysis of designing a ligand capable of sufficient enantioinduction, self-assembly towards a catalytically active host must be achieved. This poses a problem not only during initial host assembly, but in any attempts at scaffold optimization as the challenges of self-assembly must be overcome for every subsequent iteration of host. Among coordination cages, metal-organic cages are the major class utilized in enantioselective catalysis (**Figure 1.1**). Their synthetic ligands enable preparation of a variety of hosts of different sizes, geometries of M_xL_y

components, and charge properties, making them desirable targets which can theoretically be highly optimized for selectivity.⁸ The charged nature of these hosts sometimes gives rise to solubility in aqueous conditions, enabling electrostatic and hydrophobic interactions help drive catalysis.^{4,7} Very recently, interest has also grown towards the development of covalent organic coordination cages to circumvent the need for metals. These hosts are generally somewhat unstable and are bound through functional groups such as imines but can be made more stable through post-assembly modifications such as reductions.¹⁸ Thus, these hosts attempt to capture some of the advantages of metal-organic coordination cages as well as of more classical covalent organic cages. Many of these scaffolds feature organic-based ligands as well as smaller, organic macrocycles such as calixarenes. Other coordination cages are comprised of organic components and are held together solely through non-covalent interactions (**Figure 1.1**). These hosts are often comprised of smaller, organic macrocycles such as resorcinarenes and are held together by a network of hydrogen bonding interactions, generally in combination with water molecules.¹⁹

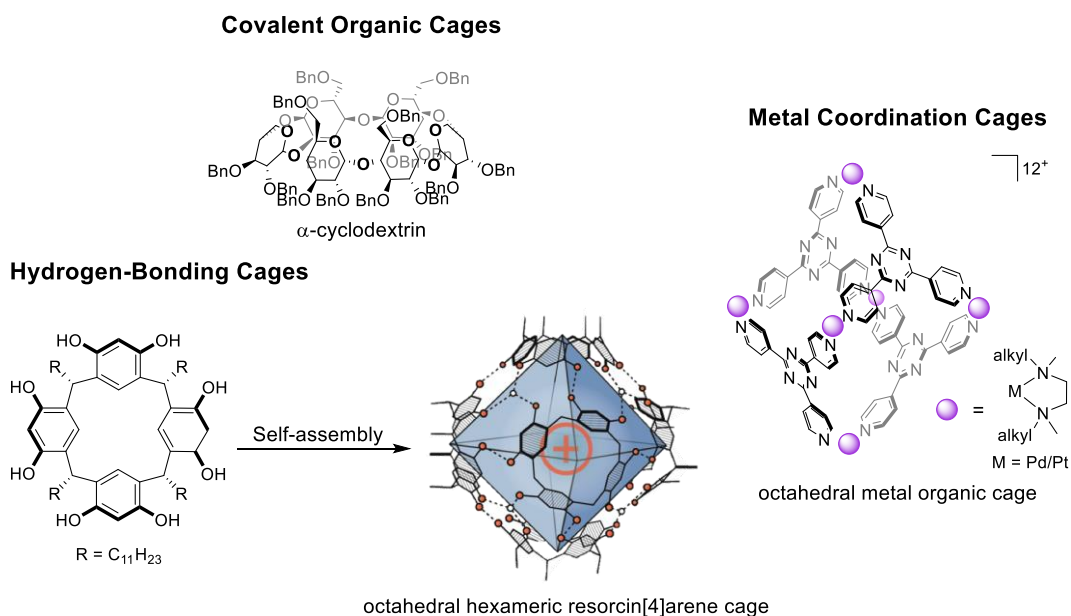


Figure 1.1. Representative examples of general classes of supramolecular hosts used for enantioselective catalysis.

1.2 Using Small Molecule Catalysts within Supramolecular Hosts for Enantioselective Catalysis

Enantioselective supramolecular catalysis is generally achieved through one of two main approaches, the first and most common of which is through the use of small molecule catalysts within supramolecular hosts. These catalysts can be merely encapsulated within the host or incorporated into the host scaffold. This approach largely seeks to mimic the behavior of co-catalysts found in some enzymatic active sites.^{8,9,20} In many instances the small molecule catalyst is chiral, leading the host to act primarily as an extended ligand system or secondary coordination sphere to further modulate the

reactivity and selectivity of the chiral small molecule catalyst. One particular advantage of using established chiral small molecule catalysts is that a baseline level of enantioselectivity can be reasonably expected, while the host acts as an additional level to further tune selectivity.

One tactic to achieve enantioselectivity in the host within this larger approach for asymmetric catalysis is through the encapsulation of chiral small molecule catalysts in achiral or racemic hosts. Given the dearth of hosts utilized for racemic catalysis, new host design is not a limiting factor for initial work; chiral small molecule catalysts must merely be able to co-encapsulate with reactants for reactivity. Hydrogen-bonding cages have primarily been used towards this aim. Tiefenbacher and coworkers have utilized this strategy extensively for the 1,4 reductions of conjugated enones.^{21–23} Using proline as the chiral small molecule catalyst and a Hantzsch ester as reductant, modest to good enantioselectivity was achieved *via* iminium catalysis in a racemic hexameric resorcin[4]arene-based host with a small number of α,β -unsaturated aldehydes (**Figure 1.2A**).²¹ The steric confinement of the host cavity was found to play a key role in enantioinduction due to the formation of (*S*) product, which is hypothesized to proceed from attack on the more sterically hindered face of the iminium due to cation- π interactions with the aryl groups of the host wall which preclude attack to the other face.^{21,22} Further mechanistic investigation revealed the aryl group of the phenylbutenal-

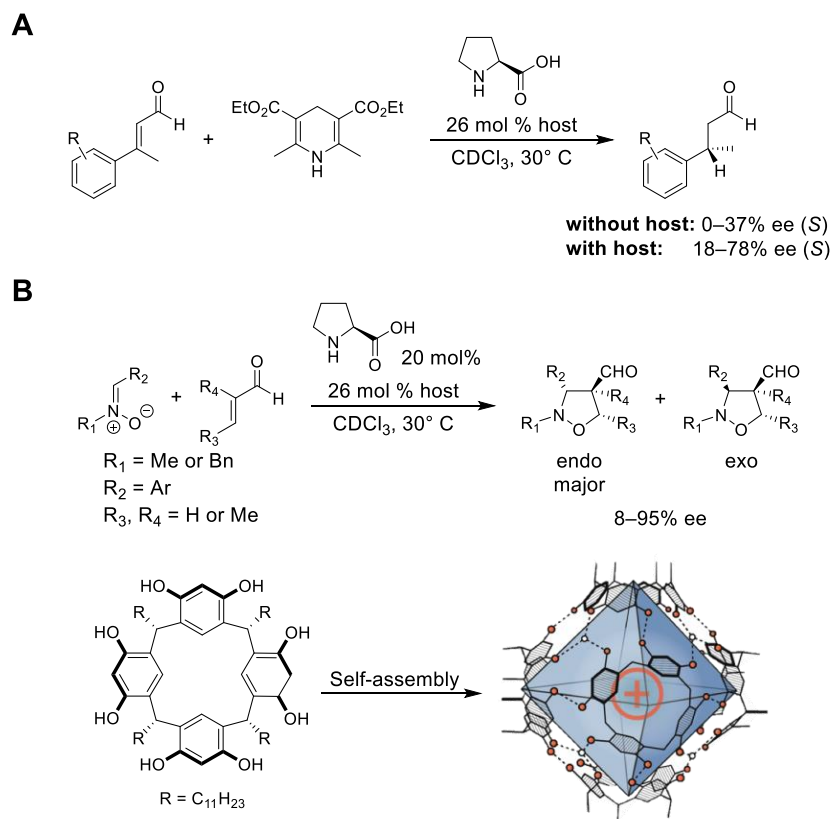


Figure 1.2. Iminium catalysis in racemic hexameric resorcinarene based hosts for **A**) 1,4-reductions of α,β -unsaturated aldehydes and **B**) dipolar cycloadditions of nitrones and α,β -unsaturated aldehydes.

derived α,β -unsaturated aldehydes was necessary for successful enantioinduction, perhaps due to π - π interactions with the host wall.²² Rescifina, Neri and coworkers similarly used proline as a co-catalyst in a hexameric resorcin[4]arene host for 1,3-dipolar cycloadditions between nitrones and α,β -unsaturated aldehydes (**Figure 1.2B**).²⁴ The reaction proved highly sensitive to aldehyde sterics and required substitution at the β position for reasonable enantioinduction but was able to achieve up to 95% ee for the major endo cyclized products. Based on reports from Tiefenbacher, cation- π interactions were speculated to play a role in the reaction. Computational work also points to stabilizing H-bonding interactions between the *H* of water molecules, which bind together the host components, and *O* of the substrates and as well as a two-center interaction between the nitrone *O* and the β carbon of carbon of the iminium before the nucleophilic attack.

Alternatively, the incorporation of active, chiral small molecule catalysts directly into the host scaffold has been the focus of much effort in the field of enantioselective supramolecular catalysis. This generally involves the use of a chiral small molecule catalyst to engender chirality within the host cavity or to facilitate formation of an enantiopure host from otherwise racemic ligands. Coordination cages have been more commonly used for this approach due to the flexibility in ligand design inherent to these structures. Work towards this aim has primarily focused on the ability to append the chiral catalyst to a portion of the ligand to generate multiple active sites within the host cavity. This strategy enables the use of scaffolds based on previously reported, racemic or achiral hosts after some ligand modifications.

Reek and coworkers were one of the first to report the use of a small molecule metal-based co-catalyst within a man-made supramolecular host. A mixed metal, tetragonal prismatic cage featuring a phosphoramidite ligand was used to generate *in situ* an encapsulated Rh(I) catalyst for the hydroformylation of styrenes.²⁵ Although the host's scaffolding ligands themselves are achiral, the top and bottoms of the host are composed of Zn(II)-based salphens which link a chiral, phosphoramidite ligand inside the cavity to generate a chiral environment. The Rh<host catalyst system formed upon addition of [Rh(acac)(CO)₂] as precatalyst yielded branched aldehydes in excellent regioselectivities and moderate to good enantioselectivity (**Figure 1.3A**). Simultaneously, Herrmann, Scherman and coworkers reported the ability of modified cucurbiturils to catalyze the Diels-Alder cycloaddition of azachalcone with cyclopentadiene.²⁶ The tight binding of amino acids to Q[n]s was exploited to encapsulate amino acids inside Q[6], Q[7] and Q[8], which served as ligands for Cu(II). All Cu<Q[n] controls, as well as free lysine and lysine+Cu<Q[6], afforded no enantioselectivity. However, selectivity was observed with aryl amino acids (AAA), particularly phenylalanine, tyrosine, tryptophan, and abrine. Decreased enantioselectivity was observed for all AAA+Cu<Q[7] relative to the AAA+Cu complex alone, and phenylalanine+Cu<Q[8] and tyrosine+Cu<Q[8] similarly afforded no improvement in enantioselectivity versus their respective AAA+Cu complexes. Very high levels of enantioselectivity were observed, however, with tryptophan+Cu<Q[8] and abrine+Cu<Q[8] species, and diastereoselectivity was also improved. The observed results in combination with guest binding and computational studies suggest that the larger Q[8] cavity size is required for co-encapsulation of guests for enantioinduction and that disfavorable steric clashes within the cavity help guide selectivity. Additional work

very recently by Cui and Lui has further demonstrated the ability to generate an active transition metal catalyst *in situ* using a chiral ligand appended within the host cavity. Covalent organic coordination cages composed of dihydrophenazine-based ligands were utilized for enantioselective Michael additions of 2-acetylazaarenes to nitroalkenes.²⁷ When ligand cores were condensed with enantioenriched cyclohexanediamines and reduced to the amine, two possible isomers of hosts featuring four dihydrophenazine ligands bridged by eight cyclohexanediamines were produced in an approximately 1:1 mixture. One isomer of the reduced host, called PN-1, adopted a Johnson-type J_{26} form, and the other isomer adopted a tetragonal prismatic form, called PN-2. The diamines served as an open coordination sites for Ni(II). When PN-1 and PN-2 were independently isolated and subjected to Ni(OAc)₂ as a precatalyst, each Ni only coordinated with one amine of the diamine ligands within the host cavity, producing eight active sites in the host cavity. Host geometry affected both reactivity and selectivity; Ni⊂PN-1 afforded the new acetylazaarene products in low to good enantioselectivity, while Ni⊂PN-2 afforded the products in higher yields with consistently improved, modest to high enantioselectivities.

In addition to transition metal catalysts, organocatalysts can also be appended to host ligands to generate active sites for enantioselective catalysis within the host cavity. Fujita and coworkers designed Pd₁₂L₂₄ spherical hosts featuring either multiple sites of TEMPO or MacMillan's imidazolidinone catalyst appended to ligand throughout the host scaffold.²⁸ Although TEMPO would typically poison the imidazolidinone Diels Alder catalyst, incorporation of the catalysts in different host cavities allowed for the co-existence of both species in solution without decomposition. When both hosts were added to solution in addition to PhI(OAc)₂ and trifluoroacetic acid, 10-phenyldeca-2,7,9-trien-1-ol, an allylic alcohol, was oxidized to an α,β -unsaturated aldehyde which cyclized upon itself to form the bicyclic product in high enantioselectivity (**Figure 1.3B**). Yuan and coworkers have utilized hosts featuring calix[4]resorcinarene vertices and pyrrolidine-2-carboxamide-based ligands as the host edges for enantioselective Aldol additions.²⁹ Two scaffolds of pyrrolidine-2-carboxamide ligands were used, each of which formed a different host. When (*S*)-*N*-(3,5-diaminophenyl)pyrrolidine 2-carboxamide was used as ligand, a tetragonal prismatic [4 + 8] host was formed while (*S*)-*N*-(4,4'-diamino-[1,1'-biphenyl]-2-yl) pyrrolidine-2-carboxamide generated a [6 + 12] octahedral assembly. Both ligand scaffolds feature an (*L*)-proline moiety for iminium catalysis. The tetragonal prismatic host showed no improvement in selectivity over free proline and the free pyrrolidine-2-carboxamide ligands alone, which each gave high levels of enantioselectivity to the *anti* product. However, the octahedral host showed a slight improvement in enantioselectivity over controls and catalyzed the addition of a small number of aliphatic ketones to aryl aldehydes with high diastereo- and enantioselectivity (**Figure 1.3C**). Cheng, Luo and coworkers also reported the synthesis of a β -cyclodextrin capped with a chiral cyclohexanediamine to act as an enamine catalyst for Aldol condensations.³⁰ Simple ketones and aryl aldehydes were studied and afforded the coupled product in moderate to excellent enantioselectivities with no Aldol dehydration or retro-Aldol side products observed. The (*R*) enantiomer of product was formed irrespective of the absolute chirality of diamine co-catalyst used, although there was appreciable erosion in observed selectivity for some diamines. Given that the CD cavity is inherently chiral, this suggests that enantioinduction is governed heavily by the host cavity, but that catalyst matching also plays a role. Further NMR spectroscopic analysis

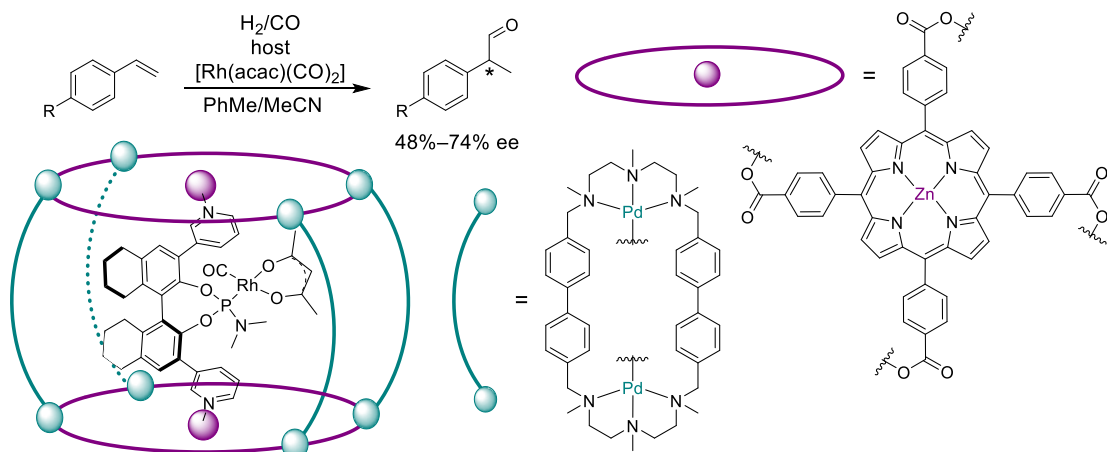
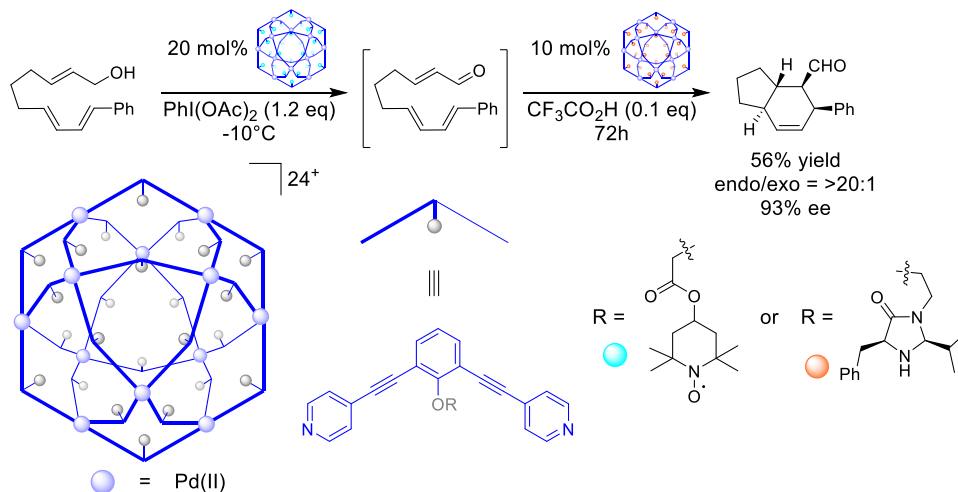
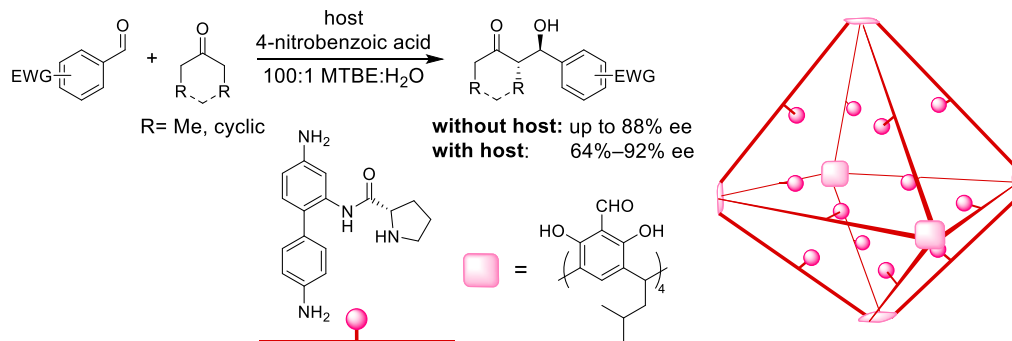
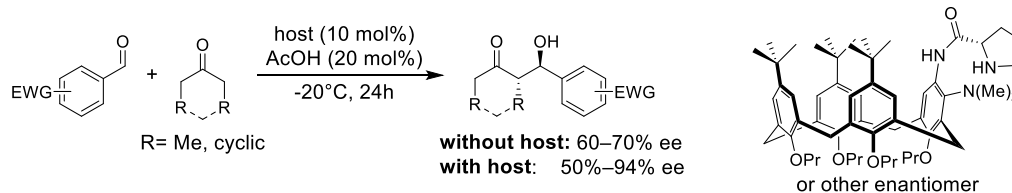
A**B****C****D**

Figure 1.3. Representative examples of chiral small molecule catalysts appended to the supramolecular host scaffold for enantioselective catalysis. **A)** Rh(phosphoramidite)

species encapsulated within a tetragonal prismatic cage for hydroformylation to branched aldehydes. **B)** TEMPO and MacMillan's Diels Alder catalyst incorporated into individual host scaffolds for tandem catalysis. Proline-catalyzed Aldol addition in **C)** an octahedral covalent organic coordination cage and **D)** functionalized calix[4]arene host.

indicated that the most selective CD+diamine combination features diamine pointing into the cavity, which might allow for increased non-covalent interactions during the enantiodetermining C–C bond forming step. Similarly, Huang, Chen, and coworkers reported a chiral, functionalized calix[4]arene host featuring an appended (*L*)-proline group, positioned near the top of the cavity, which was used to catalyze Aldol additions.³¹ Although comparable levels of enantioselectivity were observed with the free proline-containing ligand, the calixarene host was found to give a slight improvement in selectivity under optimized conditions. Cyclic and acyclic aliphatic ketones could be added to electron-deficient aryl aldehydes to give the predominantly *anti* product in generally moderate to good enantioselectivity (**Figure 1.3D**).

As an alternative to appending catalysts to the ligand, chiral small molecule catalysts can be incorporated directly into the scaffolding ligands of the host. In this way, catalytically active enantiopure supramolecular hosts can be synthesized. Su and coworkers designed an octahedral Pd-based host with a phenanthroline-based Ru(II) photocatalyst linked to pyridines as ligands. Although primarily used for photocatalyzed reactions,^{32–34} this scaffold has very recently been used as an acid-base catalyst for Diels Alder [4+2] cycloadditions of 9-alkyl anthracene and 9-anthrone derivatives with maleimides.³⁵ The overall 28+ charge and imidazole groups present throughout the scaffold can facilitate host deprotonation and H⁺ transfer to substrates. When subjected to reaction conditions, the anthracene derivatives were thought to undergo cyclization at the host aperture to give the *anti* isomer due to the acidic nature of the host exterior, while 9-anthrone reacts within the host cavity due to its basicity (**Figure 1.4A**). Su and coworkers suggested that π - π and H-bonding interactions, along with steric clash from the 9-substituent, guide the orientation and selectivity of anthracenes while π - π and electrostatic interactions guide the orientation and selectivity of anthrones to the opposite enantiomer as observed with anthracene derivatives.

Cui and coworkers have reported the application of heteroleptic C₃-symmetric Zr cluster-based tetrahedral hosts with enantiopure Mn(salen) and Cr(salen) groups incorporated into the ligand scaffold towards the epoxidation and ring opening of 2,2-dimethyl-2*H*-chromene and some derivatives.³⁶ Although high enantioselectivities were obtained using free Mn(salen) alone, reactivity was improved while enantioselectivities maintained for a handful of substrates. Slightly improved levels of reactivity and selectivity were observed when heteroleptic cages featuring both Mn(salen) and Cr(salen)-based ligands were used versus using a 1:1 mixture of Mn(salen) and Cr(salen) homoleptic hosts (**Figure 1.4B**). This principle was also concurrently applied to the synthesis of an enantiopure octahedral Zn-sulfonylcalix[4]arene host, in which only enantiopure Mn(salen) groups were incorporated into the ligand scaffold.³⁷ This host was used to successfully catalyze the oxidative kinetic resolution of alcohols and the epoxidation of 2,2-dimethyl-2*H*-chromene and its derivatives. These products were also formed in good to excellent enantioselectivities, although again enantioselectivity was not or only minimally improved over that of the free Mn(salen) species alone. Liu, Cui and coworkers

have also utilized a cationic Pd_3L_6 host with 6,6'-dipyridyl-functionalized SPINOL-based ligands for the addition of styrenylboronic acids to chalcone derivatives in the presence of Mg^{2+} cations (**Figure 1.4D**).³⁸ The free SPINOL ligand alone displayed high levels of reactivity and enantioselectivity, while the SPINOL-based host demonstrated slightly improved enantioselectivities when both electron-donating and electron-withdrawing substituents were used. The chiral alcohol of the SPINOL ligand was hypothesized to play a key role in enantiodetermination through formation of a chiral boronate intermediate by a transesterification from the starting boronic acid.

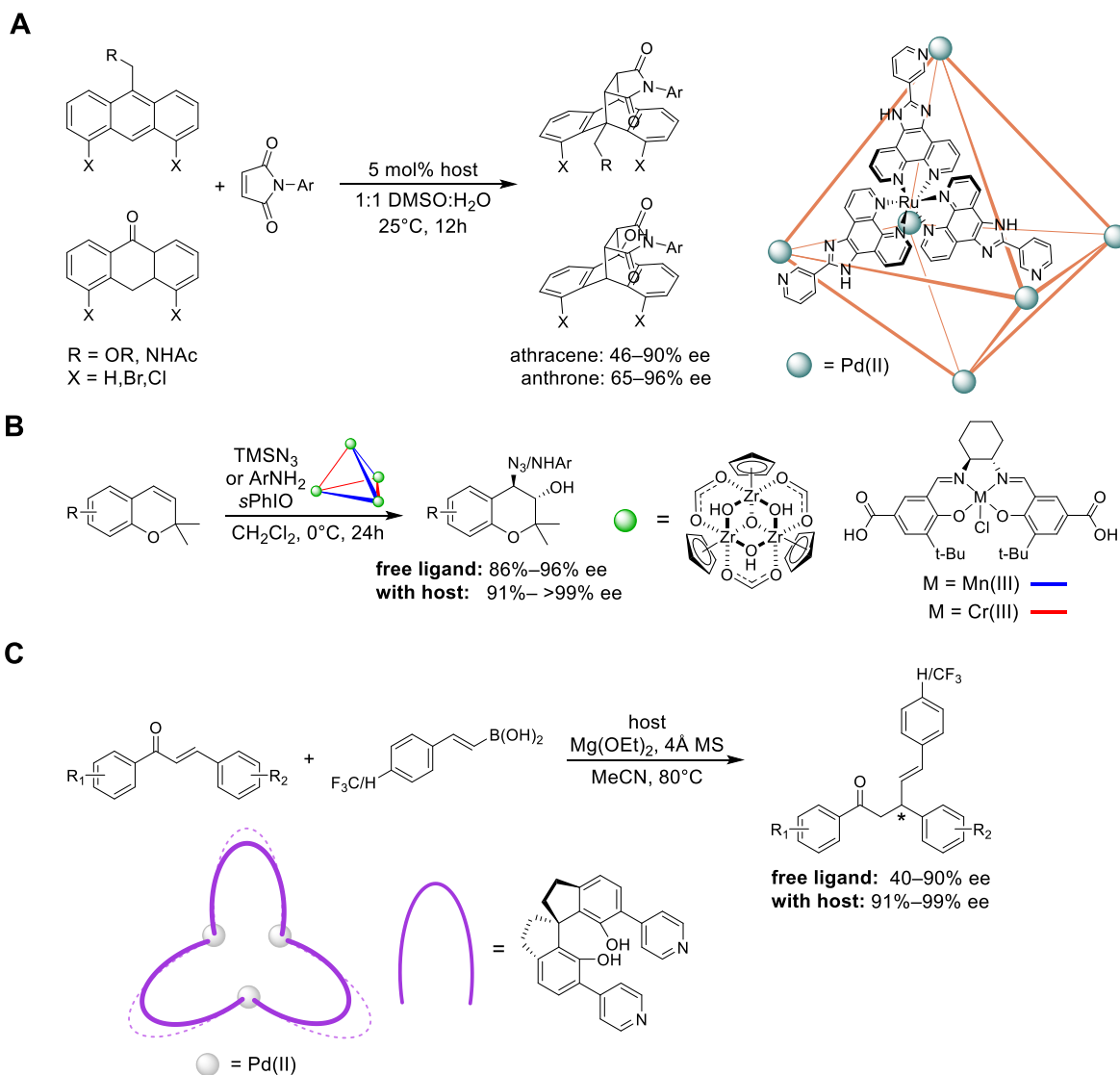


Figure 1.4. Examples of chiral small molecule catalysts used as ligands for enantiopure supramolecular catalysts. **A)** Application of a Ru photocatalyst as an acid-base catalysts for Diels Alder reactions of anthracenes. **B)** Heteroleptic Zr-based hosts featuring Mn(salen) and Cr(salen) ligands for epoxidation and subsequent ring openings. **C)** $\text{Pd}_3\text{L}_6^{6+}$ host featuring SPINOL-based ligands for addition of styrenylboronic acids to chalcones.

A third, related approach is through the use of a chiral host with a catalytically active but achiral catalyst incorporated into the host scaffold. The host scaffold may or may not be catalytically active in other contexts but is not catalytically active for the reaction of interest in the absence of the co-catalyst. This approach is perhaps most akin to that utilized in transition metal catalysis in which the host is effectively a chiral ligand bound to the nearby site of catalysis. Covalent cages, particularly cyclodextrins, have been the predominant class of supramolecular hosts to utilize this approach. Although CDs are already chiral, the addition of a co-catalyst enables a wider range of reactions to exploit confinement-driven reactivity and selectivity. Early reports with capped cyclodextrins used appended phosphine ligands for Rh-catalyzed hydrogenations.^{39,40} Rather than reactivity occurring in the CD cavity, the distally appended host primarily acted as another bulky chiral ligand. Reports generally found the steric clash of these ligands afforded moderate to high enantioselectivity for olefin hydrogenations³⁹ and hydroformylations⁴⁰ but were generally less selective than state-of-the-art ligands. Similar behavior was concurrently reported with calix[4]arenes for Rh-catalyzed olefin hydrogenations and Pd-catalyzed allylic alkylations.⁴¹

Efforts were eventually directed towards catalysis within the host cavity, first through functionalization of aperture of the CD scaffold. Sollogoub and coworkers designed α -CDs featuring diphenylphosphine groups at the top edge of the cavity for coordination to a metal catalyst.⁴² When $[\{Pd(\eta^3-C_3H_5)Pd(\mu-Cl)\}_2]$ was added to solution as a Pd(0) precatalyst in the presence of *N,O*-bis(trimethylsilyl)acetamide and AcOK, the Tsuji–Trost allylic alkylation of 1,3-diphenylallyl acetate with dimethylmalonate occurred, albeit in low levels of enantioselectivity. This report served as proof-of-concept for the application of functionalized or capped CDs for transition-metal catalyzed reactions. Armspach and coworkers then reported the incorporation of monophosphane groups into α - and β -CDs to generate unsymmetrical CDs.⁴³ Addition of $[Rh(acac)(CO)_2]$ facilitated the *in situ* generation of a Rh–host species capable of hydroformylation. NMR spectroscopy suggested the functionalized β -CD formed in such a way that the CO ligand protruded out of the host cavity, while the α -CD formed such that the CO ligand protruded into the host cavity. While different reactivities and selectivities might be expected based on differences in catalyst position within the host structure, independent subsection of each host found that the optimal conditions for both hosts were identical and the products were formed in nearly identical levels of regioselectivity, with the branched product being heavily favored, and nearly identical levels of excellent enantioselectivity.

Soon after, work focused on promoting catalysis inside the CD cavity by tethering a ligand between 2 of the amylose groups of the host to suspend a small molecule catalyst into the cavity. *N*-heterocyclic carbenes (NHCs), have been explored extensively towards this aim with α - and β -CDs. These M–NHC complexes bridge the top of the cyclodextrins such that the metal catalysts suspended within the host cavity to enforce confinement-driven reactivity and selectivity. Sollogoub and coworkers first reported the ability to use an Au-imidazolium NHC-capped perbenzylated CD for cycloisomerizations of *N*-tethered 1,6-enynes in the presence of $AgSbF_6$ salts (**Figure 1.5A**).²⁰ Although only moderate enantioselectivities were observed, the larger NHC-capped β -CD afforded the desired product in higher selectivity than the more sterically compact functionalized α -CD. Subsequent studies expanded the scope of NHC-capped CDs synthesized to include Cu,

Ag, and Au-NHC α , β , and γ -CDs.⁴⁴ Although the electronics of the NHC were found to have little effect on stereochemical outcome of the reaction, the size and shape of the cyclodextrin cavity proved influential. Again, the β -CD was found to be optimal for enantioselectivity, with α -CD showing decreased selectivity and γ -CD demonstrating further suppressed selectivity (**Figure 1.5A**). X-ray crystallography and DFT studies point to the importance of a groove in the cyclodextrin cavity in which the alkene and alkyne overlap. Unfavorable steric clashes unique to the β -CD cavity guides formation to the given enantiomer. Armspach, Bentouhami and coworkers likewise reported the enantioselective cycloisomerization of *N*-tethered 1,6-enynes using an Au-benzimidazolium NHC-capped permethylated α -cyclodextrin.⁴⁵ The previously reported benzyl groups were exchanged with methyl groups to improve guest access to the host cavity, but only low to moderate enantioselectivities were observed. Mechanistic investigation pointed to the importance of using a C_2 -symmetric host, which gives rise to further steric bias during the transition state to promote successful enantioinduction.

Following this work, Sollogoub and coworkers then turned attention to other reactions possible using these scaffolds and reported Au-imidazolium NHC-capped perbenzylated β -CDs could also be used for alkoxy cyclizations.⁴⁶ When dimethyl 2-(3-methylbut-2-en-1-yl)-2-(prop-2-yn-1-yl) malonate was employed with MeOH, the exo alkoxy cyclization product was formed exclusively in excellent enantioselectivity. However, other protic co-solvents, H₂O, *i*-PrOH, and BnOH, afforded a mixture of the 5-membered alkoxy cyclization product and 6-membered cycloisomerization product, and the desired alkoxy cyclization product suffered lower selectivity relative to the MeOH-derived product. When *N*-tethered 1,6-enynes were used instead, only the alkoxy cyclization product was formed, irrespective of the starting alcohol. After excluding electronic effects, steric effects based on CD cavity size and the relative size and nucleophilicity of the alcohol were determined to guide enantioinduction. In light of this, Sollogoub and coworkers then utilized Au imidazolium NHC-capped permethylated α - and β -CDs for a number of reactions in aqueous solutions, including enantioselective cycloisomerizations and hydroxycyclization of 1,6-enynes.⁴⁷ When results were compared to those of previously reported NHC-capped CDs for Au-catalyzed cycloisomerizations of *N*-tethered 1,6-enynes, enantioselectivity was noticeably improved for both the α - and β -CD, affording the desired product in modest and good enantioselectivity, respectively. Likewise, enantioselectivity for the hydroxycyclization of dimethyl 2-(3-methylbut-2-en-1-yl)-2-(prop-2-yn-1-yl) malonate was improved. While the α -capped CD gave only moderate enantioselectivity, β -capped CD afforded the desired product in excellent enantioselectivity. Notably, no cycloisomerization byproduct was observed and the AgSbF₆ salt previously required for other CD-catalyzed cyclizations was found unnecessary for selectivity. Simultaneously, Sollogoub and coworkers also reported imidazolium-NHC perbenzylated α - and β -CDs could be paired with a monomeric Cu-H species for hydrosilylation.⁴⁸ The NHC-capped α -CD afforded the desired product from acetophenone in high enantioselectivities with various silanes, but β -CD afforded only modest selectivity. When benzylideneacetone and some functionalized derivatives were similarly subjected to both hosts, the functionalized α -CD afforded exclusively the α , β -unsaturated alcohol product, formed *via* a 1,2-addition, in a range of very low to high enantioselectivities. However, when the functionalized β -CD was employed under identical conditions, the fully saturated alcohol product was formed in very low to modest

enantioselectivity (**Figure 1.5B**). Lowering the stoichiometry of silane in the presence of the β -CD afforded the ketone product, formed *via* a 1,4-addition. Computational studies investigating the mode of enantioinduction suggest that product selectivity arises from cavity shape, which precludes certain conformations within the cavity of the cyclodextrin. Furthermore, stabilizing hydrogen bonds between the C–H groups of the CD cavity and the ketone O also appear to play a role.

Cyclodextrins and inherently chiral, functionalized calix[4]arenes have also been similarly used to incorporate organocatalysts into the host scaffold. Shimizu and coworkers first reported a chiral calix[4]arene-based host featuring a pendant hydroxyl group and tertiary amine, which upon crystallization with mandelic acid, enabled separation of the host diastereomers.⁴⁹ The amine group was utilized to promote the Michael addition of thiophenol to 2-cyclohexen-1-one, although low levels of enantioinduction were observed with each enantiomer of host (**Figure 1.5C**). Shortly after, a per-6-amino- β -cyclodextrin was reported by Pitchumani and Suresh which could catalyze Michael additions to chalcones.⁵⁰ Poor enantioselectivity was observed with addition of nitromethane to benzylideneacetone, but chalcones were tolerated and afforded products in typically modest to good enantioselectivity, although some sensitivity to substrate sterics on the phenylacetyl group ring were observed. Aliphatic thiols could also serve as nucleophiles; while no disulfide was observed, the resulting products demonstrated generally poor enantioselectivity.

Enantiopure metal-organic cages can also be employed with achiral small molecule catalysts for enantioselective catalysis. Nguyen, Hupp and coworkers reported the use of a mixed-metal porphyrin-based box which self-assembled under reaction conditions. Chirality was imparted through distal chiral amino acids on the Sn porphyrin serving as the two sides of the host, and a catalytically active, achiral Mn-based porphyrin stretched across the middle of the cavity. Although only very low enantioselectivity was achieved for the sulfoxidation of methyl *p*-tolyl sulfide, this approach served as an early proof of concept for through-space chirality transfer in metal-organic cage systems (**Figure 1.5D**).⁵¹

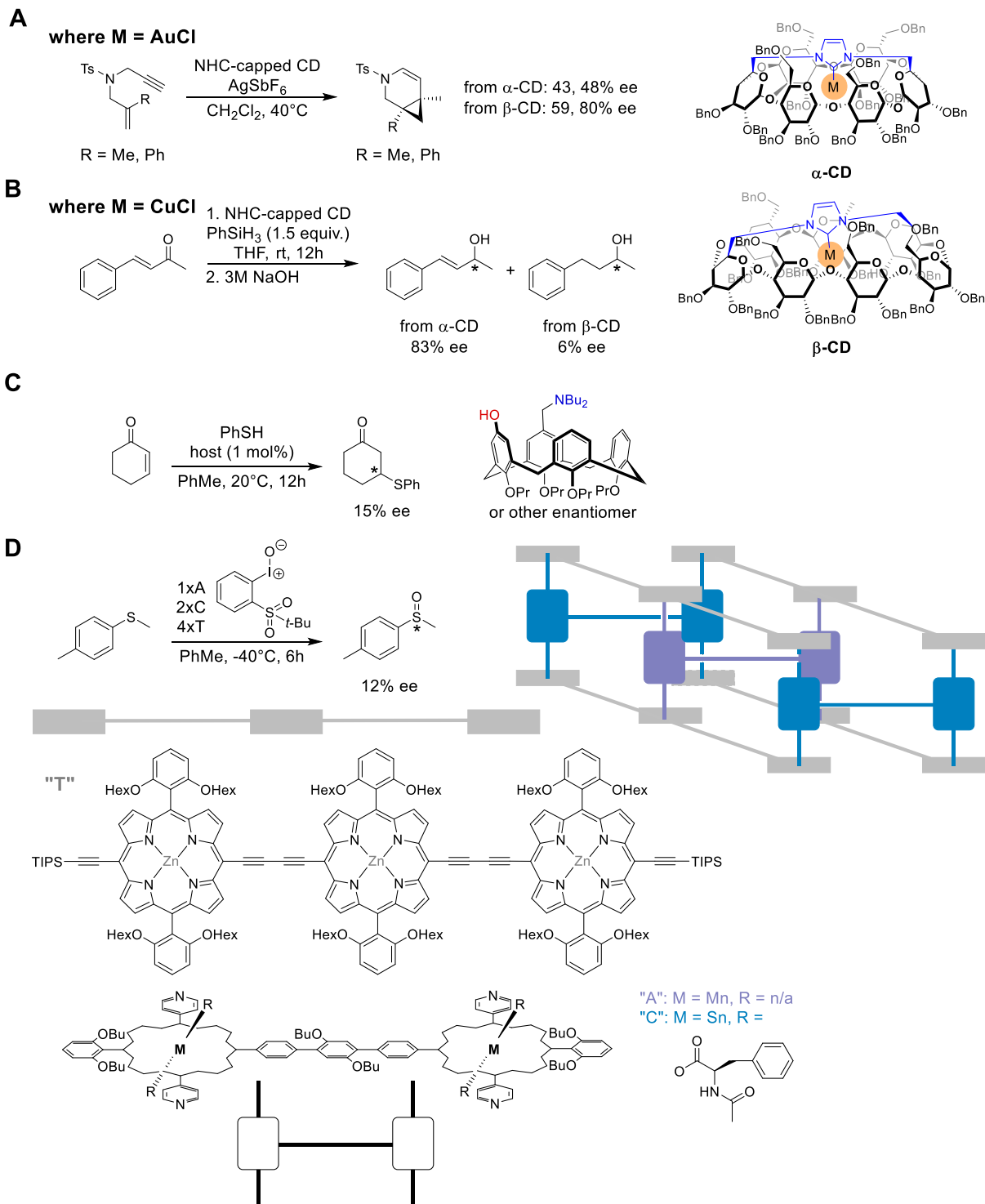


Figure 1.5. Representative examples of achiral small molecule catalysts appended to enantiopure supramolecular hosts for catalysis. **A)** Au imidazolium-NHC capped perbenzylated α - and β -CD for cycloisomerizations of 1,6-enynes. **B)** Host dependent product formation in hydrosilylations using Cu-H imidazolium-NHC capped perbenzylated α - and β -CD. **C)** Inherently chiral functionalized calix[4]arene-based host for Michael additions to cyclohexanone. **D)** Self-assembling chiral box applied for S-oxidations.

1.3 Enantiopure, Catalytically Active Supramolecular Hosts Applied for Enantioselective Catalysis

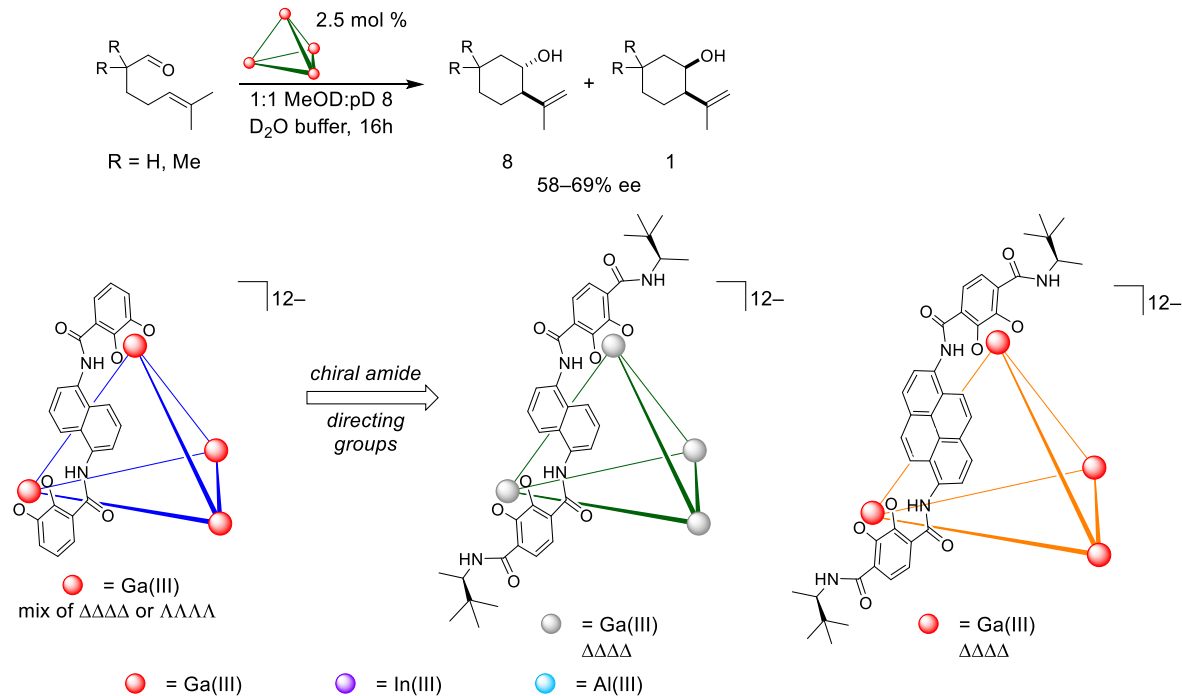
The use of enantiopure hosts to enforce chirality is another type of approach towards asymmetric catalysis within supramolecular hosts. Such an approach relies upon a distinct mode of enantioinduction in which the source of the chirality does not directly engage the substrate through covalent bonds. Because of this and the lack of a specific small molecule catalyst incorporated in the scaffold, these scaffolds may allow for more promiscuous applications of these hosts to numerous reactions. However, this approach is comparatively understudied within asymmetric supramolecular catalysis. Host design is a substantial challenge for this approach; even though the host itself is catalytically active, it is *a priori* unclear whether highly enantioselective reactivity can be achieved for a given transformation since the source of chirality is remote from the reaction site. With very little known about mechanisms of self-assembly or the interactions important in these systems for enantioinduction, designing a host capable of catalyzing one or multiple reactions with good enantioselectivities can be prohibitively difficult.

Early work towards asymmetric catalysis in enantiopure hosts focused on the use of cyclodextrins in thermal^{52,53} and photocatalyzed reactions.^{54–58} Since the 21st century, metal-organic coordination cages which lack chiral small molecule catalysts in their scaffold have been explored in thermal reactions. While many metal organic cages are inherently chiral, they are generally formed as a racemic mixture due to a lack of chiral information present during self-assembly. Isolation of a single enantiomer of host, however, is possible through two approaches. Less commonly, ligands generally utilized to form racemic host can be employed and one enantiomer of host is preferentially stabilized and isolated. Raymond, Bergman and coworkers have utilized this approach for an enantioselective aza-Cope rearrangement.^{59,60} A nicotinium salt which associates with the exterior of the racemic host to form diastereomers enabled separation and isolation of $\Delta\Delta\Delta$ and $\Lambda\Lambda\Lambda$ $\text{NMe}_4^+\text{host}$ using ion exchange chromatography.⁵⁹ Subjecting this host to aza-Cope rearrangement conditions enabled very low to good enantioselectivity. However, this approach is time-consuming and requires that the nicotinium salt remain coordinated to host to prevent host racemization.

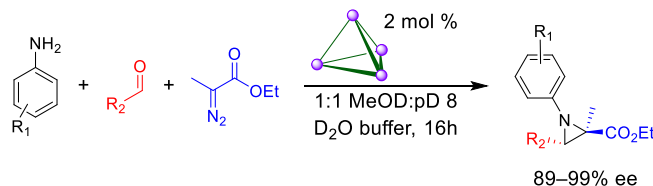
Alternatively, the use of chiral auxiliary groups incorporated into the ligand structure can give rise to inherently enantiopure hosts. Inspired by Fujita's use of chiral auxiliaries at the metal center to form an enantiopure host,⁶¹ Raymond, Bergman, Toste and coworkers employed a similar approach to their $\text{M}_4\text{L}_6^{12-}$ tetrahedral cages through the installation of distal chiral *t*-Bu-based amide groups at the ligand apices to render an enantiopure host.⁶² The host was used to catalyze an enantioselective Prins cyclization in moderate enantioselectivity (**Figure 1.6A**)⁶² and was also to impart stereoretention in a $\text{S}_{\text{N}}1$ reaction of trichloroacetimidates.⁶³ Although precise interactions involved in enantioinduction are unknown, cation- π interactions are speculated to play a role in the stereoretentive $\text{S}_{\text{N}}1$ reaction by stabilizing the cationic intermediate formed.⁶³ Changing the spacer group of the ligand from naphthalene to pyrene is possible but was found to erode enantioselectivity in the Prins cyclization, likely due to a loss of constrictive binding (**Figure 1.6A**).⁶⁴ Very recently, the development of an expanded host library featuring additional chiral amide groups and other Group 13 metals (Al, In) enabled tuning of selectivity in an aza-Darzens condensation to form aziridines in excellent

enantioselectivities.⁶⁵ In this reaction, it was found that hosts with higher guest exchange rates, particularly an $\text{In}_4\text{L}_6^{12-}$ with a *t*-Bu amide, were optimal for enantioinduction in these systems (**Figure 1.6B**). Toste and coworkers hypothesize this is due to the ability of guests to exchange more rapidly to find optimal, favorable interactions within the host.

A



B



C

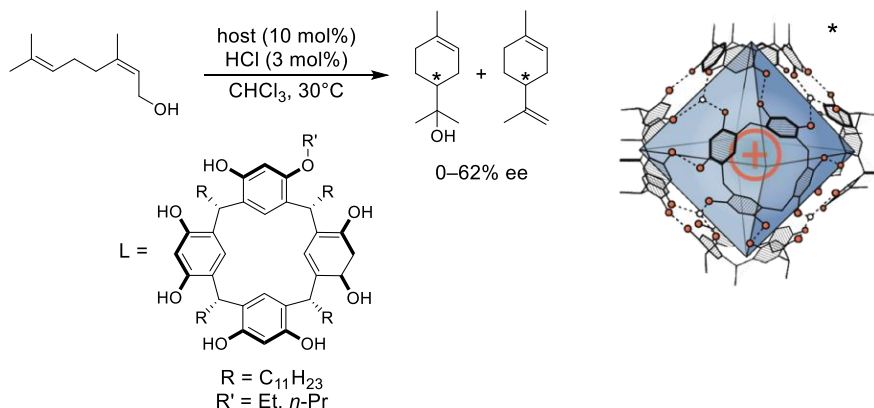


Figure 1.6. Representative examples of catalysis using catalytically active enantiopure supramolecular hosts. **A)** Prins cyclization catalyzed by an enantiopure $\text{Ga}_4\text{L}_6^{12-}$ host. **B)** Aza-Darzens condensation catalyzed by an enantiopure $\text{Ga}_4\text{L}_6^{12-}$ or $\text{In}_4\text{L}_6^{12-}$ host. **C)** Endo-

to-end terpene cyclization catalyzed by an enantiopure resorcin[4]arene-based hydrogen bonding cage.

Recent work has explored the possibility of enantioselective catalysis in hydrogen-bonded enantiopure hosts. Tiefenbacher and coworkers have used a chiral hexameric resorcin[4]arene-based host for terpene cyclizations of nerol. Modification of the resorcinarene by introducing chiral groups either to the benzylic linkers or “feet” of the ligand or by monoalkylation of one phenol group of the ligand led to assembly of chiral hosts. While the chiral feet hosts and the *n*-butyl monoalkylated host were unable to impart selectivity, the *n*-propyl monoalkylated host provided limonene and α -terpineol in good and moderate enantioselectivity, respectively (**Figure 1.6C**).⁶⁶ Notably, the host was found to be more selective than Jacobsen’s state-of-the-art urea catalyst.⁶⁷

1.4 Outlook and Conclusions

When compared to conventional small molecule catalyst scaffolds, examples of enantioselective catalysis using supramolecular hosts in the literature are few and generally focused on the ability of host molecules to catalyze well-understood reactions in order to test the capabilities of these systems. Among the range of approaches for catalysis, the primary thrust of work in this field has largely explored the ability of supramolecular cages to impart selectivity in cooperation with highly active, chiral small molecule catalysts. However, many reports currently lack the high degree of enantioselectivity often observed with state-of-the-art small molecule catalysts or demonstrate no improvements in enantioselectivity when host+small molecule catalyst are employed over baseline selectivity afforded by the small molecule catalyst alone. Although the modes of activation and key interactions involved in enantioinduction for these reported small molecule catalysts are more generally understood, there are still many questions as to the role of host in enantioinduction and the precise interactions involved. Existing studies on cyclodextrins and similar covalent organic cages point to the importance of steric interactions within the host cavity and potential hydrogen-bonding interactions involved. However, these scaffolds have limited handles to improve enantioinduction, limiting their potential use.

A growing body of work has explored the use of coordination cages in this context, perhaps due to their increased potential handles for optimization. While principles governing chemo- and regioselectivity observed in racemic systems may help guide initial investigations into enantioinduction, extensive work is needed to understand enantioselectivity in these systems. Current reports propose potential host-guest interactions involved in enantioinduction but minimal work has been reported towards more direct interrogation. Further, it is not clear whether the principles observed in covalent cages are unique to those scaffolds or may be more broadly applicable. The high degree of complexity of coordination cages complicates both experimental and computational efforts towards this aim. However, the ability to effectively utilize the non-covalent interaction-rich environment of supramolecular hosts could render these assemblies as highly selective asymmetric catalysts which complement existing catalyst scaffolds, making work in this area of both fundamental and practical significance.

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Chapter 2

A Brief Overview of Enantioselective Oxime Reductions

2.1 A Brief Introduction to Oximes and Hydroxylamines

Oximes are composed of an imine type C=N double bond but feature an –OH/R group rather than a –H or –R group bonded to the *N* as are found in imines. As such, they are also structurally related to hydrazones and nitrones. Oximes are most commonly synthesized from carbonyl compounds through a condensation with a hydroxylamine.¹ When synthesized from an unsymmetrical ketone or aldehyde, the resulting oxime can take on either the (*E*) or (*Z*) isomeric forms, and is often formed as a mixture of the two (**Figure 2.1**). Due to their N–OH group, oximes are capable of acting as a weak acid or base.² Furthermore, both the *N* and *O* atoms are nucleophilic, and the *N* is generally the most basic site of the molecule.^{2,3} This basic nitrogen, when protonated, increases the relative electrophilicity of the adjacent *C* and can make these compounds more reactive compared to carbonyl compounds, which are not as easily protonated.³ However, the identity of the atoms connected to the nitrogen can greatly influence reactivity. Most notably, the *O* atom of the oxime makes it less susceptible to nucleophilic attack than imines due to inductive effects and increased resonance.⁴ The oxime scaffold can be found in a variety of natural products and medicinally relevant compounds, and oxime isomer has been found to play an important role in biological activity.^{2,3,5} Beyond their biological importance, oximes are synthetically versatile and can be converted to a range of products, including amines, hydroxylamines, amides, nitroalkenes, and azole-type heterocycles.²

Very similar to oximes, hydroxylamines feature a single C–N bond as well as an –OH/R group attached to the *N* atom. This motif can be synthesized through a variety of approaches, including alkylations of more simple hydroxylamines,⁶ reductions of oximes⁷ or nitrones,⁸ addition to oximes, nitrones, or similar nitroso compounds,⁶ or through the oxidation of amines.⁹ Much like oximes, the *N* atom is the most basic site of the molecule, though it is still considered weakly basic.⁶ Hydroxylamines are likewise of synthetic value due to their presence in a number of natural products, pharmaceuticals, and agrochemicals.⁶ They can also be used en route to other *N*-based functional groups for synthesis or ligand design.

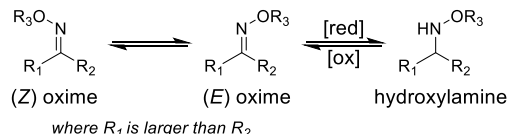


Figure 2.1. Structure of oximes and hydroxylamines.

2.2 An Overview of State-of-the-Art Approaches for Enantioselective Oxime Reductions to Hydroxylamines

Enantioselective reductions play a key role in the synthetic toolbox of chemists. Since the latter half of the 20th century, extensive efforts have enabled highly selective reductions of many functional groups using state-of-the-art transition metal catalysts and organocatalysts.^{10–12} Among ketone and imine-type functional group reductions, which are of much synthetic value and interest, are oxime reductions to hydroxylamines. Although hydroxylamines are becoming increasingly prevalent in drugs and

agrochemicals and can be used en route to a number of bioactive compounds,^{13,14} they are generally currently available as racemates. Given the ubiquity and importance of chirality in biological systems,^{15–17} there is a need for development of methodology in this area, but the synthetic challenge posed by high degree of lability of oxime N–O bonds relative to their C=N bonds has likely hindered progress. Rather than the hydroxylamine product, metal-catalyzed approaches typically yield the primary amine overreduction product or a mixture of the desired hydroxylamine and undesired primary amine.^{7,18–23} Consequently, unlike the well-established transition-metal catalyzed asymmetric reductions of imines and enamines,^{12,24} the metal-catalyzed asymmetric hydrogenation of oximes to hydroxylamines remains a comparatively unsolved challenge. Stoichiometric reductions with chiral boranes are possible but likewise suffer from mixtures of the desired hydroxylamine and the overreduction product.^{25–27}

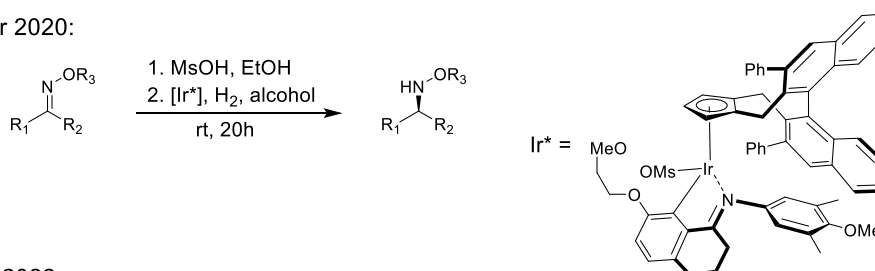
While stoichiometric amounts of achiral boranes can successfully mediate racemic reductions without overreduction, catalytic oxime reductions, whether racemic or enantioselective, have largely been a challenging reduction. A 2007 patent from Evonik Degussa GmbH reported the use of Rh catalysts featuring chiral Josiphos-type ligands for the hydrogenation of β -oxime esters with some degree of enantioselectivity.²⁸ However, these oximes can tautomerize, so reduction may proceed through tautomerization and reduction of the enamine rather than true oxime reduction.²⁹ In 2014, Oestreich and coworkers reported the application of $B(C_6F_5)_3$, an achiral boron Lewis acid catalyst, and H_2 towards racemic oxime reductions. This borane was selected due to its ability to generate borohydrides catalytically *in situ*. Free oximes and small oxime ethers were very poorly reactive or unreactive under these conditions, but oxime ethers featuring *t*-Bu or tri-isopropylsilyl (TIPS) groups were well-tolerated. Subsequent removal of the TIPS group furnished the free hydroxylamine product.³⁰ These reports, though not examples of enantioselective oxime reductions to hydroxylamines, served as proof-of-concept for the catalytic reductions of oximes to hydroxylamines.

In 2020, Cramer and coworkers reported the first transition-metal catalyzed asymmetric hydrogenation of oximes to hydroxylamines using a preformed Ir catalyst with bespoke ligands. Although free oximes were tolerated, oxime ethers were reduced with a higher degree of enantioselectivity, with oximes reported being generally reduced in good to high enantioselectivities (**Figure 2.2A**). Protonation of the oxime with MsOH before addition of the Ir catalyst activated the substrate for reduction. Two reaction regimes were presented – one in which subjecting a single isomer of oxime proved to give highest enantioselectivities and one in which (*E*):(*Z*) oxime mixtures were tolerated. When benzylic and bulky dialkyl oximes were utilized, (*E*):(*Z*) isomerization was found to be slow relative to reduction. Reactions proceeded through the thermodynamically more stable isomer, typically the (*E*) isomer, while the thermodynamically disfavored isomer was found to display lower levels of reactivity and enantioselectivity. Other oximes, particularly α -aryl and heteroaryl oxime ethers, could be subjected as mixtures while still displaying good levels of selectivity. For these substrates, (*E*):(*Z*) isomerization was found to be more rapid relative to reduction. Interestingly, in these instances, (*E*) oxime isomerized to the more reactive (*Z*) isomer to facilitate selective reduction.³¹ Little is known about the key interactions at play in these reductions, but a hydrogen bonding interaction between the

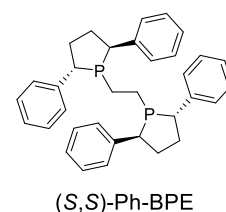
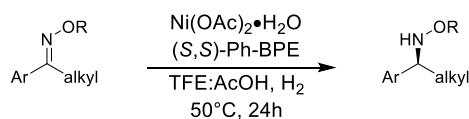
O atom of a pendant 2-methoxyethyl) ether and the oxime is hypothesized to contribute to the reaction.^{31,32}

During the course of our own work on enantioselective oxime reductions (see **Chapter 3**), a Ni-catalyzed method³³ and a second Ir-catalyzed method³⁴ were reported. Zhang and coworkers' use of Ni with (S,S)-Ph-BPE ligands enabled the reduction of α -aryl oximes in generally excellent enantioselectivities (**Figure 2.2B**). Oxime ethers and free oximes were generally reduced in good to excellent enantioselectivities. The geometry of the oxime was found to be critical to the high selectivities observed. Pure (*E*) oxime isomers gave the highest degree of enantioselectivities, while (*E*):(*Z*) mixtures led to a slight decrease, and pure (*Z*) isomer gave further decreased selectivity. Further controls indicated oxime isomerization occurred under reaction conditions due to the presence of AcOH, and that the reactivity of (*Z*) oxime was comparatively sluggish relative to the (*E*) isomer. It was hypothesized that the eroded selectivity observed with mixtures or when (*Z*) oxime was subjected to solution was therefore due to slow but concurrent reactivity of the (*Z*) isomer to the other product enantiomer. DFT indicated the poor reactivity of (*Z*) oximes was likely due to $-OH-\pi$ interactions within the oxime on the side chain phenyl group, which would preclude the substrate from sufficient interaction with the catalyst. Reactivity of the (*E*) isomer was facilitated by C-H- π and $\pi-\pi$ interactions between the aryl group of the oxime and phenyl groups of the Ph-BPE ligand. This may partially explain why heterocyclic, benzylic, and dialkyl oximes were found to be poorly reactive or give poor enantioselectivities under these conditions. Due to the very limited overlap in scope with Cramer's catalyst system, this approach was argued to be a viable catalyst system for complementary reactivity and expand the scope of oximes reducible with high selectivity.³³ Later that year, a second Ir-catalyzed method was reported by Yu,

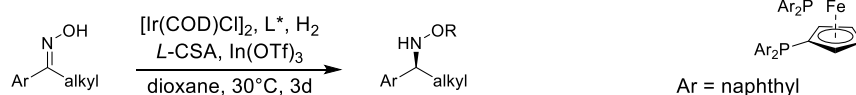
A) Cramer 2020:



B) Zhang 2022:



C) Chen & Yu 2022:



Ar = naphthyl

Figure 2.2. (A) Seminal report by Cramer and coworkers' on the use of a bespoke $[Ir^*]$ catalyst, (B) Zhang and coworker's use of a Ni catalyst and Ph-BPE ligands, and (C)

Chen and Yu's use of an [Ir*] catalyst with Lewis and Brønsted acid additives for enantioselective oxime hydrogenations.

Chen and coworkers which relied on tandem cooperativity of Lewis and Brønsted acid additives to facilitate hydrogenation. More specifically, an Ir catalyst with ferrocene–thiourea dinaphthylbisphosphine ligands was used with *L*-camphorsulfonic acid (*L*-CSA) to protonate the oxime as well as Zn(OAc)₂ or In(OTf)₃ to reduce α-aryl and heteroaryl oximes in moderate to high enantioselectivity (**Figure 2.2C**). DFT calculations suggest the Lewis acid is coordinates to the S of the thiourea to improve enantioselectivity through sterics.³⁴

2.3 Outstanding Challenges

These reports constitute substantial progress toward enantioselective oxime reductions to hydroxylamines but are largely limited to aryl and heteroaryl oximes. Very few examples are provided which showcase aliphatic oximes,³¹ presumably due to the need for π-type interactions, including π–π and CH–π interactions, with the ligand scaffold.³³ Existing metal catalysts appear to be catalytically active for these reductions, but the absence of these substrates from published reaction scopes implies they are reduced in very low to no enantioselectivities.^{29,31,33} Additionally, examples of heterocyclic oximes are limited and entirely lack *N*-containing heterocycles, presumably due to the propensity for basic nitrogens to coordinate with metal centers and poison the catalyst.³⁵ Therefore, there is certainly room for continued work within this space to further expand the scope of oximes reducible to hydroxylamines in an enantioselective fashion. Due to the heavy reliance on unfavorable steric clash for selectivity within asymmetric transition metal catalysis,^{36,37} alternative catalytic scaffolds which better utilize non-covalent interactions could be particularly appealing to address this challenge. Such catalytic platforms are also generally not poisoned by basic functionalities and might therefore present other advantages over metal catalysts. The unique features of supramolecular hosts might enable them, among other catalyst scaffolds, to act as a potential platform to broaden reaction scope.

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Chapter 3

Initial Steps Towards Probing Enantioinduction in Supramolecular Hosts Through Asymmetric Oxime Reductions

3.1 Preface

This chapter describes the development and elaboration of methodology for the enantioselective reduction of oximes to hydroxylamines catalyzed by an enantiopure $\text{Ga}_4\text{L}_6^{12-}$ supramolecular host. Particular emphasis is directed toward gaining insight into the modes of enantioinduction in the host with these substrates. Well-tolerated substrates were reduced in selectivities comparable to or greater than those reported with state-of-the-art catalysts. Furthermore, substrate types not currently accessible using reported methods were successfully reduced. Reaction scope and mechanistic study informed resulting data science analysis of potential interactions in the catalytic system. In addition to steric effects, exhibited through a high degree of size and shape recognition, electronic effects were also found to be important for enantioinduction of some substrates. This work serves as proof-of-concept for supramolecular hosts' potential to complement existing catalytic scaffolds and sets the foundation for future study into the mechanism of enantioinduction in these hosts. This work was done in collaboration with fellow graduate students Cristina Craescu, who contributed to the experimental work, and Andrew Smith, who performed computations and data science analysis.

3.2 Introduction to $\text{Ga}_4\text{L}_6^{12-}$ Hosts for Enantioselective Oxime Reductions

The development of a mechanistic understanding of enantioinduction is critical in asymmetric catalysis for the development of next generation catalysts and methods. Among the most selective catalysts, enzymes have evolved to achieve exquisite selectivity through the synergistic action of an array of highly substrate-specific non-covalent and electrostatic interactions within a confined active site. Despite advancements in directed evolution and protein engineering, widespread adoption of enzymes in asymmetric catalysis is still hampered by the limited range of reactions for which known enzyme counterparts can serve as a starting point for evolution campaigns.¹ On the other hand, chiral small molecule catalysts are generally much more substrate promiscuous and can catalyze a wide range of asymmetric reactions. While their synthetic modularity enables a high degree of tunability, achieving enzyme-like selectivity is inherently challenging since these catalysts generally rely on a limited range of interactions accessible at specific sites on the catalyst to confer selectivity.²⁻⁴ Due to their unique structure and mode of substrate engagement,^{5,6} supramolecular hosts have the potential to complement traditional asymmetric catalyst platforms by leveraging advantageous features of both enzymatic and chiral small molecule catalyst systems to engage a broad range of substrates in a non-covalent interaction-rich synthetic microenvironment (**Figure 3.1A**).

Existing approaches for asymmetric supramolecular catalysis which utilize chiral small molecule catalysts, whether encapsulated⁷⁻¹⁰ or incorporated¹¹⁻¹⁸ within the host scaffold, rely heavily on the mode of activation utilized by the small molecule catalyst, often through covalent bonding. Furthermore, the incorporation of small molecule catalysts into the scaffold results in host structures tailored to the reaction of interest which may not be applied more generally. In contrast, enantiopure hosts lacking chiral small molecule catalysts present an alternative catalytic scaffold with a distinct mode of enantioinduction – reactivity and selectivity is driven solely through non-covalent host-

guest interactions within the cavity. The host scaffold therefore is not specific to a reaction or substrate type and can utilize an ensemble of non-covalent and electrostatic interactions with substrates on a case-by-case basis to achieve selectivity for a range of reactions. The few examples of catalysis among enantiopure hosts have thus far focused largely on the development of new hosts to try to modulate enantioselectivity in well-understood model reactions.^{19–24} Given little is known of the interactions or substrate features important for enantioinduction within these hosts, the development and optimization of highly selective reactions utilizing enantiopure supramolecular hosts remains exceedingly difficult. For example, while host recognition of guest size and shape is understood to be important for guest encapsulation,^{6,25–29} its impact on enantioselectivity has been assumed rather than demonstrated. Interrogation of interactions between host and substrate through systematic study of reaction scope and mechanism is therefore a critical step in the elaboration of asymmetric supramolecular catalysis, but current reports lack the broad substrate scopes necessary to adequately study enantioinduction in these systems.

The enantiopure Raymond $\text{Ga}_4\text{L}_6^{12-}$ tetrahedron, a commonly utilized catalytically active enantiopure host, was identified as a scaffold of particular interest for study (**Figure 3.1B**). Although itself not well-understood, it maintains many of the properties of the well-studied parent racemic $\text{Ga}_4\text{L}_6^{12-}$ host. Its bis-catecholamide-based ligands are structurally analogous to the racemic host but also feature distal chiral amides proximal to the metal centers which reinforce host enantiopurity due to strong mechanical coupling, thereby preventing catalyst racemization events (**Figure 3.1B**).^{20,30} The dodecanionic charge of the host enables its solubility in polar solvents such as water, while the cavity of the host remains hydrophobic, enabling preferential encapsulation and stabilization of hydrophobic and cationic species.^{27,31,32} These properties position the host to promote numerous acid-catalyzed reactions including those proceeding through iminium-type intermediates. For example, a previous report using the racemic $\text{Ga}_4\text{L}_6^{12-}$ host towards reductive amination also reported the preparation of a small number of racemic aliphatic hydroxylamines from oximes.⁵

In light of the challenges of oxime reductions and the limited examples of their enantioselective hydrogenation using transition metal catalysts,^{33–35} with no examples using organocatalysts (see **Chapter 2**), enantioselective oxime reductions were identified as a reaction of interest. Such a synthetic challenge presents an interesting opportunity to study the capabilities of enantiopure supramolecular hosts as catalytic scaffolds, and success could serve as proof-of-concept for their use in other challenging synthetic transformations. Given the precedent for racemic host-catalyzed oxime reductions, we envisioned reductions of a broad range of oximes in the enantiopure $\text{Ga}_4\text{L}_6^{12-}$ host might help elucidate key interactions involved in enantioinduction, particularly when paired with data science. Data science-based analysis is particularly advantageous over traditional transition-state modeling in these systems due to the highly complex and therefore computationally demanding nature of supramolecular hosts. Although readily utilized in small molecule systems, this would constitute the first use of data science towards understanding enantioselectivity in an asymmetric supramolecular catalyst system.

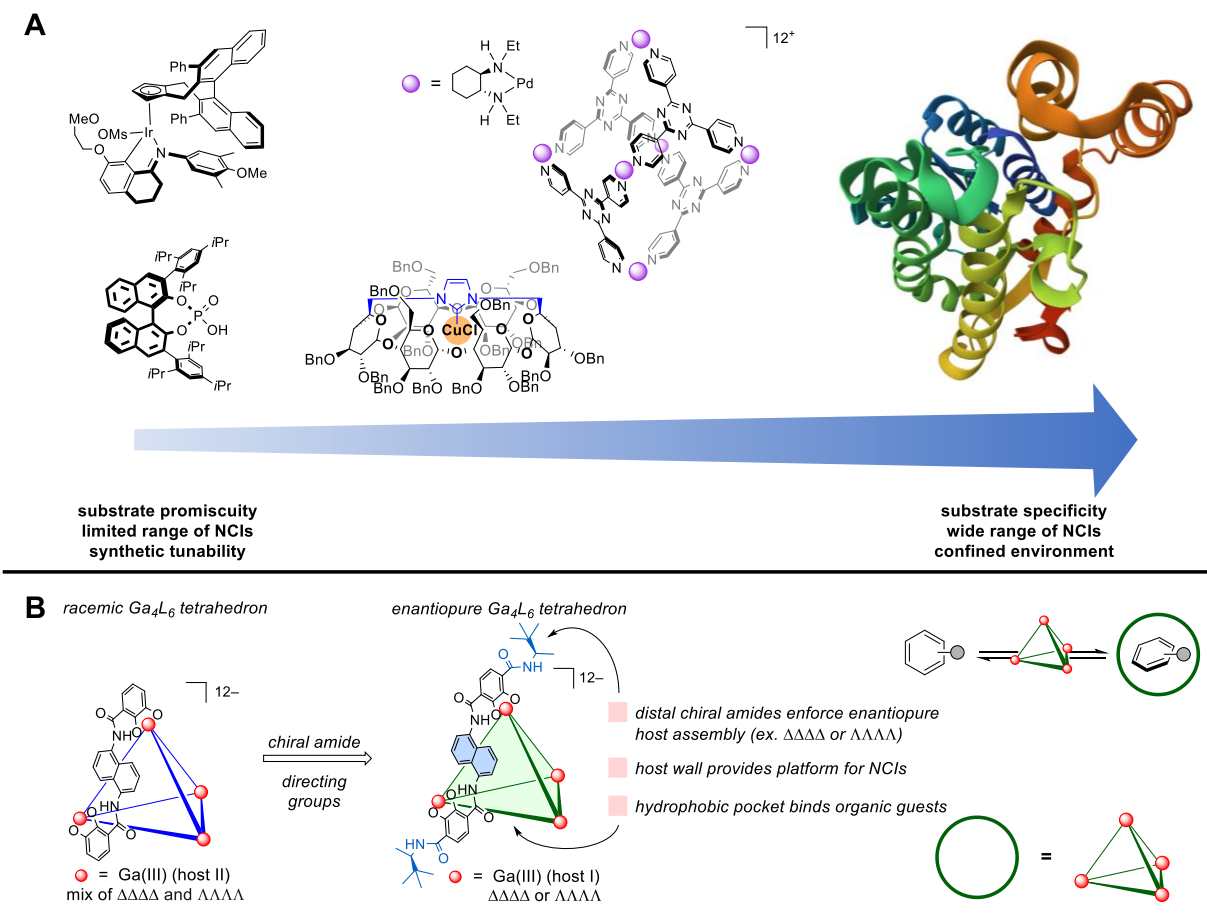


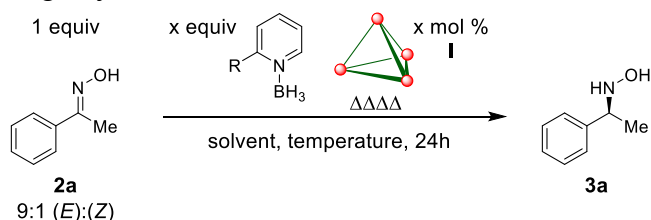
Figure 3.1. (A) Range of homogenous catalysts used in asymmetric catalysis. **(B)** Characteristics of racemic and enantiopure supramolecular M₄L₆^{12−} tetrahedron used here relevant to catalysis.

3.3 Developing the Scope of Enantioselective Host-Catalyzed Oxime Reductions

Based on literature precedent for aryl oxime reductions using transition metal catalysts and aliphatic oxime reductions using the racemic Ga₄L₆^{12−} host, initial work investigated the asymmetric reduction of acetophenone oxime (**2a**) using pyridine borane (**1a**) as reductant within enantiopure Ga₄L₆^{12−} host **I** under air. While host **I** was insoluble in 100 mM K₃PO₄ pH 8 D₂O buffer (**Table 3.1, Entry 1**), unbuffered D₂O yielded moderate amounts of the desired hydroxylamine in high enantioselectivity (**Table 3.1, Entry 2**). Under both reaction conditions, the oxime was found to be generally largely insoluble at the start of the reaction, but solubility improved over the course of the reaction. However, the reactions were generally not sufficiently homogenous to allow for NMR analysis, so CDCl₃ was used to extract and analyze the product. Notably, no overreduction to the corresponding amine was detected. Addition of co-solvents, however, did not improve reactivity (**Table 3.1, Entries 3–4**), while inclusion of lower concentrations of buffered D₂O (**Table 3.1, Entries 11–14**) and modulating temperature (**Table 3.1, Entry 3**) had minimal effect on yield and enantioselectivity. Further optimization identified that increased

pyridine borane and decreased host loading afforded (S)-1-phenylethylhydroxylamine (**3a**) in good yields and excellent enantioselectivity (**Table 3.1, Entries 6–9**). Attempts at increasing steric bulk within the host cavity using 2-methylpyridine (picoline) borane (**1c**) had minimal effect on enantioselectivity and substantially decreased yields (**Table 3.1 Entry 10**), likely due to limited borane solubility.³⁶ Comparable reactivity and high enantioselectivity was observed when using $\Delta\Delta\Delta\Delta$ host (**Table 3.1, Entry 15**), and H₂O, rather than D₂O, as solvent was tolerated (**Table 3.1, Entry 16**). Control reactions with pyridine borane in the absence of host and with host whose cavity was blocked by very strongly binding tetraethylphosphonium iodide (PEt₄I) showed no or trace conversion in

Table 3.1. Optimization of pyridine borane (**1a**)-mediated asymmetric oxime reductions catalyzed by host **I** using aryl oxime **2a**.



Entry	Solvent	Temp (°C)	R	Borane Equiv	Host Loading (mol %)	Yield(%) ^a	ee (%)
1	100 mM pD 8 K ₃ PO ₄ D ₂ O buffer	rt	H	1.1	8.5	nd	nd
2	D ₂ O	rt	H	1.1	8.5	55	94 ^b
3	D ₂ O/10% EtOH	rt	H	1.1	8.5	16	nd
4	D ₂ O/1% EtOH	rt	H	1.1	8.5	28	nd
5	D ₂ O	5	H	1.1	8.5	55	95
6	D ₂ O	rt	H	2	8.5	70	96
7	D ₂ O	rt	H	3	8.5	88	95
8	D ₂ O	rt	H	1.1	5	65	93
9	D₂O	rt	H	3	5	77	97
10	D ₂ O	rt	Me	3	5	10	93
11	20 mM pD 7 K ₃ PO ₄ D ₂ O buffer	rt	H	3	5	56	91
12	20 mM pD 8 K ₃ PO ₄ D ₂ O buffer	rt	H	3	5	55	94
13	20 mM pD 9 K ₃ PO ₄ D ₂ O buffer	rt	H	3	5	83	94
14	20 mM pD 11 K ₂ CO ₃ D ₂ O buffer	rt	H	3	5	73	95
15	D ₂ O ^c	rt	H	3	5	80	97
16	H ₂ O ^c	rt	H	3	5	65	94

^a NMR yields from CDCl₃ extract relative to internal standard ^b Average of 3 runs. ^c $\Delta\Delta\Delta\Delta$ host was used

D₂O using oxime **2a**. This is consistent with required co-encapsulation of pyridine borane and oxime within the host cavity for catalysis.

Encouraged by these results, attention was turned to 2-pentanone oxime (**2b**). Subjecting the oxime to conditions similar to those optimized for acetophenone oxime **2a** facilitated successful reduction to the desired (*S*)-*N*-(pentan-2-yl)hydroxylamine (**3b**) in modest enantioselectivity but low yields (**Table 3.2, Entry 1**). Given the smaller steric profile of this oxime compared to aryl oxime **2a**, the potential of increasing the steric bulk within host **I** to improve enantioselectivity was examined. However, picoline borane (**1c**) and 4-dimethylaminopyridine borane gave minimal reactivity, likely due to their limited D₂O solubility,³⁶ and large linear steric profile, respectively (**Table 3.2, Entries 2–3**). Lowering reaction temperature and extending reaction time was able to improve selectivity but at the expense of further decreased reactivity (**Table 3.2, Entry 4**). Additional work pointed to the loss of product *in vacuo* on the rotary evaporator so conditions were modified to improve solution solubility and eliminate excess pyridine borane to allow for *in situ* ¹H NMR analysis for yield determination (**Table 3.2, Entry 5**). However, low but detectable amounts of reactivity (15% or less) was repeatedly observed using tetraethylphosphonium bromide (PEt₄Br) blocked host **I** in D₂O alone with oxime **2b** (**see Supporting Information**). Gratifyingly, background could be eliminated under slightly buffered D₂O conditions, and the product was formed in near quantitative yields with modest enantioselectivity (**Table 3.2, Entry 6**).

Table 3.2. Optimization of pyridine borane (**1a**)-mediated asymmetric oxime reductions catalyzed by host **I** using aliphatic oxime **2b**.

Entry	Solvent	Temp (°C)	R	Borane Equiv	Time (h)	Yield(%) ^a	ee (%)
1	D ₂ O	rt	H	3	24	38	49
2	D ₂ O	rt	2-Me	3	24	9	nd
3	D ₂ O	rt	4-NMe ₂	3	24	0	nd
4	D ₂ O	5	H	2	48	21	59
5	D ₂ O	rt	H	1.2	48	96 ^b	48
6	35 mM pD 7.7 Li ₂ CO ₃ D ₂ O buffer ^c	rt	H	1.2	24	96 ^b	51

^a NMR yields from CDCl₃ extract relative to internal standard ^b *in situ* NMR yields in D₂O relative to internal standard.

^c ΔΔΔΔ host was used

Though enantioselectivity was achieved, the two oximes were reduced in disparate selectivity, which we hypothesized could be due to differing interactions accessible to each substrate during the enantiodetermining step. A wide array of 53 small, synthesizable oximes was then considered without bias to known or unknown capacity for asymmetric reduction to search for potential trends underlying reactivity and

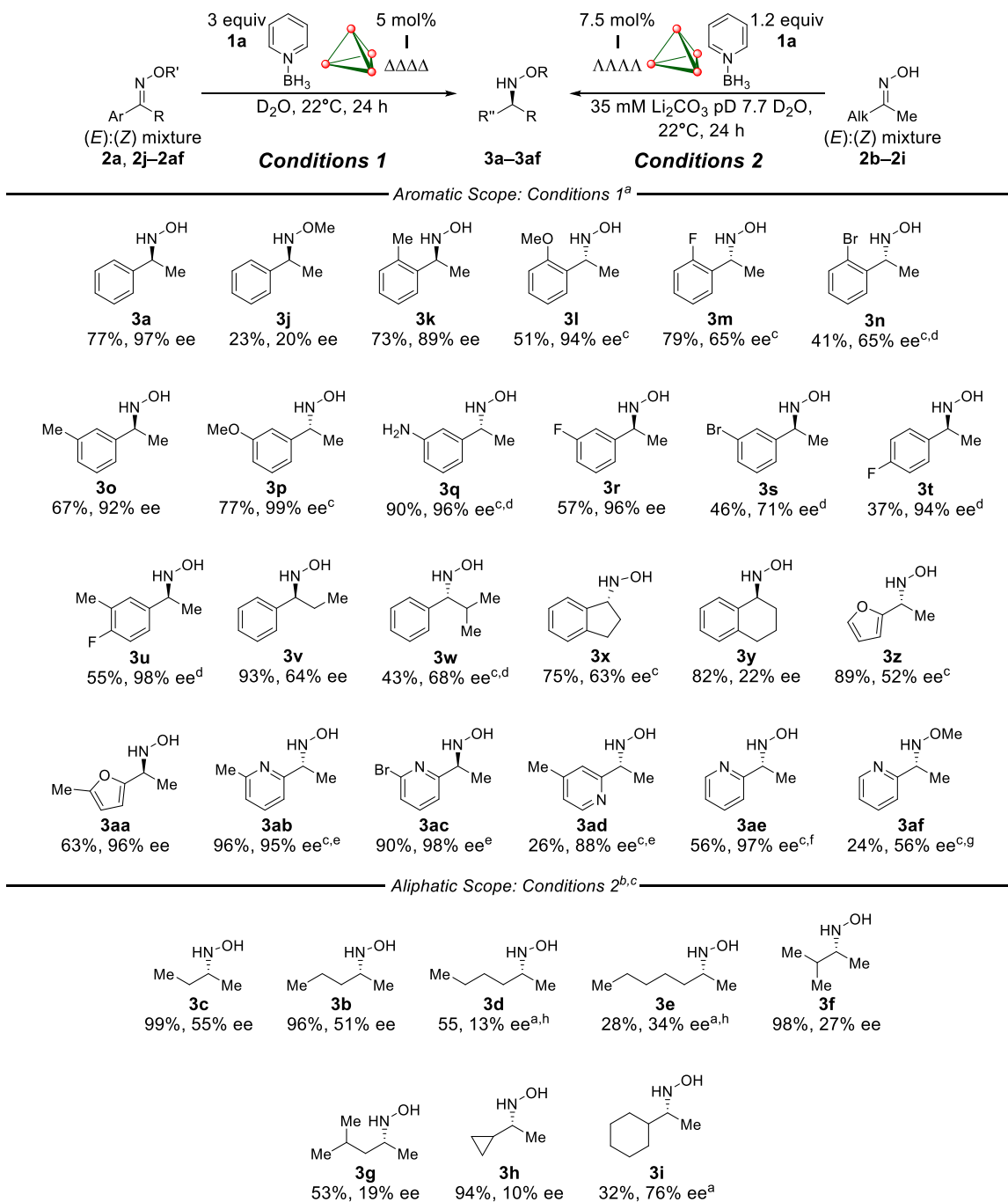
selectivity. The catalytic activity of host **1** proved highly sensitive to substrate sterics when aryl oximes, obtained as (*E*):(*Z*) mixtures of isomers, were subjected to optimized reaction conditions (**Figure 3.2**). Most notably, use of oxime ethers (**2j**) as substrate, rather than free oxime, decreased yield and enantioselectivity markedly (**Figure 3.2**). Background control using **2j** and blocked **1** showed no reactivity, suggesting the –OH group could be involved in important interactions with host or pyridine borane (see **Supporting Information**). Additionally, benzylic oximes (**2an**) were also found to be unreactive (**Figure 3.3**). Although substrates featuring ortho-methyl (**2k**) and methoxy (**2l**) groups were reduced in high enantioselectivity, substrates with ortho halogens (**2m**, **2n**) displayed noticeably attenuated enantioselectivity compared to **2a**. Meta substituents (**2o–2s**) were generally well-tolerated, with all affording excellent enantioselectivity (92–99% ee) except bromo-containing oxime **2s**, which was reduced in good selectivity (75% ee). Notably, oxime **2q**, which features a basic nitrogen, was well-tolerated. However, oxime **2aq**, featuring a CF₃ group at the meta position, was poorly reactive (**Figure 3.3**). Although very limited substitution was tolerated at the para position, and even a methyl substituent shut down reactivity (**2ao**) (**Figure 3.3**), 4-fluoro acetophenone oxime (**2t**) displayed sluggish reactivity but high enantioselectivity, which was further improved by adding a meta substituent (**2u**) (**Figure 3.2**). A competition experiment between **2a** and **2t** using 1 equivalent of pyridine borane found consumption solely of **2a**, while **2t** was fully recovered, ruling out host decomposition mediated by **2t** (see **Supporting Information**). Based on the low reactivity observed with 4-F substitutions, it is unsurprising that methyl ether oxime **2ap** was found to be nearly unreactive (**Figure 3.3**). Oximes featuring longer aliphatic side chains were generally very reactive; those with both linear (**2v**) and branched (**2w**) acyclic chains displayed moderate enantioselectivity. Interestingly, oxime **2ar**, which is highly structurally related to oxime **2w**, was poorly reactive (**Figure 3.3**). Bicyclic indanone (**2x**) likewise displayed moderate selectivity while tetralone (**2y**) oximes displayed very poor enantioselectivity. Although substrate shape appeared to clearly impact enantioselectivity, no clear intuitive stereoelectronic trends emerge upon inspection.

Additional aliphatic oximes were also explored, and it was found that linear aliphatic oximes lacking any clear steric or electronic biases (**2c–2e**) were generally reduced in higher yields and enantioselectivities than their more sterically bulky branched (**2f**, **2g**) or cyclic counterparts (**2h**) (**Figure 3.2**). Attempts at incorporating alkynes (**2as–2au**) and alkenes (**2av**, **2ax**) into the substrate were generally unsuccessful, with alkynes proving unreactive under host-catalyzed conditions while alkenes were also generally reduced under host-catalyzed conditions. Incorporation of –CF₃ (**2ax**) or –OH (**2ay**) groups which might participate in non-covalent interactions such as hydrogen bonding to help guide enantioinduction was also not tolerated (**Figure 3.3**). In fact, 2-butanone oxime **2c** (55% ee) was the most reactive and selective of all aliphatic oximes investigated. As the length of the alkyl chain in the oxime increased (**2b**, **2d**, and **2e**), the observed reactivity and enantioselectivity diminished, suggesting smaller oximes are better able to capture favorable interactions within the host cavity. However, cyclohexyl-containing oxime **2i** was a notable exception to this trend, producing the desired hydroxylamine in a reasonable 76% ee. Such a clear break in the selectivity trend suggests unique host-guest interactions for this substrate relative to other aliphatic oximes.

Given the ability of **1** and **1a** to successfully reduce oxime **2q** with excellent enantioselectivity, heterocyclic oximes were also of interest. Due to the lack of an open coordination site at the host metal, we hypothesized various heterocyclic oximes including those featuring a basic, coordinating nitrogen might also reasonably be tolerated under host-catalyzed reaction conditions. Furan **2z** was found to yield hydroxylamine in modest enantioselectivity, which was greatly improved using a pseudo-meta methyl group (**2aa**). Very limited examples of racemic reduction of pyridine-based oximes have been reported,^{37,38} and we have found no reports of their enantioselective reduction. It was noted that pyridine-containing heterocyclic oximes such as **2ab** were not reduced under conventional pyridine borane reduction conditions in the absence of host. In the presence of racemic host, however, oxime **2ab** was successfully reduced to the corresponding hydroxylamine nearly quantitatively. When subjected to enantiopure host **1** under optimized conditions, the oxime was reduced to the desired hydroxylamine (**2ab**) in near quantitative yield with excellent enantioselectivity. Subjecting oximes **2ac** and **2ae** to the host **1**-catalyzed reaction yielded similar results, and 4-substituted oxime **2ad** yielded dramatically diminished reactivity with slightly diminished selectivity. Surprisingly, methyl ether oxime **2af** was reduced with attenuated but modest selectivity compared to parent oxime **2ae**, in contrast to that observed with acetophenone-derived oximes (**2a** versus **2j**). However, 3- and 4-acetylpyridine-based oximes (**2am**, **2ba**) were only minimally reactive, as were pyrimidines (**2bb**, **2bc**) and pyrazines (**2bd**), suggesting 2-acetylpyridines are a privileged scaffold. Other basic *N*-containing heterocycles such as pyrroles, imidazoles (**2ak**, **2al**), and isatin (**2aj**) were similarly found to be unreactive (**Figure 3.3**), further corroborating this assertion.

In light of the decreased enantioselectivity observed with some oximes, background reactivity was probed by examining the reactivity of substrates **2v**, **2x**, **2y**, and **2z** in the presence of host **1** and blocking agent (PEt₄I). Under these host-inhibited conditions, only trace product was observed, thus eliminating the possibility of competing racemic background reactivity eroding enantioselectivity. The observed differences in both reactivity and enantioselectivity between even subtly different substrates therefore suggest highly specific interactions with substrates inside the host cavity may be involved in enantioinduction. However, few trends clearly emerged from initial crude analysis of the entire dataset to suggest one or more interactions involved in enantioinduction across substrates. In general, aryl and heteroaryl oximes were reduced in higher selectivity compared to aliphatic oximes. That aryl oxime ethers and non-methyl ketone derived oximes were poorly or moderately tolerated suggests added bulk around the oxime could hinder selectivity. Additional ¹⁹F NMR titration experiments in D₂O are also generally consistent with this hypothesis. Reactive aryl oximes featuring a free –OH (**2m** and **2t**) formed additional peaks upon addition of an excess of pyridine borane, while an unreactive methyl ether oxime did not display additional peaks after as many as 3 equiv. of pyridine borane were added. Furthermore, while these oximes are generally not soluble in D₂O, addition of pyridine borane appeared to facilitate the solvation of the reactive oximes, particularly upon addition of an excess (see **Supporting Information** for more details). Although this data could have multiple interpretations, one potential explanation is that it showcases difficulty by pyridine borane with interaction with methyl ether oximes. Along with empirical observations, this also suggests pyridine borane may partially act as a phase transfer catalyst under reaction conditions. Altogether, these findings combined

suggest that oxime shape, particularly with respect to steric bulk around the oxime functionality, could indeed be important for enantioinduction in the host.



^a NMR yields from CDCl₃ extract relative to internal standard. ^b *in situ* NMR yields in D₂O relative to internal standard. ^c ΛΛΛΛ host was used.
^d run for 3d with 7.5 mol% host. ^e run for 3d with 2.5 equiv. pyridine borane (added portionwise: 1.5 equiv. initial charge, 1 equiv. charge after 18h).
^f run for 48h with 1.2 equiv. pyridine borane. ^g run for 4.5d with 1.5 equiv. pyridine borane. ^h run for 40 h.

Figure 3.2. Oximes successfully reduced using pyridine borane (1a) plus enantiopure host I system.

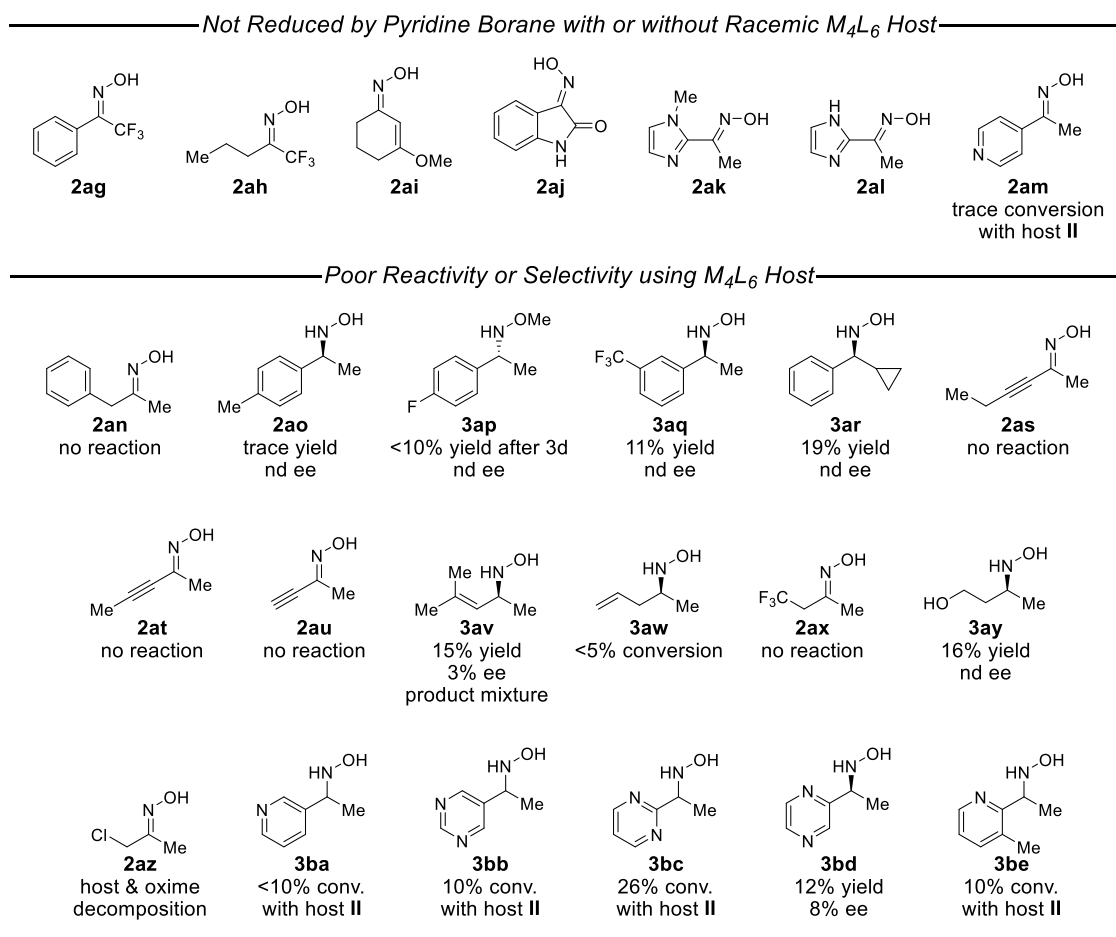


Figure 3.3. Other oximes which were attempted using pyridine borane (**1a**) with and without supramolecular host **I/II**.

3.4 Profiling the Reaction Mechanism Towards Understanding Enantioinduction

To gain a clearer mechanistic picture, a rigorous mechanistic investigation was undertaken. A series of *in situ* ^{19}F NMR kinetics experiments were conducted on substrate **2m** (see **Supporting Information** for full details) under homogenous conditions. Variable Time Normalization Analysis demonstrated that the reaction proceeds with first order in host. Varying equivalents of **1a** indicates the reductant is at saturation above 1 equiv., and ^1H NMR indicates it undergoes rapid exchange with **I** on the NMR timescale. The observed linearity of the logarithmic reaction profile in oxime beyond 50% conversion is therefore consistent with first order in oxime and suggests a rate-limiting step involving host and oxime. Kinetic isotope effect (KIE) experiments³⁹ were also conducted to more clearly define the rate-limiting step. A primary solvent KIE was observed when reductions were run in H_2O or D_2O (**Figure 3.4B**). While a weak primary KIE was observed with **2a** and **2z** (see **Supporting Information**) in one-pot, intermolecular competition experiments

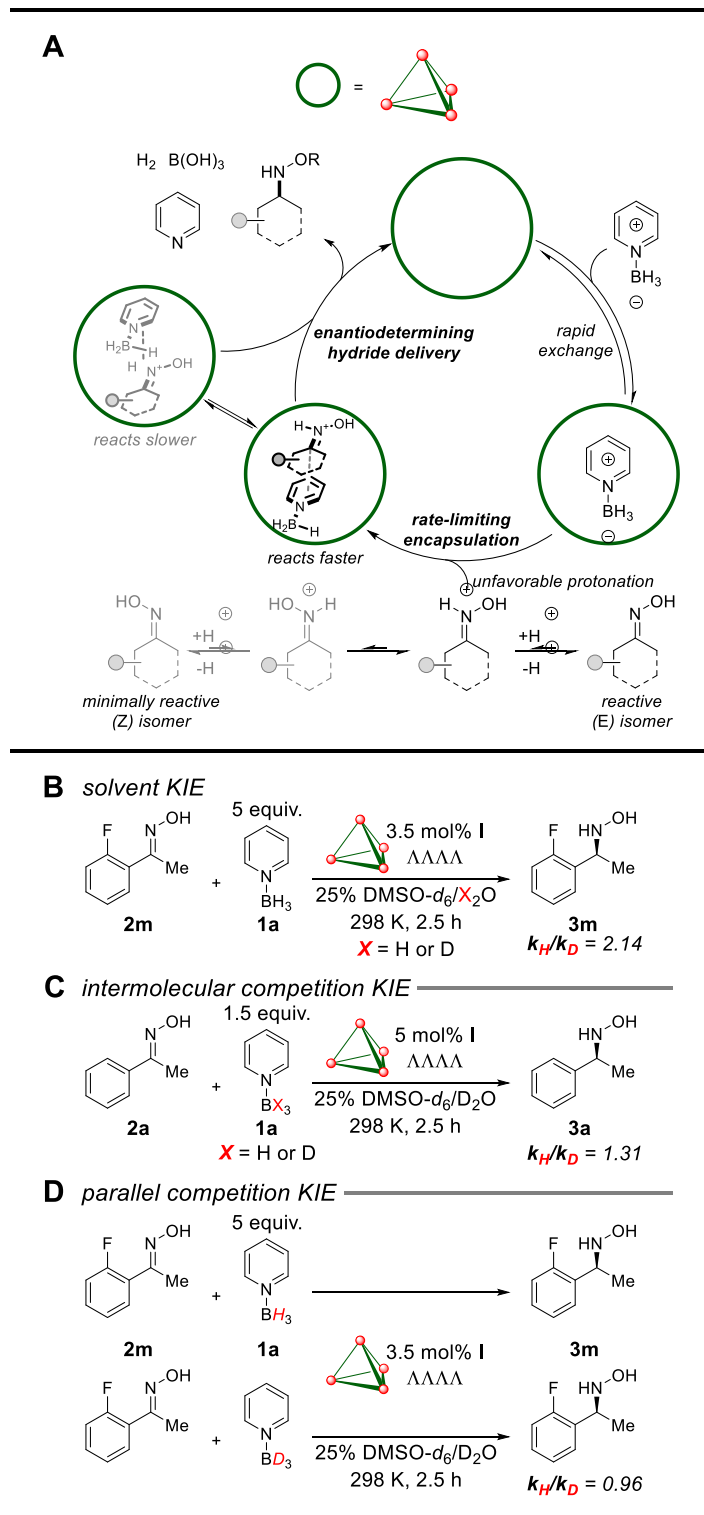


Figure 3.4. **A)** Mechanistic analysis implicates rate-limiting encapsulation and enantiodetermining hydride delivery. **(B)** Solvent KIE, **(C)** intermolecular competition KIE of reductant, and **(D)** parallel competition KIE of reductant.

using a 1:1 mixture of pyridine borane-H₃ and pyridine borane-D₃ (**Figure 3.4C**), no KIE on reaction rate was observed when pyridine borane-H₃ and pyridine borane-D₃ were independently measured in parallel using **2m**, suggesting pyridine borane is not involved in the rate-limiting step (**Figure 3.4D**). Combined, these results imply rate-determining encapsulation of protonated oxime followed by irreversible hydride delivery to furnish the desired hydroxylamine (**Figure 3.4A**). The need for stoichiometric or superstoichiometric quantities of **1a** for optimal conversion (**Table 3.1**) suggests pyridine borane delivers only one hydride before extrusion to regenerate empty host (**Figure 3.4A**). Observed H₂ evolution throughout the reaction as well as recovery of pyridine at the end of the reaction also supports this analysis.

Kinetic and thermodynamic analysis of binding behavior in **I** of (*R*) and (*S*) cationic arenes, selected to resemble protonated oxime, lends insight into the enantiodetermining step, which was hypothesized to be hydride delivery. Selective inversion recovery NMR analysis indicates **I** displays only slight differences (only 1.3 times faster) in guest exchange rates between the two enantiomers, implying encapsulation cannot be sufficiently selective to account for the observed enantioselectivities. Furthermore, a binding competition experiment between (*R*) and (*S*) arene with **I** indicated no preferential binding for one enantiomer over another, and addition of an excess of **1a** did not perturb the equilibrium (see **Supporting Information**). Therefore, while the encapsulation event is kinetically rate-limiting, enantioinduction is likely achieved through Curtin-Hammett control of the transient, prochiral reductant-oxime complexes during hydride delivery (**Figure 3.4A**). Observed enantioenrichment is therefore influenced by biased interactions, likely an array of non-covalent interactions between the reductant, oxime, and host cavity wall, to preferentially stabilized one diastereomeric transition state over the other.

We hypothesized that concurrent reactivity of both the (*E*) and (*Z*) oxime isomers within the host could be the source of the lower enantioselectivities observed with some substrates. However, many of the least selective oximes (**2j**, **2x**, and **2y**) were isolated only as the (*E*) isomer. Furthermore, during the course of kinetic analysis, the consumption of (*E*) isomer of oxime **2m** was observed while the amount of (*Z*) oxime present remained constant. To probe this finding, enriched (*Z*) oxime **2m** was subjected to reaction conditions, yielding less than 5% hydroxylamine and unreacted oxime (94% (*Z*)), consistent with only the (*E*) isomer being the reactive species and minimal to no isomerization (**Figure 3.5A**). However, when highly enriched (*Z*) oxime **2a** was similarly subjected to reaction conditions, hydroxylamine **3a** was formed in comparable yield and with high enantioselectivity to the same enantiomer as observed when an (*E*):(*Z*) mixture was used (**Table 3.1, Entry 9, Figure 3.5C**). Furthermore, an approximately 1:1 (*E*):(*Z*) ratio of **2a** was recovered, suggesting oxime isomerization can occur. Highly enriched (*E*) **2a** and **2z** also formed hydroxylamine in identical or highly comparable enantioselectivity as observed using the (*E*):(*Z*) mixture and, notably, no (*Z*) oxime was recovered (**Figure 3.5B&C**, suggesting only (*Z*) to (*E*) isomerization occurs during the reaction. Control experiments in the absence of pyridine borane suggest this isomerization is host-catalyzed, rather than a result of background reactivity (see **Supporting Information**). Combined, these results are consistent with host-catalyzed isomerization helping to funnel oxime mixtures to the much more reactive (*E*) isomer, with the possibility of

comparatively much slower (*Z*) isomer concurrently reacting with lower enantioselectivity. Oximes **2m** and **2w** appear to be exceptions to this regime, with very little to no isomerization between oxime isomers observed. Therefore, decreased enantioselectivity observed is likely due to differential interactions within the host cavity between (*E*) oxime, reductant, and host, rather than competing reactivity of oxime isomers.

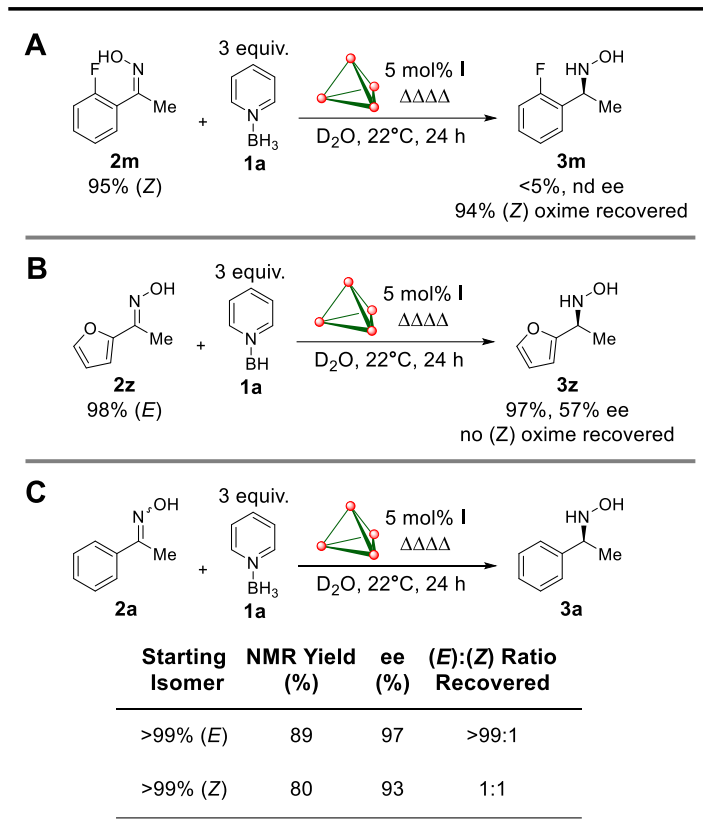


Figure 3.5. Differing reactivity of **A**) (*Z*) isomer of oxime **2m**, **B**) (*E*) isomer of oxime **2z**, and **C**) (*E*) and (*Z*) oxime isomers of **2a** under reaction conditions with host **I**.

3.5 Experimental and Data Science Analysis of Steric and Electronics Effects on Enantioselectivity

With this mechanistic information and reaction scope, we turned to data science-based analysis to help elucidate reaction features important for enantioinduction. An in-house python workflow was utilized to parameterize reactive oximes into chemically meaningful descriptors (see **Supporting Information** for complete workflow details). Although oxime isomer and protonation states were examined, parameterization of the protonated form of (*E*)-oximes provided the best correlation and, given the above data, are the most mechanistically relevant species to the reaction outcome. Principal component analysis (PCA) was then applied to condense the many-dimensional space into a more concise, holistic representation of the dataset. A *k*-means clustering algorithm on this chemical space indicated the 30-oxime substrate scope considered could be represented by four distinct classes (**Figure 3.6A**). Although some of the grouping was

largely consistent with chemical intuition, this was not true for all substrates or classes (see **Supporting Information**). Across the entire data set, a modest univariate correlation was observed with enantioselectivity using solely ground state sterimol_L, a feature conveying molecular length (see **Supporting Information**, $R^2 = 0.62$). Notably, analysis of the error associated with predictions of oximes belonging to separate clusters revealed that the largest deviations were primarily located in the largest group (see **Supporting Information** for expanded discussion). Addition of a second variable, namely ground state buried volume at the oxime α -C (4 Å radius), generated an improved correlation ($R^2 = 0.67$) with the observed enantioselectivity across the entire data set (**Figure 3.6B**). In analyzing the observed correlation, it was noted that longer molecular length, as indicated by sterimol_L, and less hindered oximes, as indicated by the buried volume descriptor, each contribute to greater enantioinduction. Given that both variables generally describe steric properties, these findings provide data-based support for the hypothesis that guest size and shape are important for host-mediated enantioinduction.

Since hydride delivery within the host cavity was identified as the enantiodetermining step, this implies that tuning reductant and host identities should affect enantioselectivity. Although non-covalent interactions with host are often hypothesized as playing key roles in racemic and enantioselective catalysis in supramolecular hosts,^{40–42} the interactions between substrates in multicomponent enantioselective reactions within supramolecular hosts has been the subject of little study. To probe for potential interactions between oxime and pyridine borane, interaction energies⁴³ were calculated between the oxime substrate and a pyridine probe molecule (see **Supporting Information** for full workflow details and calculations). Given that steric parameters correlated with enantioselectivity, we posited that they may also be important to the interaction between substrate and reductant. It was noted that oxime ground state sterimol_L also correlated with the interaction energy between pyridine and substrate ($R^2 = 0.66$). Importantly, this steric parameter captures the magnitude of a non-covalent interaction between reactants, while also correlating to the enantioselectivity of their reaction.

To further examine these interactions, four 2-substituted pyridine boranes (**1b–1e**) with differing stereoelectronic profiles were screened using a small number of oximes selected to represent a range of chemical space (**2b**, **2k**, **2m** and **2ae**). The resulting enantioselectivities were compared to that of the parent **1a**. For all substrates, 2-fluoro-containing borane **1b** gave lower selectivity compared to the isosteric parent pyridine borane **1a**. Similar behavior was also observed when comparing 2-methylpyridine borane (**1c**) and isosteric 2-aminopyridine borane (**1d**). For three of the four oximes, more electron-rich borane **1d** afforded higher levels of selectivity. Notably, the amino group of **1d** has the potential for hydrogen-bonding interactions not accessible to other boranes studied, which could also impact enantioselectivity. These results combined point to the importance of borane electronics on ee. Observed enantioselectivities with electron-rich but sterically hindered borane **1e**, featuring a 2-methoxy group, showed divergent behavior which highlighted the importance of steric interactions between reductant and oxime. Of all boranes, **1e** afforded the highest selectivity for aliphatic oxime **2b**, and improved selectivity with oxime **2m**, consistent with previous observations regarding borane electronics. However, borane **1e** provided only comparable selectivity versus **1a** for pyridine-based oxime **2ae** and dramatically diminished selectivity for oxime **2k**, which

features added steric bulk near the oxime moiety, suggesting sterics may be equally or more important for some substrates. While no borane emerged as optimal across substrates, these results empirically suggest that enantioselectivity can be affected both by steric and electronic effects of the achiral reductant.

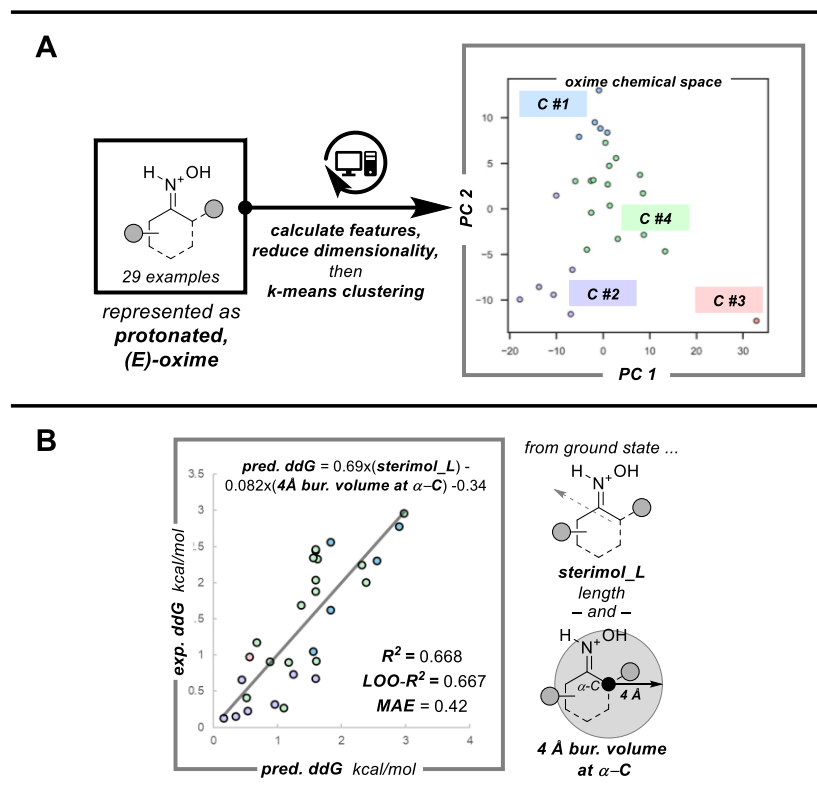


Figure 3.6. A) Oximes considered in linear regression tasks constitute four clusters (*k*-means clustering) across principal component-reduced chemical space. **(B)** Regression analysis shows the impact of oxime size and shape on interactions with host for enantioinduction as represented by ground state sterimol_L and buried volume at the oxime $\alpha\text{-C}$ (4Å). Correlations are reported with the computed R^2 , LOO- R^2 (leave one out R^2), and the mean absolute error (MAE) as a redundant, quantitative measure of error.

Data science analysis of the borane screen results generally supports these observations. Interaction energies of the Boltzmann distribution of conformations were calculated for each pyridine derivative with the protonated (*E*) isomer of the corresponding oximes (see **Supporting Information** for calculations). A positive correlation was observed between enantioselectivity and the interaction energies for pyridine-based oxime **2ae** ($R^2 = 0.77$, **Figure 4C**), suggesting that electronic effects dominate selectivity-determining interactions for this oxime. On the other hand, a negative correlation between the buried volume at the pyridine borane reductant and enantioselectivity was observed **2k** ($R^2 = 0.87$, **Figure 4D**), suggesting steric effects may be more important for selectivity of this substrate. Notably, these correlations do not exist across every oxime tested (see **Supporting Information**). Empirical observations suggest the lack of univariate correlations may be due to a combination of steric and electronic effects which impact selectivity for some substrates. Taken together, these correlations align with experimental

observations highlighting the importance of both steric and electronic features for guest interactions within the host cavity and strongly suggest that interactions important for enantioselectivity likely vary on a substrate-to-substrate basis. The unexpected disparities observed between the relative importance of steric and electronic effects on selectivity of individual substrates is the subject of future investigation.

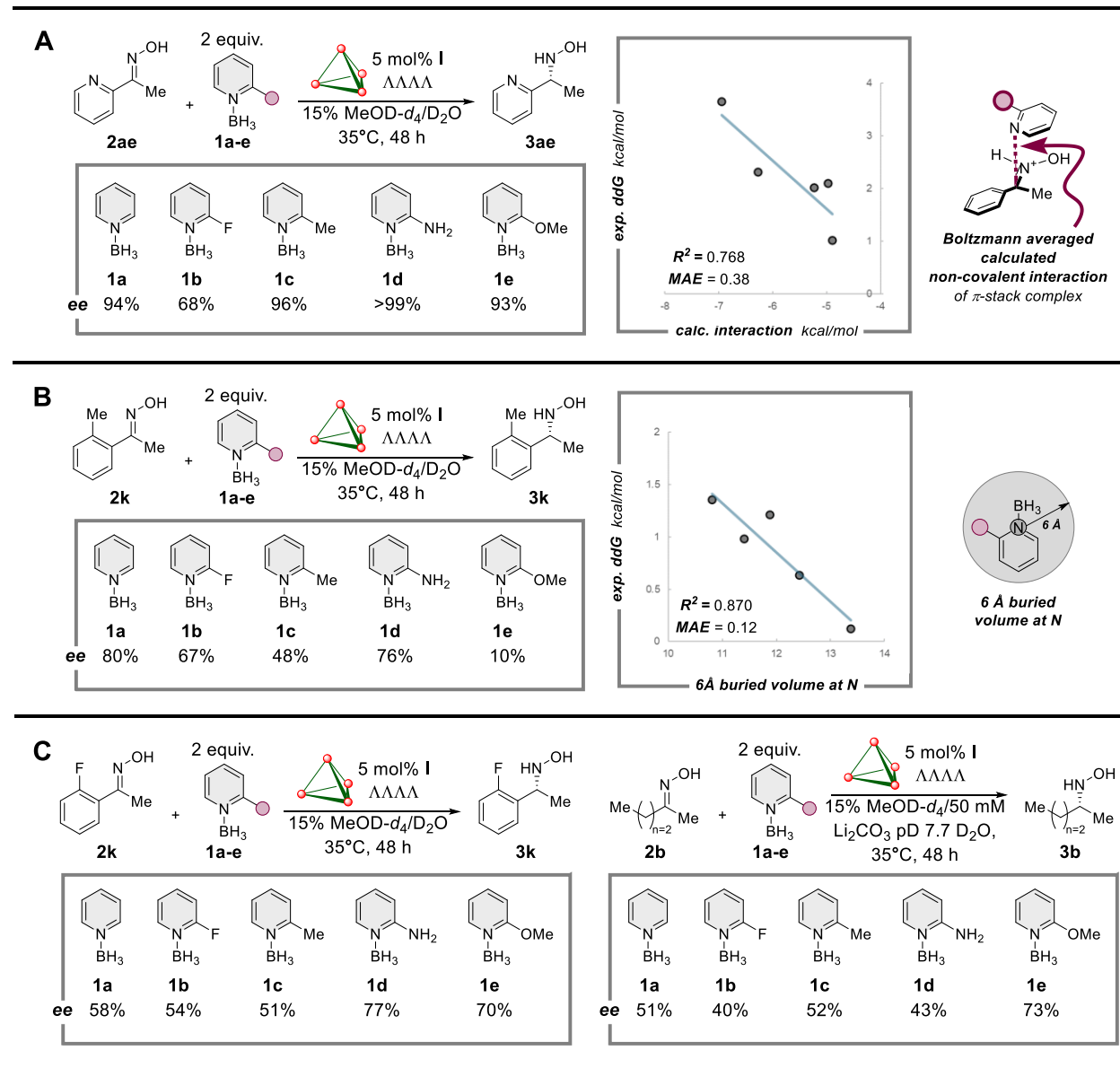


Figure 3.7. Reductant choice impacts enantioselectivity of **(A)** pyridine oxime **2ae** reduction due to borane electronics, based on correlation to calculated non-covalent interactions in the proposed enantiodetermining complex, and **(B)** aryl oxime **2k** reduction due to borane sterics, based on correlation to buried volume at the N-atom of the reductant. Correlations are reported with the computed R^2 and the mean absolute error (MAE) as a second, quantitative measure of error. **(C)** Reductant choice impacts enantioselectivity of aryl oxime **2m** and aliphatic oxime **2b**.

3.6 Conclusions

Application of an enantiopure $\text{Ga}_4\text{L}_6^{12-}$ supramolecular host enabled the enantioselective reduction of a broad range of aryl, aliphatic, and heteroaryl oximes, including the first examples of oximes featuring Lewis basic metal-coordinating pyridine-based oximes. Substrate scope and mechanistic work in combination with data science analysis demonstrate the importance of guest size and shape on interactions with the host for enantioselectivity. However, a solely steric-based model for enantioinduction in these systems paints an incomplete picture of host-guest interactions, as electronic effects are also demonstrated to be at play. Modulating the pyridine borane reductant cofactor reveals the importance of steric and electronic matching of guests on a substrate-by-substrate basis in multi-component reactions to achieve high selectivity. The scope of this reaction, coupled with the mechanistic and statistical framework described herein highlights the potential of supramolecular hosts in asymmetric catalysis due to their unique structures and mode of enantioinduction and provides a foundation for further interrogation of enantioinduction in these systems.

3.7 Supporting Information

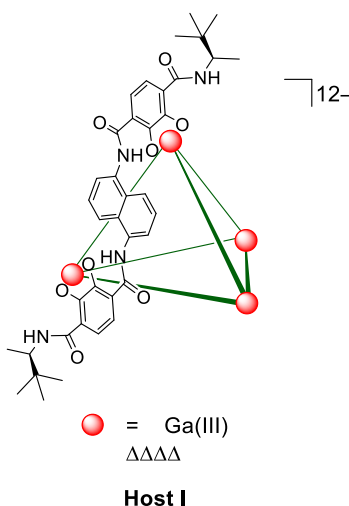
3.7.1 General Methods and Instrumentation:

All reactions were capped and performed at room temperature under ambient atmosphere with Teflon-coated magnetic stir bars unless otherwise specified. Air sensitive materials were prepared using standard Schlenk technique and handled in a wet glovebox under a nitrogen (N_2) atmosphere. All solvents were degassed for 0.5 hours by sparging before introduction into the glovebox. Flash column chromatography was performed on a Teledyne Isco CombiFlash Rf instrument using pre-packed silica gel columns unless otherwise stated. Thin layer chromatography (TLC) analysis was performed using Merck 60 pre-coated silica gel plates with F254 indicator and visualized using UV light (254 nm) or potassium permanganate (KMnO_4). Commercial grade solvents were used without further purification except as indicated. Dichloromethane (CH_2Cl_2), diethyl ether (Et_2O), tetrahydrofuran (THF), and triethylamine (Et_3N) were dried by passing the previously degassed solvents through activated alumina columns under argon. All other reagents were used directly as received without further purification. All deuterated solvents were used as received from Cambridge Isotope Laboratories, Inc. Proton nuclear magnetic resonance (^1H NMR), carbon nuclear magnetic resonance (^{13}C NMR), and fluorine nuclear magnetic resonance (^{19}F NMR) spectra were taken with Bruker AV-300, AVB-400, AVQ-400, NEO-500, NEO-501, AV-600, or AV-700 and JEOL-400 NMR spectrometers operating at 300 MHz, 400 MHz, 500 MHz, 600, or 700 MHz. Chemical shifts are reported in parts per million (ppm) with reference to the appropriate residual solvent signal. ^1H NMR: CDCl_3 : δ : 7.26 ppm, CD_2Cl_2 : δ : 5.32 ppm, $\text{DMSO}-d_6$: δ : 2.50 ppm, $\text{MeOD}-d_4$: δ : 3.31 ppm, D_2O : δ : 4.79 ppm. ^{13}C NMR: CDCl_3 : δ : 77.16 ppm, CD_2Cl_2 : δ : 53.84 ppm, $\text{DMSO}-d_6$: δ : 39.52 ppm, $\text{MeOD}-d_4$: δ : 49.00 ppm. ^1H NMR multiplicities are reported as (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, hept = heptet, oct = octet, m = multiplet; coupling constant(s) in Hz; integration). High resolution mass spectra were recorded by an Agilent 6230 ESI-TOF LC/MS and are given in m/z. The determination of enantiomeric excess was performed by chiral phase high

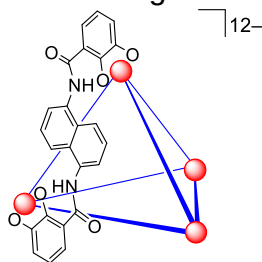
performance liquid chromatography (HPLC) using Shimadzu Prominence HPLC and Diacel ChiralCel OJ-H, AD-H and IA columns. Samples for chiral HPLC analysis were prepared in 95% hexanes/isopropanol (IPA) solutions unless otherwise stated. Optical rotation was measured with a Perkin-Elmer 241 Polarimeter on enantioenriched hydroxylamine sample reduced in host **I** to determine absolute stereochemistry. Absolute stereochemistry of other products was assigned by analogy. Oximes, hydroxylamines, and pyridine boranes were stored in a -20°C freezer when not in use. M_4L_6 hosts were stored in a wet glovebox to avoid oxidative decomposition.

3.7.2 Synthesis and Characterization of Compounds:

Host Synthesis



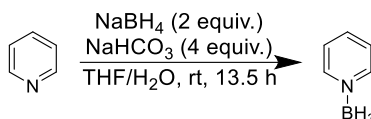
$\text{K}^{12}[\text{Ga}_4\text{L}_6]$ **Host I** was synthesized according to a reported procedure.²³



$\text{K}^{12}[\text{Ga}_4\text{L}_6]$ **Host II** was synthesized according to a previously reported procedure.⁴⁴

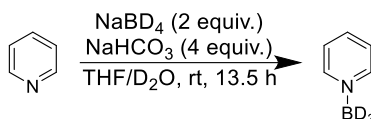
Borane Synthesis:

2-methylpyridine (picoline) **borane (1c)** was used as received from Thermo Fisher Scientific.



Pyridine borane (1a) was synthesized according to a modified procedure.⁴⁴ To a flame-dried 25 mL round bottom flask equipped with a magnetic stir bar was added sodium borohydride (207 mg, 5.46 mmol, 2 equiv.), sodium bicarbonate (888 mg, 10.57 mmol, 3.9 equiv.) and THF (4 mL). Then, pyridine (0.22 mL, 2.73 mmol, 1 equiv.) was added in a single portion, followed by a slow, dropwise addition of DI water (0.2 mL) and additional THF (0.8 mL). The heterogeneous mixture was vigorously stirred for 4 hours at room temperature. The solids were removed by vacuum filtration, and the filtrate was concentrated *in vacuo*. Purification of the crude product by column chromatography eluting with CH₂Cl₂/MeOH (0–5% MeOH) yielded the title compound as a hazy liquid. Analytical data were consistent with the literature.⁴⁴

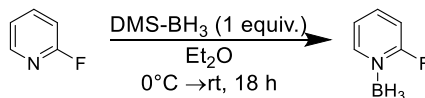
¹H NMR (300 MHz, Chloroform-*d*) δ 8.65 (d, *J* = 5.6 Hz, 2H), 8.06 – 7.88 (m, 1H), 7.64 – 7.48 (m, 2H), 2.54 (dt, *J* = 163.6, 66.0 Hz, 3H).



Pyridine BD₃ (1a-D) was synthesized under an analogous procedure as used to synthesized pyridine borane-H₃. To a flame-dried 25 mL round bottom flask equipped with a magnetic stir bar was added sodium borodeuteride (284 mg, 6.75 mmol, 2 equiv.), sodium bicarbonate (1155 mg, 13.5 mmol, 4 equiv.) and THF (5 mL). Then, pyridine (275 μL, 3.375 mmol, 1 equiv.) was added in a single portion, followed by a slow, dropwise addition of D₂O (0.25 mL) and additional THF (1 mL). The heterogeneous mixture was vigorously stirred for 13.5 hours at room temperature. The solids were removed by vacuum filtration, and the filtrate was concentrated *in vacuo*. Purification of the crude product by column chromatography eluting with CH₂Cl₂/MeOH (0–5% MeOH) yielded the title compound as a clear liquid.

¹H NMR (500 MHz, CDCl₃) δ 8.60 (d, *J* = 6.4 Hz, 2H), 7.93 (tt, *J* = 7.8, 1.6 Hz, 1H), 7.55 – 7.48 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 147.64, 139.19, 125.45.



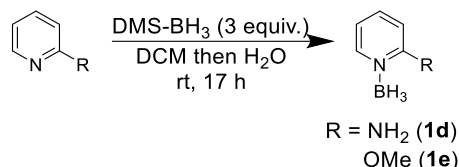
2-fluoropyridine borane (1b) was synthesized according to a modified procedure.⁴⁵ To a flame-dried 25 mL round bottom flask equipped with a magnetic stir bar was added Et₂O (6 mL) and 2-fluoropyridine (515 μL, 6.00 mmol, 1.0 equiv.) under N₂. The reaction was cooled to 0°C before dimethyl sulfide borane (DMS-BH₃) (570 μL, 6.00 mmol, 1.0 equiv.) was slowly added and kept at 0°C for 1h before being allowed to slowly warm to room temperature and stopped after 17h, after which time the reaction was filtered. The reaction flask was washed with Et₂O and the rinse also filtered. To the filtrate was added a large excess of hexanes to precipitate out a white solid, which was filtered off and washed twice with H₂O (2x15 mL). The solid was allowed to dry on the fritted glass funnel

briefly before drying on high vacuum overnight and isolation in 95% purity. The solid was found to be poorly stable, particularly in protic solvents.

^1H NMR (600 MHz, CDCl_3) δ 8.51 (s, 1H), 8.12 – 8.00 (m, 1H), 7.36 (t, J = 6.1 Hz, 1H), 7.23 (d, J = 8.3 Hz, 1H), 2.91 – 2.04 (m, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 161.01 (d), 148.14 (d), 144.50 (d), 121.55 (d), 112.39 (d).

^{19}F NMR (565 MHz, CDCl_3) δ -68.45.



2- NH_2 pyridine borane (1d**) and 2-OMe pyridine borane (**1e**)** were synthesized according to a modified procedure.⁴⁶ To a flame-dried 25 mL round bottom flask equipped with a magnetic stir bar was added CH_2Cl_2 (5 mL) and pyridine (2.8 mmol, 1.0 equiv.) under N_2 before slow addition of DMS-BH_3 (8.4 mmol, 3.0 equiv.). The reaction was allowed to stir at room temperature for 13h, after which H_2O (10 mL) was slowly added. A vent needle was also added to the flask. The reaction was then allowed to stir another 4h before it was further diluted with H_2O (5 mL) and extracted three times with CH_2Cl_2 (3x10 mL). The organic layers were backwashed once with NaHCO_3 (1x15 mL). The resulting organic layers were combined and dried over MgSO_4 , filtered, and concentrated *via* rotary evaporation. Purification of the crude product by column chromatography eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (0–30% MeOH) yielded the title compound.

2-aminopyridine borane (1d**):** Prepared according to the general procedure and isolated as a white solid.

^1H NMR (600 MHz, CDCl_3) δ 8.15 (s, 1H), 7.60 – 7.52 (t, J = 7.7 Hz, 1H), 6.65 (d, J = 8.0 Hz, 2H), 5.57 (s, 2H), 2.60 – 1.79 (m, 3H).

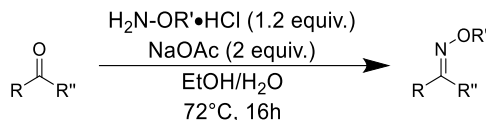
^{13}C NMR (151 MHz, CDCl_3) δ 155.38, 146.05, 139.99, 113.11, 111.43.

2-methoxypyridine borane (1e**):** Prepared according to the general procedure and isolated as a white solid. Analytical data were consistent with literature reports.^{46,47}

^1H NMR (600 MHz, CDCl_3) δ 8.51 (d, J = 5.2 Hz, 1H), 7.96 – 7.89 (m, 1H), 7.06 – 7.01 (m, 1H), 6.96 (d, J = 8.5 Hz, 1H), 4.10 (s, 3H), 2.82 – 2.02 (m, 3H).

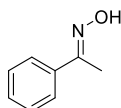
^{13}C NMR (151 MHz, CDCl_3) δ 163.15, 148.65, 142.76, 116.98, 107.65, 57.06.

General Procedure A for the Synthesis of Aryl and Heteroaryl Oximes:



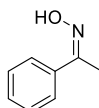
Synthesized based on a modified procedure.⁴⁴ To a 100 mL round bottomed flask equipped with a stir bar was added hydroxylamine HCl (4.8 mmol, 1.2 equiv.) and NaOAc (8 mmol, 2 equiv.), followed by EtOH (28 mL) and H_2O (12 mL). The ketone was then added, and the solution was brought to reflux. After overnight reflux, the solution was cooled and concentrated *via* rotary evaporation to remove most of the EtOH. The

remaining residue was diluted with H₂O (15 mL) and transferred to a separatory funnel and extracted twice with EtOAc (2x20 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated *via* rotary evaporation. Purification of the crude product by column chromatography eluting with hexanes/EtOAc (0–50% EtOAc) yielded the title compound.



(E)-1-phenylethan-1-one oxime (2a-(E)): Prepared according to General Procedure A and isolated as a white solid in 98% purity. Analytical data were consistent with literature reports.^{48–50}

¹H NMR (600 MHz, CDCl₃) δ 7.70–7.57 (m, 2H), 7.42–7.31 (m, 3H), 2.31 (s, 3H).

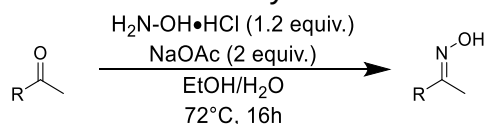


(Z)-1-phenylethan-1-one oxime (2a-(Z)): Prepared according to a modified procedure.⁵¹ To a 25 mL RBF was added finely ground hydroxylamine HCl (541 mg, 7.79 mmol, 1.3 equiv.), EtOH (6 mL), acetophenone (700 μL, 5.99 mmol, 1.0 equiv.), and dry Et₃N (1.1 mL, 7.89 mmol, 1.32 equiv.). The heterogeneous solution was sonicated for 1 min then stirred vigorously for 2.25h. The resulting mixture was partially concentrated to dryness *via* rotary evaporation, then diluted with H₂O (20 mL) and extracted twice with EtOAc (2x20 mL). The organic layers were combined and dried over MgSO₄, filtered, and concentrated *via* rotary evaporation. Oxime was found to rapidly isomerize in the presence of trace acid to the more stable (E) isomer, including on silica and in the presence of CDCl₃, consistent with literature reports.⁴⁸ Oxime was not found to isomerize to (E) in CD₂Cl₂ over the course of 1h. Therefore, crude product was purified *via* flash column chromatography using 0–40% EtOAc/hexanes on basic Al₂O₃. Fractions which were found to be enriched in the (Z) isomer were immediately concentrated to dryness *via* rotary evaporation. The oxime mixture was immediately redissolved in minimal CH₂Cl₂ and purified *via* prep TLC in 30% EtOAc/hexanes with 1% Et₃N (prep TLC plate was pre-washed with 30% EtOAc/hexanes with 1% Et₃N). The plate was immediately scraped, and the product was eluted with CH₂Cl₂ and concentrated to dryness *via* rotary evaporation. The resulting product was dried on high vacuum for at least 2 hours before being stored in a freezer (found to be stable for at least 2 days).

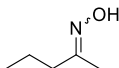
¹H NMR (600 MHz, CD₂Cl₂) δ 7.50 (d, J = 7.1 Hz, 2H), 7.45 – 7.39 (m, 2H), 7.37 (t, J = 7.3 Hz, 1H), 7.31 (br s, 1H), 2.18 (s, 3H).

¹³C NMR (151 MHz, CD₂Cl₂) δ 155.39, 134.66, 129.26, 128.51, 128.22, 21.76.

General Procedure B for the Synthesis of Aliphatic Oximes: A modified version of General Procedure A due to substrate volatility.



To a 100 mL round bottomed flask equipped with a stir bar was added hydroxylamine HCl (2.4 mmol, 1.2 equiv.) and NaOAc (4 mmol, 2 equiv.), followed by EtOH (14 mL) and H₂O (6 mL). The ketone (2 mmol, 1 equiv.) was then added, and the solution was brought to reflux. After overnight reflux, the solution was cooled and partially concentrated *via* rotary evaporation. To minimize product loss but remove as much EtOH as possible, the rotovap bath temperature was kept below 14°C. The remaining residue was diluted with H₂O (15 mL) and transferred to a separatory funnel and washed with DCM (20 mL) x2. The combined organic layers were dried over MgSO₄, filtered, and concentrated *via* rotary evaporation. To minimize product loss, the rotovap bath temperature was kept below 7°C. The resulting crude product still generally contained small amounts of acetic acid, so the product was diluted with DCM (20 mL), returned to the separatory funnel and washed with H₂O (20 mL) x2. The organic layer was dried over MgSO₄, filtered, concentrated *via* rotary evaporation below 10°C, and then briefly dried on high vacuum to remove any remaining residual solvent.



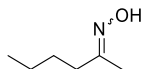
(E)- and-(Z)-pentan-2-one oxime (2b): Prepared according to General Procedure B with slight modification. Rather than repeated washing with H₂O, the crude product was purified *via* Hickman distillation and isolated as a colorless oil in a 3:1 (*E*):(*Z*) isomer mixture. Analytical data were consistent with literature reports.^{44,52}

¹H NMR (600 MHz, CDCl₃) δ 8.67 (br s, 1H), 2.38 – 2.32 (m, 2H, minor), 2.19 – 2.13 (m, 2H, major), 1.87 (s, 3H, major), 1.86 (s, 3H, minor), 1.54 (m, 4H, major and minor), 0.96 (t, *J* = 7.4 Hz, 3H, minor), 0.92 (t, *J* = 22.4, 7.4 Hz, 3H, major).



(E)- and-(Z)-butan-2-one oxime (2c): Prepared according to General Procedure B with slight modification. Rather than repeated washing with H₂O, the crude product was purified *via* Hickman distillation and isolated as a colorless oil in a 3.4:1 (*E*):(*Z*) isomer mixture. Analytical data were consistent with literature reports.^{53,54}

¹H NMR (500 MHz, CDCl₃) δ 8.62 (br s, 1H), major: 2.22 (q, *J* = 7.5 Hz, 2H), 1.88 (s, 3H, major), 1.09 (t, *J* = 7.5 Hz, 3H, major), minor: 2.39 (q, *J* = 7.7 Hz, 2H), 1.86 (s, 3H), 1.08 (t, *J* = 7.7 Hz, 3H).

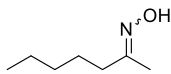


(E)- and-(Z)-hexan-2-one oxime (2d): Prepared according to General Procedure B and isolated as a colorless oil in a 2.5:1 (*E*):(*Z*) isomer ratio (64% yield).

¹H NMR (600 MHz, CDCl₃) δ 8.29 (br s, 1H), 2.40 – 2.34 (m, 2H, minor), 2.21 – 2.16 (m, 2H, major), 1.88 (s, 3H, major), 1.86 (s, 3H, minor), 1.53 – 1.45 (m, 2H, major and minor), 1.41 – 1.33 (m, 2H, minor), 1.36 – 1.28 (m, 2H, major), 0.93 (t, *J* = 7.3 Hz, 3H, minor), 0.91 (t, *J* = 7.4 Hz, 3H, major).

¹³C NMR (151 MHz, CDCl₃) δ 159.37 (minor), 158.93 (minor), 35.66 (major), 28.48 (major), 28.43, 27.79, 22.96, 22.42 (major), 19.98, 13.98, 13.94 (major), 13.45.

HRMS (ESI+): *m/z* calcd for C₆H₁₃NO [*M*+H]⁺ 116.1070, found 116.1075.



(E)- and (Z)-heptan-2-one oxime (2e): Prepared according to General Procedure B and isolated as a light yellow oil in a 10.1:1 (*E*):(*Z*) isomer ratio (78% yield).

^1H NMR (600 MHz, CDCl_3) δ 7.75 (br s, 1H), 2.39 – 2.32 (m, 2H, minor), 2.20 – 2.15 (m, 2H, major), 1.88 (s, 3H, major), 1.86 (s, 3H, minor), 1.55 – 1.47 (m, 2H, major and minor), 1.37 – 1.24 (m, 4H, major and minor), 0.93 (t, J = 7.5 Hz, 3H, minor) 0.89 (t, J = 7.1 Hz, 3H, major).

^{13}C NMR (151 MHz, CDCl_3) δ major: 158.95, 35.91, 31.48, 26.04, 22.53, 14.09, 13.49, minor: 31.99, 28.68, 25.30, 20.97, 19.96.

HRMS (ESI+): m/z calcd for $\text{C}_7\text{H}_{15}\text{NO}$ [$\text{M}+\text{H}$] $^+$ 130.1226, found 130.1232.

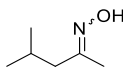


(E)- and (Z)-3-methylbutan-2-one oxime (2f): Prepared according to General Procedure B and isolated as a colorless liquid in a 6.6:1 (*E*):(*Z*) isomer ratio (62% yield).

^1H NMR (600 MHz, CDCl_3) δ 8.69 (br s, 1H), major: 2.49 (hept, J = 6.9 Hz, 1H), 1.85 (s, 3H), 1.09 (d, J = 6.9 Hz, 6H), minor: 3.47 (sept, J = 6.9 Hz, 1H), 1.78 (s, 3H), 1.05 (d, J = 6.9 Hz, 6H).

^{13}C NMR (151 MHz, CDCl_3) δ 163.39, 162.78, 34.62, 25.86, 19.83, 18.98, 15.52, 11.20.

HRMS (ESI+): m/z calcd for $\text{C}_5\text{H}_{11}\text{NO}$ [$\text{M}+\text{H}$] $^+$ 102.0913, found 102.0915.

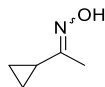


(E)- and (Z)-4-methyl-pentan-2-one oxime (2g): Prepared according to General Procedure B with some modifications. Rather than repeated washing with H_2O , the crude product was purified *via* column chromatography and isolated as a very pale yellow liquid in a 3.5:1 (*E*):(*Z*) isomer ratio (98% yield).

^1H NMR (600 MHz, CDCl_3) δ 7.81 (br s, 1H), 2.28 (d, J = 7.5 Hz, 2H, minor), 2.05 (d, J = 7.3 Hz, 2H, major), 2.03 – 1.96 (m, 1H, minor), 1.94 – 1.87 (m, 1H, major), 1.87 (s, 3H, major), 1.86 (s, 3H, minor), 0.94 (d, J = 6.6 Hz, 6H, minor), 0.91 (d, J = 6.6 Hz, 6H, major).

^{13}C NMR (151 MHz, CDCl_3) δ 158.53, 158.25, 44.93, 37.62, 25.94, 25.89, 22.84, 22.51, 20.59, 13.62.

HRMS (ESI+): m/z calcd for $\text{C}_6\text{H}_{13}\text{NO}$ [$\text{M}+\text{H}$] $^+$ 116.1070, found 116.1072.

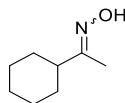


(E)- and (Z)-1-cyclopropylethan-1-one oxime (2h): Prepared according to General Procedure B with some modifications. Rather than repeated washing with H_2O , the crude product was purified *via* column chromatography and isolated as a light yellow liquid in a 10:1 (*E*):(*Z*) isomer ratio (99% yield).

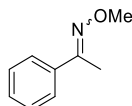
^1H NMR (600 MHz, CDCl_3) δ 6.29 (s, 1H), 2.46 (tt, J = 8.6, 5.2 Hz, 1H, minor), 1.72 (s, 3H, major), 1.61 (tt, J = 8.4, 5.2 Hz, 1H, major), 1.57 (s, 3H, minor), 0.89 (dd, J = 8.7, 2.2 Hz, 1H), 0.078 – 0.66 (m, 4H, major and minor).

^{13}C NMR (151 MHz, CDCl_3) δ 159.76, 15.21 (major), 14.61 (minor), 10.83 (major), 8.91 (minor), 5.16 (minor), 4.64 (major).

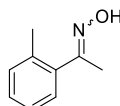
HRMS (ESI⁺): m/z calcd for C₅H₉NO [M+H]⁺ 100.07569, found 100.07564.



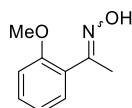
(E)-1-cyclohexylethan-1-one oxime (2i): Prepared according to General Procedure B and isolated as a white solid. Analytical data were consistent with literature reports.⁵⁵
¹H NMR (600 MHz, CDCl₃) δ 8.14 (br s, 1H), 2.20 – 2.08 (m, 1H), 1.85 (s, 3H), 1.79 (dd, J = 6.5, 3.3 Hz, 4H), 1.69 (d, J = 10.8 Hz, 1H), 1.33 – 1.23 (m, 4H), 1.22 – 1.13 (m, 1H).



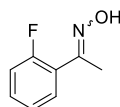
(E)- and (Z)-1-phenylethan-1-one O-methyl oxime (2j): Prepared according to General Procedure A and isolated as a very pale yellow oil as a mixture of isomers (16:1 *E:Z*). Analytical data were consistent with literature reports.^{56,57}
¹H NMR (500 MHz, CDCl₃) δ 7.69 – 7.61 (m, 2H, major), 7.50 – 7.45 (m, 2 H, minor), 7.43 – 7.31 (m, 3H, major and minor), 4.01 (s, 3H, major), 3.86 (s, 3H, minor), 2.24 (s, 3H, major), 2.21 (s, 3H, minor).



(E)- and (Z)-1-(4-methylphenyl)ethanone oxime (2k): Prepared according to General Procedure A and isolated as a white solid as a 3:1 (*E*):(*Z*) mixture. Analytical data were consistent with literature reports.⁵⁸
¹H NMR (500 MHz, CDCl₃) δ 8.19 (br s, 1H), 7.25 (ddp, J = 7.5, 5.0, 2.5 Hz, 2H, major and minor), 7.23 – 7.16 (m, 2H, major and minor), 7.09 – 7.05 (m, 1H, minor), 2.35 (s, 3H, major), 2.27 (s, 3H, minor), 2.22 (s, 3H, major), 2.15 (s, 3H, minor).

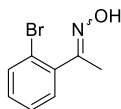


(E)- and (Z)-1-(2-methoxyphenyl)ethanone oxime (2l): Prepared according to General Procedure A and isolated as a white solid as a 8.5:1 (*E*):(*Z*) mixture. Analytical data were consistent with literature reports.⁵⁹
¹H NMR (600 MHz, CDCl₃): δ 7.34 (ddd, J = 8.3, 7.5, 1.8 Hz, 1H, major), 7.29 (dd, J = 7.5, 1.7 Hz, 1H, major), 7.16 (dd, J = 1.7 Hz, 1H, minor), 7.00 (td, J = 7.4, 0.9 Hz, 1H, minor), 6.95 (td, J = 7.4, 1.0 Hz, 1H, major), 6.92 (dd, J = 8.3, 1.1 Hz, 1H, major), 3.84 (s, 3H, major), 3.84 (s, 3H, minor), 2.23 (s, 3H, major), 2.17 (s, 3H, minor).



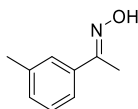
(E)- and (Z)-1-(2-fluorophenyl)ethanone oxime (2m): Prepared according to General Procedure A and isolated as a white solid as a mixture of isomers 14:1 (*E*):(*Z*). Analytical data were consistent with literature reports of the (*E*) isomer.⁴⁹

¹H NMR (500 MHz, CDCl₃) δ 9.17 (br, 1H), 7.46 (td, *J* = 7.6, 1.8 Hz, 1H, major), 7.35 (dddd, *J* = 8.2, 7.1, 5.1, 1.8 Hz, 1H, major), 7.30 (td, *J* = 7.6, 1.8 Hz, 1H minor), 7.20 – 7.06 (m, 2H major, 3H minor), 2.30 (d, *J* = 2.4 Hz, 3H, major), 2.23 (s, 3H, minor).



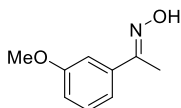
(E)- and (Z)-1-(2-bromophenyl)ethanone oxime (2n): Prepared according to General Procedure A and isolated as a white solid as a 4.1:1 (*E*):(*Z*) mixture. Analytical data were consistent with literature reports.^{59,60}

¹H NMR (500 MHz, CDCl₃) δ 8.11 (br s, 1H), major: 7.61 (dd, *J* = 7.1, 1.0 Hz, 1H), 7.33 – 7.26 (m, 2H), 7.26 – 7.19 (m, 1H), 2.26 (s, 3H), minor: 7.62 (dd, *J* = 7.0, 1.2 Hz, 1H), 7.39 – 7.33 (m, 2H), 7.14 (dd, *J* = 6.0, 1.60 Hz, 1H), 2.20 (s, 3H).



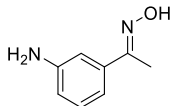
(E)-1-(3-methylphenyl)ethanone oxime (2o): Prepared according to General Procedure A and isolated as a white solid. Analytical data were consistent with literature reports.^{48,61}

¹H NMR (600 MHz, CDCl₃) δ 8.76 (br, 1H), 7.45 (s, 1H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 2.39 (s, 3H), 2.30 (s, 3H).



(E)-1-(3-methoxyphenyl)ethanone oxime (2p): Prepared according to General Procedure A and isolated as a white solid. Analytical data were consistent with literature reports.⁶¹

¹H NMR (500 MHz, CDCl₃) δ 8.39 (br s, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.19 (s, 1H), 6.93 (ddd, *J* = 8.2, 2.6, 1.1 Hz, 1H), 3.84 (s, 3H), 2.28 (s, 3H).

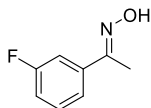


(E)-1-(3-aminophenyl)ethanone oxime (2q): Prepared according to General Procedure A and isolated as a brown solid (65% yield).

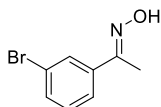
¹H NMR (600 MHz, DMSO) δ 10.96 (s, 1H), 7.00 (t, *J* = 7.8 Hz, 1H), 6.87 (t, *J* = 2.0 Hz, 1H), 6.77 (ddd, *J* = 7.7, 1.7, 1.0 Hz, 1H), 6.55 (ddd, *J* = 7.9, 2.3, 1.0 Hz, 1H), 5.08 (s, 2H), 2.07 (s, 3H).

¹³C NMR (151 MHz, DMSO) δ 153.25, 148.52, 137.58, 128.70, 114.30, 113.42, 111.02, 11.62.

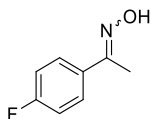
HRMS (ESI⁺): *m/z* calcd for C₈H₁₀N₂O [M+H]⁺ 151.0866, found 151.0871.



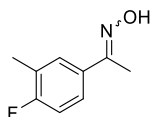
(E)-1-(3-fluorophenyl)ethanone oxime (2r): Prepared according to General Procedure A and isolated as a white solid. Analytical data were consistent with literature reports.⁴⁹
¹H NMR (600 MHz, CDCl₃) δ 8.89 (br s, 1H), 7.41 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.40 – 7.30 (m, 2H), 7.08 (tdd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 2.29 (s, 3H).



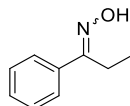
(E)-1-(3-bromophenyl)ethanone oxime (2s): Prepared according to General Procedure A and isolated as a white solid. Analytical data were consistent with literature reports.⁶¹
¹H NMR (600 MHz, CDCl₃) δ 7.89 (br s, 1H), 7.79 (t, *J* = 1.9 Hz, 1H), 7.56 (ddd, *J* = 7.8, 1.7, 1.0 Hz, 1H), 7.50 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.25 (t, *J* = 7.9 Hz, 1H), 2.26 (s, 3H).



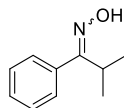
(E)- and (Z)-1-(4-fluorophenyl)ethanone oxime (2t): Prepared according to General Procedure A and isolated as a white solid as a mixture of 51:1 (*E*):(*Z*) isomers. Analytical data were consistent with literature reports of the (*E*) isomer.^{48,62}
¹H NMR (600 MHz, CDCl₃) δ 8.55 (br s, 1H), 7.71 – 7.51 (m, 2H, major and minor), 7.13 – 7.02 (m, 2H, major and minor), 2.28 (s, 3H, major), 2.23 (s, 3H, minor).



(E)-1-(4-fluoro-3-methyl-phenyl)-ethanone oxime (2u): Prepared according to General Procedure A and isolated as a white solid (84% yield).
¹H NMR (600 MHz, CDCl₃) δ 8.32 (s, 1H), 7.46 (d, *J* = 7.3 Hz, 1H), 7.41 (m, 1H), 7.00 (t, *J* = 8.9 Hz, 1H), 2.30 (s, 3H), 2.27 (s, 3H).
¹³C NMR (151 MHz, CDCl₃) δ 162.03 (d, *J* = 247.6 Hz) 155.44, 132.32 (d, *J* = 3.6 Hz), 129.26 (d, *J* = 5.5 Hz), 125.22 (d, *J* = 8.3 Hz), 124.98 (d, *J* = 17.7 Hz), 115.07 (d, *J* = 22.9 Hz), 14.63 (d, *J* = 3.4 Hz), 12.20.
¹⁹F NMR (565 MHz, CDCl₃) δ -116.36 (s).
 HRMS (ESI⁺): *m/z* calcd for C₉H₁₀FNO [M+H]⁺ 168.0819, found 168.0825.

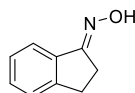


(E)-1-phenyl-1-propanone oxime (2v): Prepared according to General Procedure A and isolated as a white solid. Analytical data were consistent with literature reports.^{48,63}
¹H NMR (500 MHz, CDCl₃) δ 7.65 – 7.58 (m, 2H), 7.38 (dd, *J* = 5.2, 1.9 Hz, 3H), 2.82 (q, *J* = 7.6 Hz, 2H), 1.18 (t, *J* = 7.6 Hz, 3H).



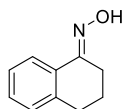
(E)- and (Z)-2-methyl-1-phenylpropan-1-one oxime (2w): Prepared according to General Procedure A and isolated as a white solid as a 1:1.25 (*E*):(*Z*) ratio. Analytical data were consistent with literature reports.^{64,65}

¹H NMR (600 MHz, CDCl₃) δ 7.46 – 7.39 (m, 1H, major and minor), 7.41 – 7.32 (m, 3H, major and minor), 7.29 – 7.25 (m, 1H, major and minor), 3.60 (hept, *J* = 7.1 Hz, 1H, minor), 2.83 (hept, *J* = 6.9 Hz, 1H, major), 1.22 (d, *J* = 7.1 Hz, 6H, minor), 1.13 (d, *J* = 6.9 Hz, 6H, major).



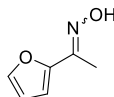
(E)-2,3-dihydro-1H-inden-1-one oxime (2x): Prepared according to General Procedure A and isolated as a white solid. Analytical data were consistent with literature reports.⁶⁶

¹H NMR (600 MHz, CDCl₃) δ 8.43 (br s, 1H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.37 – 7.31 (m, 2H), 7.26 (t, *J* = 6.9 Hz, 1H), 3.11 – 3.05 (m, 2H), 3.02 – 2.95 (m, 2H).



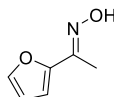
(E)-3,4-dihydronaphthalen-1(2H)-one oxime (2y): Prepared according to General Procedure A and isolated as an off-white solid. Analytical data were consistent with literature reports.^{59,66}

¹H NMR (500 MHz, CDCl₃) δ 8.38 (br s, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.34 – 7.22 (m, 2H), 7.19 (d, *J* = 7.5 Hz, 1H), 2.87 (t, *J* = 6.7 Hz, 2H), 2.81 (t, *J* = 6.0 Hz, 2H), 1.92 (q, *J* = 6.5 Hz, 2H).



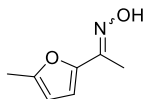
(E)- and (Z)-1-(furan-2-yl)ethanone oxime (2z): Prepared according to General Procedure A and isolated as a white solid as a 3.8:1 (*E*):(*Z*) isomer mixture. Analytical data were consistent with literature reports.^{67,68}

¹H NMR (600 MHz, CDCl₃) δ 8.17 (br s, 1H), major: 7.46 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.63 (d, *J* = 3.4 Hz, 1H), 6.44 (dd, *J* = 3.4, 1.8 Hz, 1H), 2.21 (s, 3H), minor: 7.47 (dd, *J* = 1.8, 0.7 Hz, 1H), 7.42 (m, 1H), 6.54 (dd, *J* = 3.5, 1.8 Hz, 1H), 2.27 (s, 3H).



(E)-1-(furan-2-yl)ethanone oxime (2z-(E)): Prepared according to General Procedure A and isolated as a white solid in 99% purity.

¹H NMR (600 MHz, CDCl₃) δ 7.46 (dd, *J* = 1.8, 0.7 Hz, 1H), 6.64 (dd, *J* = 3.4, 0.8 Hz, 1H), 6.44 (dd, *J* = 3.4, 1.8 Hz, 1H), 2.21 (s, 3H).

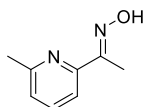


(E)- and (Z)-1-(5-methyl-2-furanyl)ethanone oxime (2aa): Prepared according to General Procedure A and isolated as white solid as a 3:1 (*E*):(*Z*) isomer mixture (80% yield).

^1H NMR (600 MHz, CDCl_3) δ 8.66 (br s, 1H), major: 6.51 (d, J = 3.3 Hz, 1H), 6.03 (dq, J = 3.2, 1.0 Hz, 1H), 2.34 (s, 3H), 2.17 (s, 3H); minor: 7.34 (d, J = 3.3 Hz, 1H), 6.14 (dq, J = 3.3, 0.9 Hz, 1H), 2.35 (s, 3H), 2.24 (s, 1H).

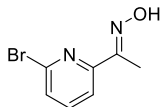
^{13}C NMR (151 MHz, CDCl_3) δ major: 153.96, 148.45, 147.71, 111.53, 107.45, 13.74, 10.97, minor: 152.84, 144.54, 144.42, 119.28, 108.60, 17.33, 13.71.

HRMS (ESI⁺): m/z calcd for $\text{C}_7\text{H}_9\text{NO}_2$ [$\text{M}+\text{Na}$]⁺ 162.0525, found 162.0525.



(E)-1-(6-methylpyridin-2-yl)ethanone oxime (2ab): Prepared according to General Procedure A and isolated as a white solid (82% yield). Analytical data were consistent with literature reports.⁶⁹

^1H NMR (600 MHz, CDCl_3) δ 7.59 (dd, J = 8.1, 1.4 Hz, 1H), 7.59 – 7.54 (m, 1H), 7.15 – 7.10 (m, 1H), 2.58 (s, 3H), 2.38 (s, 3H).

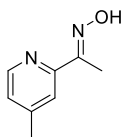


(E)-1-(6-bromo-2-pyridinyl)ethanone oxime (2ac): Prepared according to General Procedure A with some modifications. After reflux, the reaction was cooled to room temperature and diluted with water until extensive precipitation was observed, after which the solution was frozen overnight. The product was filtered and isolated as a white crystalline powder (90% yield).

^1H NMR (500 MHz, CDCl_3) δ 7.80 (d, J = 7.6 Hz, 1H), 7.53 (t, J = 7.8 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H), 2.34 (s, 3H), (1.61 br s, 1H).

^{13}C NMR (126 MHz, CDCl_3) δ 156.40, 155.31, 141.26, 138.52, 128.05, 119.17, 10.50.

HRMS (ESI⁺): m/z calcd for $\text{C}_7\text{H}_7\text{BrN}_2\text{O}$ [$\text{M}+\text{H}$]⁺ 214.9815, found 214.9821.

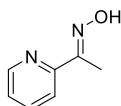


(E)- and (Z)-1-(4-Methyl-2-pyridinyl)ethanone oxime (2ad): Prepared from [ketone] according to General Procedure A and isolated as a white solid as an approximately 1:1 (*E*):(*Z*) isomer mixture (94% yield).

^1H NMR (600 MHz, CDCl_3) δ 8.48 (d, J = 5.0 Hz, 1H), 8.00 (s, 1H), 7.66 (s, 1H), 7.10 (d, J = 5.0 Hz, 1H), 2.38 (s, 3H), 2.37 (s, 3H).

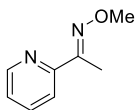
^{13}C NMR (151 MHz, CDCl_3) δ 157.36, 154.21, 148.76, 147.76, 124.96, 121.45, 21.25, 10.83.

HRMS (ESI⁺): m/z calcd for $\text{C}_8\text{H}_{10}\text{N}_2\text{O}$ [$\text{M}+\text{H}$]⁺ 151.0866, found 151.0867.



(E)-1-pyridin-2-yl-ethanone oxime (2ae): Prepared according to General Procedure A with some modifications. After reflux, the reaction was cooled to room temperature and allowed to crystallize overnight. The next day, the product was filtered, washed with H₂O, and isolated as crystalline white needles. Analytical data were consistent with literature reports.⁴⁸

¹H NMR (500 MHz, CDCl₃) δ 8.63 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H), 8.58 (br s, 1H), 7.84 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.69 (td, *J* = 7.8, 1.8 Hz, 1H), 7.31 – 7.26 (m, 1H), 2.40 (s, 3H).



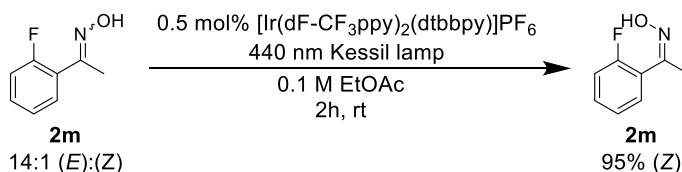
(E)- and (Z)-1-(2-pyridinyl)ethanone O-methyloxime (2af): Prepared according to General Procedure A with slight modification. The reaction was heated to reflux for 12.5h before workup and was isolated as a clear oil as an 8:1 (*E*):(*Z*) isomer mixture (64% yield).

¹H NMR (600 MHz, CDCl₃) δ 8.66 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H, minor), 8.59 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H, major), 7.90 (dt, *J* = 8.0, 1.1 Hz, 1H, major), 7.81 (dt, *J* = 8.0, 1.1 Hz, 1H, minor), 7.70 (td, *J* = 7.7, 1.8 Hz, 1H, minor), 7.68 – 7.62 (m, 1H), 7.26 – 7.21 (m, 1H, major and minor), 4.03 (s, 3H, major), 3.88 (s, 3H, minor), 2.32 (s, 3H, major), 2.29 (s, 3H, minor).

¹³C NMR (151 MHz, CDCl₃) δ 155.82, 154.51, 149.38 (minor), 148.96 (major), 136.29 (major), 135.86 (minor), 125.49 (minor), 123.74 (minor), 123.64 (major), 120.71 (major), 62.40 (major), 62.09 (minor), 20.17 (minor), 11.23 (major).

HRMS (ESI⁺): *m/z* calcd for C₈H₁₀N₂O [*M*+*H*]⁺ 151.0866, found 151.0866.

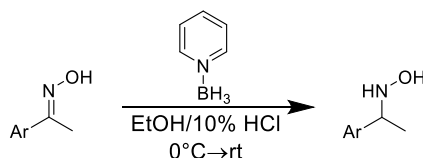
Photocatalyzed Oxime 2m Isomerization



Oxime **2m** was isomerized according to a modified procedure.⁵⁷ An (*E*):(*Z*) oxime mixture (7.6 mg, 0.0496 mmol, 1.0 equiv.), and [Ir(dF-CF₃ppy)₂(dtbbpy)]PF₆ (0.33 mg, 0.270 μmol, 0.5 mol%) were added to a 1 dram (dr) vial with septa cap electrical taped shut and equipped with a stirbar. The vial was placed under an atmosphere of N₂. To the 1 dr vial was added sparged EtOAc (600 μL) and the resulting solution was sparged for 45 min. The resulting solution was irradiated with a blue LED (Kessil, 440 nm, 40W) for 2 hours, with a fan set up to maintain room temperature. Solvent was removed by rotary evaporation with a water bath temperature of 24°C to avoid (*Z*) to (*E*) isomerization to afford *Z*-oxime product without further purification. The crude product was used as-is in the host-catalyzed reaction.

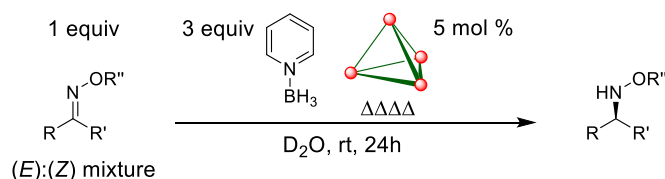
Racemic and Enantioenriched Hydroxylamine Synthesis:

General Procedure C for the Racemic Synthesis of Aryl Hydroxylamines:



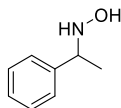
Synthesized based on a modified procedure.⁴⁴ To a 25 mL round bottomed flask equipped with a stir bar containing oxime (0.62 mmol, 1 equiv.) was added EtOH (5 mL) and pyridine borane (1.90 mmol, 3.05 equiv.). The flask was cooled to 0°C before dropwise addition of 10% HCl (10 mL). The reaction was allowed to slowly warm to rt until stopped. The resulting solution was transferred to a separatory funnel and washed twice with Et₂O (2x15 mL). To the aqueous layer was added 5M KOH until the aqueous solution pH was between 12 and 14. The basic aqueous layer was then washed three times with EtOAc (3x15 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated *via* rotary evaporation. The resulting crude product was purified by prep TLC in 2.5% MeOH/DCM.

General Procedure D for Ga₄L₆¹²⁻ Host I-Catalyzed Reductions of Aryl and Heteroaryl Oximes



To a 1 dr vial containing $\Delta\Delta\Delta\Delta$ host I (5 mol%) was added D₂O *via* Eppendorf pipette. The host solution was transferred to a second 1 dr vial equipped with a magnetic stir bar containing oxime (1.0 equiv.). The 1 dr vial containing host was rinsed with D₂O and the rinse was also transferred to the 1 dr vial containing oxime. The final concentration of solution was 55 mM in oxime. The heterogeneous solution was allowed to stir at rt for 5 minutes before addition of pyridine borane (3.0 equiv.) *via* Hamilton syringe. The reaction was then stirred at rt until the reaction time was complete, at which point the reaction was stopped by adding a large unmeasured excess of tetraethylphosphonium iodide (PEt₄I) or bromide (PEt₄Br). The stir bar was removed using a stir bar magnet and rinsed with CDCl₃. Additional CDCl₃ was added to the vial to extract the product and the CDCl₃ rinse was transferred to a 2 dr vial. The reaction solution was washed at least 3 times with CDCl₃. Solvent in the 2 dr vial from the combined rinses was removed *via* rotary evaporation to be less than 500 μ L, but not to full dryness. Internal standard, 1,3,5-trimethoxybenzene (2.00 mg, 0.0119 mmol), as a stock solution in CDCl₃ (594.5 mM) was added *via* Hamilton syringe to the 2 dr vial and the solution was transferred to an NMR tube for ¹H NMR analysis to determine yield.

Following NMR analysis of the crude reaction mixture extract, the product was returned to the 2 dr vial and the NMR tube was rinsed with EtOAc and CH₂Cl₂. Solvent in the vial was removed to near-dryness *via* rotary evaporation. The crude product was isolated *via* prep TLC.



N-hydroxy-α-methylbenzenemethanamine (3a): Racemic material was prepared according to General Procedure C. The reaction was run for 2h before workup and isolation as a white solid. Analytical data were consistent with literature reports.^{56,70}

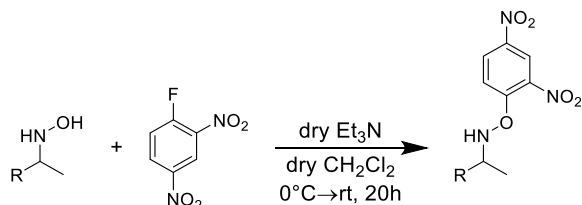
¹H NMR (600 MHz, CDCl₃) δ 7.38 – 7.30 (m, 4H), 7.32 – 7.24 (m, 1H), 6.01 (br s, 1H), 5.35 (br s, 1H), 4.12 (q, *J* = 6.7 Hz, 1H), 1.38 (d, *J* = 6.7 Hz, 3H).

ChiralCel OJ-H column (97:3 hexanes/*i*PrOH, 1 mL/min), *t*_r = 16.3 min (minor), *t*_r = 20.0 min (major).

Sample for optical rotation was prepared using ΛΛΛΛ host I: [α]_D²⁵ +22.9 (*c* = 0.8, CHCl₃). 92% ee

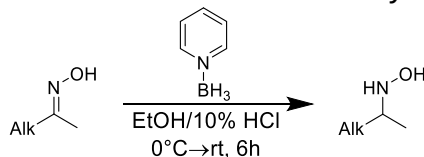
Enantioenriched material was prepared from oxime **2a** (4.05 mg, 0.0300 mmol) according to General Procedure D. The reaction was stopped with PEt₄I after 24h. Following extraction, the crude extract solution was analyzed by ¹H NMR (77% NMR yield), and the product was purified by prep TLC in 2.5% MeOH/DCM and isolated as a white solid for HPLC analysis (97% ee).

General Procedure E for Hydroxylamine Protection for HPLC Analysis



Based on a modified procedure.⁷¹ To a 1 or 2 dr vial containing crude hydroxylamine was added dry CH₂Cl₂ (0.09 mM). The vial was cooled to 0°C before addition of 2,4-dinitrofluorobenzene (1.05 equiv.) and dry Et₃N (1.0 equiv.). The reaction was allowed to slowly warm to room temperature overnight. After approximately 20h, the reaction was stopped and the organic layer diluted with CH₂Cl₂. The organic layer was washed with H₂O, and the aqueous layer was then back extracted with EtOAc. The combined organic layers were dried with MgSO₄ and solvent removed *via* rotary evaporator. The hydroxylamine was purified and isolated by prep TLC in 30% EtOAc/hexanes before being dissolved in 5% hexanes/IPA for chiral HPLC analysis.

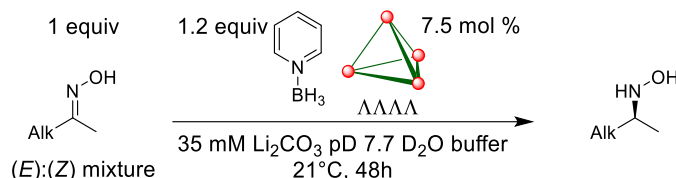
General Procedure F for the Synthesis of Aliphatic Hydroxylamines: Modified version of General Procedure C due to substrate volatility.



To a 25 mL round bottomed flask equipped with a stir bar containing oxime (0.62 mmol, 1 equiv.) was added EtOH (5 mL) and pyridine borane (1.85 mmol, 3.00 equiv.). The flask was cooled to 0°C before dropwise addition of 10% HCl (10 mL). The reaction was kept at 0°C for 2h, after which it was allowed to slowly warm to rt overnight and was stopped

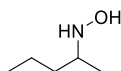
after 16h. The resulting solution was transferred to a separatory funnel and washed with Et₂O (15 mL) x2. To the aqueous layer was added 2k KOH until the solution pH was 12–13. The aqueous layer was then washed with DCM (15 mL) x3. The combined organic layers were dried over MgSO₄, filtered, and concentrated *via* rotary evaporation. To minimize product loss, the rotovap bath temperature was kept below 8°C. Characterized products were purified by prep TLC in 2.5% MeOH/DCM with 0.5% Et₃N and visualized using KMnO₄.

General Procedure G for Ga₄L₆¹²⁻ Host I-Catalyzed Reactions of Aliphatic Oximes



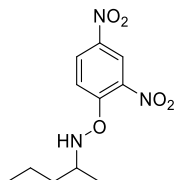
To a 1 dr vial containing $\Delta\Delta\Delta\Delta$ host **I** (7.5 mol%) was added D₂O then 50 mM Li₂CO₃ pD 7.7 D₂O buffer *via* Eppendorf pipette. The host solution was transferred to an NMR tube. The 1 dr vial was rinsed with D₂O then 50 mM Li₂CO₃ pD 7.7 D₂O buffer and the rinse was also transferred to the NMR tube. The resulting solution was host **I** in 35 mM Li₂CO₃ pD 7.7 D₂O buffer. Oxime (1.0 equiv.) was then added *via* Hamilton syringe to the NMR tube and capped with a septa cap before addition of pyridine borane (1.2 equiv.) *via* Hamilton syringe. The final concentration of solution was 55 mM in oxime. The tube was electrical taped, inverted two or three times to mix the solution, and briefly vortexed then allowed to sit at rt. After 48h, the reaction was stopped by adding tetraethylphosphonium bromide (PEt₄Br) (9 mol%) as a stock solution in D₂O. Internal standard, 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt (2.50 mg, 0.01145 mmol), as a stock solution in D₂O (176 mM) was added *via* Hamilton syringe to the NMR tube for ¹H NMR analysis.

Following ¹H NMR analysis, the reaction mixture was transferred to a 1 dr vial. The NMR tube was rinsed with CH₂Cl₂. Additional CH₂Cl₂ was added to the vial to extract the product and the CH₂Cl₂ rinse was transferred to a 1 dr vial. The reaction solution was washed at least 3 times with CH₂Cl₂. Organic solvent in the 1 dr vial from the combined rinses was removed to dryness *via* rotary evaporation below 7°C. Then a small portion of NaCl was added to the host solution in the 1 dr vial and aqueous layer was again washed at least 3 times with CH₂Cl₂. Again the rinses were transferred to the 1 dr vial and solvent was removed to dryness *via* rotary evaporation. The crude product was assumed to be extracted quantitatively and subjected to General Procedure E with a slight modification, through the use of increased amounts of 2,4,-dinitrofluorobenzene (1.4 equiv.) and dry Et₃N (1.4 equiv.).



N-hydroxy-2-pentanamine (3b): Racemic material was prepared from oxime **2b** according to General Procedure F and isolated as white solid. Analytical data were consistent with literature reports.⁴⁴

^1H NMR (600 MHz, CDCl_3) δ 5.00 (br s, 2H), 2.98 (dq, J = 12.6, 6.3 Hz, 1H), 1.52 (ddt, J = 13.0, 9.6, 5.7 Hz, 1H), 1.41 – 1.20 (m, 3H), 1.08 (d, J = 6.4 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H).



A portion of the purified product (6.7 mg, 0.065 mmol) was functionalized for chiral HPLC analysis using General Procedure E with a slight modification. Increased 2,4-dinitrofluorobenzene (1.5 equiv.) was used. After workup the product was isolated as a yellow solid.

ChiralPak IA column (98.5:1.5 hexanes/*i*PrOH, 1 mL/min), t_r = 15.4 min (minor), t_r = 17.0 min (major).

Enantioenriched material was prepared from oxime **2b** (3.60 mg, 0.0361 mmol) according to General Procedure G and allowed to react at room temperature for 24h before quenching. Following *in situ* ^1H NMR analysis (96% NMR yield), the product was extracted and subjected to a modified version of General Procedure E using dry CH_2Cl_2 (550 μL), 2,4-dinitrofluorobenzene (7.10 μL , 0.0565 mmol, 1.55 equiv.), and dry Et_3N (7.65 μL , 0.0549 mmol, 1.52 equiv.). The crude functionalized product was purified by prep TLC in 30% EtOAc/hexanes and isolated as yellow solid for HPLC analysis (51% ee).

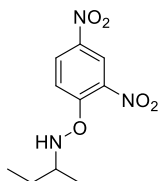


N-hydroxy-2-butanamine (3c): Racemic material was prepared from oxime **2c** according to General Procedure F and isolated as white solid.

^1H NMR (600 MHz, CDCl_3) δ 4.71 (br s, 2H), 2.91 (dq, J = 12.7, 6.3 Hz, 1H), 1.59 (dq, J = 12.9, 7.5, 5.4 Hz, 1H), 1.36 – 1.27 (m, 1H), 1.07 (d, J = 6.3 Hz, 3H), 0.92 (t, J = 7.5 Hz, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 58.83, 26.57, 17.36, 10.33.

HRMS (ESI⁺): m/z calcd for $\text{C}_4\text{H}_{11}\text{NO}$ [$\text{M}+\text{H}$]⁺ 90.0913, found 90.0921.

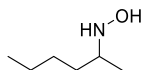


A portion of the purified product (5.35 mg, 0.60 mmol) was functionalized for chiral HPLC analysis using General Procedure E and isolated as a yellow solid.

ChiralPak AD-H column (99:1 hexanes/*i*PrOH, 1 mL/min), t_r = 25.7 min (minor), t_r = 28.6 min (major).

Enantioenriched material was prepared from oxime **2c** (3.00 mg, 0.0344 mmol) according to General Procedure G and allowed to react at room temperature for 24h before

quenching. Following *in situ* ^1H NMR analysis (99% NMR yield), the product was extracted and subjected to a modified version of General Procedure E using dry CH_2Cl_2 (450 μL), 2,4,-dinitrofluorobenzene (6.05 μL , 0.0482 mmol, 1.40 equiv.), and dry Et_3N (6.70 μL , 0.0481 mmol, 1.40 equiv.). The crude functionalized product was purified by prep TLC in 30% EtOAc/hexanes and isolated as yellow solid for HPLC analysis (55% ee).

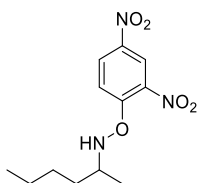


N-hydroxy-2-hexanamine (3d): Racemic material was prepared from oxime **2d** according to General Procedure F and isolated as white solid.

^1H NMR (500 MHz, CDCl_3) δ 4.11 (br s, 2H), 2.97 (h, J = 6.4 Hz, 1H), 1.54 (m, 1H), 1.29 (m, 5H), 1.08 (d, J = 6.3 Hz, 3H), 0.90 (t, J = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 57.47, 33.61, 28.31, 23.03, 23.03, 17.94, 14.18.

HRMS (ESI $^+$): m/z calcd for $\text{C}_6\text{H}_{15}\text{NO}$ $[\text{M}+\text{H}]^+$ 118.1226, found 118.1230.

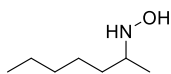


A portion of the purified product (23 mg, 0.200 mmol) was functionalized for chiral HPLC analysis using General Procedure E and isolated as a yellow solid.

ChiralPak AD-H column (99.6:0.4 hexanes/ iPrOH , 1 mL/min), t_r = 50.4 min (minor), t_r = 57.4 min (major).

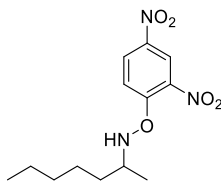
Enantioenriched material was prepared from oxime **2d** according to General Procedure D with some modifications. To a 1 dr vial containing $\Delta\Delta\Delta\Delta$ host **I** (18.10 mg, 3.75 μmol , 7.5 mol%) was added D_2O (200 μL) then 50 mM Li_2CO_3 pD 7.7 D_2O buffer (530 μL) *via* Eppendorf pipette. The host solution was transferred to a second dr vial equipped with a magnetic stir bar containing oxime **2d** (5.74 mg, 0.0498 mmol, 1.0 equiv.). The 1 dr vial containing host **I** was rinsed with D_2O (75 μL) and 50 mM Li_2CO_3 pD 7.7 D_2O buffer (100 μL) and the rinse was also transferred to the 1 dr vial containing oxime. The final concentration of solution was 55 mM in oxime and 35 mM Li_2CO_3 pD 7.7 D_2O buffer. To the heterogeneous solution was added pyridine borane (6.00 μL , 0.0600 mmol, 1.20 equiv.) *via* Hamilton syringe. The reaction was then stirred at rt for 40h, then the reaction was stopped by adding an unmeasured excess of PET_4Br . The stir bar was removed using a stir bar magnet and rinsed with CDCl_3 . Additional CDCl_3 was added to the vial to extract the product and the CDCl_3 rinse was transferred to a 2 dr vial. The reaction solution was washed at least 3 times with CDCl_3 . Solvent in the 2 dr vial from the combined rinses was removed *via* rotary evaporation to be less than 500 μL , but not to full dryness. To minimize product loss, the rotovap bath temperature was kept below 7°C . To the 1 dr reaction vial was added a small, unmeasured amount of NaCl. The extraction process was repeated once more and the resulting solution from rinses partially removed *via* rotary evaporation. Internal standard was added, and the solution was transferred to an NMR tube for ^1H NMR analysis (55% NMR yield).

Following NMR analysis of the crude reaction mixture extract, the product was returned to the 2 dr vial and the NMR tube was rinsed with CH₂Cl₂. Solvent in the vial was removed to near-dryness (<50 μ L solution) *via* rotary evaporation, still below 7°C. Dry CH₂Cl₂ (200 μ L) was added to the 2 dr vial and the solution transferred to a new 1 dr vial equipped with a magnetic stir bar. The 2 dr vial was rinsed with additional CH₂Cl₂ (100 μ L) and the rinse transferred to the 1 dr vial. The crude product was assumed to be transferred quantitatively and subjected to General Procedure E with a slight modification, through the use of increased amounts of 2,4,-dinitrofluorobenzene (5.15 μ L, 0.0410 mmol, 1.50 equiv.), and dry Et₃N (5.70 μ L, 0.0409 mmol, 1.49 equiv.). The crude functionalized product was purified by prep TLC in 30% EtOAc/hexanes and isolated as yellow solid for HPLC analysis (34% ee).



N-hydroxy-2-heptanamine (3e): Racemic material was prepared from oxime **2e** according to General Procedure F and isolated as a white solid. Analytical data were consistent with literature reports.⁷²

¹H NMR (600 MHz, CDCl₃) δ 5.13 (s, 2H), 2.96 (h, *J* = 6.3 Hz, 1H), 1.52 (ddd, *J* = 12.6, 9.7, 5.7 Hz, 1H), 1.35 – 1.22 (m, 7H), 1.08 (d, *J* = 6.3 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H).



A portion of the purified product (28.8 mg, 0.219 mmol) was functionalized for chiral HPLC analysis using General Procedure E and isolated as a yellow solid.

ChiralPak AD-H column (99.4:0.6 hexanes/*i*-PrOH, 1 mL/min), *t_r* = 26.4 min (minor), *t_r* = 29.7 min (major).

Enantioenriched material was prepared from oxime **2e** according to General Procedure D with some modifications. To a 1 dr vial containing $\Delta\Delta\Delta$ host **I** (20.75 mg, 4.29 μ mol, 7.5 mol%) was added D₂O (240 μ L) then 50 mM Li₂CO₃ pD 7.7 D₂O buffer (600 μ L) *via* Eppendorf pipette. The host solution was transferred to a second dr vial equipped with a magnetic stir bar containing oxime **2e** (7.38 mg, 0.0571 mmol, 1.0 equiv.). The 1 dr vial containing host **I** was rinsed with D₂O (70 μ L) and 50 mM Li₂CO₃ pD 7.7 D₂O buffer (125 μ L) and the rinse was also transferred to the 1 dr vial containing oxime. The final concentration of solution was 55 mM in oxime and 35 mM Li₂CO₃ pD 7.7 D₂O buffer. To the heterogeneous solution was added pyridine borane (6.85 μ L, 0.0685 mmol, 1.20 equiv.) *via* Hamilton syringe. The reaction was then stirred at rt for 40h, then the reaction was stopped by adding an unmeasured excess of PET₄Br. The stir bar was removed using a stir bar magnet and rinsed with CDCl₃. Additional CDCl₃ was added to the vial to extract the product and the CDCl₃ rinse was transferred to a 2 dr vial. The reaction solution was washed at least 3 times with CDCl₃. Solvent in the 2 dr vial from the combined rinses was removed *via* rotary evaporation to be less than 500 μ L, but not to full dryness. To minimize product loss, the rotovap bath temperature was kept below 7°C. To the 1 dr reaction vial

was added a small, unmeasured amount of NaCl. The extraction process was repeated once more and the resulting solution from rinses partially removed *via* rotary evaporation. Internal standard was added, and the solution was transferred to an NMR tube for ^1H NMR analysis (28% NMR yield).

Following NMR analysis of the crude reaction mixture extract, the product was returned to the 2 dr vial and the NMR tube was rinsed with CH_2Cl_2 . Solvent in the vial was removed to near-dryness (<50 μL solution) *via* rotary evaporation, still below 7°C . Dry CH_2Cl_2 (150 μL) was added to the 2 dr vial and the solution transferred to a new 1 dr vial equipped with a magnetic stir bar. The 2 dr vial was rinsed with additional CH_2Cl_2 (100 μL) and the rinse transferred to the 1 dr vial. The crude product was assumed to be transferred quantitatively and subjected to General Procedure E with a slight modification, through the use of increased amounts of 2,4,-dinitrofluorobenzene (4.00 μL , 0.0319 mmol, 1.99 equiv.), and dry Et_3N (4.45 μL , 0.0319 mmol, 2.00 equiv.). The crude functionalized product was purified by prep TLC in 30% EtOAc/hexanes and isolated as yellow solid for HPLC analysis (34% ee).

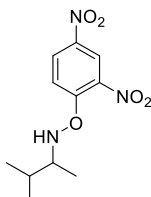


N-Hydroxy-3-methyl-2-butanamine (3f): Racemic material was prepared from oxime **2f** according to General Procedure F and isolated as a white solid.

^1H NMR (600 MHz, CDCl_3) δ 2.83 (qd, J = 6.5, 5.1 Hz, 1H), 1.84 (hept, J = 6.9, 5.0 Hz, 1H), 1.01 (d, J = 6.5 Hz, 3H), 0.93 (d, J = 6.9 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 62.44, 29.75, 19.61, 17.35, 13.64.

HRMS (ESI+): m/z calcd for $\text{C}_5\text{H}_{13}\text{NO}$ $[\text{M}+\text{H}]^+$ 104.1070, found 104.1068.

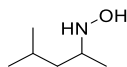


A portion of the purified product (12.0 mg, 0.116 mmol) was functionalized for chiral HPLC analysis using General Procedure E with a slight modification. Increased 2,4-dinitrofluorobenzene (1.2 equiv.) and Et_3N (1.2 equiv.) were used. After workup the product was isolated as a yellow solid.

ChiralPak AD-H column (99:1 hexanes/ PrOH , 1 mL/min), t_r = 20.4 min (minor), t_r = 22.9 min (major).

Enantioenriched material was prepared from oxime **2f** (4.23 mg, 0.0418 mmol) according to General Procedure G and allowed to react at room temperature for 24h before quenching. Following *in situ* ^1H NMR analysis (98% NMR yield), the product was extracted and subjected to a modified version of General Procedure E using dry CH_2Cl_2 (500 μL), 2,4,-dinitrofluorobenzene (7.40 μL , 0.0589 mmol, 1.40 equiv.), and dry Et_3N (8.15 μL , 0.0585 mmol, 1.40 equiv.). The crude functionalized product was purified by

prep TLC in 30% EtOAc/hexanes and isolated as yellow solid for HPLC analysis (27% ee).

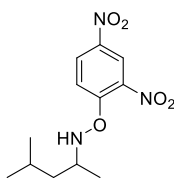


N-Hydroxy-4-methyl-2-pentanamine (3g): Racemic material was prepared from oxime **2g** according to General Procedure F and isolated as a white solid.

^1H NMR (600 MHz, CDCl_3) δ 4.94 (br s, 2H), 3.05 (dp, $J = 7.6, 6.2$ Hz, 1H), 1.66 (dh, $J = 7.9, 6.5$ Hz, 1H), 1.38 (ddd, $J = 13.7, 7.9, 6.0$ Hz, 1H), 1.13 (ddd, $J = 13.8, 7.6, 6.5$ Hz, 1H), 1.09 (d, $J = 6.3$ Hz, 3H), 0.92 (d, $J = 6.6$ Hz, 3H), 0.89 (d, $J = 6.6$ Hz, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 55.49, 43.19, 25.12, 23.38, 22.60, 18.26.

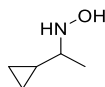
HRMS (ESI $^+$): m/z calcd for $\text{C}_6\text{H}_{15}\text{NO}$ $[\text{M}+\text{H}]^+$ 118.1226, found 118.1228.



A portion of the purified product (14.6 mg, 0.125 mmol) was functionalized for chiral HPLC analysis using General Procedure E with a slight modification. Increased 2,4-dinitrofluorobenzene (1.1 equiv.) and Et_3N (1.1 equiv.) were used. After workup the product was isolated as a yellow solid.

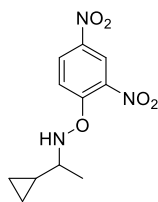
ChiralPak AD-H column (98.5:1.5 hexanes/ i PrOH, 1 mL/min), $t_r = 10.5$ min (minor), $t_r = 11.9$ min (major).

Enantioenriched material was prepared from oxime **2g** (5.18 mg, 0.0450 mmol) according to General Procedure G and allowed to react at room temperature for 24h before quenching. Following *in situ* ^1H NMR analysis (53% NMR yield), the product was extracted and subjected to a modified version of General Procedure E using dry CH_2Cl_2 (500 μL), 2,4-dinitrofluorobenzene (7.90 μL , 0.0629 mmol, 1.40 equiv.), and dry Et_3N (8.70 μL , 0.0624 mmol, 1.39 equiv.). The crude functionalized product was purified by prep TLC in 30% EtOAc/hexanes and isolated as yellow solid for HPLC analysis (19% ee).



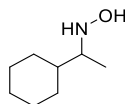
N-Hydroxy- α -methylcyclopropanemethanamine (3h): Racemic material was prepared from oxime **2h** according to General Procedure F and isolated as a white solid. Analytical data were consistent with literature reports.⁷³

^1H NMR (600 MHz, CDCl_3) δ 5.29 (s, 2H), 2.26 – 2.16 (m, 1H), 1.20 (d, $J = 6.4$ Hz, 3H), 0.76 – 0.68 (m, 1H), 0.49 (d, $J = 8.8$ Hz, 2H), 0.31 – 0.23 (m, 1H), 0.19 – 0.10 (m, 1H).



A portion of the purified product (17.3 mg, 0.171 mmol) was functionalized for chiral HPLC analysis using General Procedure E and isolated as a yellow solid. ChiralPak IA column (96:4 hexanes/*i*PrOH, 1 mL/min), t_r = 12.4 min (major), t_r = 14.0 min (minor).

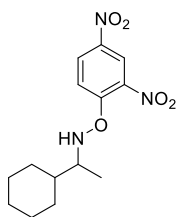
Enantioenriched material was prepared from oxime **2h** (4.03 mg, 0.0407 mmol) according to General Procedure G and allowed to react at room temperature for 24h before quenching. Following *in situ* ^1H NMR analysis (94% NMR yield), the product was extracted and subjected to a modified version of General Procedure E using dry CH_2Cl_2 (550 μL), 2,4,-dinitrofluorobenzene (7.15 μL , 0.0569 mmol, 1.40 equiv.), and dry Et_3N (7.90 μL , 0.0567 mmol, 1.39 equiv.). The crude functionalized product was purified by prep TLC in 30% EtOAc/hexanes and isolated as yellow solid for HPLC analysis (10% ee).



***N*-Hydroxy- α -methylcyclohexanemethanamine (**3i**):** Racemic material was prepared from oxime **2i** according to General Procedure F and isolated as a white solid. Analytical data were consistent with literature reports.⁷²

^1H NMR (600 MHz, CDCl_3) δ 5.45 (br s, 2H), 2.81 (qd, J = 6.5, 5.2 Hz, 1H), 1.80 – 1.71 (m, 2H), 1.74 – 1.63 (m, 3H), 1.47 (tdt, J = 11.8, 5.2, 3.2 Hz, 1H), 1.30 – 1.17 (m, 2H), 1.12 (qt, J = 12.9, 3.4 Hz, 1H), 1.05 (d, J = 6.5 Hz, 3H), 1.04 – 0.93 (m, 2H).

^{13}C NMR (151 MHz, CDCl_3) δ 61.95, 40.21, 29.99, 28.23, 26.75, 26.65, 26.51, 14.52.



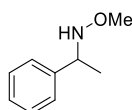
A portion of the purified product (8.9 mg, 0.062 mmol) was functionalized for chiral HPLC analysis using General Procedure E with a slight modification. Increased 2,4-dinitrofluorobenzene (1.1 equiv.) was used. After workup the product was isolated as a yellow solid.

ChiralPak AD-H column (98:2 hexanes/*i*PrOH, 1 mL/min), t_r = 12.3 min (major), t_r = 13.8 min (minor).

Enantioenriched material was prepared from oxime **2i** according to General Procedure D with some modifications. To a 1 dr vial containing $\Delta\Delta\Delta\Delta$ host **I** (12.60 mg, 2.61 μmol , 7.5 mol%) was added D_2O (130 μL) then 50 mM Li_2CO_3 pD 7.7 D_2O buffer (400 μL) *via*

Eppendorf pipette. The host solution was transferred to a second dr vial equipped with a magnetic stir bar containing oxime **2i** (4.90 mg, 0.0347 mmol, 1.0 equiv.). The 1 dr vial containing host **1** was rinsed with D₂O (60 μ L) and 50 mM Li₂CO₃ pD 7.7 D₂O buffer (40 μ L) and the rinse was also transferred to the 1 dr vial containing oxime. The final concentration of solution was 55 mM in oxime and 35 mM Li₂CO₃ pD 7.7 D₂O buffer. To the heterogeneous solution was added pyridine borane (4.20 μ L, 0.0420 mmol, 1.21 equiv.) *via* Hamilton syringe. The reaction was then stirred at rt for 24h, then the reaction was stopped by adding an unmeasured excess of PET₄Br. The stir bar was removed using a stir bar magnet and rinsed with CDCl₃. Additional CDCl₃ was added to the vial to extract the product and the CDCl₃ rinse was transferred to a 2 dr vial. The reaction solution was washed at least 3 times with CDCl₃. Solvent in the 2 dr vial from the combined rinses was removed *via* rotary evaporation to be less than 500 μ L, but not to full dryness. To minimize product loss, the rotovap bath temperature was kept below 7°C. To the 1 dr reaction vial was added a small, unmeasured amount of NaCl. The extraction process was repeated once more and the resulting solution from rinses partially removed *via* rotary evaporation. Internal standard was added, and the solution was transferred to an NMR tube for ¹H NMR analysis (32% NMR yield).

Following NMR analysis of the crude reaction mixture extract, the product was returned to the 2 dr vial and the NMR tube was rinsed with CH₂Cl₂. Solvent in the vial was removed to near-dryness (<50 μ L solution) *via* rotary evaporation, still below 7°C. Dry CH₂Cl₂ (80 μ L) was added to the 2 dr vial and the solution transferred to a new 1 dr vial equipped with a magnetic stir bar. The 2 dr vial was rinsed with additional CH₂Cl₂ (50 μ L) and the rinse transferred to the 1 dr vial. The crude product was assumed to be transferred quantitatively and subjected to General Procedure E with a slight modification, through the use of increased amounts of 2,4,-dinitrofluorobenzene (2.20 μ L, 0.0175 mmol, 1.58 equiv.), and dry Et₃N (2.40 μ L, 0.0172 mmol, 1.55 equiv.). The crude functionalized product was purified by prep TLC in 30% EtOAc/hexanes and isolated as yellow solid for HPLC analysis (76% ee).



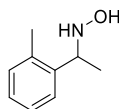
N-methoxy- α -methylbenzenemethanamine (3j): Racemic material was prepared from oxime **2j** according to General Procedure C. The reaction was run for 7.5h, with the reaction kept at 0°C for the first 2.33h. The crude product was purified by prep TLC in 1.25% MeOH/DCM and isolated as a clear oil. Analytical data were consistent with literature reports.⁷⁴

¹H NMR (600 MHz, CDCl₃) δ 7.38 – 7.31 (m, 4H), 7.29 – 7.26 (m, 1H), 5.61 (br s, 1H), 4.14 (q, *J* = 6.7 Hz, 1H), 3.49 (s, 3H), 1.37 (d, *J* = 6.6 Hz, 3H).

ChiralCel OJ-H column (99.9:0.1 hexanes/*i*PrOH, 1 mL/min), *t_r* = 8.8 min (minor), *t_r* = 11.4 min (major).

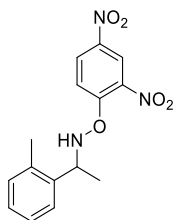
Enantioenriched material was prepared from oxime **2j** (10.60 mg, 0.07105 mmol) according to General Procedure D with a slight modification. The reaction was stopped with PET₄I after 24h. Following extraction, the crude extract solution was analyzed by ¹H

NMR (23% NMR yield), and the product was purified by prep TLC in 1.25% MeOH/DCM and isolated as a clear oil for HPLC analysis (20% ee).



N-hydroxy-α,2-dimethylbenzenemethanamine (3k): Racemic material was prepared from oxime **2k** (48 mg, 0.32 mmol) according to General Procedure C. The reaction was run for 6h. The crude product was purified for characterization by prep TLC in 2% MeOH/DCM and isolated as a white solid. Analytical data were consistent with literature reports.⁷⁵

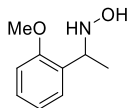
¹H NMR (600 MHz, CDCl₃) δ 7.38 (d, *J* = 7.2 Hz, 1H), 7.24 – 7.14 (m, 3H), 5.65 (br s, 1H), 4.43 (q, *J* = 6.6 Hz, 1H), 2.38 (s, 3H), 1.36 (d, *J* = 6.6 Hz, 3H).



A portion of the crude product (12.0 mg, 0.0794 mmol) was functionalized for chiral HPLC analysis using General Procedure E with a slight modification. Increased 2,4-dinitrofluorobenzene (1.4 equiv.) and Et₃N (1.4 equiv.) were used. After workup, the product was isolated as a yellow solid.

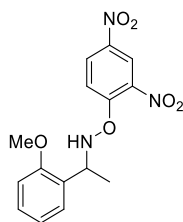
ChiralPak AD-H column (98:2 hexanes/*i*PrOH, 1 mL/min), *t*_r = 12.8 min (minor), *t*_r = 14.3 min (major).

Enantioenriched material was prepared from oxime **2k** (6.18 mg, 0.0414 mmol) according to General Procedure D with some modifications. The reaction was stopped with PEt₄Br after 24h. Following extraction, the crude extract solution was analyzed by ¹H NMR (73% NMR yield), then the reaction mixture was transferred to a 1 dr vial and solvent was removed to dryness *via* rotary evaporation. The crude product was subjected to General Procedure E with a slight modification. Quantitative transfer was assumed before addition of dry CH₂Cl₂ (300 μL) and increased amounts of 2,4-dinitrofluorobenzene (5.50 μL, 0.0420 mmol, 1.39 equiv.) and dry Et₃N (6.00 μL, 0.0420 mmol, 1.39 equiv.). The crude functionalized product was purified by prep TLC in 2.5% MeOH/DCM and isolated as yellow solid for HPLC analysis (89% ee).



N-(1-(2-methoxyphenyl)ethyl)hydroxylamine (3l): Racemic material was prepared from oxime **2l** (51 mg, 0.31 mmol) according to General Procedure C. The reaction was run for 6h. The crude product was purified for characterization by prep TLC in 2% MeOH/DCM and isolated as a white solid. Analytical data were consistent with literature reports.⁷⁰

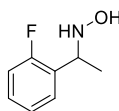
^1H NMR (600 MHz, CDCl_3) δ 7.30 (dd, J = 7.6, 1.7 Hz, 1H), 7.28 – 7.22 (m, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 5.86 (br s, 2H) 4.48 (q, J = 6.7 Hz, 1H), 3.84 (s, 3H), 1.42 (d, J = 6.7 Hz, 3H).



A portion of the crude product (11.0 mg, 0.066 mmol) was functionalized for chiral HPLC analysis using General Procedure E with a slight modification. Increased 2,4-dinitrofluorobenzene (1.4 equiv.) and Et_3N (1.6 equiv.) were used. After workup, the product was purified by prep TLC in 30% EtOAc/hexanes, and isolated as a dark yellow solid.

ChiralCel AD-H column (99.5:0.05 hexanes/ i PrOH, 1 mL/min), t_r = 38.2 min (major), t_r = 43.3 min (minor).

Enantioenriched material was prepared from oxime **2l** (4.46 mg, 0.0270 mmol) according to General Procedure D with some modifications. To the 1 dr vial containing oxime and a magnetic stir bar was added $\Delta\Delta\Delta\Delta$ host **l** (6.55 mg, 1.36 μmol , 5.0 mol%) as a solution in D_2O . The reaction was stopped with PEt_4Br after 24h. Following extraction, the crude extract solution was analyzed by ^1H NMR (51% NMR yield), then the reaction mixture was transferred to a 1 dr vial and solvent was removed to dryness *via* rotary evaporation. The crude product was subjected to General Procedure E with a slight modification. Quantitative transfer was assumed before addition of dry CH_2Cl_2 (300 μL) and increased amounts of 2,4-dinitrofluorobenzene (2.25 μL , 0.0179 mmol, 1.31 equiv.) and dry Et_3N (2.50 μL , 0.0179 mmol, 1.31 equiv.). The crude functionalized product was purified by prep TLC in 35% EtOAc/hexanes and isolated as yellow solid for HPLC analysis (94% ee).



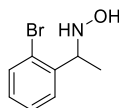
2-fluoro-*N*-hydroxy- α -methylbenzenemethanamine (3m): Racemic material was prepared from oxime **2m** according to General Procedure C. The reaction was run for 5h and the product was isolated as a white solid. Analytical data were consistent with literature reports.⁷⁵

^1H NMR (600 MHz, CDCl_3) δ 7.37 (td, J = 7.5, 1.8 Hz, 1H), 7.28 – 7.21 (m, 1H), 7.13 (td, J = 7.5, 1.2 Hz, 1H), 7.04 (ddd, J = 10.6, 8.2, 1.2 Hz, 1H), 5.84 (br, 2H), 4.46 (q, J = 6.8 Hz, 1H), 1.40 (d, J = 6.8 Hz, 3H).

ChiralCel OJ-H column (98:2 hexanes/ i PrOH, 1 mL/min), t_r = 19.9 min (major), t_r = 23.3 min (minor).

Enantioenriched material was prepared from oxime **2m** (3.98 mg, 0.0260 mmol) according to General Procedure D using $\Delta\Delta\Delta\Delta$ host **l** (6.29 mg, 1.30 μmol , 5.0 mol%).

The reaction was stopped with PEt_4Br after 24h. Following extraction, the crude extract solution was analyzed by ^1H NMR (79% NMR yield), then the product was purified by prep TLC in 2.25% MeOH/DCM and isolated as a white solid for HPLC analysis (65% ee).



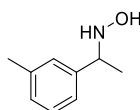
2-bromo-N-hydroxy-α-methylbenzenemethanamine (3n): Racemic material was prepared from oxime **2n** according to General Procedure C with a slight modification. The crude product was purified by prep TLC in 3% MeOH/DCM and isolated as a white solid. ^1H NMR (600 MHz, CDCl_3) δ 7.56 (dd, J = 8.0, 1.3 Hz, 1H), 7.51 (dd, J = 7.8, 1.7 Hz, 1H), 7.33 (td, J = 7.7, 1.3 Hz, 1H), 7.15 – 7.11 (m, 1H), 4.92 (br s, 1H), 4.63 (q, J = 6.7 Hz, 1H), 1.35 (d, J = 6.6 Hz, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 141.54, 133.19, 128.91, 127.87, 127.66, 124.12, 60.31, 18.60.

HRMS (ESI+): m/z calcd for $\text{C}_8\text{H}_{10}\text{BrNO}$ ($[\text{M}+\text{H}]^+$ 216.0019, found 216.0026.

ChiralCel OJ-H column (95:5 hexanes/ i PrOH, 1 mL/min), t_r = 16.2 min (major), t_r = 23.6 min (minor).

Enantioenriched material was prepared from oxime **2n** (7.07 mg, 0.0330 mmol) according to General Procedure D with some modifications. To the 1 dr vial containing oxime and a magnetic stir bar was added $\Delta\Delta\Delta\Delta$ host **1** (11.97 mg, 2.48 μmol , 7.5 mol%) as a solution in D_2O . The reaction was stopped with PEt_4Br after 72h. Following extraction, the crude extract solution was analyzed by ^1H NMR (41% NMR yield). The desired product was purified by prep TLC in 3% MeOH/DCM and isolated as a white solid for HPLC analysis (65% ee).

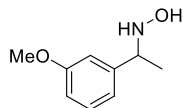


N-hydroxy-α,3-dimethylbenzenemethanamine (3o): Racemic material was prepared from oxime **2o** according to General Procedure C. The reaction was run for 1.25h before workup and isolation as a white solid. Analytical data were consistent with literature reports.⁷⁵

^1H NMR (600 MHz, CDCl_3) δ 7.24 (t, J = 7.5 Hz, 1H), 7.17 – 7.04 (m, 3H), 5.70 (s, 2H), 4.08 (q, J = 6.7 Hz, 1H), 2.36 (s, 3H), 1.38 (d, J = 6.7 Hz, 3H).

ChiralCel OJ-H column (97:3 hexanes/ i PrOH, 1 mL/min), t_r = 13.1 min (minor), t_r = 16.1 min (major).

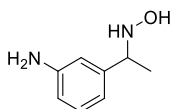
Enantioenriched material was prepared from oxime **2o** (7.75 mg, 0.0520 mmol) according to General Procedure D. The reaction was stopped with PEt_4I after 24h. Following extraction, the crude extract solution was analyzed by ^1H NMR (67% NMR yield), then the product was purified by prep TLC in 2.5% MeOH/DCM and isolated as a white solid for HPLC analysis (92% ee).



N-hydroxy-3-methoxy- α -methylbenzenemethanamine (3p): Racemic material was prepared from oxime **2p** according to General Procedure C. The reaction was allowed to warm overnight and ran for 16h before workup and isolation as white solid. Analytical data were consistent with literature reports.⁷²

¹H NMR (400 MHz, CDCl₃) δ 7.25 (t, J = 8.0 Hz, 1H), 6.96 – 6.85 (m, 2H), 6.82 (d, J = 8.2 Hz, 1H), 5.76 (br s, 2H), 4.10 (q, J = 6.7 Hz, 1H), 3.81 (s, 3H), 1.37 (d, J = 6.8 Hz, 3H). ChiralCel AD-H column (96:4 hexanes/*i*PrOH, 1 mL/min), t_r = 24.9 min (minor), t_r = 31.2 min (major).

Enantioenriched material was prepared from oxime **2p** (3.98 mg, 0.0260 mmol) according to General Procedure D using $\Delta\Delta\Delta\Delta$ host **I** (6.59 mg, 1.36 μ mol, 5.0 mol%). The reaction was stopped with PEt₄Br after 24h. Following extraction, the crude extract solution was analyzed by ¹H NMR (77% NMR yield), then the product was purified by prep TLC 2.5% MeOH/DCM and isolated as a white solid for HPLC analysis (99% ee).

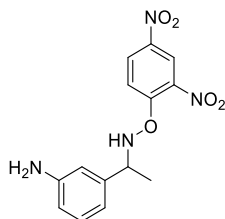


3-amino-N-hydroxy- α -methylbenzenemethanamine (3q): Racemic material was prepared from oxime **2q** (31 mg, 0.21 mmol) according to General Procedure C with some modifications. The reaction was allowed to warm overnight and run for 16h. The crude product was purified for characterization by prep TLC in 3% MeOH/DCM and isolated as a white solid.

¹H NMR (600 MHz, CDCl₃) δ 7.11 (t, J = 7.8 Hz, 1H), 6.72 (d, J = 7.6 Hz, 1H), 6.65 (t, J = 2.0 Hz, 1H), 6.59 (dd, J = 7.9, 2.4 Hz, 1H), 5.59 (br s, 1H), 4.02 (q, J = 6.6 Hz, 1H), 3.66 (br s, 2H), 1.35 (d, J = 6.7 Hz, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 146.73, 143.77, 129.63, 117.53, 114.55, 113.91, 61.99, 19.55.

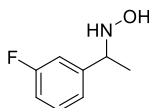
HRMS (ESI⁺): m/z calcd for C₈H₁₂N₂O [M+H]⁺ 153.1022, found 153.1023.



A portion of the crude product (10 mg, 0.066 mmol) was functionalized for chiral HPLC analysis using General Procedure E with a slight modification. Increased 2,4-dinitrofluorobenzene (2.3 equiv.) and Et₃N (2.3 equiv.) were used. After workup, the product was purified by prep TLC in 35% EtOAc/hexanes, and isolated as a dark yellow solid. The functionalized product was found to exhibit limited solubility in 95% hexanes/IPA, so samples were prepared in 90% hexanes/IPA. Small amounts of DCM as co-solvent were added to help solubilize product for HPLC analysis.

ChiralCel AD-H column (40:60 hexanes/EtOH, 1 mL/min), t_r = 34.2 min (major), t_r = 46.1 min (minor).

Enantioenriched material was prepared from oxime **2q** (6.07 mg, 0.0404 mmol) according to General Procedure D with some modifications. To the 1 dr vial containing oxime and a magnetic stir bar was added $\Lambda\Lambda\Lambda\Lambda$ host **1** (14.68 mg, 3.038 μ mol, 7.5 mol%) as a solution in D₂O. The reaction was stopped with PEt₄Br after 72h. Following extraction, the crude extract solution was analyzed by ¹H NMR (90% NMR yield), then transferred to a 1 dr vial and solvent was removed to dryness *via* rotary evaporation. The crude product was subjected to General Procedure E with a slight modification. Quantitative transfer was assumed before addition of dry CH₂Cl₂ (400 μ L) and increased amounts of 2,4-dinitrofluorobenzene (11.43 μ L, 0.0908 mmol, 2.5 equiv.) and dry Et₃N (12.68 μ L, 0.0908 mmol, 1.4 equiv.). The crude functionalized product was purified by prep TLC in 35% EtOAc/hexanes and isolated as yellow solid for HPLC analysis (96% ee).

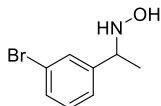


3-fluoro-N-hydroxy- α -methylbenzenemethanamine (3r): Racemic material was prepared from oxime **2r** according to General Procedure C. The reaction was run for 3h before workup and isolation as a white solid. Analytical data were consistent with literature reports.⁷⁵

¹H NMR (600 MHz, CDCl₃) δ 7.29 (td, J = 8.0, 5.9 Hz, 1H), 7.09 (dt, J = 7.7, 1.3 Hz, 1H), 7.05 (ddd, J = 9.9, 2.6, 1.6 Hz, 1H), 6.96 (tdd, J = 8.4, 2.6, 1.0 Hz, 1H), 5.84 (br s, 1H), 4.09 (q, J = 6.7 Hz, 1H), 1.34 (d, J = 6.7 Hz, 3H).

ChiralCel OJ-H column (99:1 hexanes/*i*PrOH, 1 mL/min), t_r = 37.9 min (minor), t_r = 43.5 min (major).

Enantioenriched material was prepared from oxime **2r** (6.07 mg, 0.0396 mmol) according to General Procedure D. The reaction was stopped with PEt₄I after 24h. Following extraction, the crude extract solution was analyzed by ¹H NMR (57% NMR yield), then the product was purified by prep TLC in 2.5% MeOH/DCM and isolated as a white solid for HPLC analysis (96% ee).

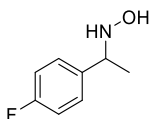


3-bromo-N-hydroxy- α -methylbenzenemethanamine (3s): Racemic material was prepared from oxime **2s** according to General Procedure C. The reaction ran for 1.5h and the crude product was purified and isolated as white solid. Analytical data were consistent with literature reports.⁷⁰

¹H NMR (600 MHz, CDCl₃) δ 7.51 (s, J = 1.8 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.30 – 7.20 (m, 2H), 5.82 (br s, 2H), 4.07 (q, J = 6.7 Hz, 1H), 1.36 (d, J = 6.7 Hz, 2H).

ChiralCel OJ-H column (99:1 hexanes/*i*PrOH, 1 mL/min), t_r = 45.4 min (major), t_r = 52.9 min (minor).

Enantioenriched material was prepared from oxime **2s** (6.92 mg, 0.0323 mmol) according to General Procedure D with a few modifications. To the 1 dr vial containing oxime and a magnetic stir bar was added $\Lambda\Lambda\Lambda\Lambda$ host **I** (11.73 mg, 2.428 μ mol, 7.5 mol%) as a solution in D₂O. The reaction was stopped with PEt₄Br after 72h. Following extraction, the crude extract solution was analyzed by ¹H NMR (46% NMR yield), then the product was purified by prep TLC in 2.5% MeOH/DCM and isolated as a white solid for HPLC analysis (71% ee).

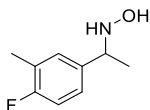


4-fluoro-N-hydroxy-α-methylbenzenemethanamine (3t): Racemic material was prepared from oxime **2t** according to General Procedure C. The reaction was allowed to run for 2.66h and the product was isolated as white solid. Analytical data were consistent with literature reports.⁷⁰

¹H NMR (600 MHz, CDCl₃) δ 7.32 – 7.26 (m, 2H), 7.04 – 6.98 (m, 2H), 5.35 (br, 2H), 4.08 (q, J = 6.7 Hz, 1H), 1.35 (d, J = 6.7 Hz, 3H).

ChiralCel OJ-H column (98:2 hexanes/*i*PrOH, 1 mL/min), t_r = 19.9 min (minor), t_r = 22.0 min (major)

Enantioenriched material was prepared from oxime **2t** (6.45 mg, 0.0421 mmol) according to General Procedure D with a few modifications. To the 1 dr vial containing oxime and a magnetic stir bar was added host **I** (15.26 mg, 3.158 μ mol, 7.5 mol%) as a solution in D₂O. The reaction was stopped with PEt₄Br after 72h. Following extraction, the crude extract solution was analyzed by ¹H NMR (37% NMR yield), then the product was purified by prep TLC in 2.5% MeOH/DCM and isolated as a white solid for HPLC analysis (94% ee).



4-fluoro-N-hydroxy-α,3-dimethylbenzenemethanamine (3u): Racemic material was prepared from oxime **2u** according to General Procedure C. The reaction was allowed to run for 4h and the product was isolated as white solid.

¹H NMR (600 MHz, CDCl₃) δ 7.15 – 7.07 (m, 2H), 6.96 (t, J = 9.2 Hz, 1H), 5.69 (br s, 2H), 4.05 (q, J = 6.7 Hz, 1H), 2.26 (d, J = 1.9 Hz, 3H), 1.34 (d, J = 6.7 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 160.88 (d, J = 244.3 Hz), 137.79 (d, J = 3.4 Hz), 130.36 (d, J = 5.0 Hz), 126.07 (d, J = 8.0 Hz), 124.96 (d, J = 17.3 Hz), 115.10 (d, J = 20.6 Hz), 61.25, 19.56, 14.71 (d, J = 3.9 Hz).

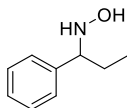
¹⁹F NMR (565 MHz, CDCl₃) δ -119.32 (s).

HRMS (ESI⁺): m/z calcd for C₉H₁₂FNO [M+H]⁺ 170.0976, found 170.0973.

ChiralCel OJ-H column (98:2 hexanes/*i*PrOH, 1 mL/min) t_r = 17.5 min (minor), t_r = 19.9 min (major).

Enantioenriched material was prepared from oxime **2u** (4.95 mg, 0.0296 mmol) according to General Procedure D with a few modifications. To the 1 dr vial containing oxime and a

magnetic stir bar was added host **1** (10.75 mg, 2.225 μ mol, 7.5 mol%) as a solution in D₂O. The reaction was stopped with PEt₄Br after 72h. Following extraction, the crude extract solution was analyzed by ¹H NMR (55% NMR yield), then the product was purified by prep TLC in 2.5% MeOH/DCM and isolated as a white solid for HPLC analysis (98% ee).

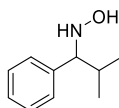


α-ethyl-N-hydroxybenzenemethanamine (3v): Racemic material was prepared from oxime **2v** according to General Procedure C. The reaction was run for 2h before workup. The crude product was purified by prep TLC in 2% MeOH/DCM and isolated as a white solid. Analytical data were consistent with literature reports.⁷⁶

¹H NMR (600 MHz, CDCl₃) δ 7.37 – 7.31 (m, 2H), 7.31 – 7.25 (m, 3H), 5.61 (br, 1H), 3.83 (dd, *J* = 8.7, 5.4 Hz, 1H), 1.88 (dtd, *J* = 13.1, 7.5, 5.6 Hz, 1H), 1.68 – 1.55 (m, 1H), 0.82 (t, *J* = 7.4 Hz, 3H).

ChiralCel OJ-H column (97:3 hexanes/*i*PrOH, 1 mL/min), *t_r* = 14.5 min (minor), *t_r* = 19.0 min (major).

Enantioenriched material was prepared from oxime **2v** (4.03 mg, 0.0270 mmol) according to General Procedure D. The reaction was stopped with PEt₄I after 24h. Following extraction, the crude extract solution was analyzed by ¹H NMR (93% NMR yield), then the product was purified by prep TLC in 2% MeOH/DCM and isolated as a white solid for HPLC analysis (64% ee).



N-(2-methyl-1-phenylpropyl)hydroxylamine (3w): Racemic material was prepared from oxime **2w** (34 mg, 0.21 mmol) according to General Procedure C with a slight modification. The reaction was allowed to warm overnight and run for 16h. The crude product was purified by prep TLC in 1.75% MeOH/DCM and isolated as a white solid.

¹H NMR (600 MHz, CDCl₃) δ 7.35 – 7.31 (m, 2H), 7.30 – 7.26 (m, 3H), 5.53 (br s, 2H), 3.69 (d, *J* = 7.5 Hz, 1H), 1.98 (oct, *J* = 6.8 Hz, 1H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.74 (d, *J* = 6.8 Hz, 3H).

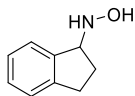
¹³C NMR (151 MHz, CDCl₃) δ 140.81, 128.31, 127.43, 73.19, 31.04, 20.03, 19.38.

HRMS (ESI⁺): *m/z* calcd for C₁₀H₁₅NO [M+H]⁺ 166.1226, found 166.1232.

ChiralCel OJ-H column (97:3 hexanes/*i*PrOH, 1 mL/min), *t_r* = 13.9 min (major), *t_r* = 17.8 min (minor).

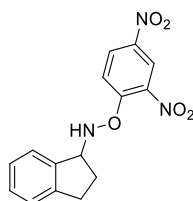
Enantioenriched material was prepared from oxime **2w** (7.03 mg, 0.0431 mmol) according to General Procedure D with a few modifications. To the 1 dr vial containing oxime and a magnetic stir bar was added host **1** (15.64 mg, 3.237 μ mol, 7.5 mol%) as a solution in D₂O. The reaction was stopped with PEt₄Br after 72h. Following extraction, the crude extract solution was analyzed by ¹H NMR (43% NMR yield), then the product was purified

by prep TLC in 1.75% MeOH/DCM and isolated as a white solid for HPLC analysis (68% ee).



2,3-dihydro-*N*-hydroxy-1H-inden-1-amine (3x): Racemic material was prepared from oxime **2x** (31 mg, 0.21 mmol) according to General Procedure C with a slight modification. The reaction was allowed to warm overnight and run for 16h. The crude product was purified by prep TLC in 2.0% MeOH/DCM and isolated as a white solid. Analytical data were consistent with literature reports.⁷⁰

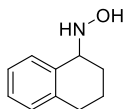
¹H NMR (600 MHz, CDCl₃) δ 7.41 (d, J = 7.5 Hz, 1H), 7.26 – 7.22 (m, 2H), 7.22 – 7.16 (m, 1H), 5.53 (br, 1H), 4.54 (dd, J = 7.3, 4.1 Hz, 1H), 3.05 (ddd, J = 15.6, 8.6, 6.7 Hz, 1H), 2.86 (ddd, J = 15.9, 8.9, 4.9 Hz, 1H), 2.31 (ddt, J = 13.8, 8.9, 7.0 Hz, 1H), 2.09 (ddq, J = 13.3, 8.8, 4.5 Hz, 1H).



A portion of the purified product (9.0 mg, 0.060 mmol) was functionalized for chiral HPLC analysis using General Procedure E with a slight modification. Increased 2,4-dinitrofluorobenzene (1.2 equiv.) and Et₃N (1.2 equiv.) were used. After workup, the product was isolated as a yellow solid.

ChiralPak AD-H column (98:2 hexanes/*i*-PrOH, 1 mL/min), t_r = 47.6 min (minor), t_r = 52.4 min (major).

Enantioenriched material was prepared from oxime **2x** (5.26 mg, 0.0357 mmol) according to General Procedure D with some modifications. To the 1 dr vial containing oxime and a magnetic stir bar was added $\Lambda\Lambda\Lambda\Lambda$ host **1** (10.45 mg, 2.163 μ mol, 5.0 mol%) as a solution in D₂O. The reaction was stopped with PEt₄Br after 24h. Following extraction, the crude extract solution was analyzed by ¹H NMR (75% NMR yield), then the product was purified by prep TLC in 2.0% MeOH/DCM and isolated as a white solid. The purified product was subjected to General Procedure E with a slight modification. Quantitative recovery was assumed before addition of dry CH₂Cl₂ (350 μ L) and increased amounts of 2,4-dinitrofluorobenzene (3.90 μ L, 0.0311 mmol, 1.19 equiv.) and dry Et₃N (4.35 μ L, 0.0312 mmol, 1.20 equiv.). The crude functionalized product was purified by prep TLC in 35% EtOAc/hexanes and isolated as yellow solid for HPLC analysis (63% ee).



1,2,3,4-tetrahydro-*N*-hydroxy-1-naphthalenamine (3y): Racemic material was prepared from oxime **2y** according to General Procedure C. The reaction was run for 3h

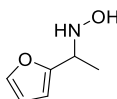
before workup. The crude product was purified by prep TLC in 2.0% MeOH/DCM and isolated as a white solid. Analytical data were consistent with literature reports.⁷⁰

¹H NMR (600 MHz, CDCl₃) δ 7.34 (dd, *J* = 7.2, 1.9 Hz, 1H), 7.21 – 7.14 (m, 2H), 7.13 – 7.09 (m, 1H), 5.30 (s, 1H), 4.11 (t, *J* = 4.3 Hz, 1H), 2.85 – 2.69 (m, 2H), 2.26 – 2.18 (m, 1H), 2.01 – 1.71 (m, 3H).

Although the purified product was found to exhibit moderate solubility in 95% hexanes/IPA, the addition of small amounts of THF to improve solubility was found to lead to rapid product decomposition. To avoid product decomposition before analysis, co-solvents were avoided and prepared HPLC samples were immediately run on chiral HPLC.

ChiralCel OJ-H column (98:2 hexanes/*i*PrOH, 1 mL/min), *t_r* = 26.3 min (major), *t_r* = 34.0 min (minor).

Enantioenriched material was prepared from oxime **2y** (4.42 mg, 0.0274 mmol) according to General Procedure D. The reaction was stopped with PEt₄I after 24h. Following extraction, the crude extract solution was analyzed by ¹H NMR (82% NMR yield), then the product was purified by prep TLC in 2% MeOH/DCM and isolated as a white solid for HPLC analysis (22% ee).

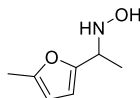


N-hydroxy-α-methyl-2-furanmethanamine (3z): Racemic material was prepared from oxime **2z** (26 mg, 0.21 mmol) according to General Procedure C with a slight modification. The reaction was allowed to warm overnight and run for 16h. The crude product was purified by prep TLC in 2% MeOH/DCM and isolated as a white solid. Analytical data were consistent with literature reports.⁷⁰

¹H NMR (600 MHz, CDCl₃) δ 7.37 (dd, *J* = 1.8, 0.9 Hz, 1H), 6.33 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.24 (dt, *J* = 3.2, 0.8 Hz, 1H), 5.66 (br s, 1H), 5.36 (br s, 1H), 4.18 (q, *J* = 6.7 Hz, 1H), 1.44 (d, *J* = 6.8 Hz, 3H).

ChiralCel AD-H column (98:2 hexanes/*i*PrOH, 1 mL/min), *t_r* = 28.4 min (minor), *t_r* = 33.6 min (major).

Enantioenriched material was prepared from oxime **2z** (3.78 mg, 0.0302 mmol) according to General Procedure D using ΛΛΛΛ host **1** (3.78 mg, 0.0302 mmol). The reaction was stopped with PEt₄Br after 24h. Following extraction, the crude extract solution was analyzed by ¹H NMR (89% NMR yield), then the product was purified by prep TLC in 1.75% MeOH/DCM and isolated as a white solid for HPLC analysis (52% ee).



N-hydroxy-α,5-dimethyl-2-furanmethanamine (3aa): Racemic material was prepared from oxime **2aa** according to General Procedure C with slight modifications. The reaction was allowed to run for 6h. The crude product was purified by prep TLC in 2% MeOH/DCM with 1% Et₃N and isolated as a white solid.

^1H NMR (600 MHz, CDCl_3) δ 6.11 (d, J = 3.1 Hz, 1H), 5.91 – 5.88 (m, 1H), 5.04 (br s, 2H), 4.12 (q, J = 6.8 Hz, 1H), 2.27 (s, 1H), 1.42 (d, J = 6.8 Hz, 3H).

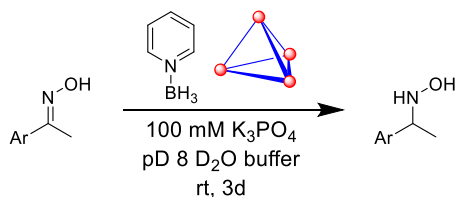
^{13}C NMR (151 MHz, CDCl_3) δ 153.17, 151.73, 107.73, 106.17, 55.46, 16.39, 13.69.

HRMS (ESI $^+$): m/z calcd for $\text{C}_7\text{H}_{11}\text{NO}_2$ ($[\text{M}+\text{Na}]^+$) 164.0682, found 164.0678.

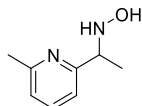
ChiralCel OJ-H column (99:1 hexanes/ i PrOH, 1 mL/min), t_r = 31.0 min (minor), t_r = 37.4 min (major).

Enantioenriched material was prepared from oxime **2aa** (5.77 mg, 0.0417 mmol) according to General Procedure D. The reaction was stopped with PET_4I after 24h. Following extraction, the crude extract solution was analyzed by ^1H NMR (63% NMR yield), then the product was purified by prep TLC in 2% MeOH/DCM and isolated as a white solid for HPLC analysis (96% ee).

General Procedure H for the Racemic Synthesis of *N*-Heterocyclic Hydroxylamines:



In an air-free wet box to a 2 dr vial containing host **4** (0.15 equiv.) was added 100 mM K_3PO_4 pH 8 D_2O buffer. The solution was transferred to a second 2 dr vial equipped with a stir bar containing oxime (1 equiv.). The first 2 dr vial was rinsed with 100 mM K_3PO_4 pH 8 D_2O buffer and the rinse was also transferred to the second 2 dr vial. The resulting solution was 42 mM in oxime. The reaction mixture vial was capped with a Teflon coated vial septa cap and sealed with electrical tape, removed from the wet box, and allowed to stir for 2–3 minutes before addition of pyridine borane. The resulting solution was allowed to stir at rt for 2.5–3 days, after which an excess of PET_4Br was added to stop the reaction.

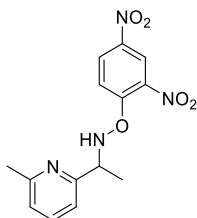


***N*-hydroxy-1-(6-methylpyridin-2-yl)ethanamine (3ab):** Racemic material was prepared from oxime **2ab** (10.02 mg, 0.0667 mmol) according to General Procedure H. After removal from the glovebox, pyridine borane (7.43 mg, 8.00 μL , 0.0800 mmol, 1.2 equiv.) was added *via* Hamilton syringe. The resulting solution was allowed to stir at rt for 3 days before PET_4Br was added to stop the reaction. Subsequent *in situ* ^1H NMR analysis showed full conversion. The stir bar was removed using a stir bar magnet and rinsed with CH_2Cl_2 . Additional CH_2Cl_2 was added to the vial to extract the product and the organic layer was transferred to a 2 dr vial. The reaction solution was washed at least 3 times with CH_2Cl_2 . NaCl was added to the reaction mixture after quenching to help improve extraction of product from solution. Solvent in the 2 dr vial from the combined rinses was removed *via* rotary evaporation to dryness. The extraction process was repeated with EtOAc. Then CH_2Cl_2 was added to the reaction vial and the extraction process was repeated. The crude material was purified using 5% MeOH in DCM for characterization and isolated as a white solid.

^1H NMR (600 MHz, CDCl_3) δ 7.56 (t, J = 7.7 Hz, 1H), 7.05 (t, J = 7.4 Hz, 2H), 6.00 (br s, 1H), 4.22 (q, J = 6.9 Hz, 1H), 2.55 (s, 3H), 1.40 (d, J = 6.9 Hz, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 162.13, 158.10, 137.18, 121.96, 118.51, 61.82, 24.62, 18.60.

HRMS (ESI $^+$): m/z calcd for $\text{C}_8\text{H}_{12}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 153.1022, found 153.1024.

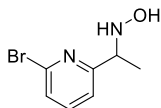


The crude extracted product (8.0 mg, 0.053 mmol) was functionalized for chiral HPLC analysis using General Procedure E with a slight modification. Increased 2,4-dinitrofluorobenzene (1.5 equiv.) and Et_3N (1.5 equiv.) were used. After workup, the product was isolated as a yellow solid.

ChiralPak AD-H column (92:8 hexanes/ i -PrOH, 1 mL/min), t_r = 19.6 min (minor), t_r = 25.8 min (major).

Enantioenriched material was prepared from oxime **2ab** (14.70 mg, 0.0979 mmol) according to a modified version of General Procedure D. To the 1 dr vial containing oxime and a magnetic stir bar was added $\Delta\Delta\Delta$ host **1** (24.00 mg, 4.968 μmol , 5.0 mol%) as a solution in D_2O . The heterogeneous solution was allowed to stir before addition of pyridine borane (13.60 mg, 14.60 μL , 0.146 mmol, 1.5 equiv.) *via* Hamilton syringe. The reaction was then stirred at rt for 18h, at which point an additional charge of pyridine borane (9.29 mg, 10.00 μL , 0.100 mmol, 1.0 equiv.) was added. The reaction was stopped with PEt_4Br (1.23 mg, 5.40 μmol , 5.5 mol%) as a stock solution in D_2O after a total of 72h from the initial charge of pyridine borane. Internal standard, 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt (2.73 mg, 0.0125 mmol), as a stock solution in D_2O (0.25 M) was added to the reaction vial *via* Hamilton syringe for ^1H NMR analysis (96% NMR yield).

Following NMR analysis, the reaction mixture was returned to the reaction vial and the NMR tube was rinsed with CH_2Cl_2 . Additional CH_2Cl_2 was added to the vial to extract the product and the CH_2Cl_2 rinse was transferred to a 1 dr vial. The reaction solution was washed at least 3 times with CH_2Cl_2 . Solvent in the 1 dr vial from the combined rinses was removed to dryness *via* rotary evaporation. Then the NMR tube was rinsed with EtOAc and the rinse was transferred to the 1 dr vial. More EtOAc was added to the 1 dr vial and the extraction process repeated at least once more with THF. Again, solvent was removed to dryness *via* rotary evaporation. A portion of the crude product (7.12 mg, 0.047 mmol, 1.0 equiv.) was subjected to General Procedure E with a slight modification, through the use of increased amounts of 2,4,-dinitrofluorobenzene (8.2 μL , 0.065 mmol, 1.4 equiv.) and dry Et_3N (9.1 μL , 0.065 mmol, 1.4 equiv.). After 18 hrs, the crude reaction mixture was concentrated down *via* rotary evaporation and the product was purified and isolated by prep TLC in 5% MeOH/DCM and then in 2% MeOH/DCM and isolated as a yellow solid for chiral HPLC analysis (95% ee).

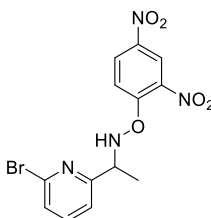


N-hydroxy-1-(6-bromopyridin-2-yl)ethanamine (3ac): Racemic material was prepared from oxime **2ac** (15.03 mg, 0.0699 mmol) according to General Procedure H. After removal from the glovebox, pyridine borane (13.00 mg, 14.00 μ L, 0.1400 mmol, 2.0 equiv.) was added *via* Hamilton syringe. The resulting solution was allowed to stir at rt for 2.5 days before PEt_4Br was added to stop the reaction. The stir bar was removed using a stir bar magnet and rinsed with CDCl_3 . Additional CDCl_3 was added to the vial to extract the product and the CDCl_3 rinse was transferred to a 2 dr vial. The reaction solution was washed at least 6 times with CDCl_3 . Solvent in the 2 dr vial from the combined rinses was removed *via* rotary evaporation to be less than 500 μ L, but not to full dryness. Following extraction, the crude extract solution was analyzed by ^1H NMR and showed 95% conversion to the desired product. The crude product was purified for characterization by prep TLC in 5% MeOH/DCM and isolated as a white solid.

^1H NMR (600 MHz, CDCl_3) δ 7.53 (t, J = 7.7 Hz, 1H), 7.38 (dd, J = 7.9, 0.9 Hz, 1H), 7.27 (d, J = 8.2 Hz, 1H), 5.07 (br s, 1H), 4.21 (q, J = 6.9 Hz, 1H), 1.57 (br s, 1H), 1.37 (d, J = 6.9 Hz, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 164.19, 142.11, 139.07, 126.89, 120.66, 62.32, 18.32.

HRMS (ESI+): m/z calcd for $\text{C}_7\text{H}_9\text{BrN}_2\text{O}$ $[\text{M}+\text{H}]^+$ 216.9971, found 216.9969.

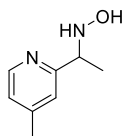


The crude product (13.0 mg, 0.060 mmol) was functionalized for chiral HPLC analysis using General Procedure E with a slight modification. Increased 2,4-dinitrofluorobenzene (1.4 equiv.) and Et_3N (1.4 equiv.) were used. After workup, the product was isolated as a yellow solid.

ChiralPak AD-H column (94:6 hexanes/ i PrOH, 1 mL/min), t_r = 22.6 min (major), t_r = 28.3 min (minor).

Enantioenriched material was prepared from oxime **2ac** (7.43 mg, 0.0346 mmol) according to General Procedure D with some modifications. The heterogeneous solution was allowed to stir before addition of pyridine borane (4.83 mg, 5.20 μ L, 0.0520 mmol, 1.5 equiv.) *via* Hamilton syringe. The reaction was then stirred at rt for 18 h, at which point additional pyridine borane (3.21 mg, 3.45 μ L, 0.0345 mmol, 1.0 equiv.) was added. The reaction was stopped with PEt_4Br after a total of 72h from the initial charge of pyridine borane. Following extraction, the crude extract solution was analyzed by ^1H NMR (90% NMR yield), then transferred to a 1 dr vial and solvent was removed to dryness *via* rotary evaporation. The crude product was subjected to General Procedure E with a slight modification. Quantitative transfer was assumed before addition of dry CH_2Cl_2 (400 μ L) and increased amounts of 2,4,-dinitrofluorobenzene (5.50 μ L, 0.0438 mmol, 1.41 equiv.) and dry Et_3N (6.10 μ L, 0.0438 mmol, 1.41 equiv.). The crude functionalized product was

purified by prep TLC in 30% EtOAc/hexanes and isolated as yellow solid for HPLC analysis (98% ee).

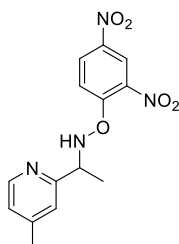


N-hydroxy-1-(4-methylpyridin-2-yl)ethanamine (3ad): Racemic material was prepared from oxime **2ad** (20.0 mg, 0.133 mmol) according to General Procedure H with some modifications. After removal from the glovebox, pyridine borane (37.16 mg, 40.0 μ L, 0.40 mmol, 3.0 equiv.) was added *via* Hamilton syringe. The resulting solution was allowed to stir at 45°C for 3 days before PEt_4Br was added to stop the reaction. The stir bar was removed using a stir bar magnet and rinsed with CH_2Cl_2 . Additional CH_2Cl_2 was added to the vial to extract the product and the rinse was transferred to a 2 dr vial. The reaction solution was washed at least 6 times with CH_2Cl_2 . Solvent in the 2 dr vial from the combined rinses was removed *via* rotary evaporation. The process was repeated again, and the resulting solution from combined rinses was again removed *via* rotary evaporation. This process was repeated a third time, this time using EtOAc. The resulting solution from combined rinses was again removed *via* rotary evaporation. The solution was dissolved in CDCl_3 and the crude solution was analyzed by ^1H NMR, which showed >95% conversion to the desired product. The crude product was purified for characterization by prep TLC in 6% MeOH/DCM and isolated as a white solid.

^1H NMR (600 MHz, CDCl_3) δ 8.42 (d, J = 5.0 Hz, 1H), 7.09 (s, 1H), 7.01 (d, J = 5.0 Hz, 1H), 4.21 (q, J = 6.9 Hz, 1H), 2.35 (s, 3H), 1.38 (d, J = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 162.32, 149.11, 148.13, 123.49, 122.77, 62.10, 21.26, 18.52.

HRMS (ESI⁺): m/z calcd for $\text{C}_8\text{H}_{12}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 153.1022, found 153.1023.

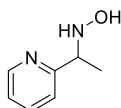


The crude product (11.9 mg, 0.078 mmol) was functionalized for chiral HPLC analysis using General Procedure E with a slight modification. Increased 2,4-dinitrofluorobenzene (1.4 equiv.) and Et_3N (1.4 equiv.) were used. After workup, the product was isolated as a yellow solid.

ChiralPak IA column (85:15 hexanes/ PrOH , 1 mL/min), t_r = 12.3 min (minor), t_r = 21.2 min (major).

Enantioenriched material was prepared from oxime **2ad** (6.50 mg, 0.0433 mmol) according to General Procedure D with some modifications. To the 1 dr vial containing oxime and a magnetic stir bar was added $\Delta\Delta\Delta\Delta$ host **I** (10.50 mg, 2.173 μ mol, 5.0 mol%) as a solution in D_2O . The heterogeneous solution was allowed to stir before addition of pyridine borane (6.04 mg, 6.50 μ L, 0.0650 mmol, 1.5 equiv.) *via* Hamilton syringe. The

reaction was then stirred at rt for 18 h, at which point additional pyridine borane (4.04 mg, 4.35 μ L, 0.0435 mmol, 1.0 equiv.) was added. The reaction was stopped with PEt_4Br after a total of 72h from the initial charge of pyridine borane. Following extraction, the crude extract solution was analyzed by ^1H NMR (26% NMR yield), then transferred to a 1 dr vial and solvent was removed to dryness *via* rotary evaporation. The crude product was subjected to General Procedure E with a slight modification. Quantitative transfer was assumed before addition of dry CH_2Cl_2 (250 μ L) and increased amounts of 2,4-dinitrofluorobenzene (2.10 μ L, 0.0167 mmol, 1.49 equiv.) and dry Et_3N (2.35 μ L, 0.0619 mmol, 1.50 equiv.). The crude functionalized product was purified by prep TLC in 30% EtOAc /hexanes and isolated as yellow solid for HPLC analysis (88% ee).

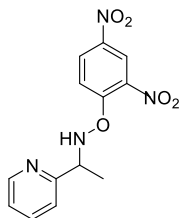


N-hydroxy-1-(2-pyridyl)ethanamine (3ae): Racemic material was prepared from oxime **2ae** (12.14 mg, 0.08917 mmol) according to General Procedure H. After removal from the glovebox, pyridine borane (12.50 mg, 13.50 μ L, 0.0800 mmol, 1.5 equiv.) was added *via* Hamilton syringe. The resulting solution was allowed to stir at rt for 3 days before PEt_4Br was added to stop the reaction. Subsequent *in situ* ^1H NMR analysis showed 86% conversion. The stir bar was removed using a stir bar magnet and rinsed with CH_2Cl_2 . Additional CH_2Cl_2 was added to the vial to extract the product and the organic layer was transferred to a 2 dr vial. The reaction solution was washed at least 3 times with CH_2Cl_2 . NaCl was added to the reaction mixture after quenching to help improve extraction of product from solution. Solvent in the 2 dr vial from the combined rinses was removed *via* rotary evaporation to dryness. The extraction process was repeated with EtOAc . Then THF was added to the reaction vial and the extraction process was repeated. The crude material was purified using 10% MeOH in EtOAc for characterization and isolated as a white solid.

^1H NMR (600 MHz, MeOD) δ 8.48 (ddd, J = 5.0, 1.8, 1.0 Hz, 1H), 7.80 (td, J = 7.7, 1.8 Hz, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.29 (ddd, J = 7.5, 5.0, 1.2 Hz, 1H), 4.17 (q, J = 6.9 Hz, 1H), 1.32 (d, J = 6.8 Hz, 3H).

^{13}C NMR (151 MHz, MeOD) δ 164.12, 149.55, 138.60, 123.71, 122.93, 63.90, 18.75.

HRMS (ESI $^+$): m/z calcd for $\text{C}_7\text{H}_{10}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 139.0866, found 139.0869.

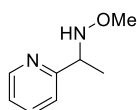


The crude product (10.49 mg, 0.076 mmol) was functionalized for chiral HPLC analysis using a modified version of General Procedure E. To a 1 dr vial containing crude hydroxylamine was added dry THF (760 μ L). The vial was cooled to 0°C before addition of 2,4-dinitrofluorobenzene (13.5 μ L, 0.107 mmol, 1.4 equiv.) and dry Et_3N (15.0 μ L, 0.107 mmol, 1.4 equiv.). The reaction was allowed to slowly warm to room temperature overnight. After approximately 22h, the reaction was stopped, the crude mixture was

concentrated down via rotary evaporator, and the resulting solid was redissolved in MeOH. The hydroxylamine was purified and isolated by subjecting the crude material twice to prep TLC in 10% MeOH/DCM and isolated as a yellow solid. ChiralPak AD-H column (92:8 hexanes/*i*PrOH, 0.6 mL/min), *t_r* = 38.7 min (minor), *t_r* = 42.0 min (major).

Enantioenriched material was prepared from oxime **2ae** (5.01 mg, 0.0368 mmol) according to a modified version of General Procedure D. To the 1 dr vial containing oxime and a magnetic stir bar was added $\Delta\Delta\Delta\Delta$ host **I** (8.92 mg, 1.846 μ mol, 5.0 mol%) as a solution in D₂O. The heterogeneous solution was allowed to stir before addition of pyridine borane (4.09 mg, 4.40 μ L, 0.0440 mmol, 1.20 equiv.) *via* Hamilton syringe. The reaction was stopped with PEt₄Br (0.46 mg, 2.03 μ mol, 5.5 mol%) as a stock solution in D₂O after 48h. Internal standard, 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt (2.50 mg, 0.01145 mmol), as a stock solution in D₂O (0.25 M) was added to the reaction vial *via* Hamilton syringe for ¹H NMR analysis (56% NMR yield).

Following NMR analysis, the reaction mixture was returned to the reaction vial and the NMR tube was rinsed with CH₂Cl₂. Additional CH₂Cl₂ was added to the vial to extract the product and the CH₂Cl₂ rinse was transferred to a 1 dr vial. The reaction solution was washed at least 3 times with CH₂Cl₂. Solvent in the 1 dr vial from the combined rinses was removed to dryness *via* rotary evaporation. Then the NMR tube was rinsed with CH₂Cl₂ and the rinse was transferred to the 1 dr vial. More CH₂Cl₂ was added to the 1 dr vial and the extraction process repeated. Again, solvent was removed to dryness *via* rotary evaporation. The crude product was subjected to General Procedure E with a slight modification. Quantitative transfer was assumed before addition of dry CH₂Cl₂ (250 μ L) and increased amounts of 2,4,-dinitrofluorobenzene (5.15 μ L, 0.0410 mmol, 1.99 equiv.) and dry Et₃N (5.75 μ L, 0.0413 mmol, 2.00 equiv.). The crude functionalized product was purified by prep TLC in 35% EtOAc/hexanes and isolated as yellow solid for HPLC analysis (97% ee).



N-Methoxy- α -methyl-2-pyridinemethanamine (3af): Racemic material was prepared from oxime **2af** (13.00 mg, 0.0866 mmol) according to General Procedure H. After removal from the glovebox, pyridine borane (12.08 mg, 13.00 μ L, 0.130 mmol, 1.5 equiv.) was added *via* Hamilton syringe. The resulting solution was allowed to stir at rt for 2.7 days before PEt₄Br was added to stop the reaction. The stir bar was removed using a stir bar magnet and rinsed with CDCl₃. Additional CDCl₃ was added to the vial to extract the product and the CDCl₃ rinse was transferred to a 2 dr vial. The reaction solution was washed at least 6 times with CDCl₃. Solvent in the 2 dr vial from the combined rinses was removed *via* rotary evaporation to be less than 500 μ L, but not to full dryness. Following extraction, the crude extract solution was analyzed by ¹H NMR and showed 53% conversion to the desired product. The crude product was purified for characterization by prep TLC in 3% MeOH/DCM and isolated as a white solid.

^1H NMR (600 MHz, CDCl_3) δ 8.58 (d, J = 4.0 Hz, 1H), 7.67 (td, J = 7.7, 1.8 Hz, 1H), 7.31 (d, J = 7.8 Hz, 1H), 7.19 (d, J = 1.5 Hz, 1H), 6.12 (s, 1H), 4.27 (q, J = 6.9 Hz, 1H), 3.51 (s, 3H), 1.37 (d, J = 6.8 Hz, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 162.42, 149.28, 136.88, 122.46, 121.91, 62.19, 61.06, 18.69.

HRMS (ESI $^+$): m/z calcd for $\text{C}_8\text{H}_{12}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 153.1022, found 153.1017.

ChiralPak AD-H column (99.5:1.5 hexanes/ i PrOH, 0.5 mL/min), t_r = 22.8 min (minor), t_r = 26.7 min (major).

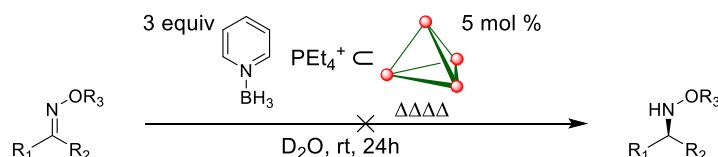
Enantioenriched material was prepared from oxime **2af** (6.50 mg, 0.0433 mmol) according to General Procedure D with some modifications. To the 1 dr vial containing oxime and a magnetic stir bar was added $\Delta\Delta\Delta\Delta$ host **I** (10.45 mg, 2.163 μmol , 5.0 mol%) as a solution in D_2O . The heterogeneous solution was allowed to stir before addition of pyridine borane (6.04 mg, 6.50 μL , 0.0650 mmol, 1.5 equiv.) *via* Hamilton syringe. The reaction was stopped with PEt_4Br (0.54 mg, 2.38 μmol , 5.5 mol%) as a stock solution in D_2O after 4.5d. Internal standard, 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt (2.50 mg, 0.01145 mmol), as a stock solution in D_2O (0.25 M) was added to the reaction vial *via* Hamilton syringe for ^1H NMR analysis (24% NMR yield). Following NMR analysis, the reaction mixture was returned to the reaction vial and the NMR tube was rinsed with CH_2Cl_2 . Additional CH_2Cl_2 was added to the vial to extract the product and the CH_2Cl_2 rinse was transferred to a 1 dr vial. The reaction solution was washed at least 3 times with CH_2Cl_2 . Solvent in the 1 dr vial from the combined rinses was removed to dryness *via* rotary evaporation. Then the NMR tube was rinsed with EtOAc and the rinse was transferred to the 1 dr vial. More EtOAc was added to the 1 dr vial and the extraction process repeated at least once more. Again, solvent was removed to dryness *via* rotary evaporation. The product was purified and isolated by prep TLC 1.5% MeOH/DCM and isolated as a white solid for HPLC analysis (56% ee).

3.7.3 Reactivity in $\text{Ga}_4\text{L}_6^{12-}$ Host **I**

Optimization of Reaction Conditions:

Reactions for substrate optimization were performed according to the respective general procedures for each substrate.

General Procedure **I** for Blocked Host Control Experiments with $\text{Ga}_4\text{L}_6^{12-}$ Host **I**



To probe background reactivity, blocked host controls were performed in a manner nearly identical to that of the General Procedures applicable for the respective oxime, with the addition of PEt_4I or PEt_4Br :

To a 1 dr vial containing host **I** (5 mol%) was added D_2O *via* Eppendorf pipette. A portion from a second 1 dr vial containing PEt_4I or PEt_4Br (6 mol%) as a stock solution in D_2O was added to the vial containing host. The blocked host solution was transferred to a third

1 dr vial equipped with a magnetic stir bar containing oxime (1 equiv.). The 1 dr vial containing blocked host was rinsed with D₂O and the rinse was also transferred to the 1 dr vial containing oxime before addition of pyridine borane (3 equiv.) and subsequent workup 24h later.

Blocked host controls in D₂O for oximes **2a**, **2j**, **2v**, **2y**, and **2z** all found <5% NMR yield vs. internal standard (1,3,5-trimethoxybenzene). However, similar blocked host controls in D₂O using oxime **2b** with increased amounts of host **I** (7.5 mol%) and PEt₄Br (8–9 mol%) found approximately 15–20% *in situ* NMR yields vs. internal standard (3-(trimethylsilyl)-1-propanesulfonic acid sodium salt). When a similar experiment using oxime **2b** and increased amounts of host **I** (7.5 mol%) and PEt₄Br (9 mol%) was performed using 35mM pD 7.7 Li₂CO₃ D₂O buffer, no product was observed via *in situ* ¹H NMR vs. internal standard.

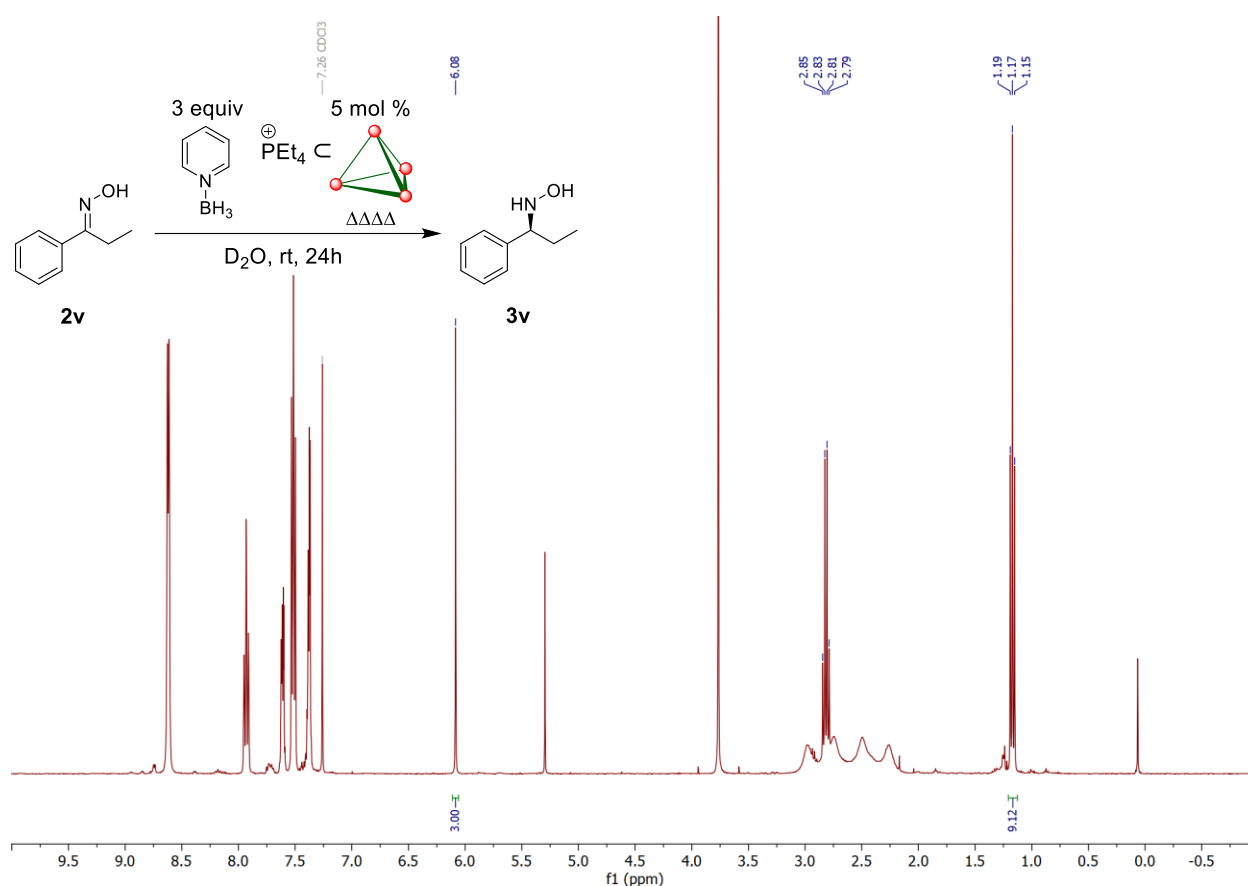


Figure S3.1. Representative ¹H NMR spectra of blocked host experiment with oxime **2v** and host **I**.

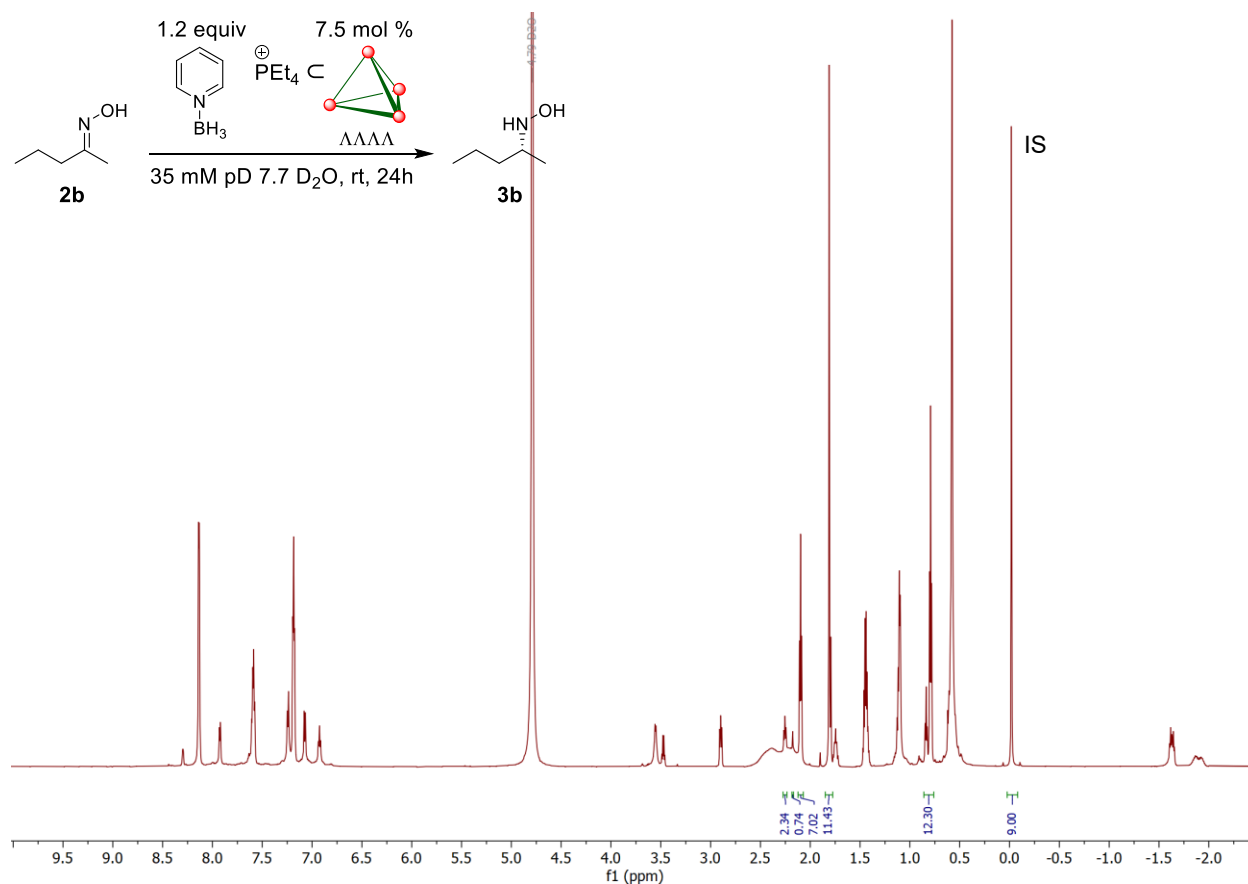
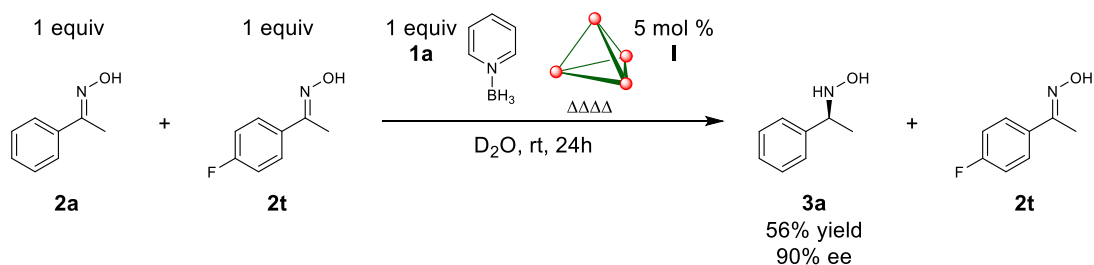


Figure S3.2. Representative ^1H NMR spectra of blocked host experiment with oxime **2b** and host **I**.

Competition experiment with oxime **2a** and **2t**



The competition experiment was performed in a manner nearly identical to that of the General Procedure D: To a 1 dr vial containing host **I** (8.36 mg, 1.73 μmol , 5 mol%) was added D_2O (500 μL) *via* Eppendorf pipette. The host solution was transferred to a second 1 dr vial equipped with a magnetic stir bar containing oxime **2a** (4.68 mg, 0.0346 mmol, 1 equiv.) and **2t** (5.30 mg, 0.0346 mmol, 1 equiv.). The 1 dr vial containing host was rinsed with D_2O (125 μL) and the rinse was also transferred to the 1 dr vial containing oxime. The heterogeneous solution was allowed to stir before addition of pyridine borane **1a** (3.20 mg, 3.45 μL , 0.0345 mmol, 1 equiv.) *via* Hamilton syringe. The reaction was then stirred at rt for 24 h, at which point the reaction was stopped by adding a large excess of PEt_4I . Following extraction, the crude extract solution was analyzed by ^1H NMR against internal standard. Although peak overlap prevented accurate integration of remaining

oxime peaks, ^1H NMR was consistent with preferential conversion of oxime **2b** to hydroxylamine **3a** (56% yield), while oxime **2t** remained unreactive. Unreacted pyridine borane was also recovered. **3a** was purified by prep TLC in 2.5% MeOH/DCM and isolated as a white solid for HPLC analysis (90% ee). Similar results were found when using 3 equiv. of pyridine borane, although **3a** was formed in greater yield (69% yield, 91% ee). These results suggest poor reactivity of *p*-substituted oximes is due to factors such as steric bulk rather than host decomposition.

Representative ^1H NMR Spectra for Yield Determination

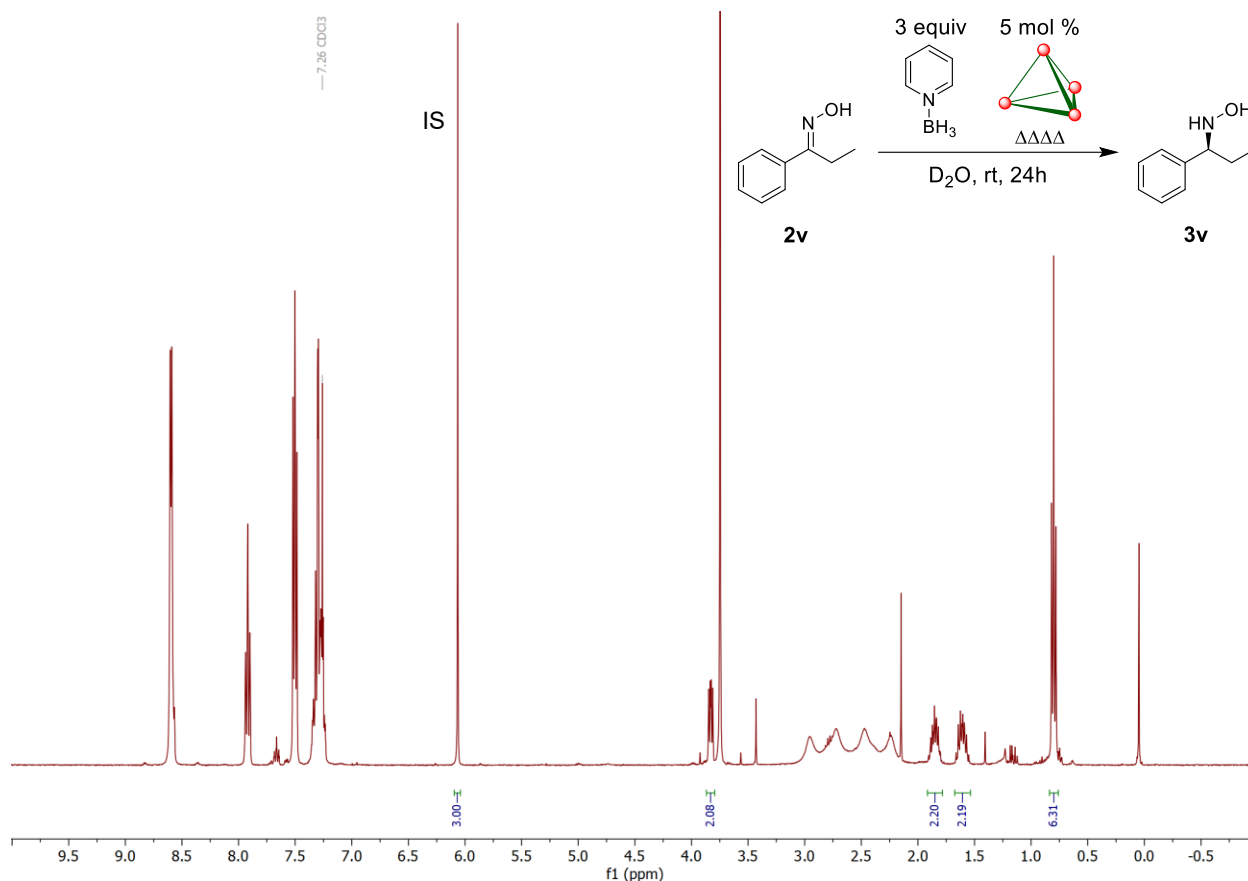


Figure S3.3. Representative crude ^1H NMR spectrum in CDCl_3 extract after enantiopure host **I**-catalyzed reduction of oxime **2v**. Contains 1,3,5-trimethoxybenzene as internal standard, used to determine extract NMR yields.

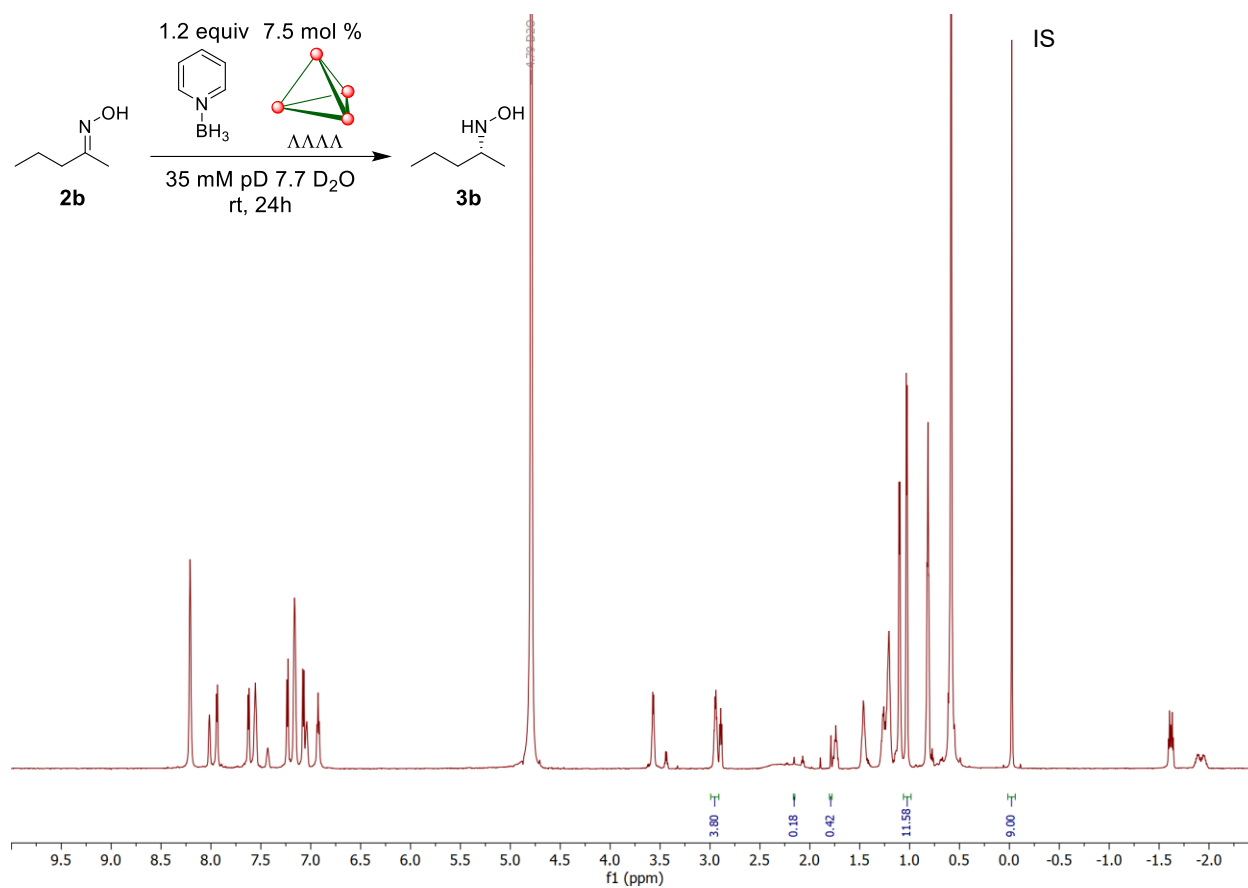


Figure S3.4. Representative crude ¹H NMR spectrum in D₂O of enantiopure host **I**-catalyzed reduction of oxime **2b** after quenching with PEt₄Br and with 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt as internal standard, used to determine *in situ* NMR yields.

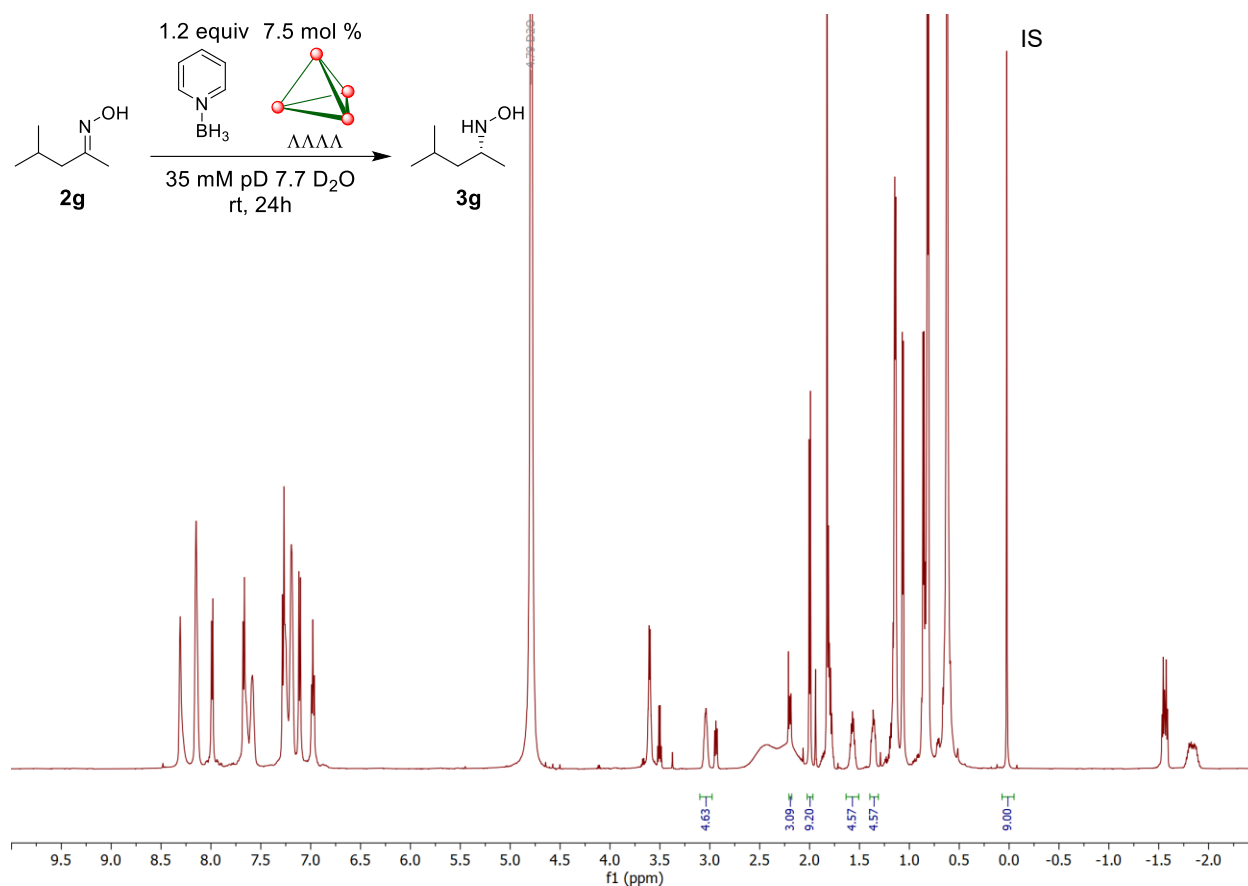


Figure S3.5. Representative crude ¹H NMR spectrum in D₂O of enantiopure host **I**-catalyzed reduction of oxime **2g** after quenching with PEt₄Br and with 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt as internal standard, used to determine *in situ* yields.

To help corroborate *in situ* yields of aliphatic oximes, solutions were prepared in NMR tube composed of blocked host **I**, oxime, and independently synthesized racemic hydroxylamine for analysis by ¹H NMR. To a 1 dr vial containing host **I** (0.001 mmol, 0.035 equiv.) was added D₂O (500 μL), PEt₄Br (0.001 mmol, 0.042 equiv.) as a stock solution, and internal standard, 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt (0.007 mmol, 0.25 equiv.) as a stock solution *via* Eppendorf pipette. The resulting solution was transferred to an NMR tube to which oxime (0.03 mmol, 1.0 equiv.) was added *via* Hamilton syringe. The sample was analyzed by ¹H NMR, and then transferred to a 1 dr vial containing hydroxylamine. The resulting solution was returned to the NMR tube, the vial was rinsed with 30 μL of MeOD-*d*₄, and the rinse was transferred to an NMR tube. The final solution was again analyzed by ¹H NMR.

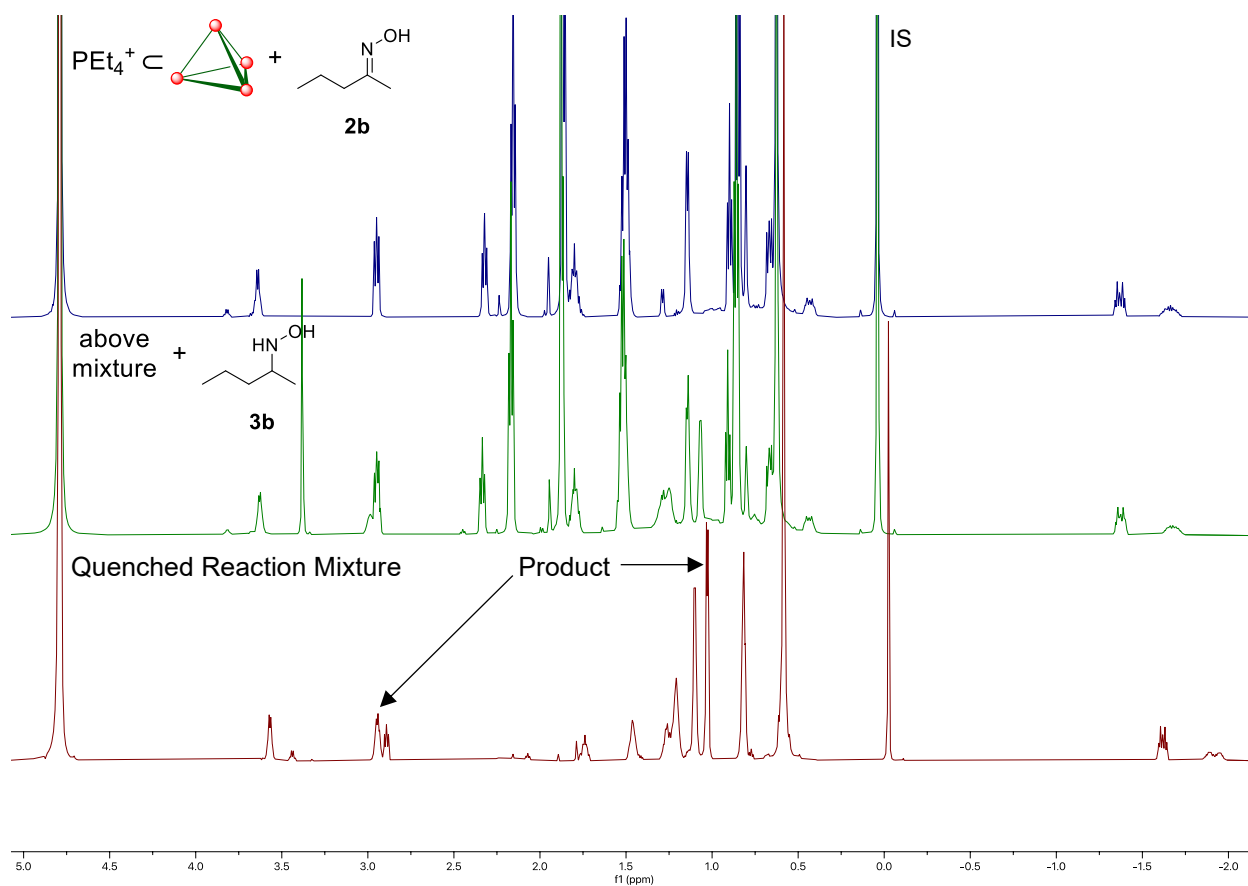


Figure S3.6. Representative ^1H NMR stacked spectra in D_2O of 1) mixture of PET_4Br blocked host **I** and oxime **1a** (top), 2) mixture of PET_4Br blocked host **I**, oxime **2b**, and independently synthesized hydroxylamine **3b** (middle) and 3) enantiopure host **I**-catalyzed reduction of oxime **2b** after quenching with PET_4Br (bottom).

3.7.4 Kinetic and Mechanistic Analysis

General Procedure J for Pyridine Borane ^{19}F NMR Titrations:

Oxime was weighed directly into an NMR tube. To the NMR tube was then added sodium 4-fluorobenzoate as internal standard (0.008387 mmol, 0.116 mM) as a pre-made stock solution in D_2O . Additional components were added as necessary, and the resulting heterogeneous solution was 55 mM concentration in oxime. The NMR tube was capped with a septa cap and the solution mixed by inversion twice before being taken to a NMR spectrometer held at 298K. The sample was locked, tuned and shimmed, and spectra acquired. The sample was ejected and additional pyridine borane quickly added to reach the next desired stoichiometry. The resulting sample was mixed by inversion at least three times and spectra acquired. This process was repeated until 3 equiv. of pyridine borane was added in total. The equivalents of pyridine borane added were: 0, 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0. The solution remained heterogeneous throughout acquisition.

Acquisition parameters:

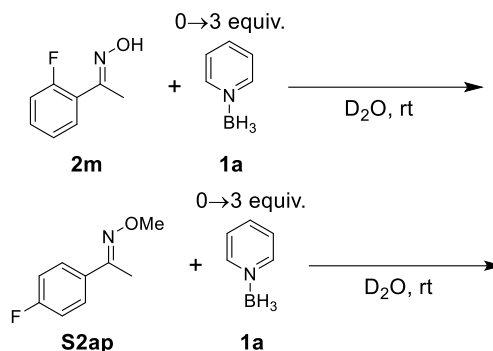
o1p = -115

sw = 30

d1 = 15

ns = 8

acq. = 1.0 sec



No Host Experiments

Two no host experiments were performed with oxime **2m** (5.89 mg, 0.0385 mmol) according to General Procedure J. Additional D₂O was added until the solution was at appropriate concentration and the samples taken to the NMR spectrometer for analysis. One included sodium 4-fluorobenzoate as internal standard and one was run in the absence of internal standard. The same behavior was observed in both experiments. Additional peaks attributed to the (*E*) and (*Z*) isomers of oxime when coordinating or interacting with another substrate appeared at 1.5 equiv. of pyridine borane (**1a**) added and continued to grow in with further addition of pyridine borane. Consistent with previous no host and blocked host control experiments, no product formation was observed.

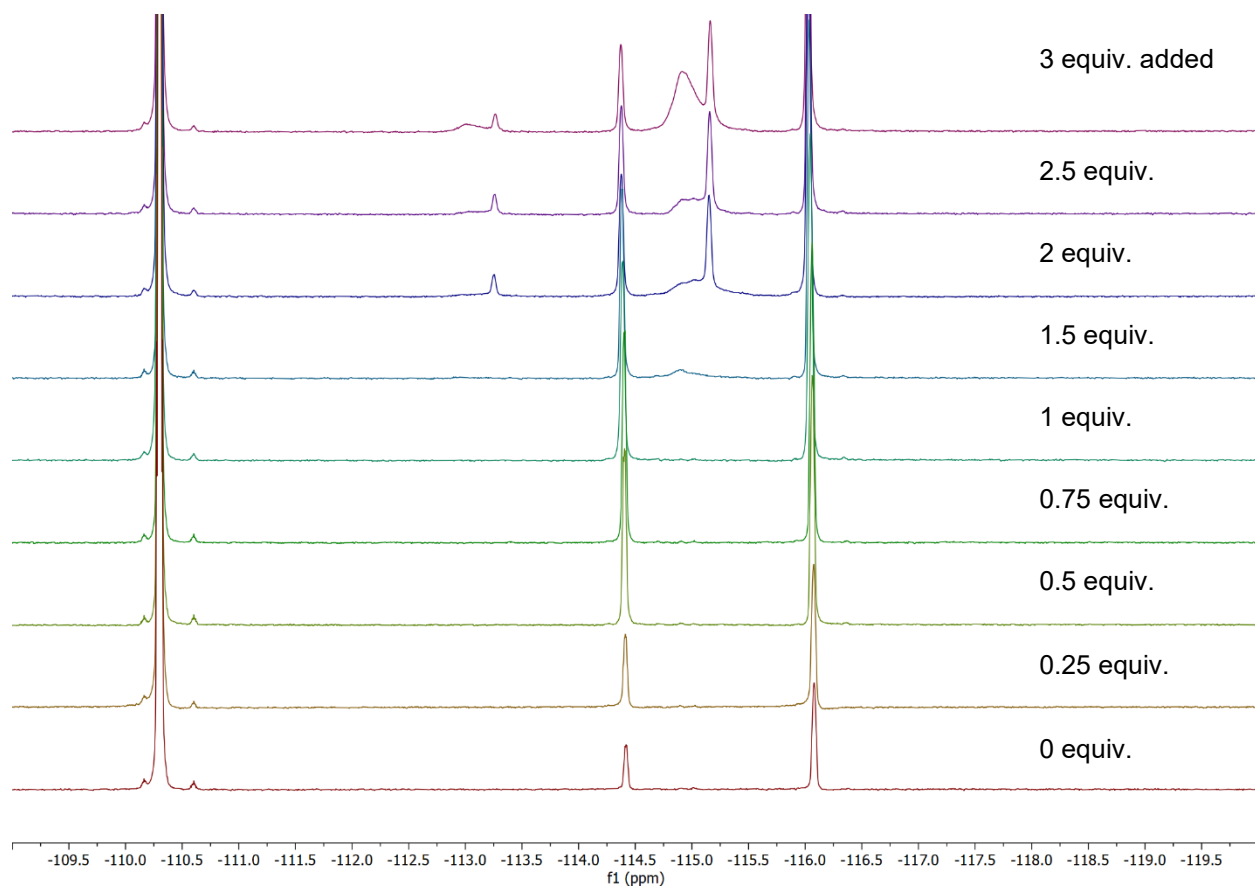


Figure S3.7. Representative ^{19}F NMR stack plot of oxime **2m** in a D_2O solution in the absence of host **I** throughout addition of pyridine borane.

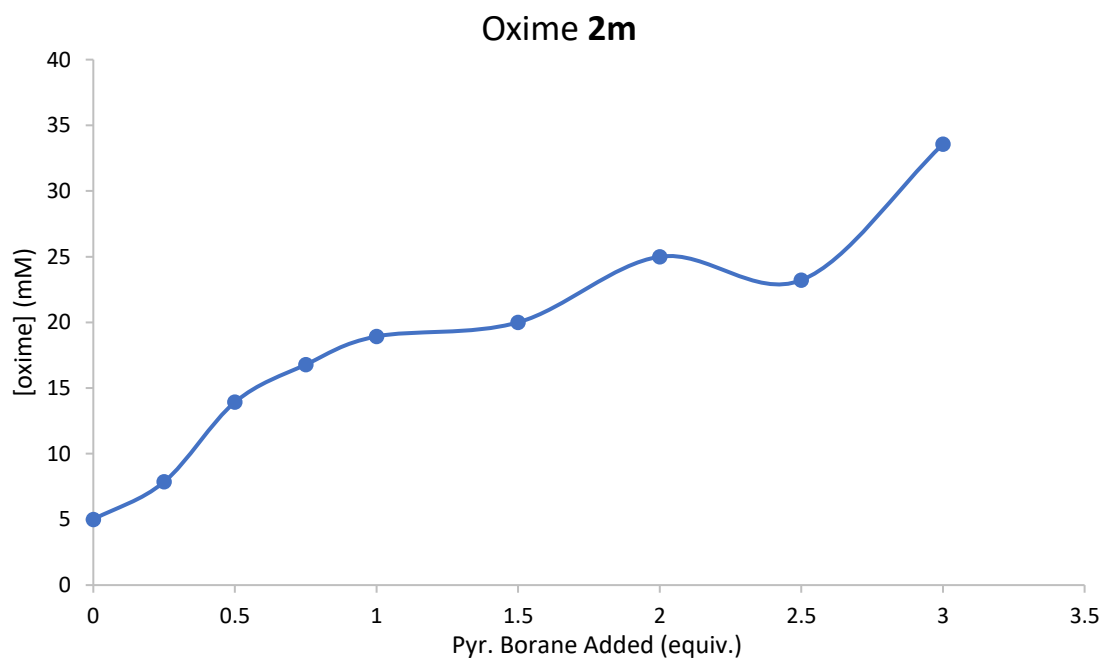


Figure S3.8. Amount of combined (*E*) and (*Z*) oxime **2m** present in a D_2O solution in the absence of host as a function of the amount of pyridine borane added.

An identical no host experiment was also performed using oxime **S2ap** (6.95 mg, 0.0416 mmol) according to General Procedure J. Additional D₂O was added until the solution was at appropriate concentration and the samples taken to the NMR spectrometer for analysis. The formation of additional peaks was not observed throughout acquisition.

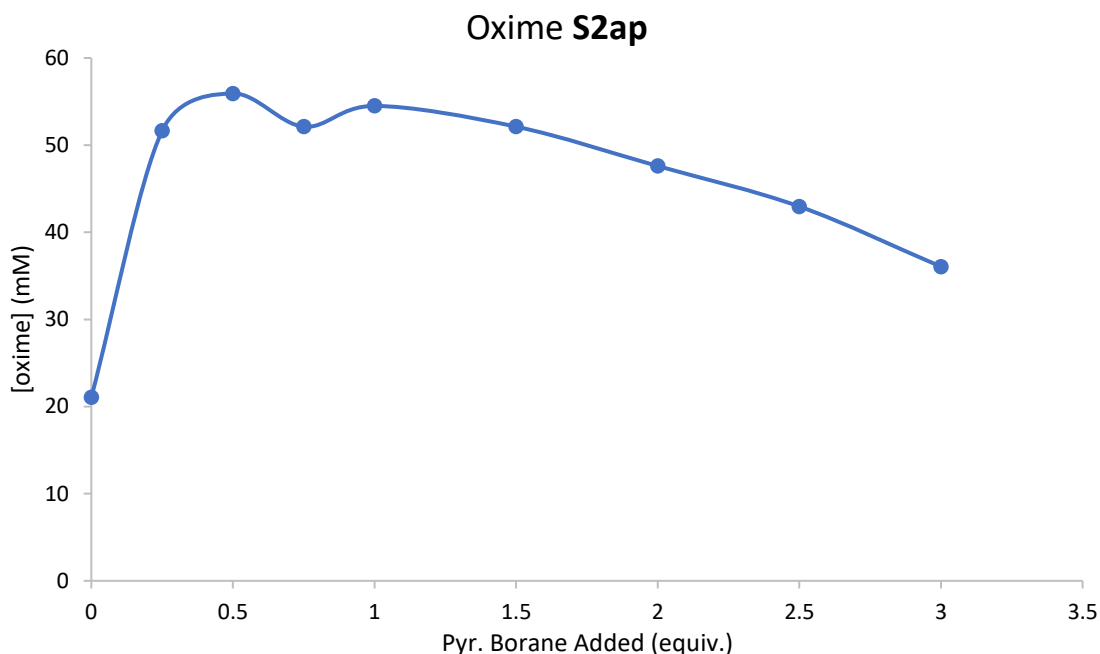
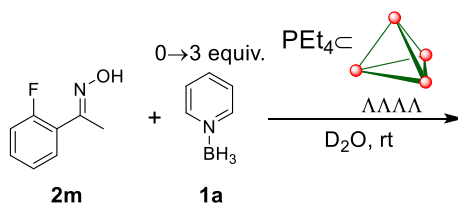


Figure S3.9. Amount of combined (*E*) and (*Z*) oxime **S2ap** present in a D₂O solution in the absence of host as a function of the amount of pyridine borane added.



Blocked Host Experiment

A blocked host experiment was performed with oxime **2m** (5.86 mg, 0.0383 mmol) according to General Procedure J. To a 1 dr vial was added $\Delta\Delta\Delta\Delta$ host **I** (9.27 mg, 1.918 μmol , 5.0 mol%). A portion of PET₄Br (0.48 mg, 2.110 μmol , 5.5 mol%) as a stock solution in D₂O was added to the vial, and additional D₂O was added. The resulting solution was transferred to the NMR tube, and the 1 dr vial was rinsed with D₂O. This rinse was transferred to the NMR tube and the resulting sample was taken to the NMR spectrometer for analysis. Additional peaks attributed to the (*E*) and (*Z*) isomers of oxime when coordinating or interacting with another substrate appeared at 1.5 equiv. of pyridine borane (**1a**) added and continued to grow in with further addition of pyridine borane. Consistent with previous no host and blocked host control experiments, no product formation was observed.

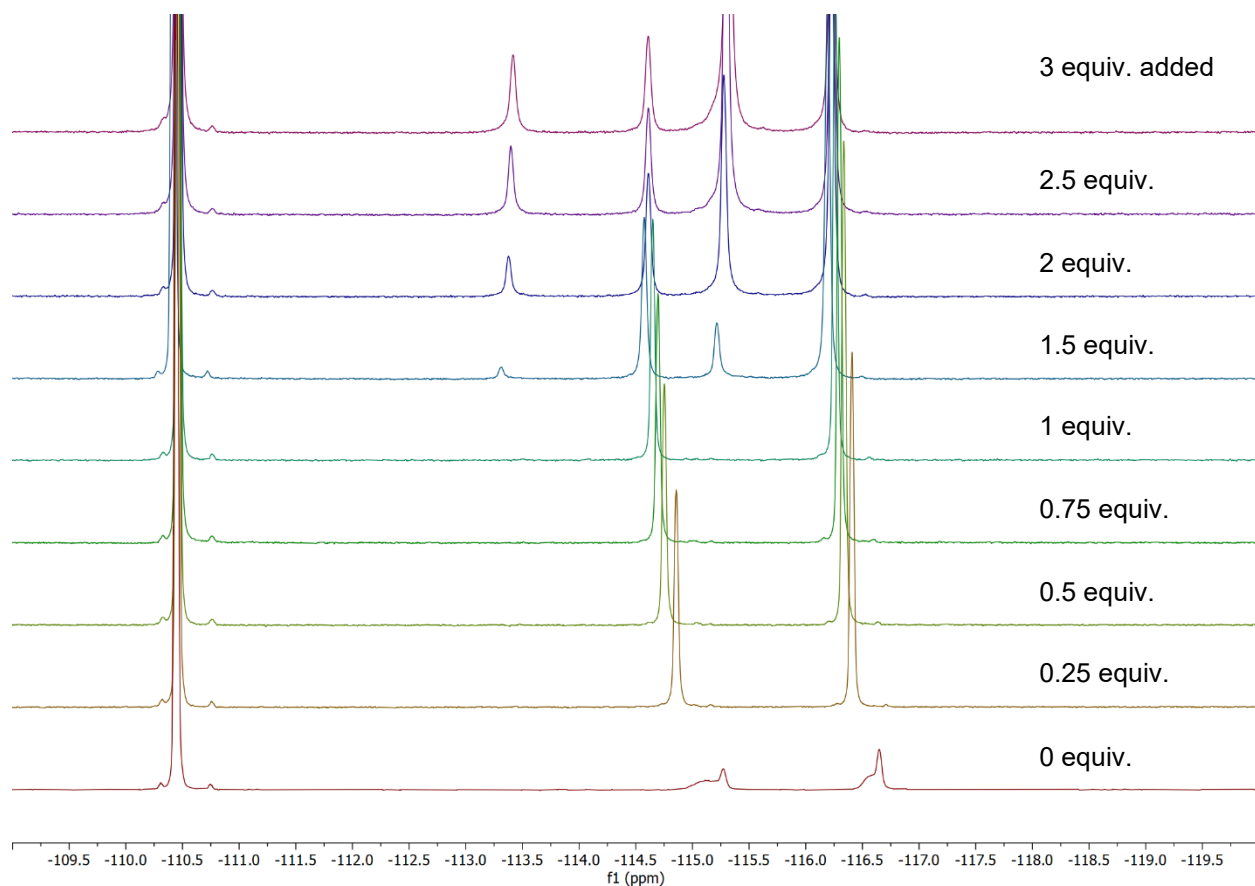


Figure S3.10. Representative ^{19}F NMR stack plot of oxime **2m** in a D_2O solution in the presence of blocked host **I** throughout addition of pyridine borane.

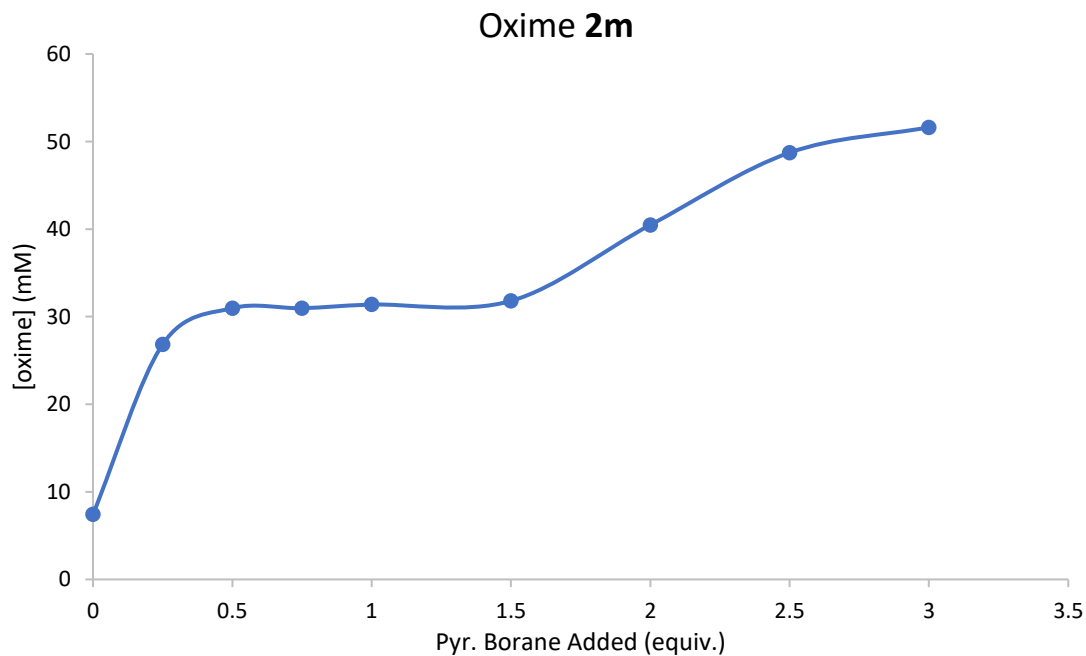
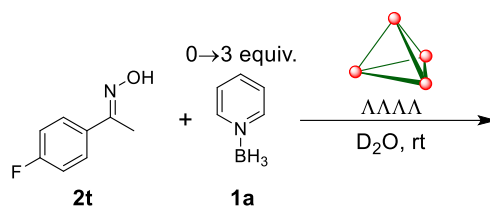


Figure S3.11. Amount of combined (*E*) and (*Z*) oxime **2m** present in a D_2O solution in the presence of blocked host **I** as a function of the amount of pyridine borane added.



Empty Host Experiment

An empty host experiment was performed with oxime **2t** (5.92 mg, 0.0386 mmol) according to General Procedure J. To a 1 dr vial was added $\Delta\Delta\Delta\Delta$ host **I** (9.36 mg, 1.937 μmol , 5.0 mol%) and D_2O was added to the vial. The resulting solution was transferred to the NMR tube, and the 1 dr vial was rinsed with D_2O . This rinse was transferred to the NMR tube and the resulting sample was taken to the NMR spectrometer for analysis. Trace amounts of product formation of the hydroxylamine **3t** was observed beginning at 0.5 equiv. of pyridine borane added and grew in very slowly. Additional peaks attributed to the (*E*) oxime isomer when coordinating or interacting with another substrate appeared at 2.0 equiv. of pyridine borane (**1a**) added and continued to grow in with further addition of pyridine borane.

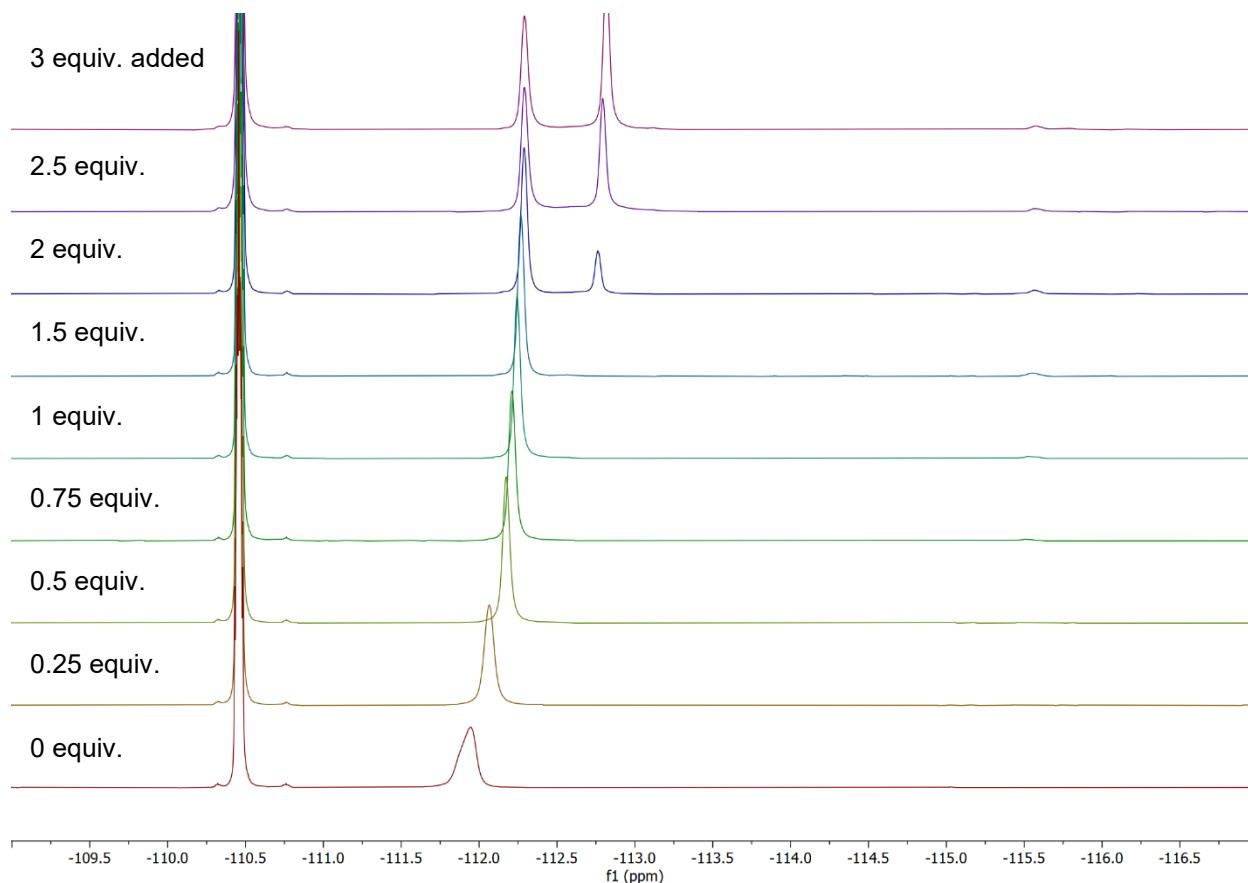


Figure S3.12. Representative ^{19}F NMR stack plot of oxime **2t** in a D_2O solution in the presence of host **I** throughout addition of pyridine borane.

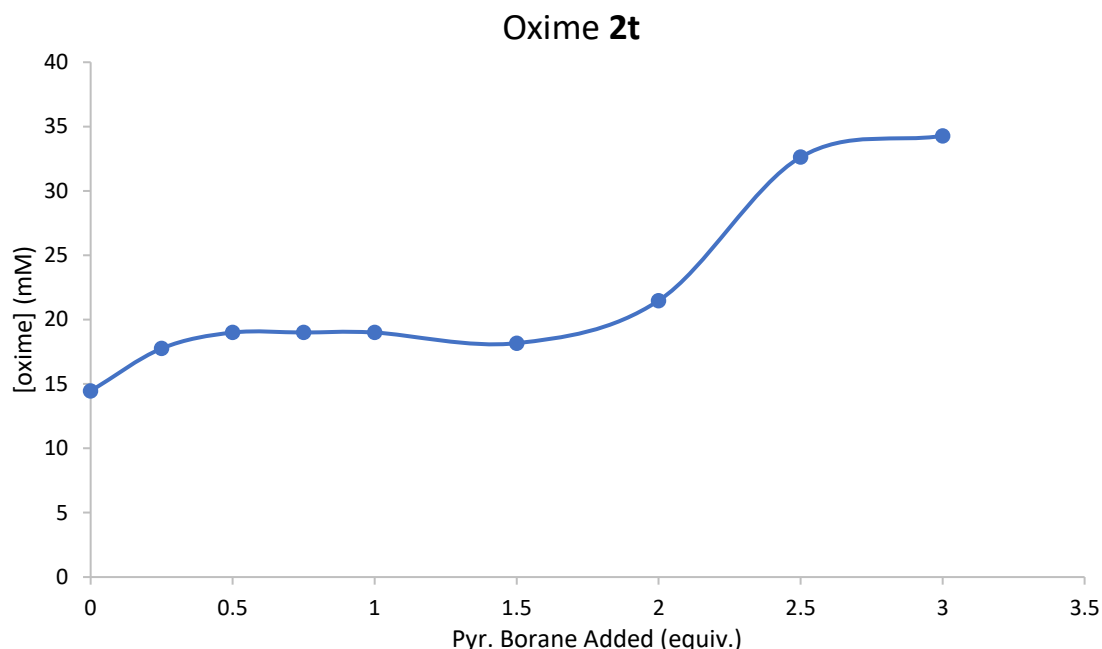
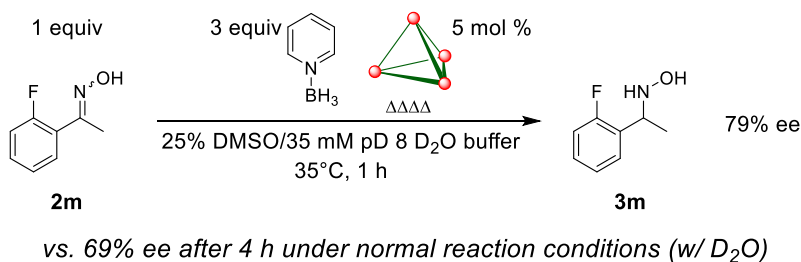


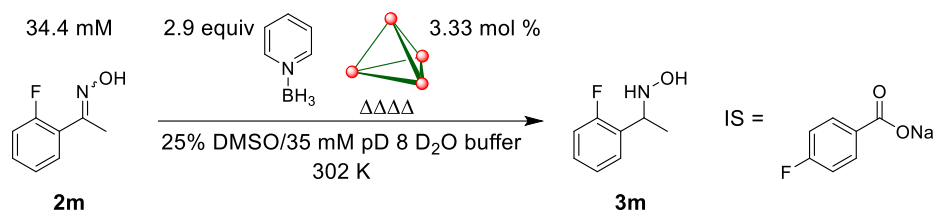
Figure S3.13. Amount of (*E*) oxime **2t** present in a D₂O solution in the presence of empty host as a function of the amount of pyridine borane added.

Kinetics Experiments

Due to the heterogeneity of the reaction mixture under normal reaction conditions with respect to oxime, pyridine borane, and H₂ evolution resulting from reduction, varying amounts of co-solvents were added to find optimal conditions for solubility. Moderate quantities of DMSO-*d*₆ (25%) were found to increase homogeneity such that the sample could be monitored *in situ* by NMR. Although chiral host **I** exhibits poor solubility in 100 mM K₃PO₄ D₂O buffers, 35mM buffer was found to be well-tolerated under reaction conditions. To increase rates of reaction to be more easily analyzed on the NMR time scale, the reaction was heated slightly to increase rate of reactivity while not promoting excessive H₂ evolution. To ensure the mechanism of the reaction did not change substantially under kinetics conditions, the reaction was stopped after 1h to observe enantioselectivity and found slightly improved (79% ee) but generally comparable enantioselectivity to that observed under normal reaction conditions without heating in D₂O after 4h (69% ee).



General Procedure K for Kinetic Experiments:



In an air-free wet glovebox, to an NMR tube was added host **I** (2.83 μ M) as a pre-made stock solution in D₂O, followed by sodium 4-fluorobenzoate as internal standard (0.008387 mmol, 0.116 mM) as a pre-made stock solution in 100 mM K₃PO₄ pD 8 D₂O buffer. Additional amounts of D₂O and 100 mM K₃PO₄ pD 8 D₂O buffer were added to dilute the reaction to the appropriate concentration as needed. The tube was capped with an NMR septa cap and sealed with electrical tape. The NMR tube was removed from the glovebox and oxime **2m** (0.628 mM) as a pre-made stock solution in DMSO-*d*₆ was added to the NMR tube. The final concentration of solution was 34.4 mM in oxime. The reaction tube was placed in a water bath heated to 29°C and allowed to equilibrate for at least 15 minutes. After equilibration, pyridine borane (**1a**) (0.981 mM) as a pre-made stock solution in DMSO-*d*₆ was added. The total volume of solution in the NMR tube was 600 μ L. The tube was shaken and inverted at least twice before being immediately taken to the NMR spectrometer, which was heated to 302K. The sample was allowed to equilibrate in the probe for 2 minutes before acquisition time began. A dummy sample prepared in an identical matter was used to tune and shim the spectrometer probe before the reaction run(s). Oxime and pyridine borane stock solutions were stored in vials with a Teflon cap and sealed with electrical taped in a -20°C freezer to prolong stability. Host and internal standard stock solutions were stored in vials with Teflon cap and sealed with electrical taped at room temperature in an air-free wet glovebox.

Acquisition parameters:

o1p = -115

sw = 30

d1 = 1

ns = 1

acq. = 0.489 sec

with forced 30 second delay between scans

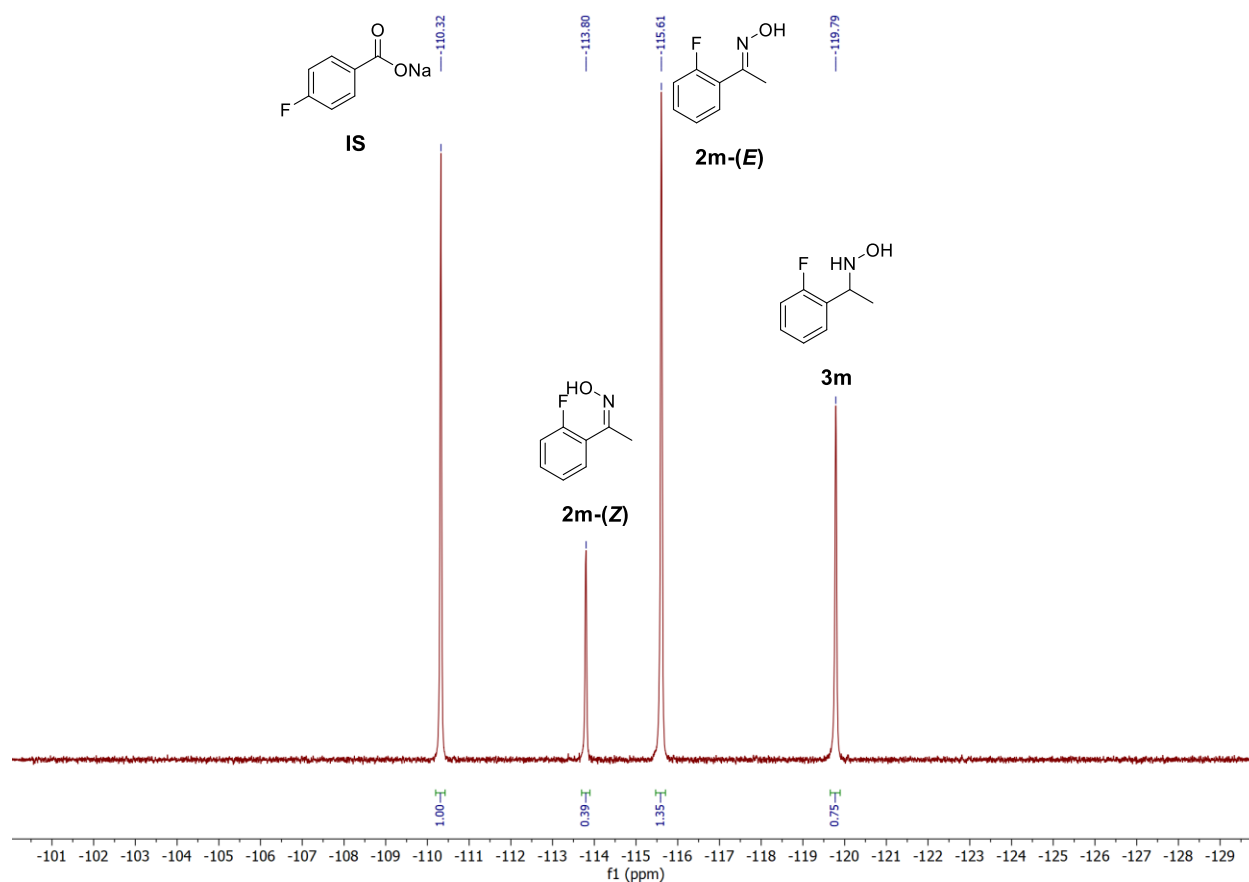


Figure S3.14. Representative ^{19}F NMR of reaction using 3.33 mol% host and 2.9 equiv. pyridine borane with 1 equiv. of oxime at 30% conversion after 5204 s.

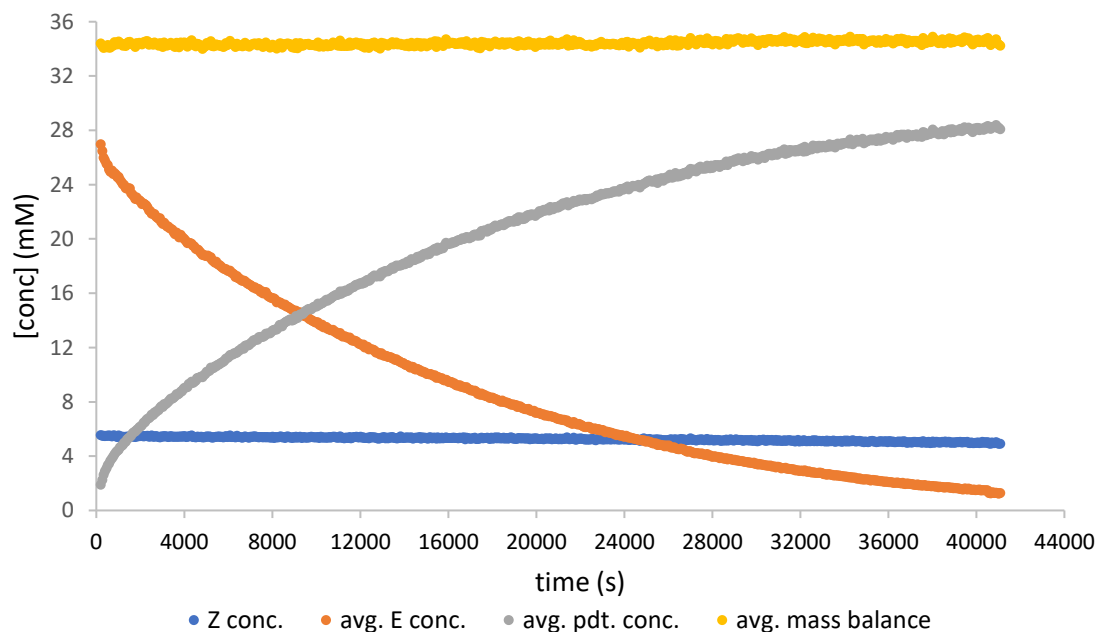


Figure S3.15. Sample kinetic trace of reaction using 3.33 mol% host **I** and 2.9 equiv. pyridine borane **1a** with 1 equiv. of oxime **2m** (average of 2 runs) up to 82% conversion.

Approximate order in host was determined using Variable Time Normalization Analysis (VTNA) as reported by Burés *et al.*⁷⁷ Each concentration is reported as an average of 2 runs. Runs for 3.33 mol% host were acquired up to 81% and 82% conversion while runs for 2.4 mol% host I were acquired up to 77% and 68% conversion. Acquisition parameters used were as reported above but with a forced 60 second delay between scans. While 1.0 order in host was found to generally give a good fit, 1.2 order was found to give optimal fit.

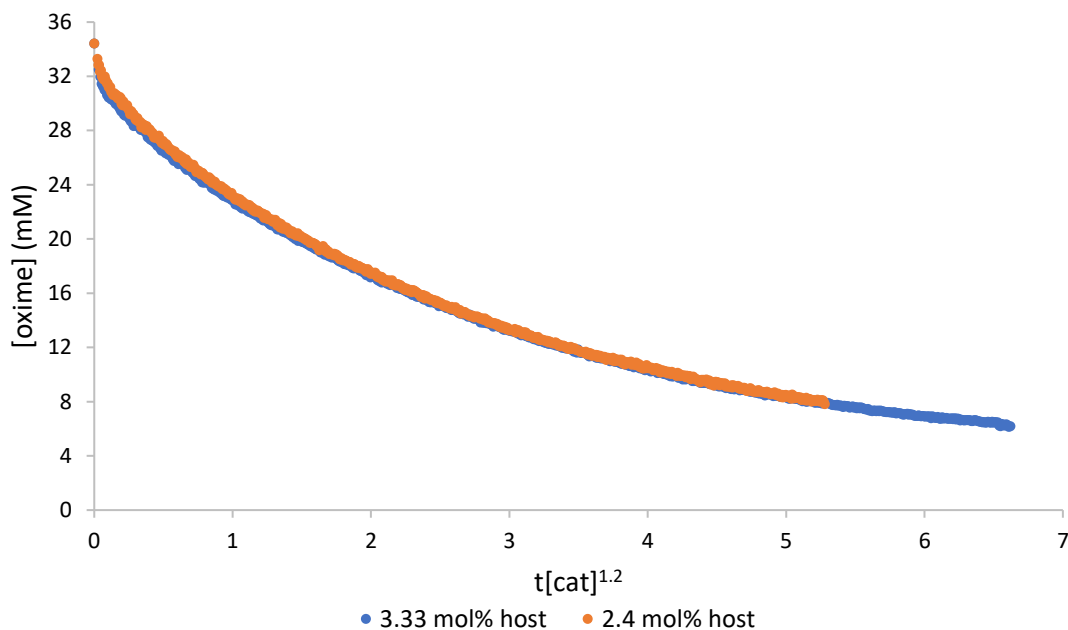


Figure S3.16. VTNA using host I to approximate 1st order in host

To determine order in pyridine borane, initial rates kinetics were performed until approx. 16.7% conversion (5 catalytic turnovers) at varying concentrations of pyridine borane. Initial temperature equilibration issues of the internal standard, which caused temporary broadening of the peak, led to data from the first 500s being excluded for determination of initial rates. Each data point represents an average of 3 runs, except for data for 1 equiv. of pyridine borane, which is an average of 2 runs.

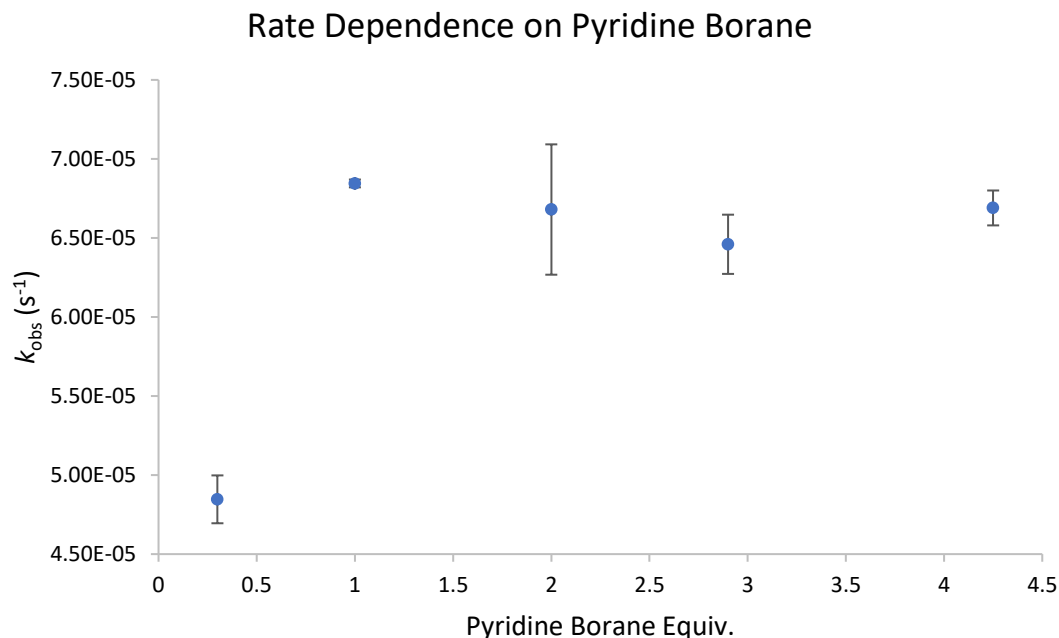


Figure S3.17. Initial rates of reactivity with varying concentrations of pyridine borane

Order in oxime was determined by monitoring reaction progress up to 51% conversion of oxime when using a constant amount of pyridine borane (40.4 mM) and host **1** (0.464 mM). Once again data from the first 500s was excluded due to temperature equilibration issues with the internal standard. First order kinetics behavior was observed using both 1.0 equiv. and 0.5 equiv of oxime. For 1.0 equiv. of oxime, $k_{\text{obs}} = 4.78 \times 10^{-5} \pm 8.14 \times 10^{-7} \text{ s}^{-1}$ an average of 3 runs and for 0.5 equiv. of oxime, $k_{\text{obs}} = 1.04 \times 10^{-4} \pm 7.67 \times 10^{-6} \text{ s}^{-1}$ as an average of 2 runs.

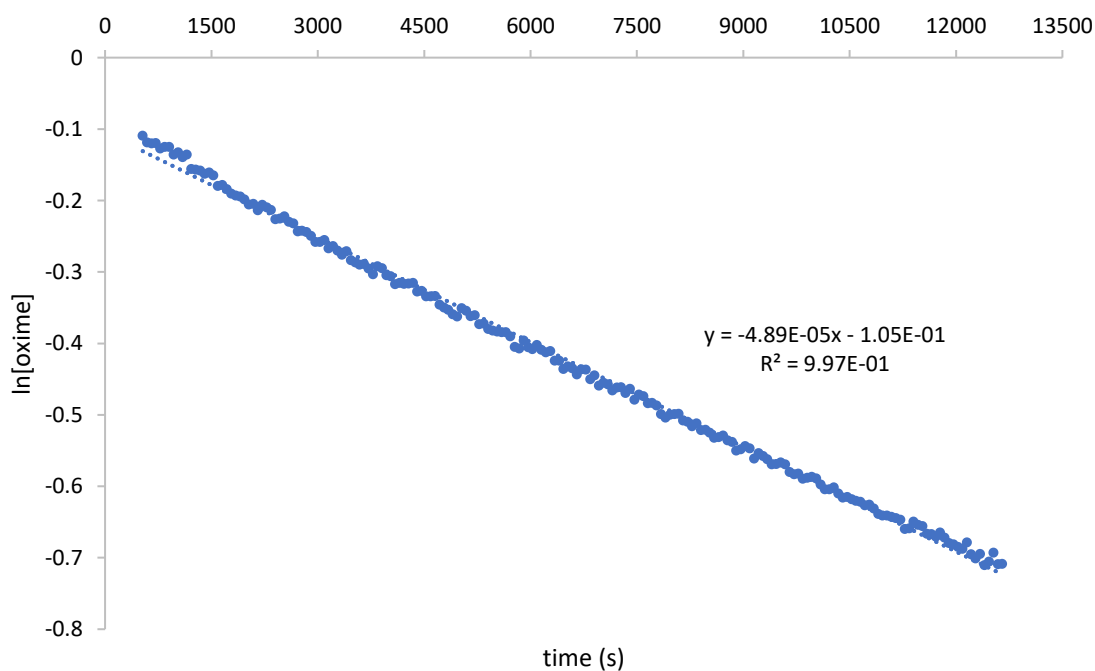


Figure S3.18. Representative first order kinetic plot of oxime concentration vs. time using 1.0 equiv. of oxime up to 51% conversion showing first order behavior in oxime.

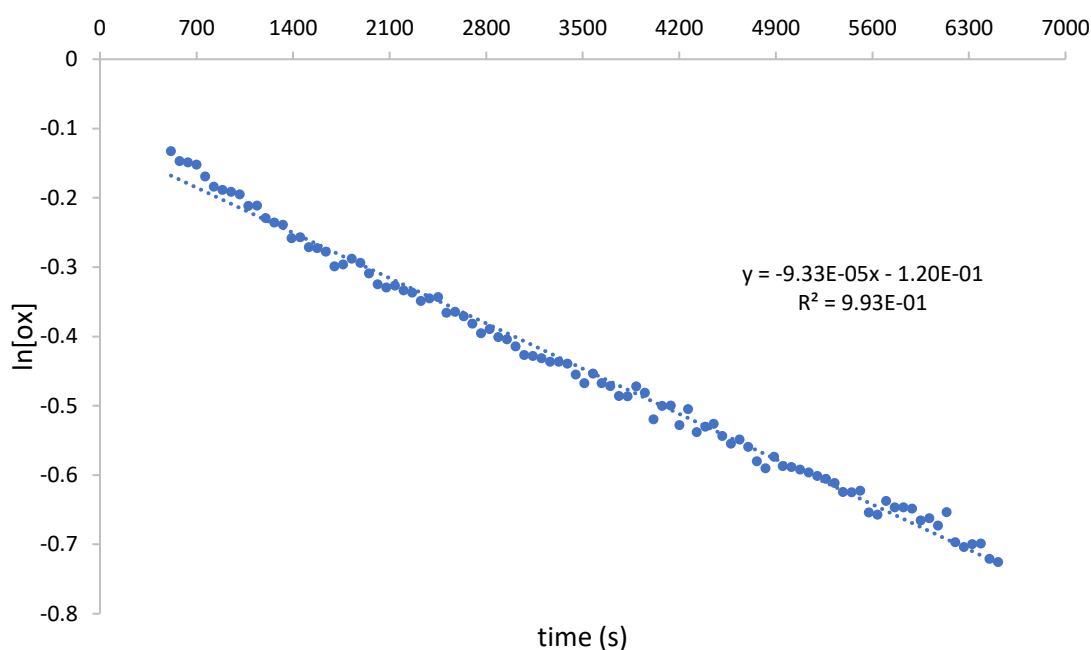
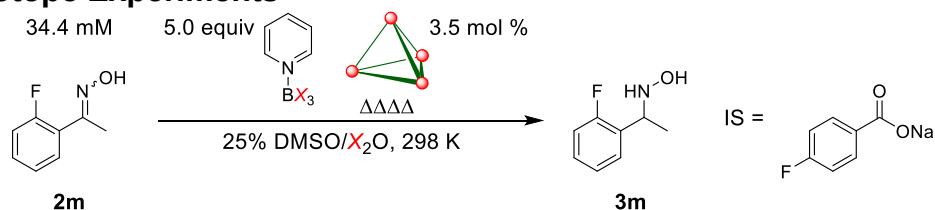


Figure S3.19. Representative first order kinetic plot of oxime concentration vs. time using 0.5 equiv. of oxime up to 51% conversion showing first order behavior in oxime.

Kinetic Isotope Experiments



Solvent and Parallel Competition KIEs

Experiments were performed in duplicate according to General Procedure K with some modifications. Reactions were set up in ambient conditions outside of an air-free wet glovebox. To an NMR tube was added host **I** (2.83 μM) as a pre-made stock solution in D_2O or H_2O accordingly, followed by sodium 4-fluorobenzoate as internal standard (0.008387 mmol, 0.116 mM) as a pre-made stock solution in D_2O or H_2O accordingly. Additional amounts of D_2O or H_2O were added to dilute the reaction to the appropriate concentration as needed. Then to the NMR tube was added oxime **2m** (34.4 mM) as a pre-made stock solution in $\text{DMSO-}d_6$, and an additional portion of $\text{DMSO-}d_6$ was added to dilute the reaction to the appropriate concentration. The tube was capped with an NMR septa cap, sealed with electrical tape, and mixed by inversion twice. Immediately before acquisition, pyridine borane (**1a** or **1a-D**) (5.0 equiv.) as a pre-made stock solution in $\text{DMSO-}d_6$ was added. The total volume of solution in the NMR tube was 600 μL . The tube was shaken and inverted at least twice before being immediately taken to the NMR spectrometer. The sample was allowed to equilibrate in the probe for 2 minutes before acquisition time began. Samples were run for 28 total scans. A dummy sample prepared

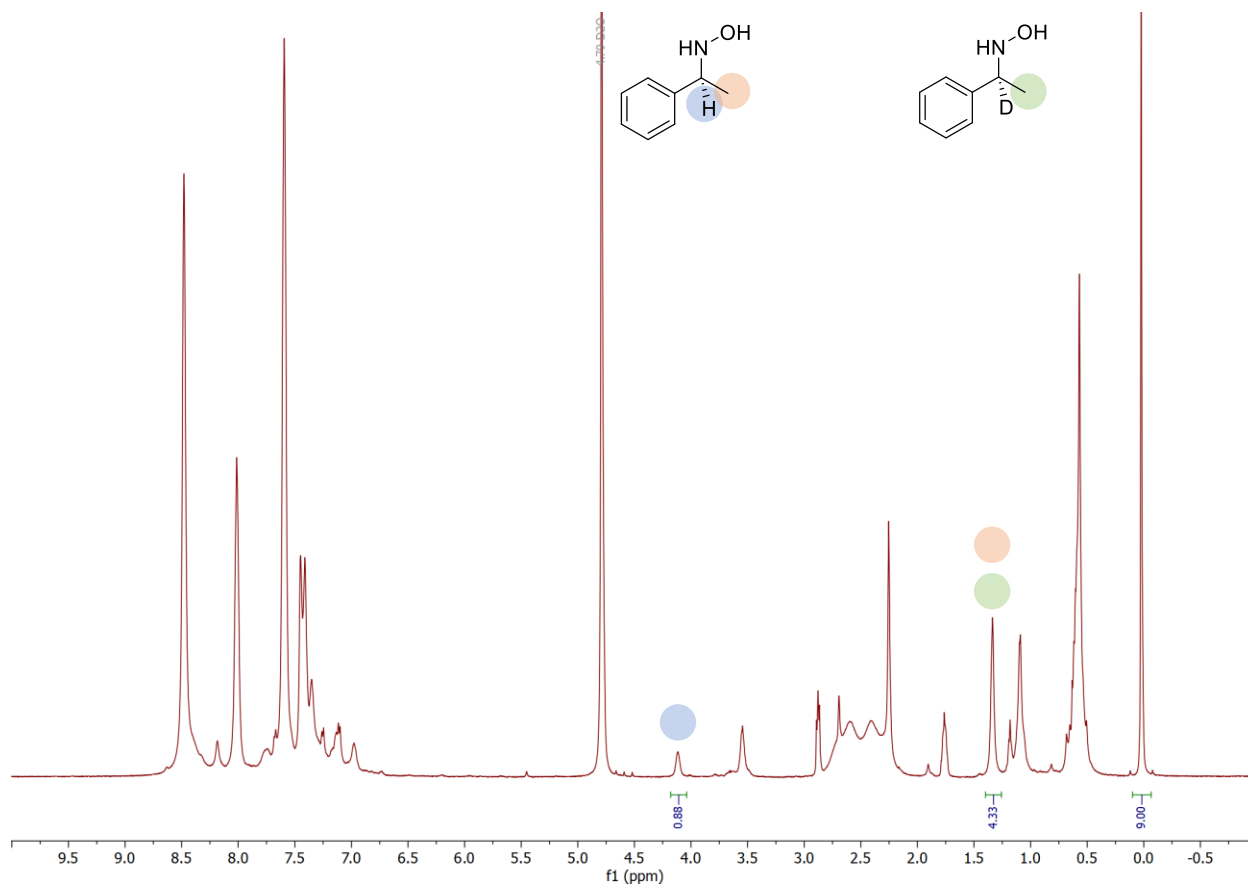
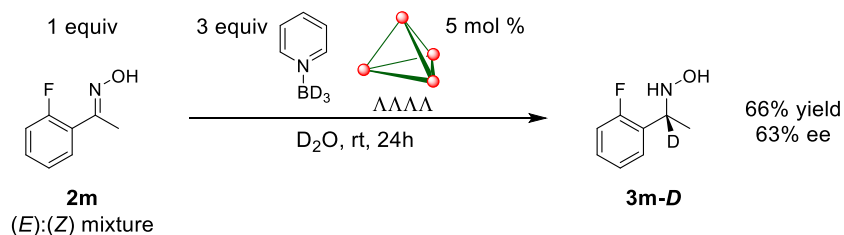


Figure S3.20. Representative crude ^1H NMR spectrum of competition KIE with host **I**, oxime **2a**, pyridine borane- H_3 (**1a**), and pyridine borane- D_3 (**1a-D**) with 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt as internal standard after 100 min.

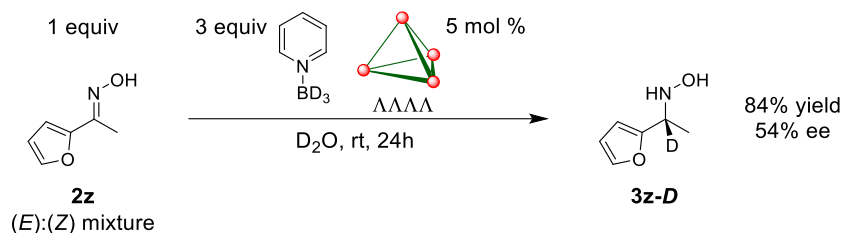
KIE on Enantioselectivity

Enantioselectivity KIE experiments were performed on oximes **2m** and **2z** using General Procedure D with a few modifications, through the use of $\Delta\Delta\Delta\Delta$ host **I** and pyridine borane- D_3 . No discernable difference was observed in enantioselectivity when using pyridine borane- D_3 .



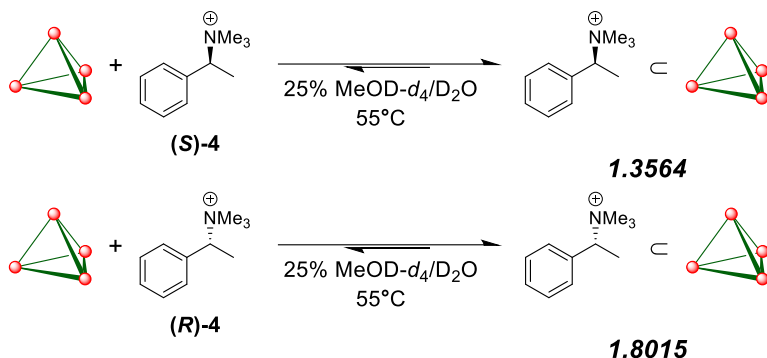
Enantioenriched material was prepared from oxime **2m** (3.81 mg, 0.0249 mmol) with $\Delta\Delta\Delta\Delta$ host **I** (6.03 mg, 1.24 μmol , 5 mol%). The heterogeneous solution in a 1 dr vial with magnetic stir bar was allowed to stir before addition of pyridine borane- D_3 (7.15 mg, 7.50 μL , 0.0746 mmol, 3.0 equiv.) *via* Hamilton syringe. The reaction was then stirred at rt for 24 h, at which point the reaction was stopped by adding a large excess of PEt_4Br . Following extraction, the crude extract solution was analyzed by ^1H NMR (66% NMR

yield), then the product was purified by prep TLC in 2.5% MeOH/DCM and isolated as a white solid for HPLC analysis (63% ee).



Enantioenriched material was prepared from oxime **2z** (4.18 mg, 0.0334 mmol) with $\Lambda\Lambda\Lambda\Lambda$ host **I** (8.08 mg, 1.67 μmol , 5 mol%). The heterogeneous solution in a 1 dr vial with magnetic stir bar was allowed to stir before addition of pyridine borane- D_3 (9.60 mg, 10.00 μL , 0.100 mmol, 3.0 equiv.) *via* Hamilton syringe. The reaction was then stirred at rt for 24 h, at which point the reaction was stopped by adding a large excess of PET_4Br . NaCl was added to the reaction mixture after quenching to help improve extraction of product from solution. Following extraction, the crude extract solution was analyzed by ^1H NMR (84% NMR yield), then the product was purified by prep TLC in 1.75% MeOH/DCM and isolated as a white solid for HPLC analysis (54% ee).

Selective Inversion Recovery (SIR) NMR Experiments:



Sample preparation:

An NMR tube was charged with $\Lambda\Lambda\Lambda\Lambda$ host **I** (0.9 μmol , 1.5 mM), chiral salt **4** (9 μmol , 15 mM), MeOD (150 μL) and D_2O (450 μL). The sample was sealed with an NMR septum cap and allowed to equilibrate overnight prior to measurement. The SIR NMR spectra were then acquired at 310K with variable delay list: 0.00001, 0.0001, 0.0005, 0.001, 0.005, 0.01, 0.015, 0.02, 0.025, 0.035, 0.05, 0.065, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 0.7, 1, 1.5, 2, 2.5, 3 s.

Example SIR NMR stack plot:

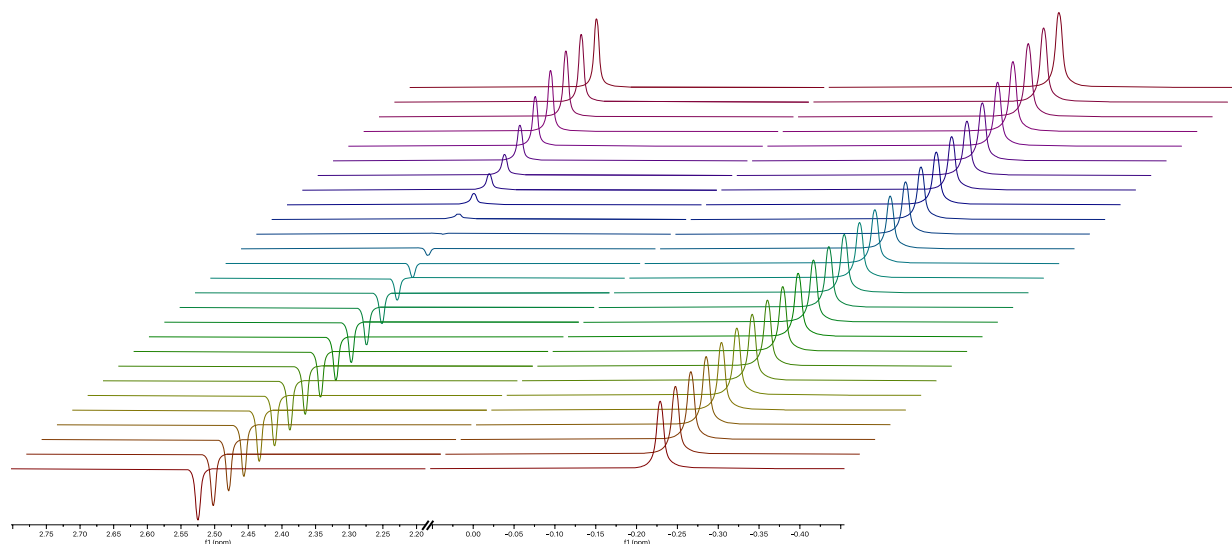


Figure S3.21. Total magnetization (difference in integration at equilibrium and various mixing times) for the selectively inverted proton resonance (2.53 ppm) of chiral salt and a resonance related by chemical exchange (−0.23 ppm) for a representative SIR experiment.

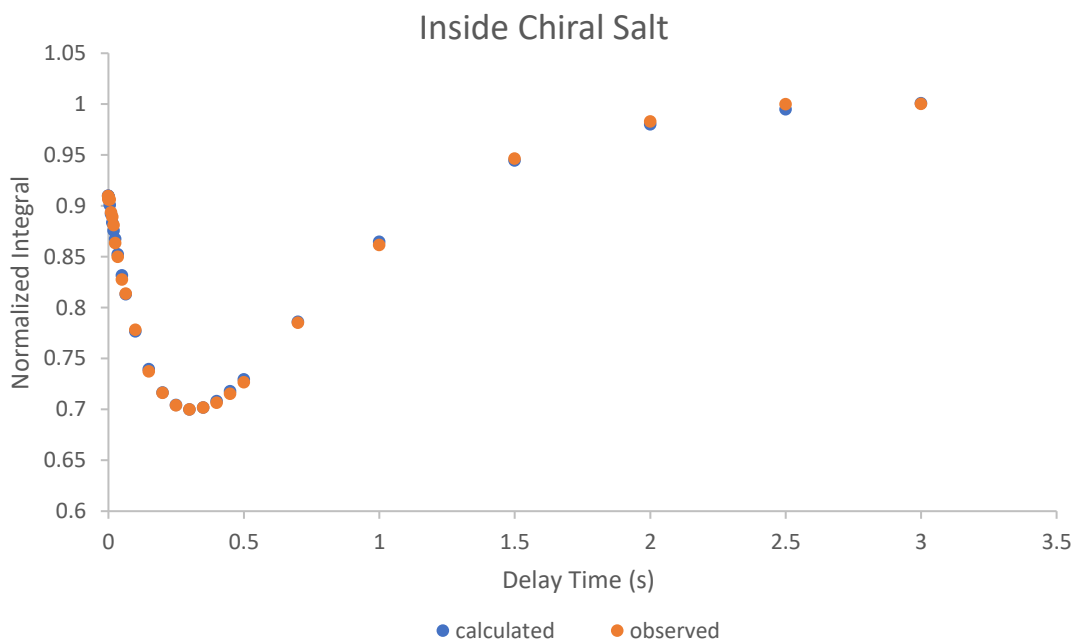


Figure S3.22. Example plot of the normalized integrals vs. delay time of the chiral salt (S)-4 NMe₃ peak while encapsulated in host I. Orange is experimentally determined, and blue is calculated with the CIFIT program.

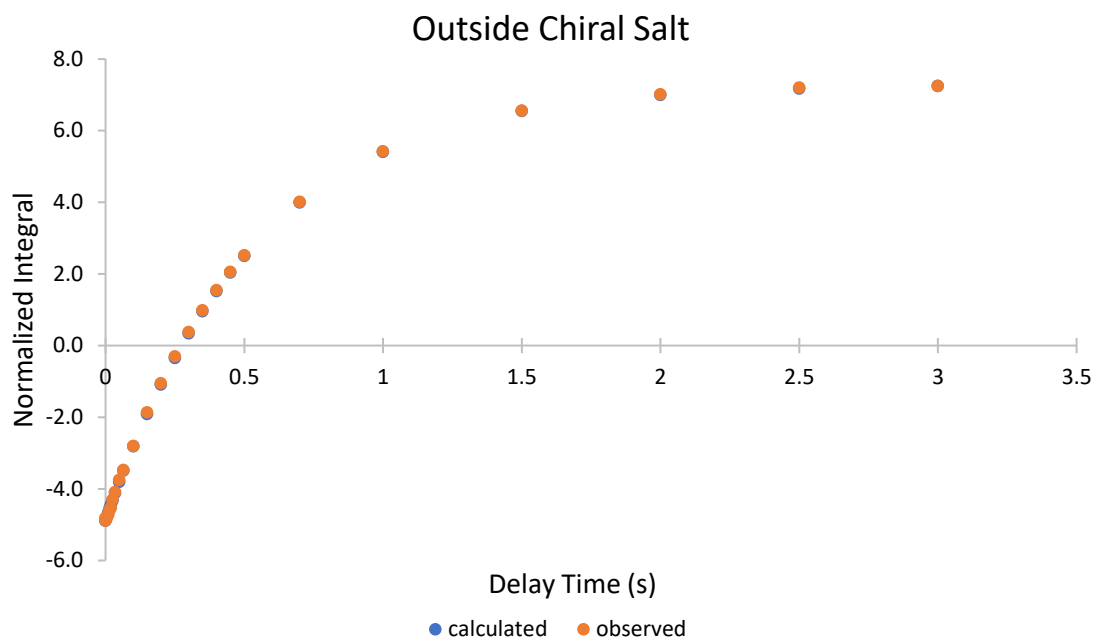
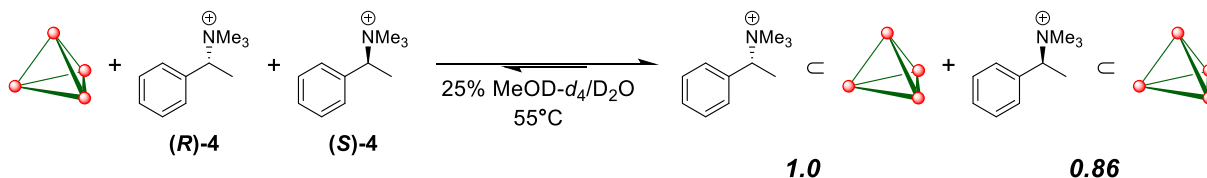


Figure S3.23. Example plot of the normalized integrals vs. delay time of the chiral salt (**S**)-**4** NMe₃ peak while not encapsulated in host **I**. Orange is experimentally determined, and blue is calculated with the CIFIT program.

Table S3.1. Measured rate of exchange (SIR NMR) for the host with (*R*) and (*S*)-model cationic salt **4**.

Guest	k_{ex} (s ⁻¹) run 1	k_{ex} (s ⁻¹) run 2	k_{ex} (s ⁻¹) run 3	k_{ex} (s ⁻¹) average	std dev
(<i>R</i>)	1.82	1.75	1.83	1.80	0.04
(<i>S</i>)	1.32	1.42	1.33	1.36	0.06

Equilibrium Competition Experiments with a Model Chiral Guest



Sample preparation:

An NMR tube was charged with $\Lambda\Lambda\Lambda\Lambda$ host **I** (1.1 μmol , 2.2 mM, 1 equiv.), chiral salt (**R**)-**4** (1.1 μmol , 2.2 mM, 1 equiv.), chiral salt (**S**)-**4** (1.1 μmol , 2.2 mM, 1 equiv.), MeOD (125 μL) and D₂O (375 μL). The sample was sealed with a septum and allowed to equilibrate overnight prior to measurement. Quantitative NMR was analyzed with $d_1=15\text{s}$ and 8 scans to obtain the ratio of encapsulated (*R*) and (*S*) chiral salts. Then, pyridine borane (6.6 μmol , 0.6 μL , 6 equiv.) was added to the NMR tube and was allowed to equilibrate

for another 16 hours. The quantitative NMR spectrum was acquired to measure the thermodynamic ratio in the presence of pyridine borane.

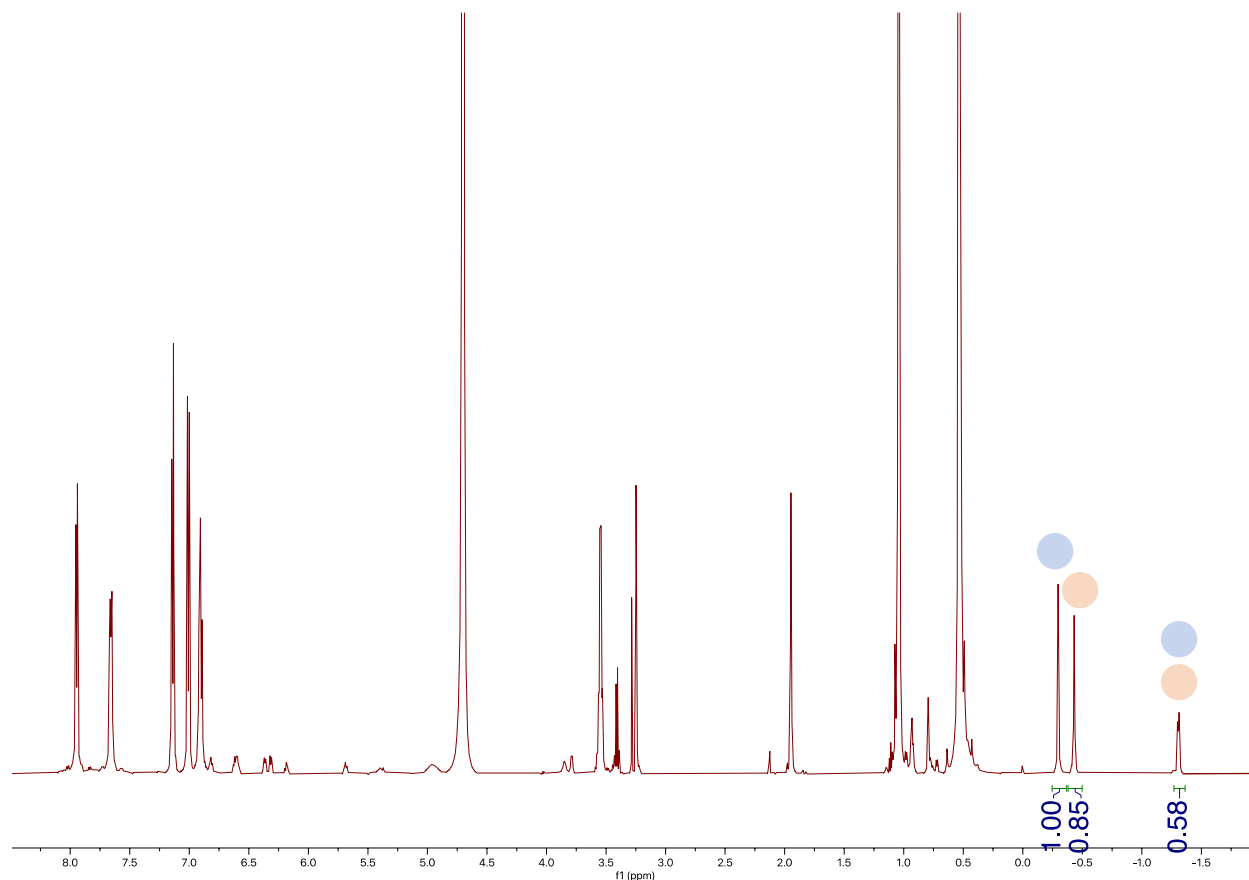
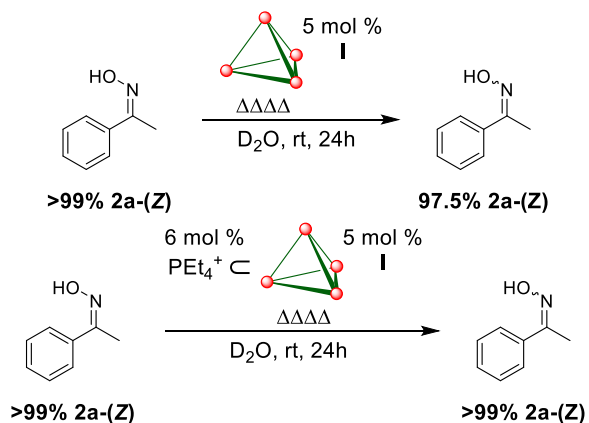


Figure S3.24. ^1H -NMR spectrum of the competition equilibrium study between host **I** with (R) -**4** (blue) and (S) -**4** (orange) cationic guest enantiomers before pyridine borane addition.

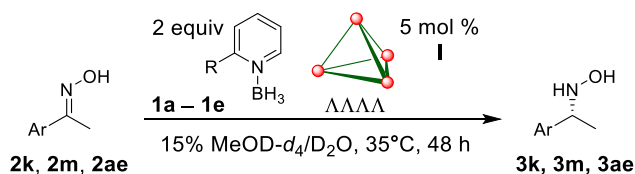
Oxime Isomerization Control Experiments



Control experiments to determine the source of oxime isomerization in the presence of empty and blocked host were performed using oxime **2a-(Z)** under modified versions of General Procedure D and General Procedure I, respectively. In each case, pyridine borane was omitted. No isomerization was observed when blocked host was used, but small amounts of isomerization was observed when empty host was used. The low amount of isomerization observed with empty host is likely due to mass transfer issues, as oxime **2b** is not soluble in D₂O in the presence or absence of host. Despite the slow rate of isomerization observed under these conditions, these results combined support host **I**-mediated isomerization and are consistent with isomerization of oxime **2a-(Z)** in the presence of trace acid.

Procedure for Pyridine Borane Reductant Screen

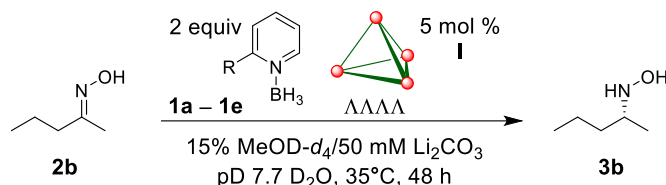
Aryl and Heteroaryl Oximes



Reductant screens were performed using a modified version of General Procedure D. To a 1 dr vial containing host **I** (5 mol%) was added D₂O *via* Eppendorf pipette. The host solution was transferred to a second 1 dr vial equipped with a magnetic stir bar containing oxime (1 equiv.) and MeOD-*d*₆ (15% by volume). The 1 dr vial containing host was rinsed with D₂O and the rinse was also transferred to the 1 dr vial containing oxime. The final concentration of solution was 55 mM in oxime. The heterogeneous solution was allowed to sit at rt for 5 minutes before addition of borane (2.0 equiv.). The reaction was then capped, sealed with electrical tape, and heated at 35°C for 48h, after which point the reaction was stopped by adding an excess of tetraethylphosphonium bromide (PEt₄Br). Internal standard, 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt (2.50 mg, 0.01145 mmol), as a stock solution in D₂O (176 mM) was added *via* Hamilton syringe to the 1 dr reaction vial. If the quenched reaction solution was found to be partially heterogeneous, minimal amounts of MeOD-*d*₆ were added to make the solution homogeneous. The solution was mixed briefly by pipetting and an aliquot taken for ¹H NMR analysis.

Following NMR analysis of the crude reaction mixture, the product was returned to the 1 dr vial and the NMR tube was rinsed with CH₂Cl₂. Solvent in the vial was removed to near-dryness *via* rotary evaporation. The crude product was then treated according to the respective preps for each oxime. Hydroxylamine **3m** was purified and isolated via prep TLC. Hydroxylamines **3k** and **3ae** were functionalized according to General Procedure E using 2,4,-dinitrofluorobenzene (1.4 equiv.) and dry Et₃N (1.4 equiv.).

Aliphatic Oxime 2b



Reductant screen was performed using a modified version of General Procedure D on oxime **2b**. To a 1 dr vial equipped with a magnetic stir bar and containing host **I** (7.5 mol%) was added MeOD-*d*₆ (15% by volume) then 50 mM Li₂CO₃ pD 7.7 D₂O buffer *via* Eppendorf pipette. Oxime (1.0 equiv.) was then added *via* Hamilton syringe to the 1 dr vial. The final concentration of solution was 55 mM in oxime. The heterogeneous solution was allowed to sit at rt for 5 minutes before addition of borane (2.0 equiv.). The reaction was then capped, sealed with electrical tape, and heated at 35°C for 48h, after which point the reaction was stopped by adding an excess of tetraethylphosphonium bromide (PEt₄Br). Internal standard, 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt (2.50 mg, 0.01145 mmol), as a stock solution in D₂O (176 mM) was added *via* Hamilton syringe to the 1 dr reaction vial. If the quenched reaction solution was found to be partially heterogenous, minimal amounts of MeOD-*d*₆ were added to make the solution homogenous. The solution was mixed briefly by pipetting and an aliquot taken for ¹H NMR analysis.

Following NMR analysis, the reaction mixture was returned to the 1 dr vial. The NMR tube was rinsed with CH₂Cl₂. Additional CH₂Cl₂ was added to the vial to extract the product and the CH₂Cl₂ rinse was transferred to a 1 dr vial. The reaction solution was washed at least 3 times with CH₂Cl₂. Organic solvent in the 1 dr vial from the combined rinses was removed to dryness *via* rotary evaporation below 8°C. Then a small portion of NaCl was added to the host solution in the 1 dr vial and aqueous layer was again washed at least 3 times with CH₂Cl₂. Again the rinses were transferred to the 1 dr vial and solvent was removed to dryness *via* rotary evaporation. The crude product was assumed to be extracted quantitatively and subjected to General Procedure E with a slight modification, through the use of increased amounts of 2,4,-dinitrofluorobenzene (1.4 equiv.) and dry Et₃N (1.4 equiv.).

3.7.5 Chiral HPLC Traces of Hydroxylamines

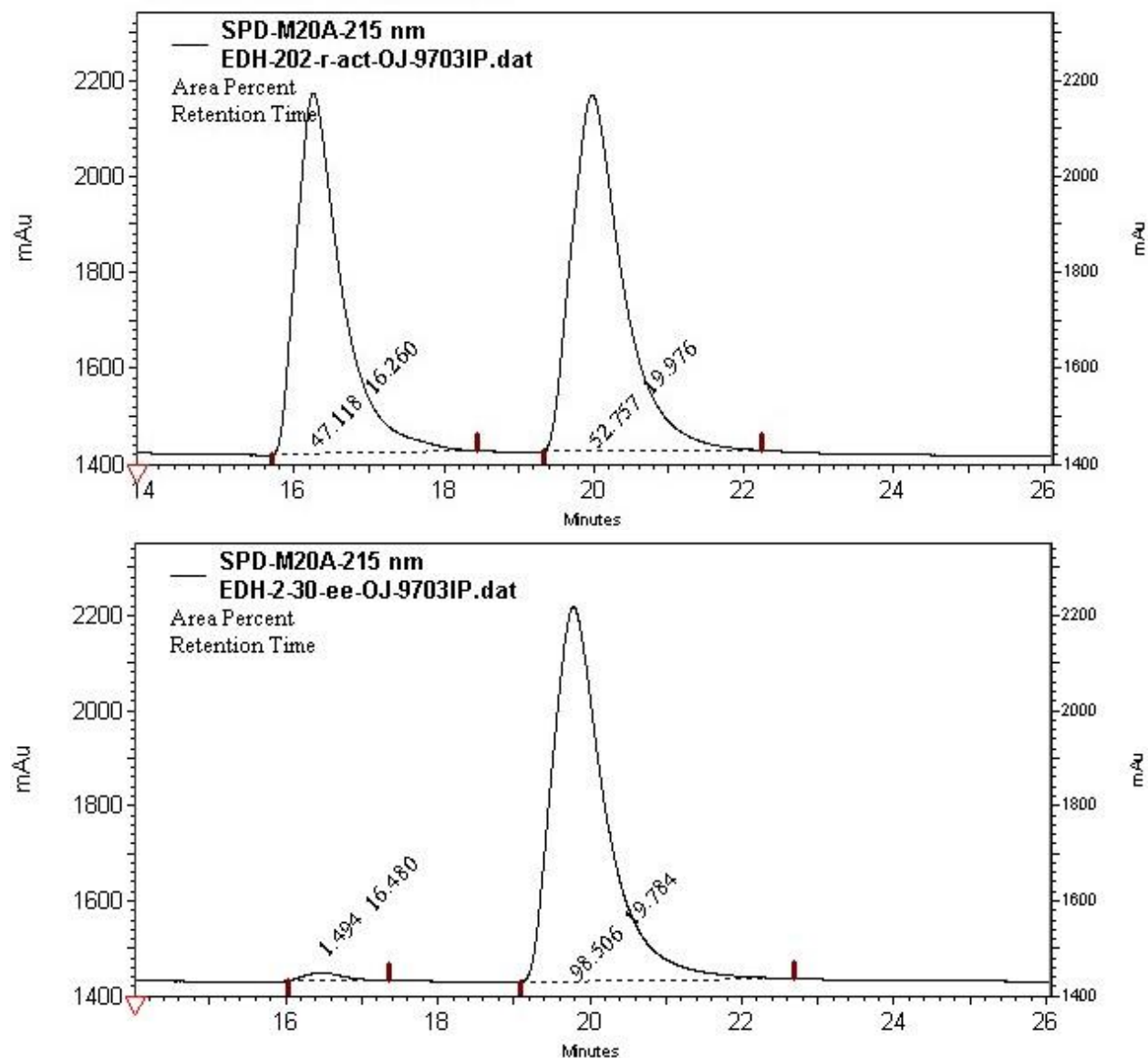


Figure S3.25. Racemic trace (top) and enantioenriched trace (bottom) for hydroxylamine **3a**.

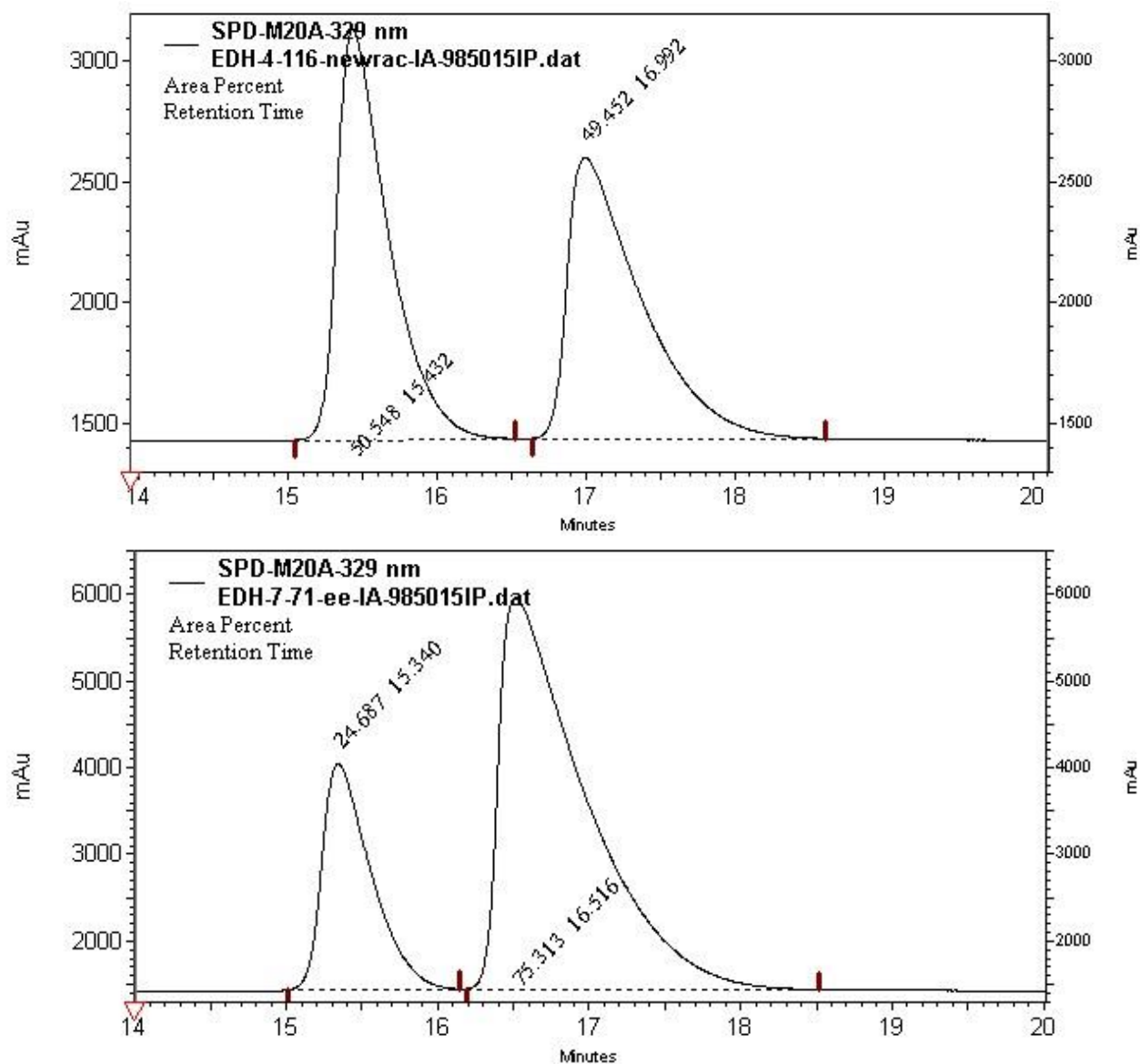


Figure S3.26. Racemic trace (top) and enantioenriched trace (bottom) for functionalized hydroxylamine **3b**.

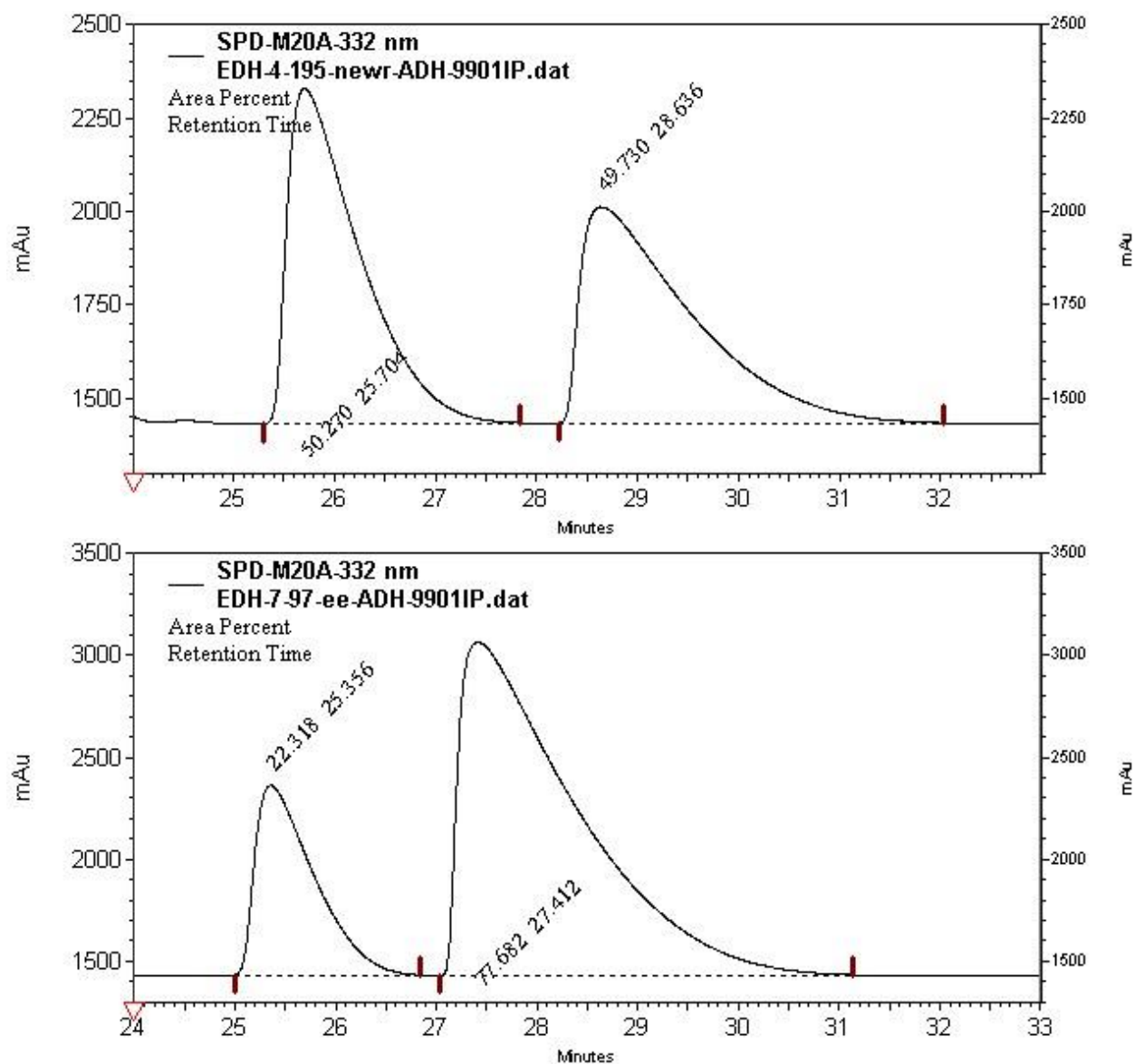


Figure S3.27. Racemic trace (top) and enantioenriched trace (bottom) for functionalized hydroxylamine **3c**.

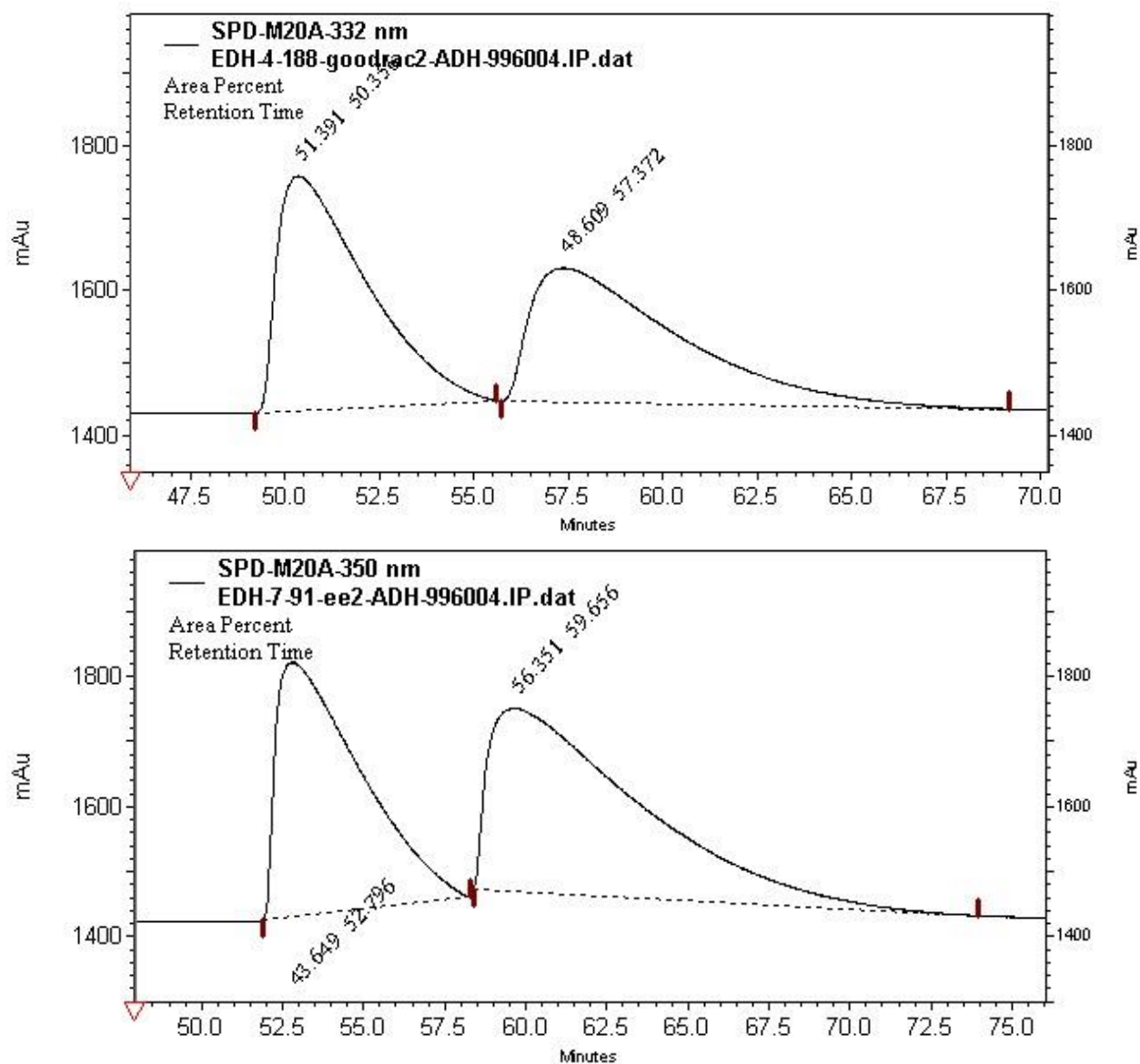


Figure S3.28. Racemic trace (top) and enantioenriched trace (bottom) for functionalized hydroxylamine **3d**.

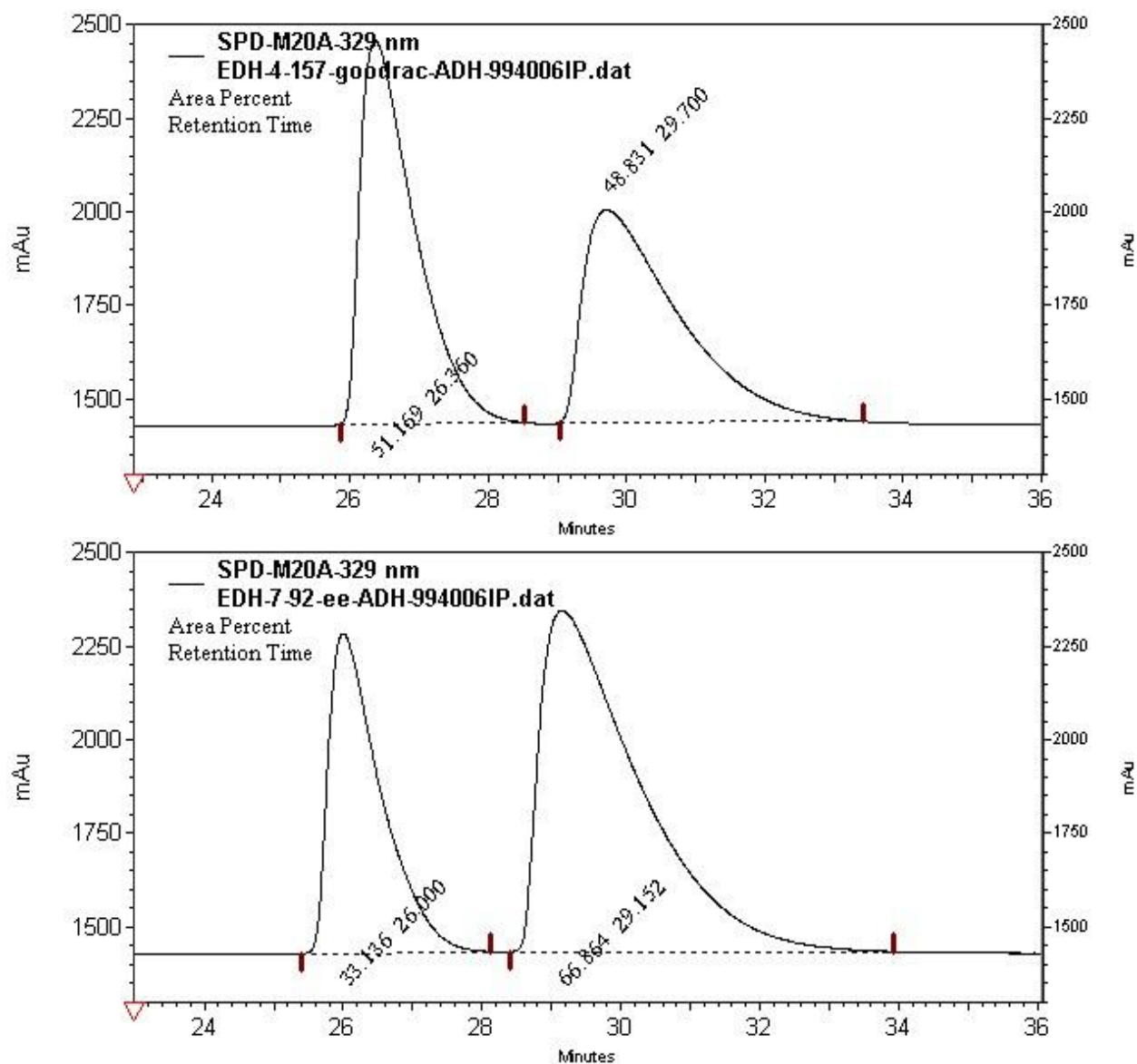


Figure S3.29. Racemic trace (top) and enantioenriched trace (bottom) for functionalized hydroxylamine **3e**.

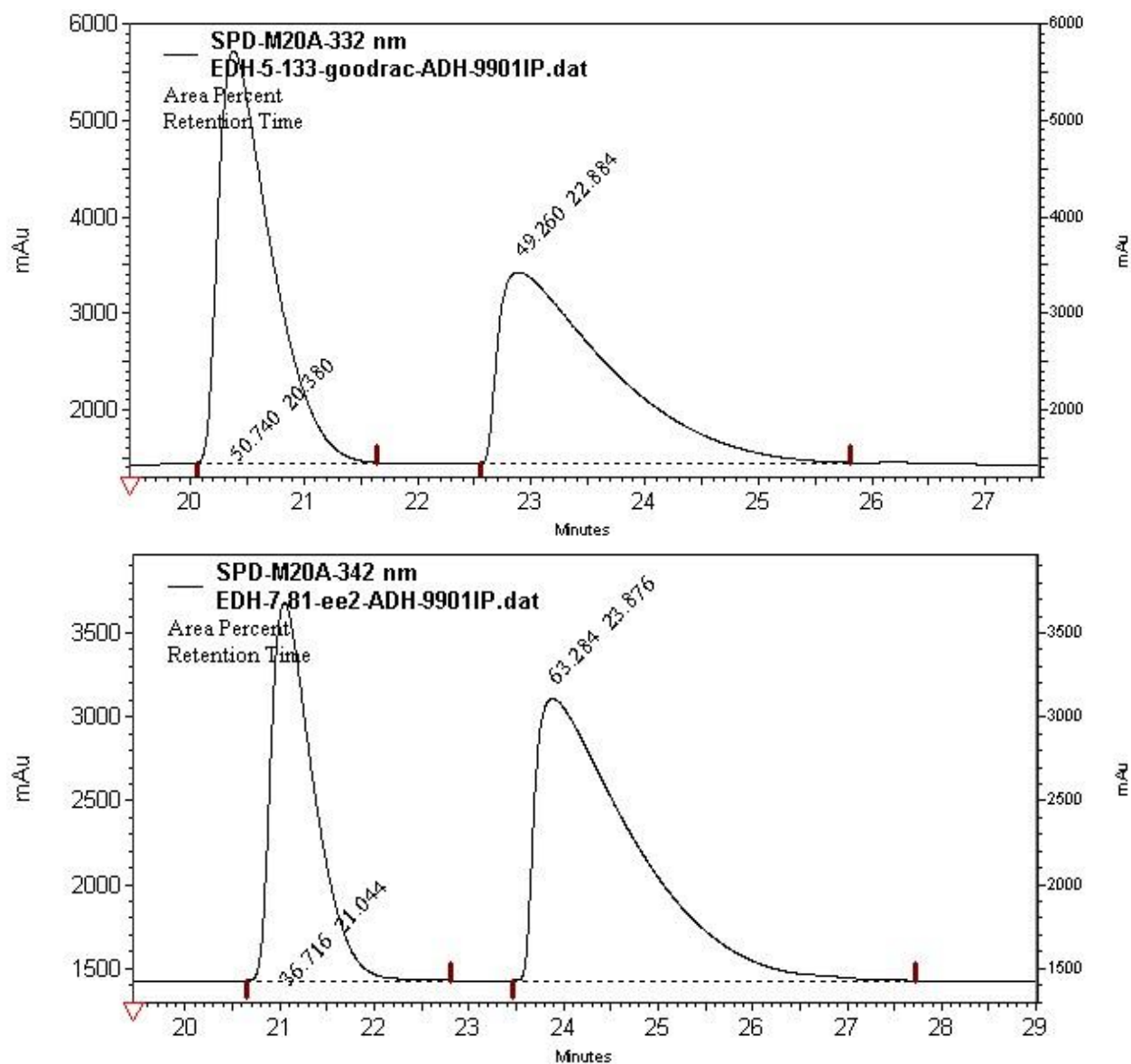


Figure S3.30. Racemic trace (top) and enantioenriched trace (bottom) for functionalized hydroxylamine **3f**.

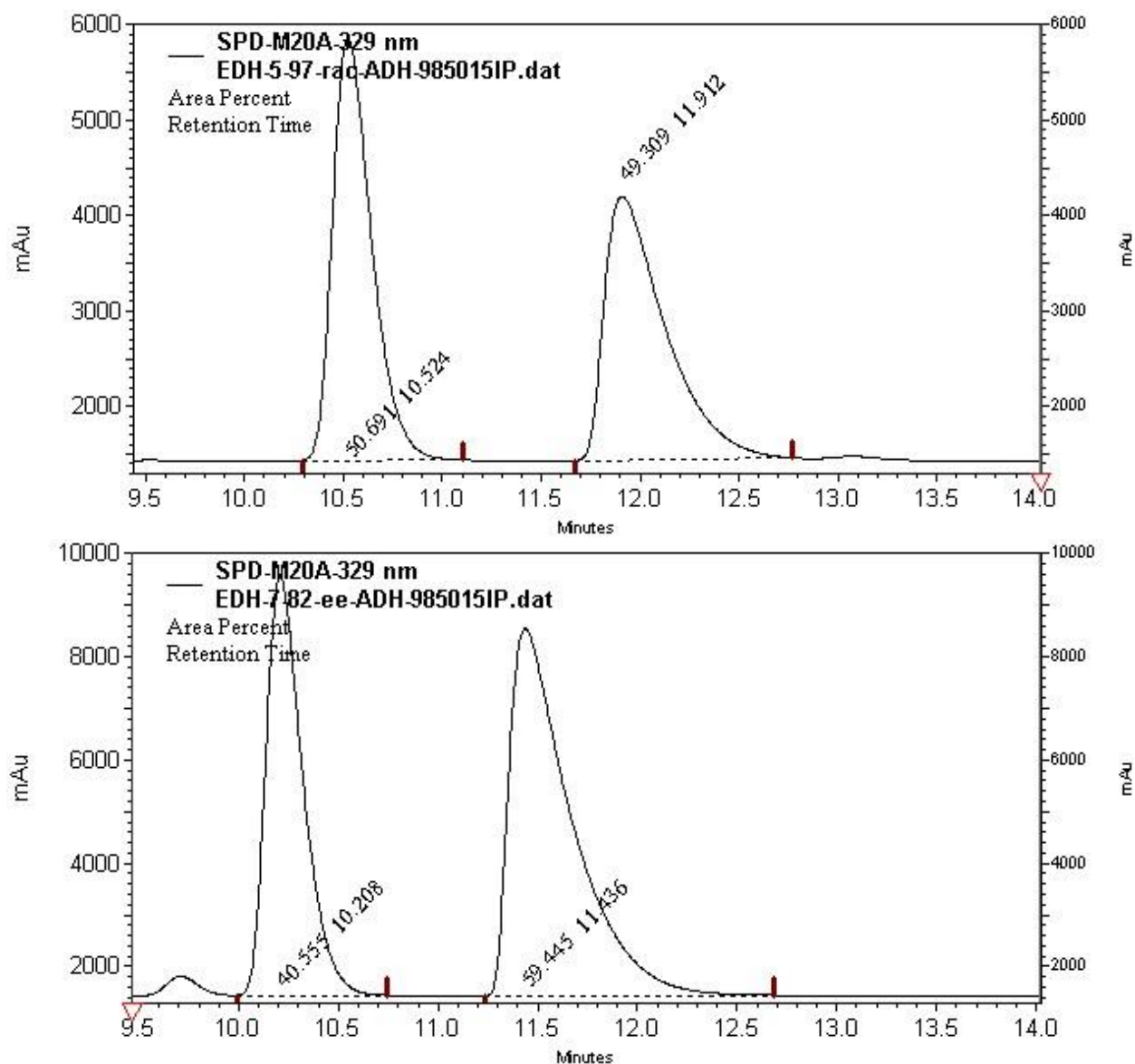


Figure S3.31. Racemic trace (top) and enantioenriched trace (bottom) for functionalized hydroxylamine **3g**.

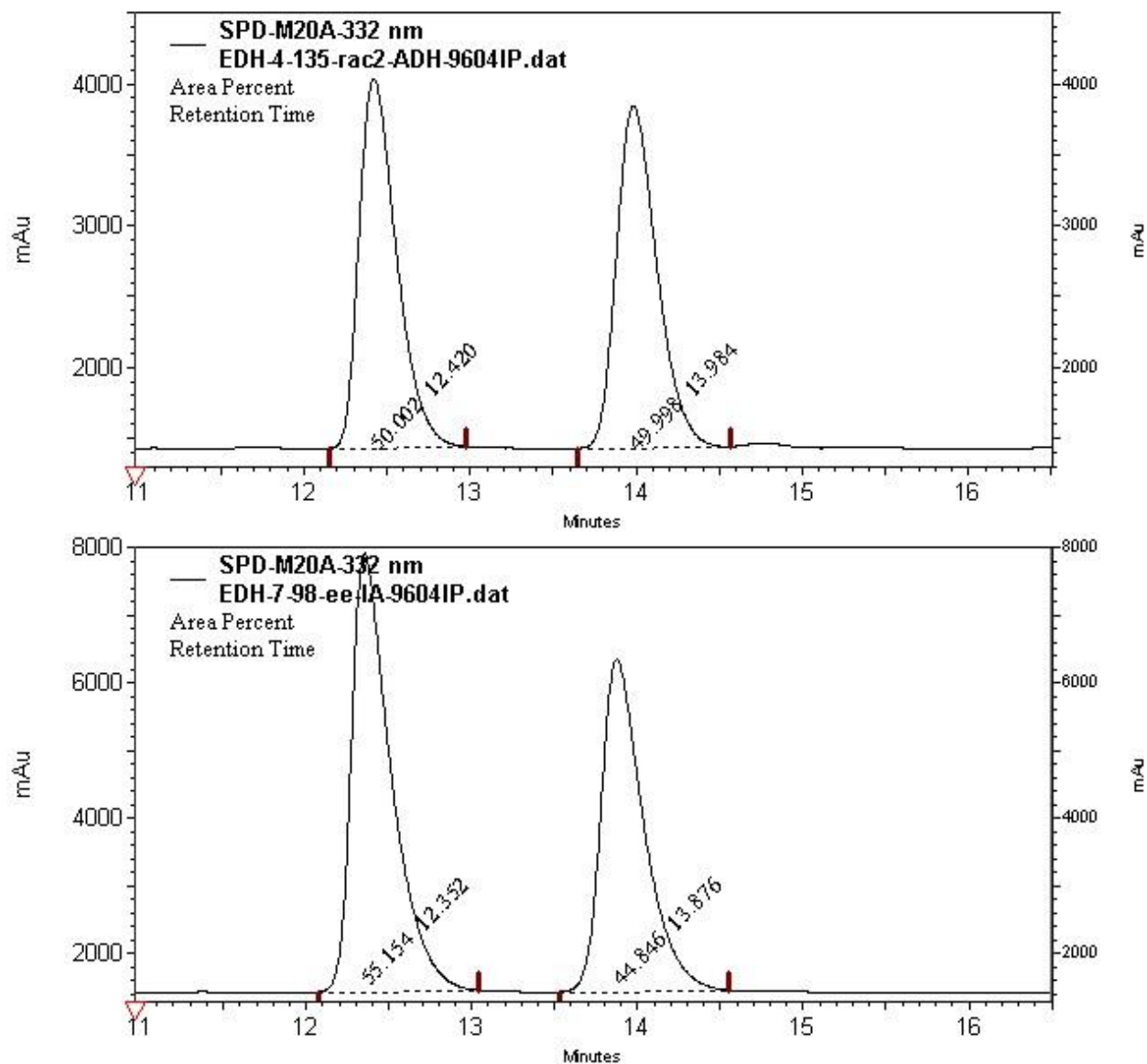


Figure S3.32. Racemic trace (top) and enantioenriched trace (bottom) for functionalized hydroxylamine **3h**.

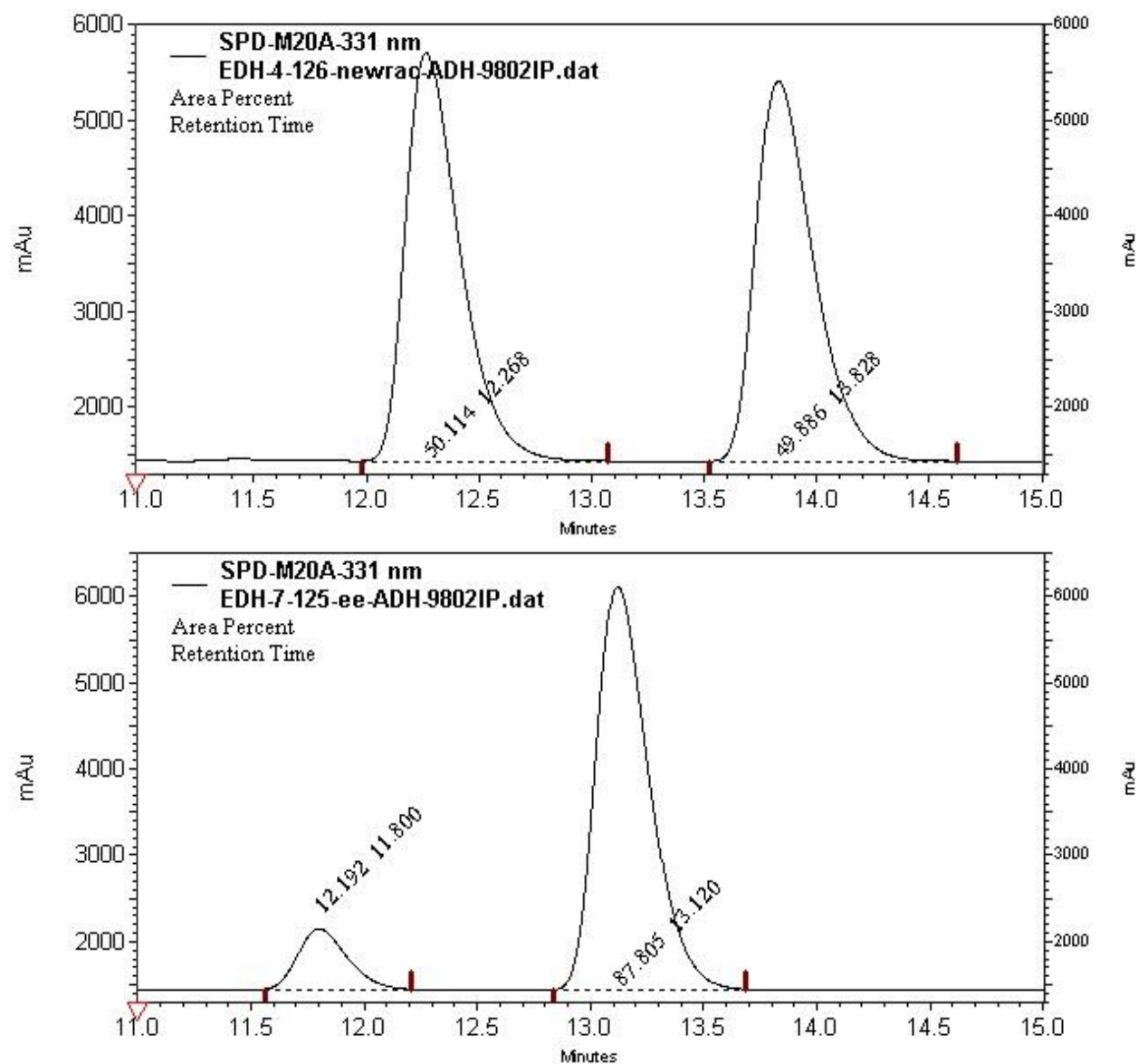


Figure S3.33. Racemic trace (top) and enantioenriched trace (bottom) for functionalized hydroxylamine **3i**.

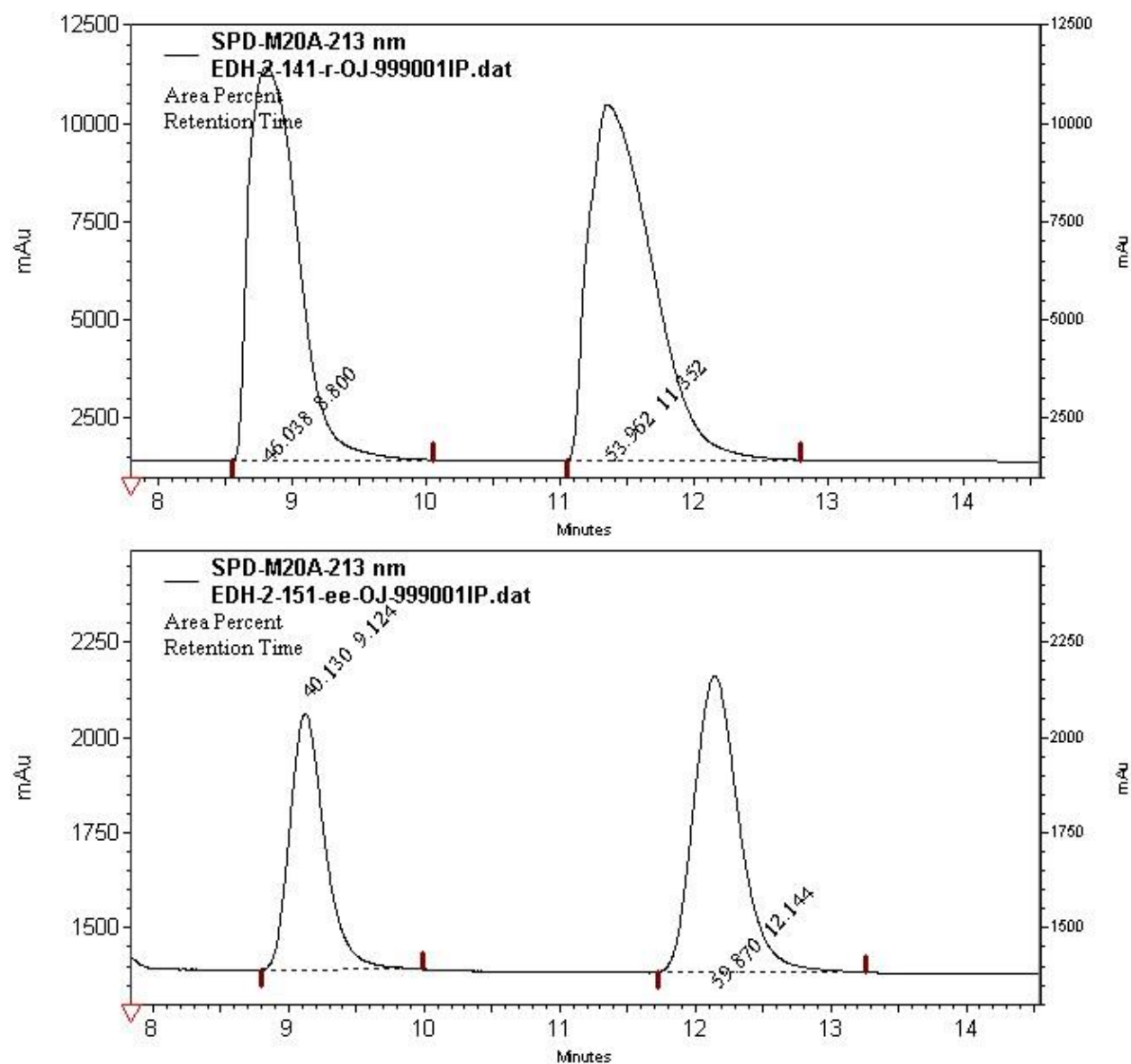


Figure S3.34. Racemic trace (top) and enantioenriched trace (bottom) for hydroxylamine **3j**.

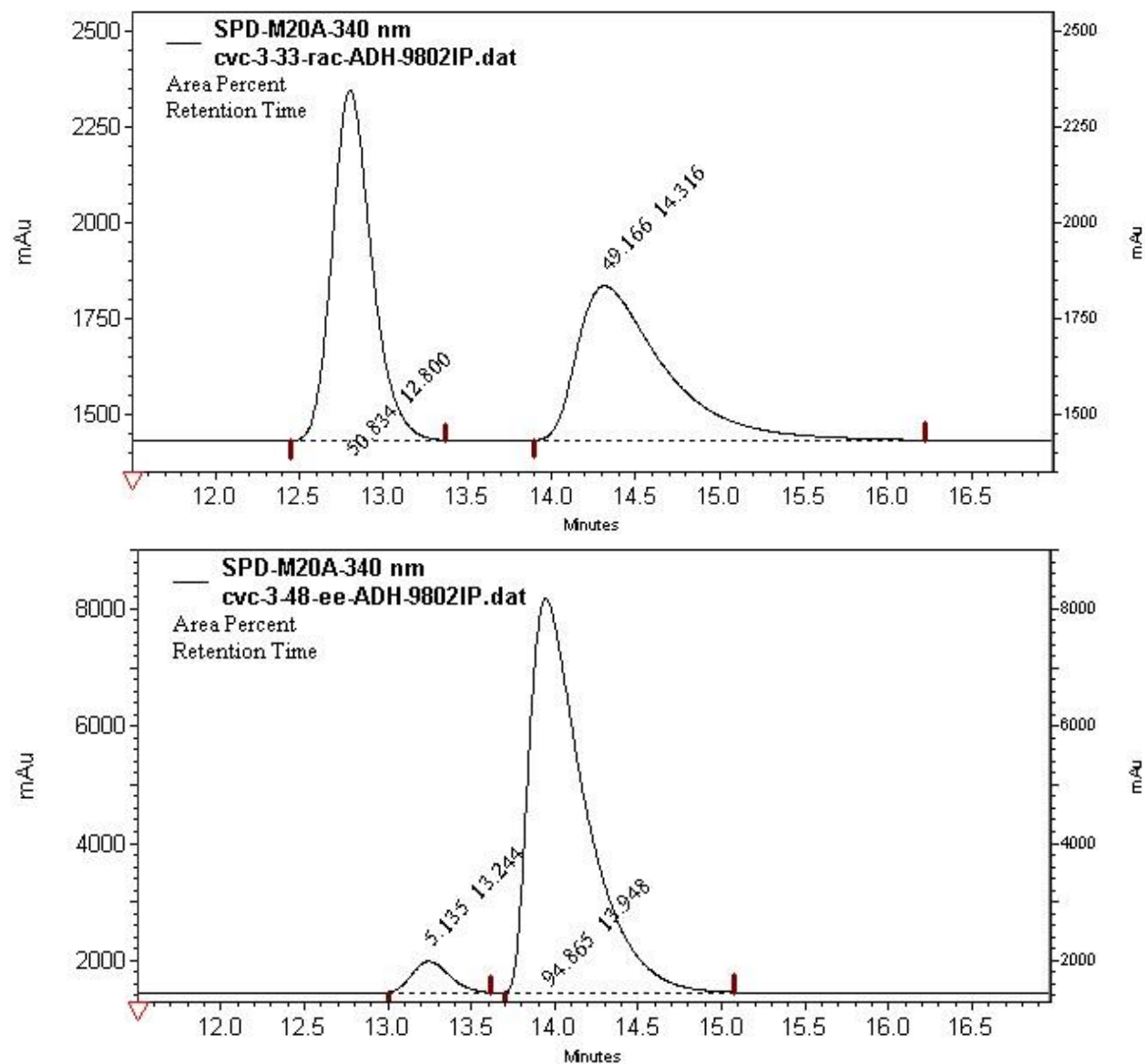


Figure S3.35. Racemic trace (top) and enantioenriched trace (bottom) for functionalized hydroxylamine **3k**.

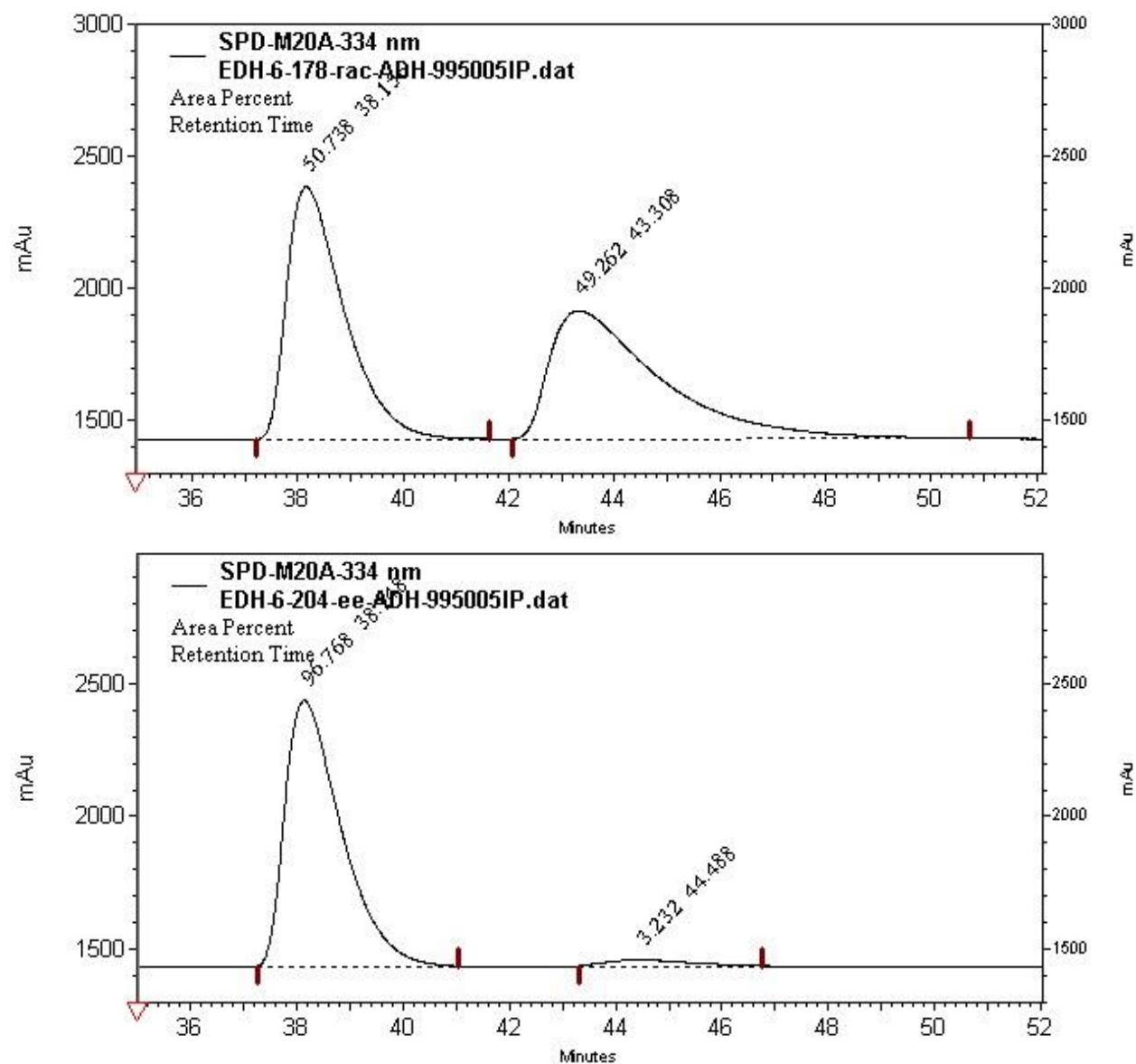


Figure S3.36. Racemic trace (top) and enantioenriched trace (bottom) for functionalized hydroxylamine **3l**.

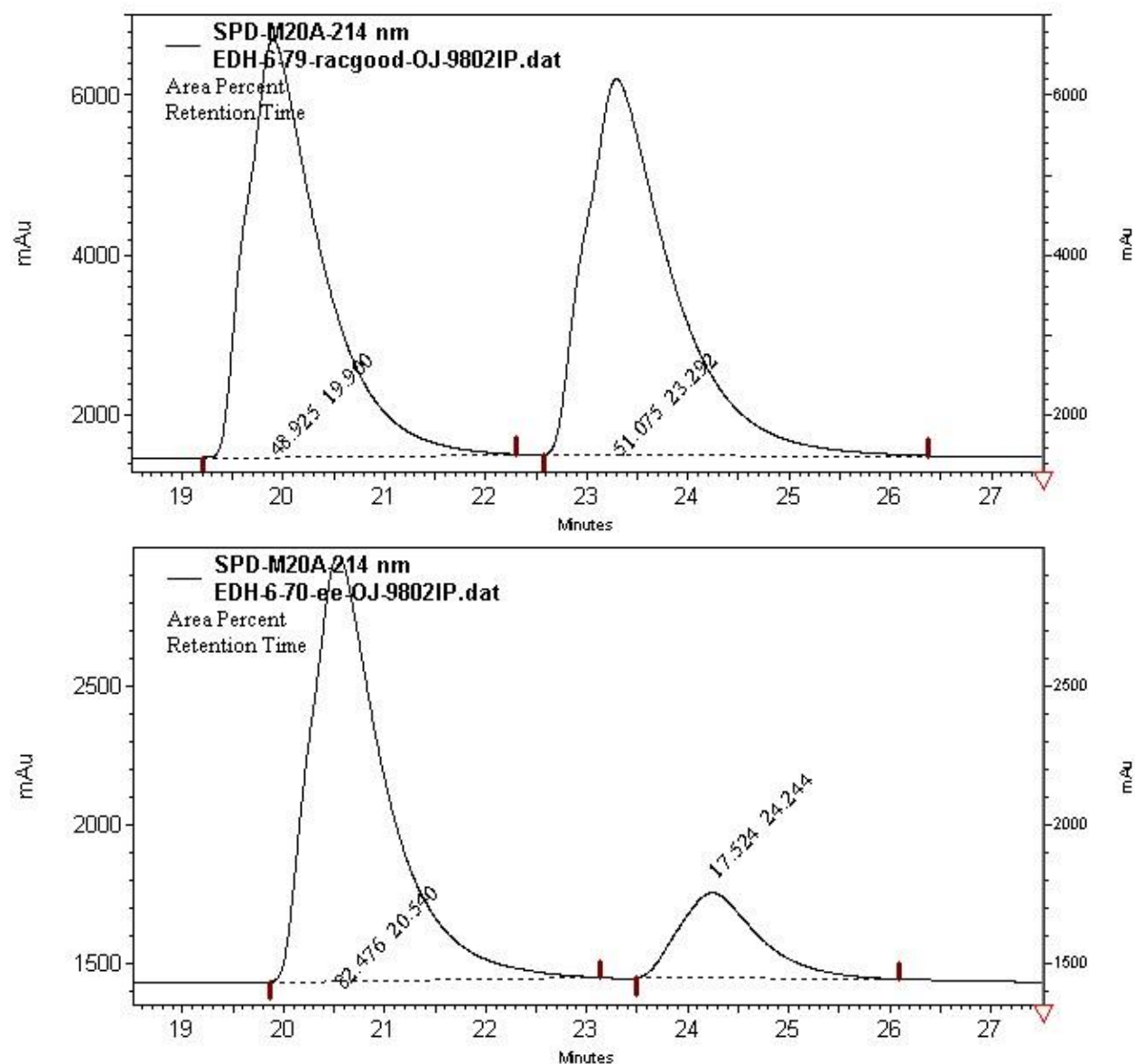


Figure S3.37. Racemic trace (top) and enantioenriched trace (bottom) for hydroxylamine **3m**.

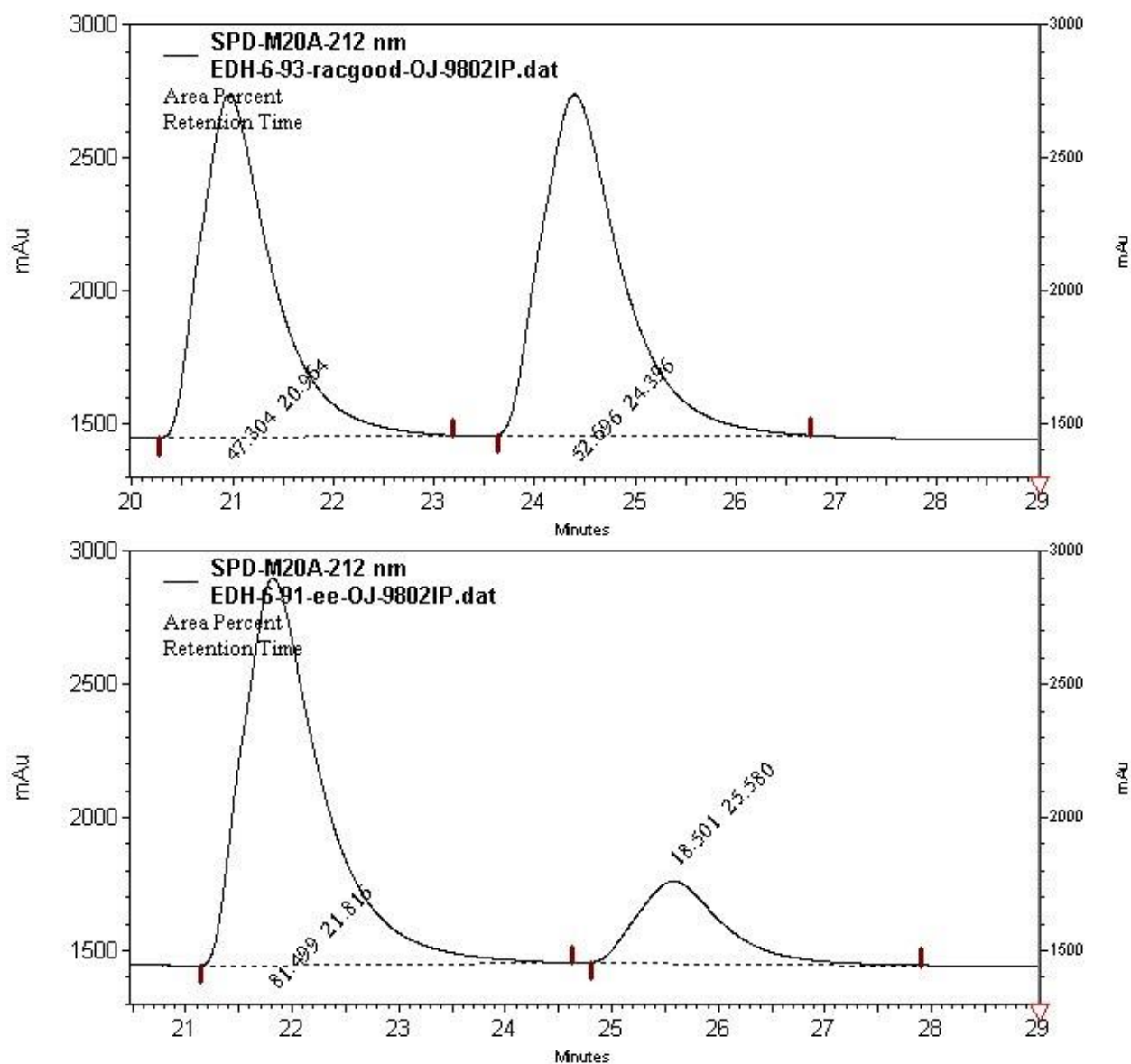


Figure S3.38. Racemic trace (top) and enantioenriched trace (bottom) for hydroxylamine **3m-D**.

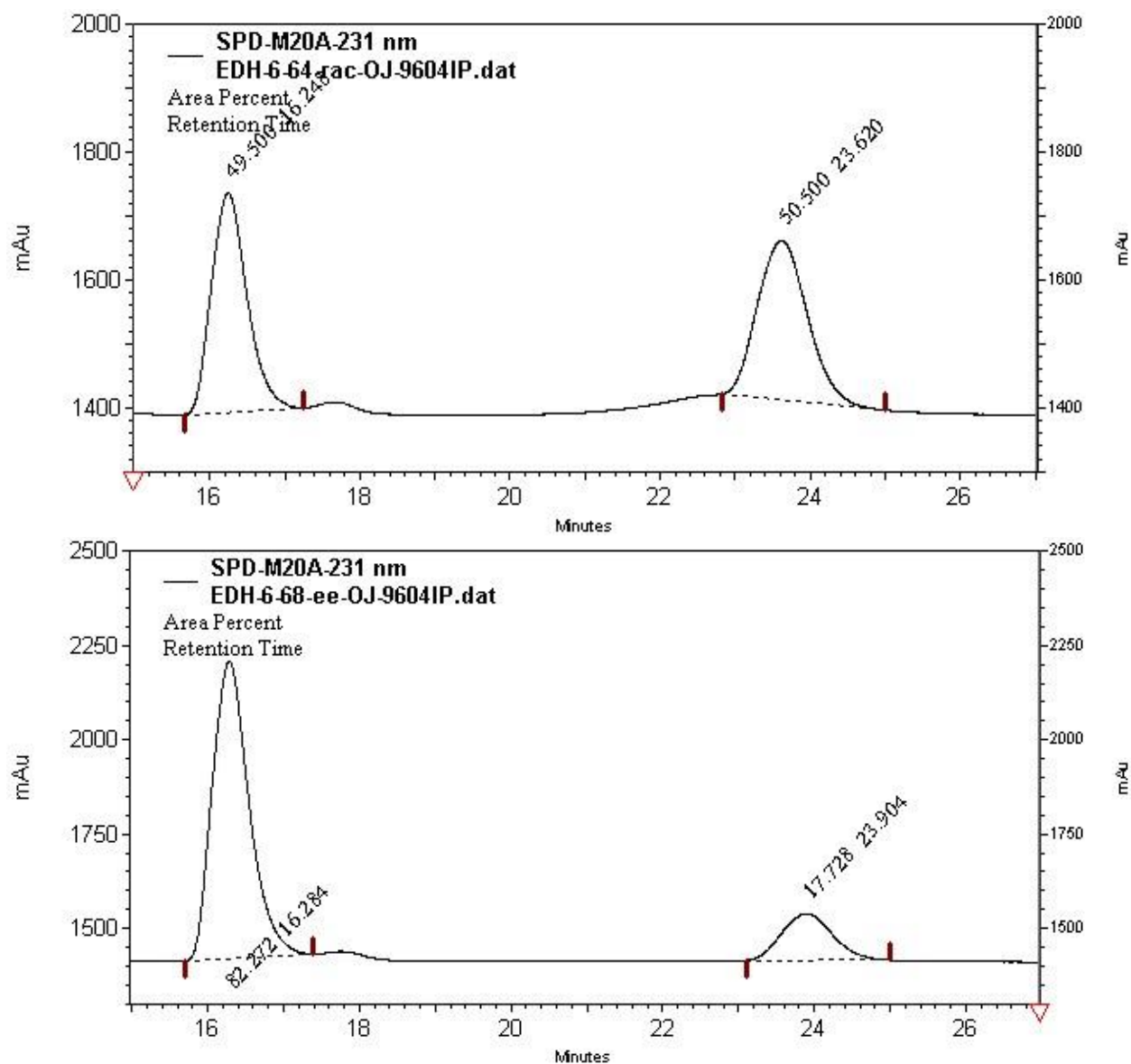


Figure S3.39. Racemic trace (top) and enantioenriched trace (bottom) for hydroxylamine **3n**.

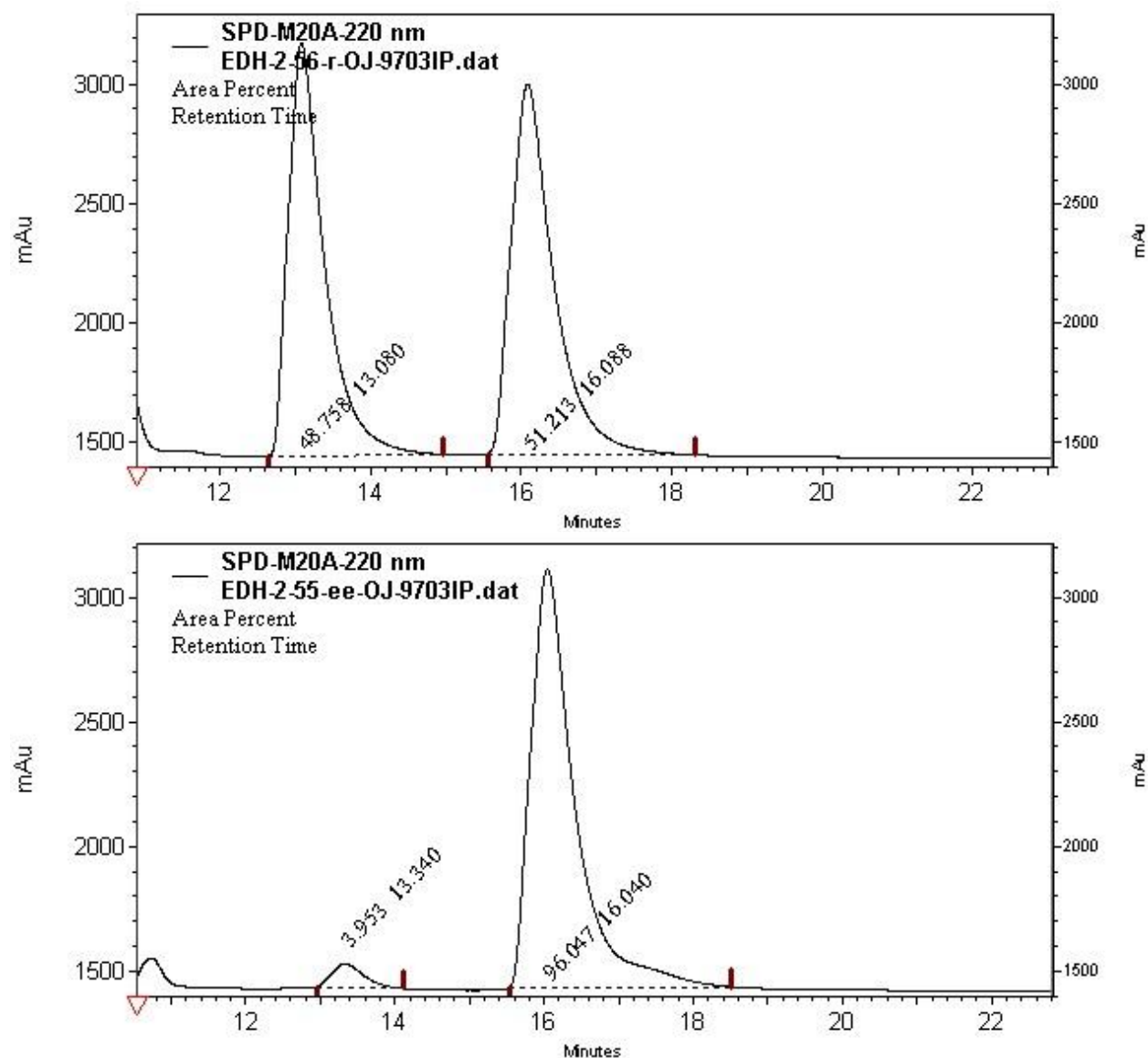


Figure S3.40. Racemic trace (top) and enantioenriched trace (bottom) for hydroxylamine **30**.

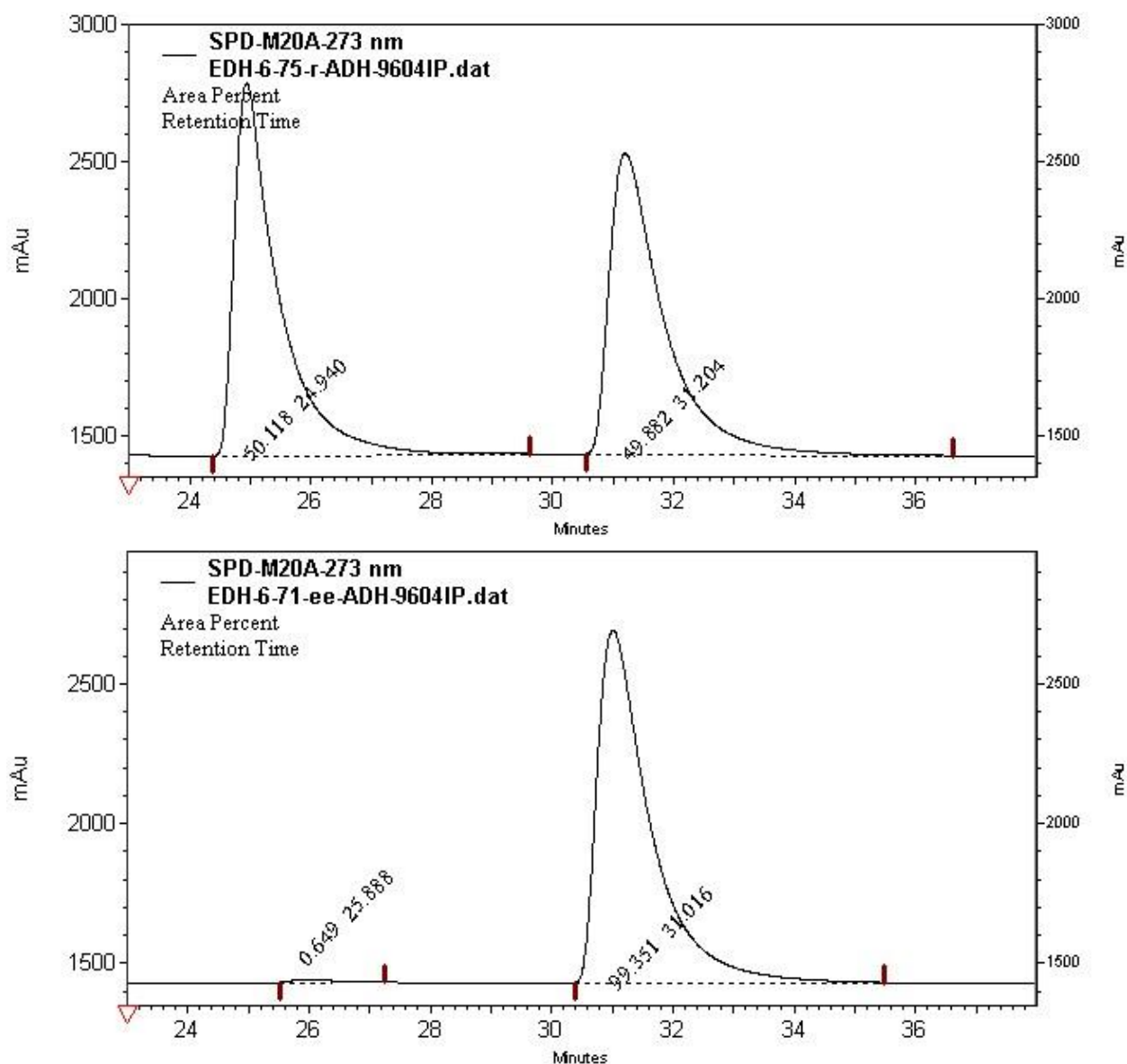


Figure S3.41. Racemic trace (top) and enantioenriched trace (bottom) for hydroxylamine **3p**.

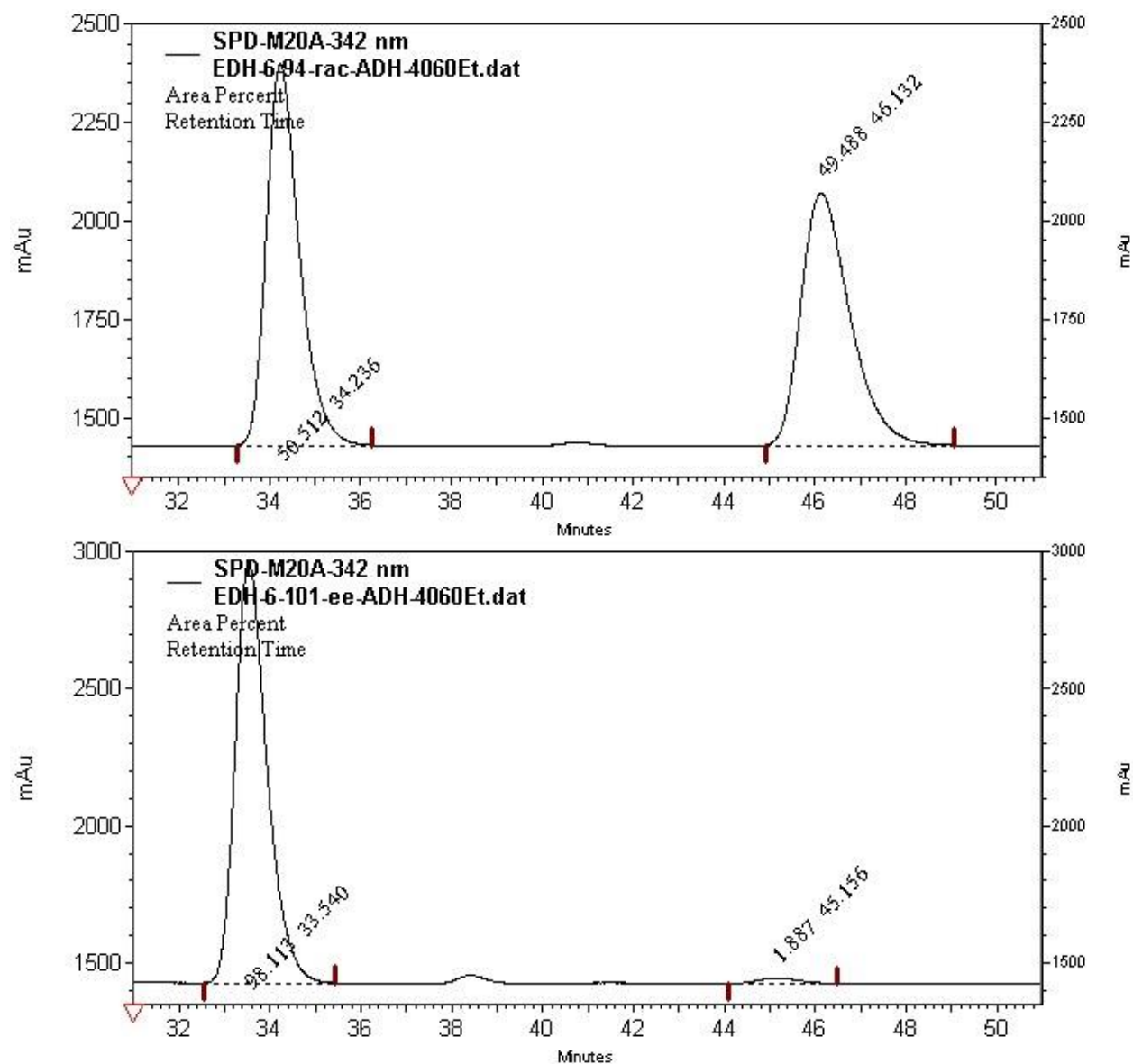


Figure S3.42. Racemic trace (top) and enantioenriched trace (bottom) for functionalized hydroxylamine **3q**.

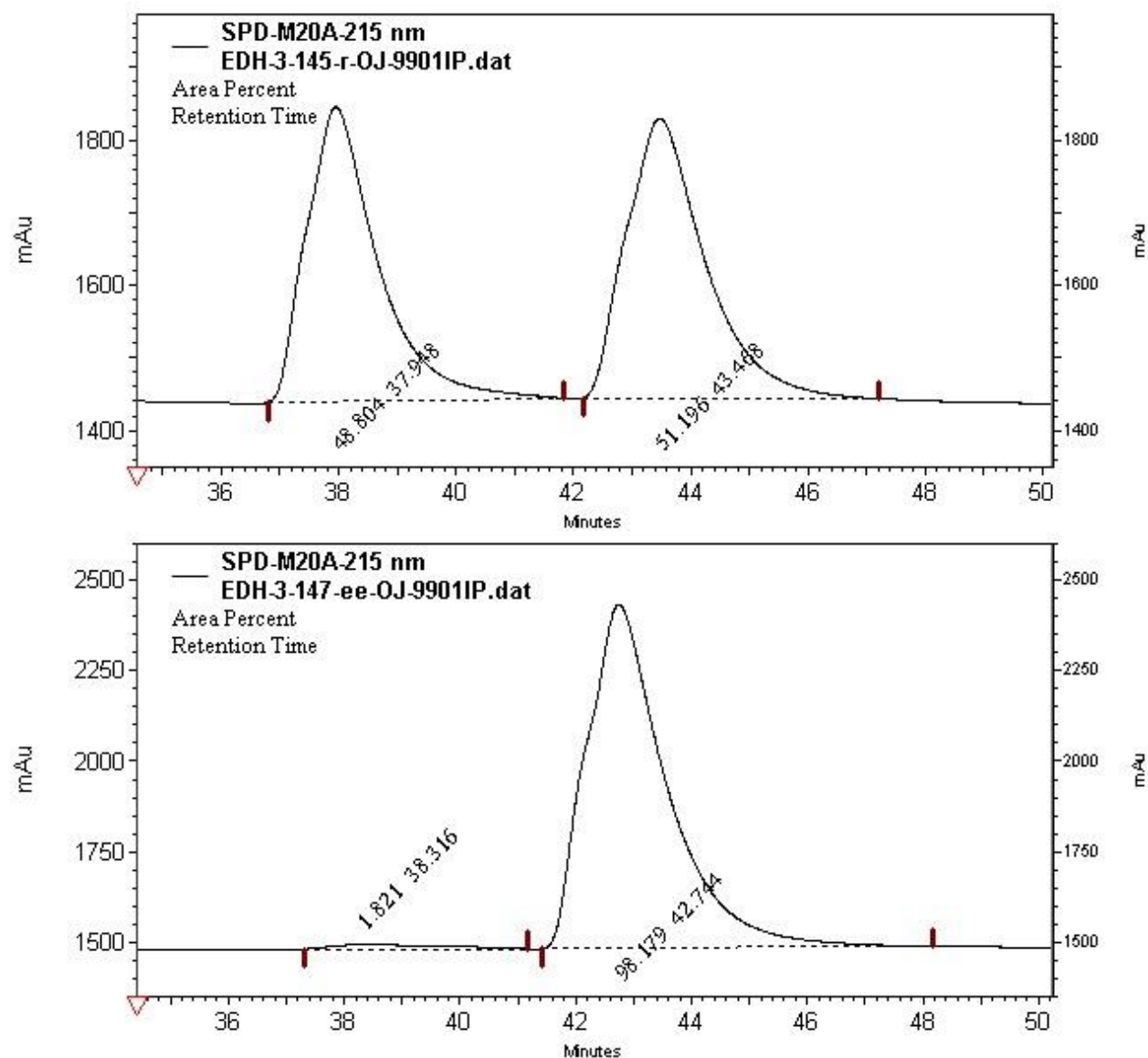


Figure S3.43. Racemic trace (top) and enantioenriched trace (bottom) for hydroxylamine **3r**.

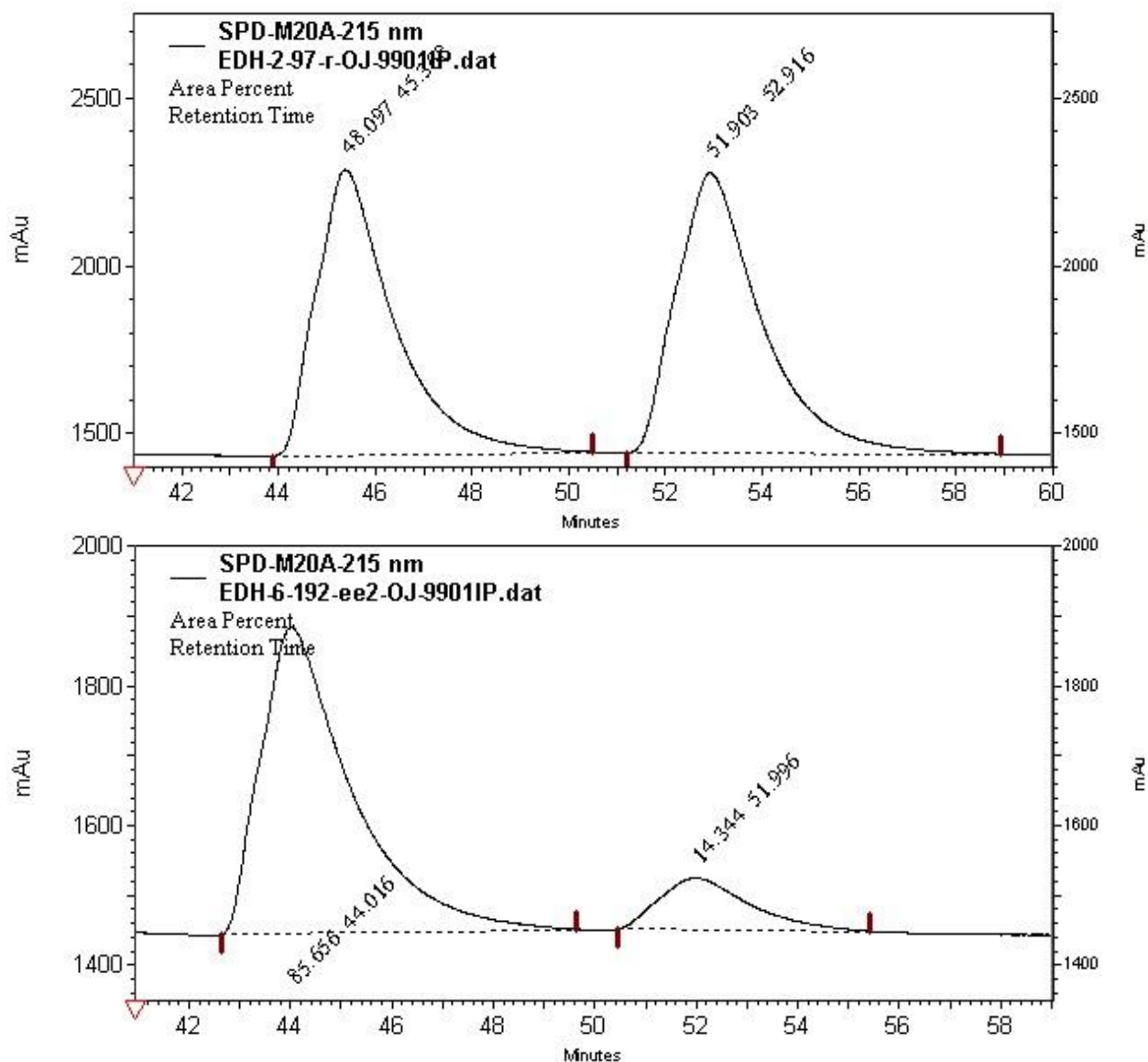


Figure S3.44. Racemic trace (top) and enantioenriched trace (bottom) for hydroxylamine **3s**.

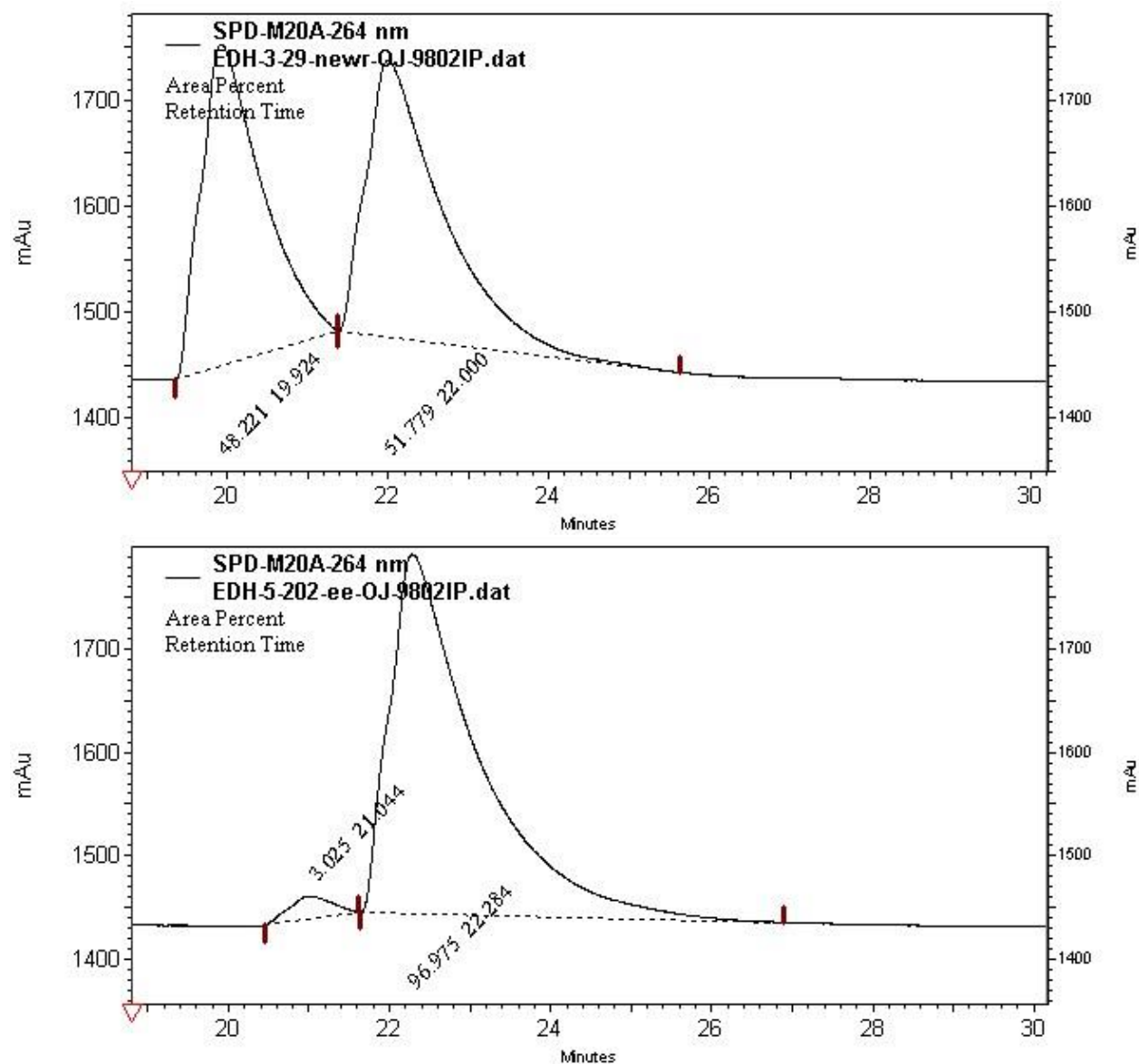


Figure S3.45. Racemic trace (top) and enantioenriched trace (bottom) for hydroxylamine **3t**.

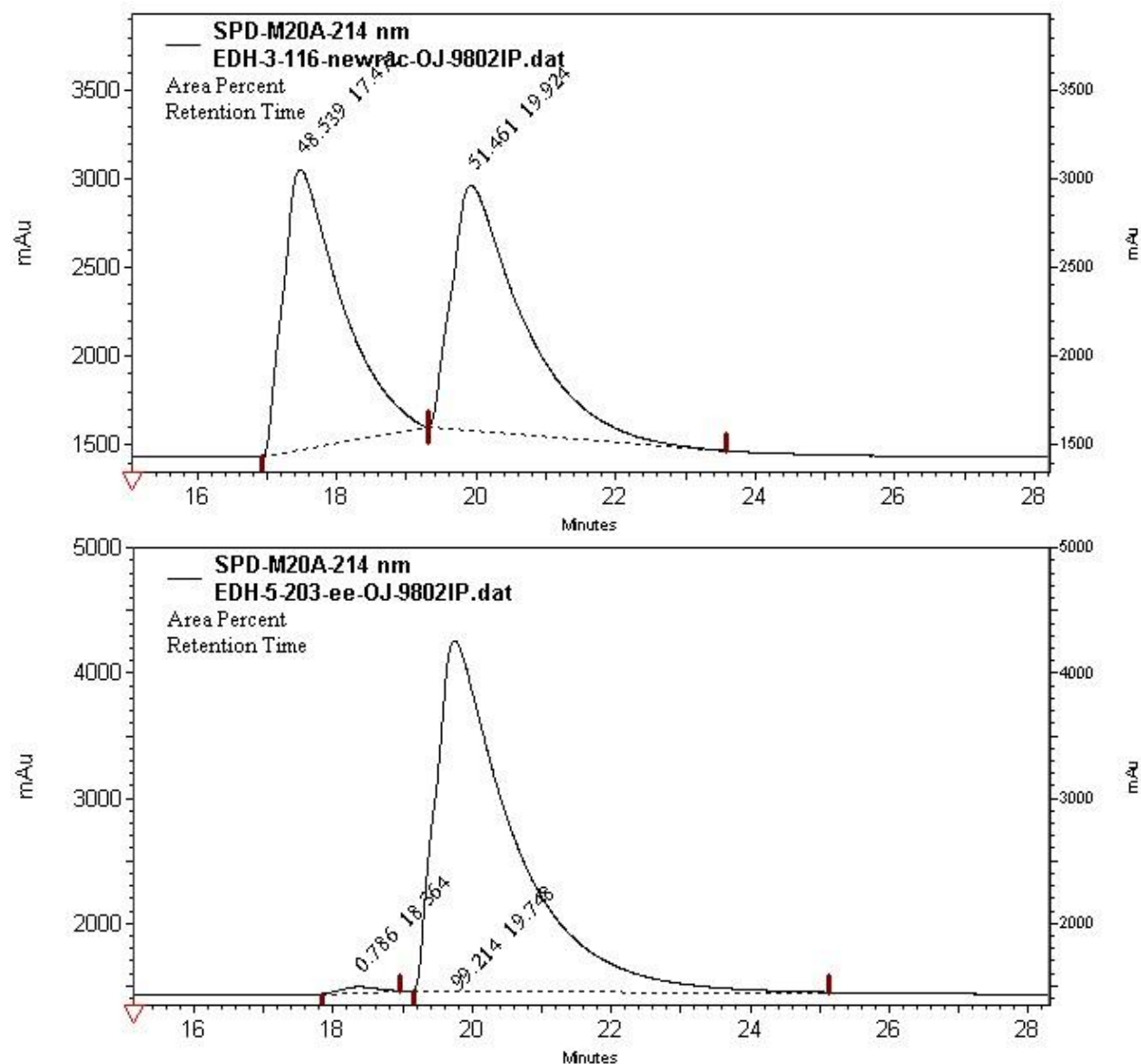


Figure S3.46. Racemic trace (top) and enantioenriched trace (bottom) for hydroxylamine **3u**.

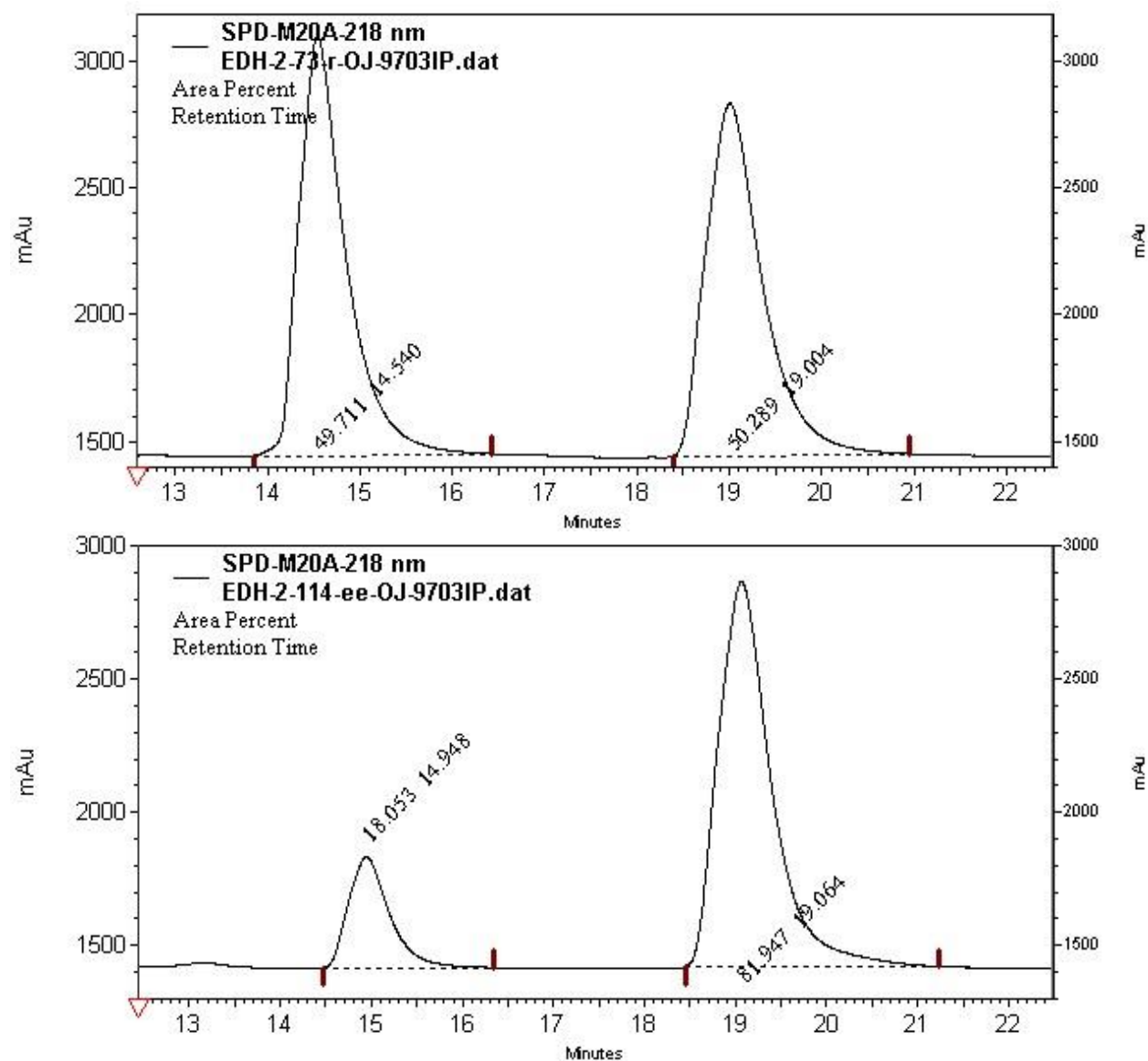


Figure S3.47. Racemic trace (top) and enantioenriched trace (bottom) for hydroxylamine **3v**.

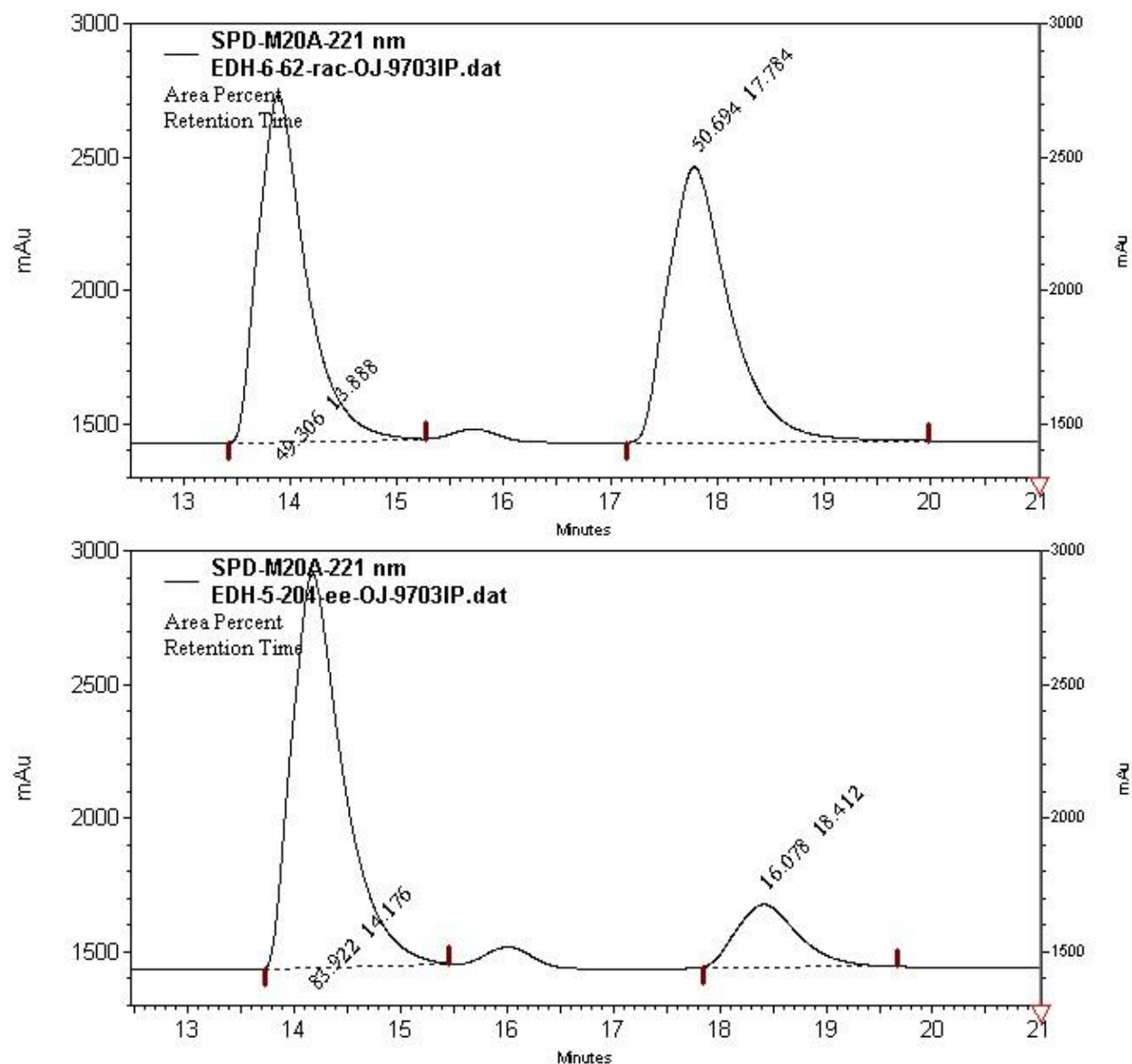


Figure S3.48. Racemic trace (top) and enantioenriched trace (bottom) for hydroxylamine **3w**.

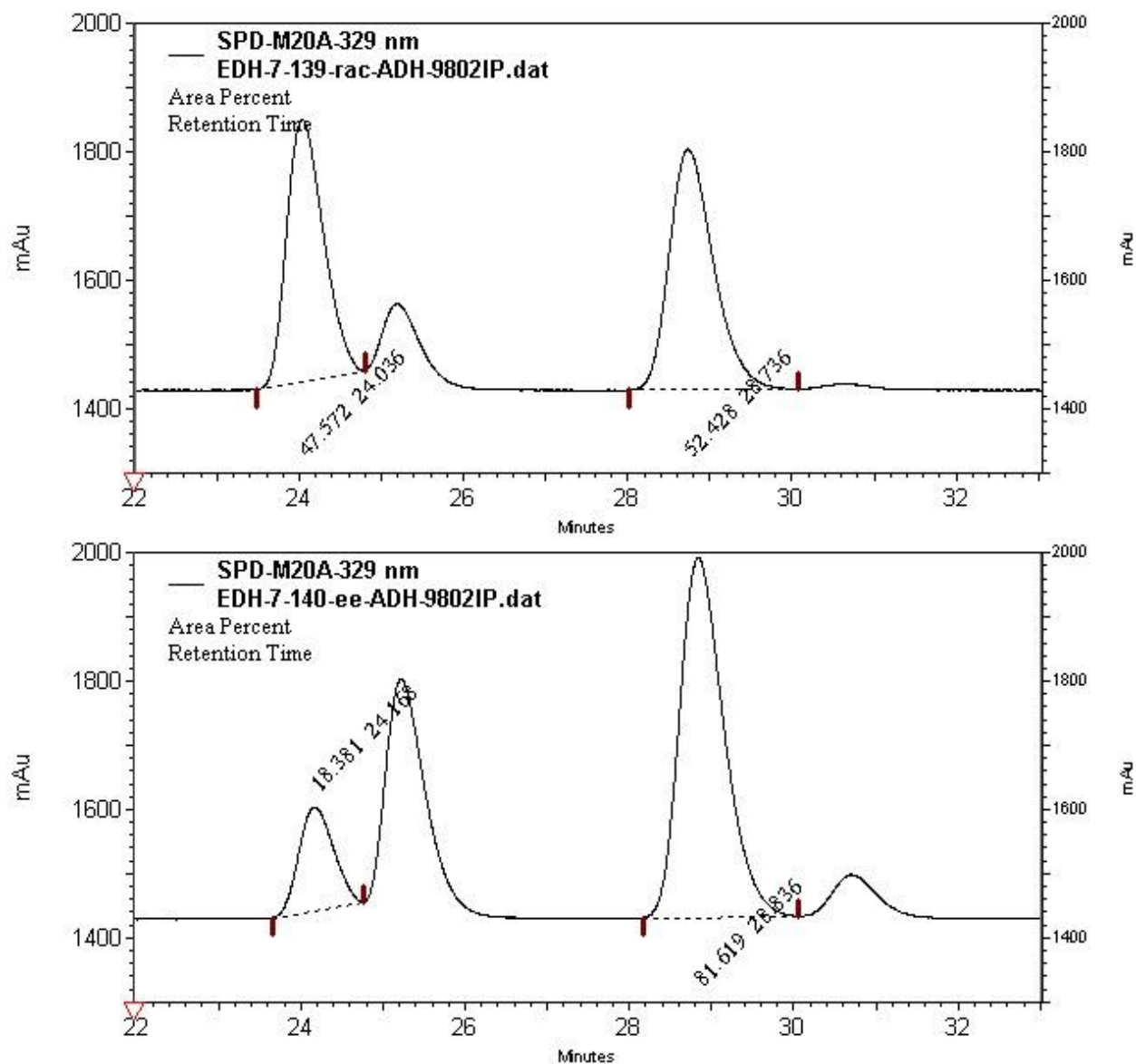


Figure S3.49. Racemic trace (top) and enantioenriched trace (bottom) for functionalized hydroxylamine **3x**.

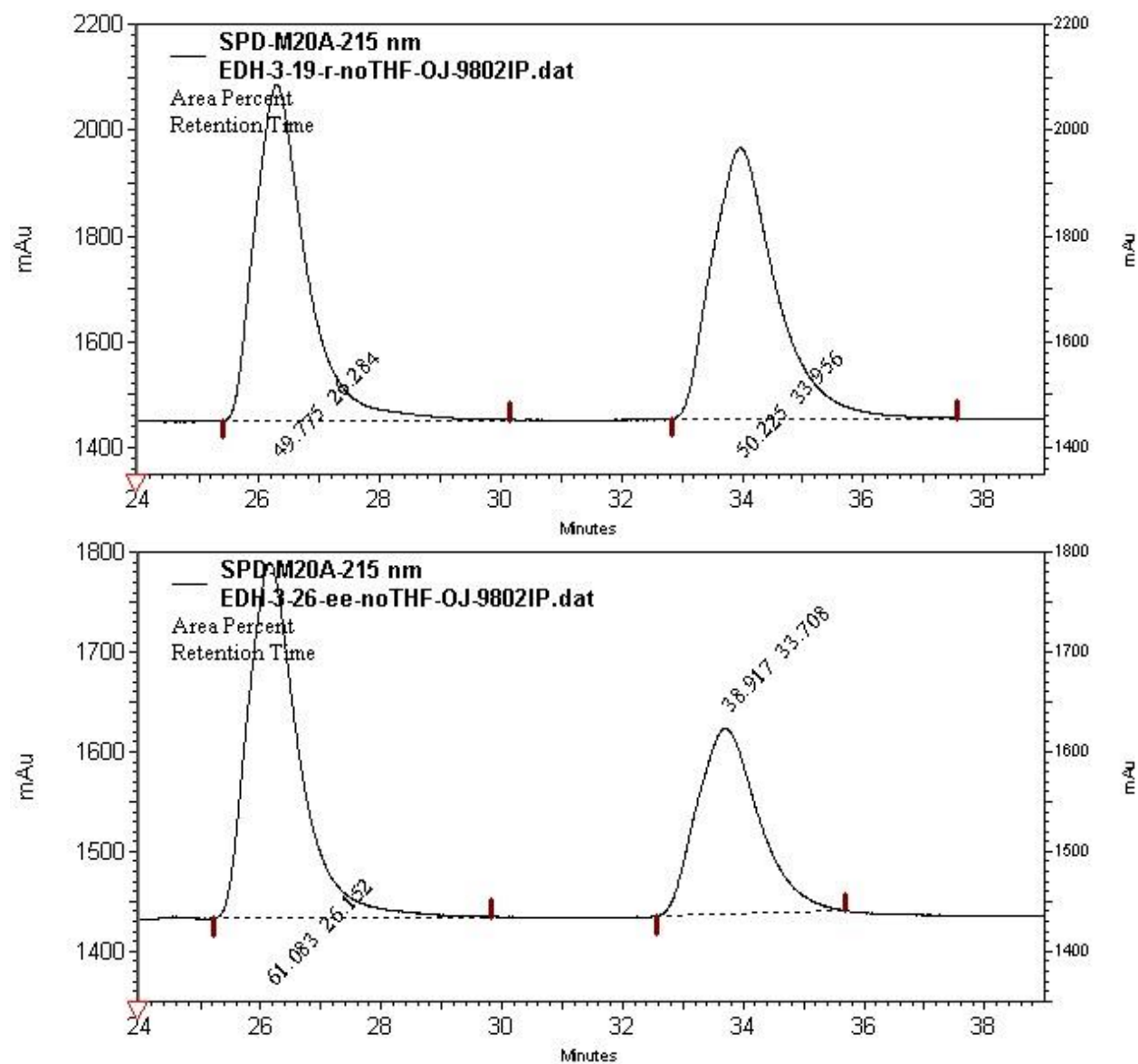


Figure S3.50. Racemic trace (top) and enantioenriched trace (bottom) for hydroxylamine **3y**.

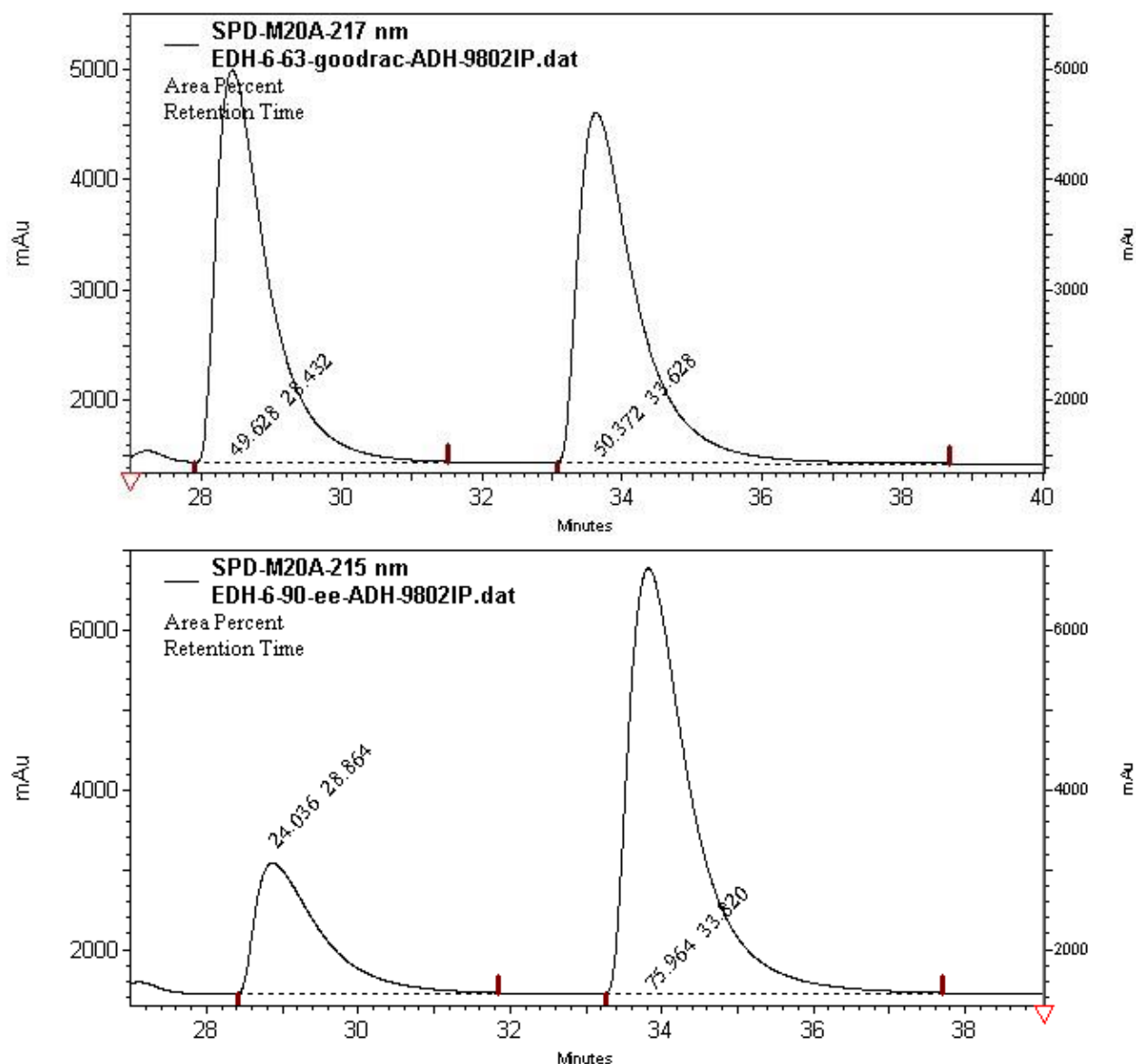


Figure S3.51. Racemic trace (top) and enantioenriched trace (bottom) for hydroxylamine **3z**.

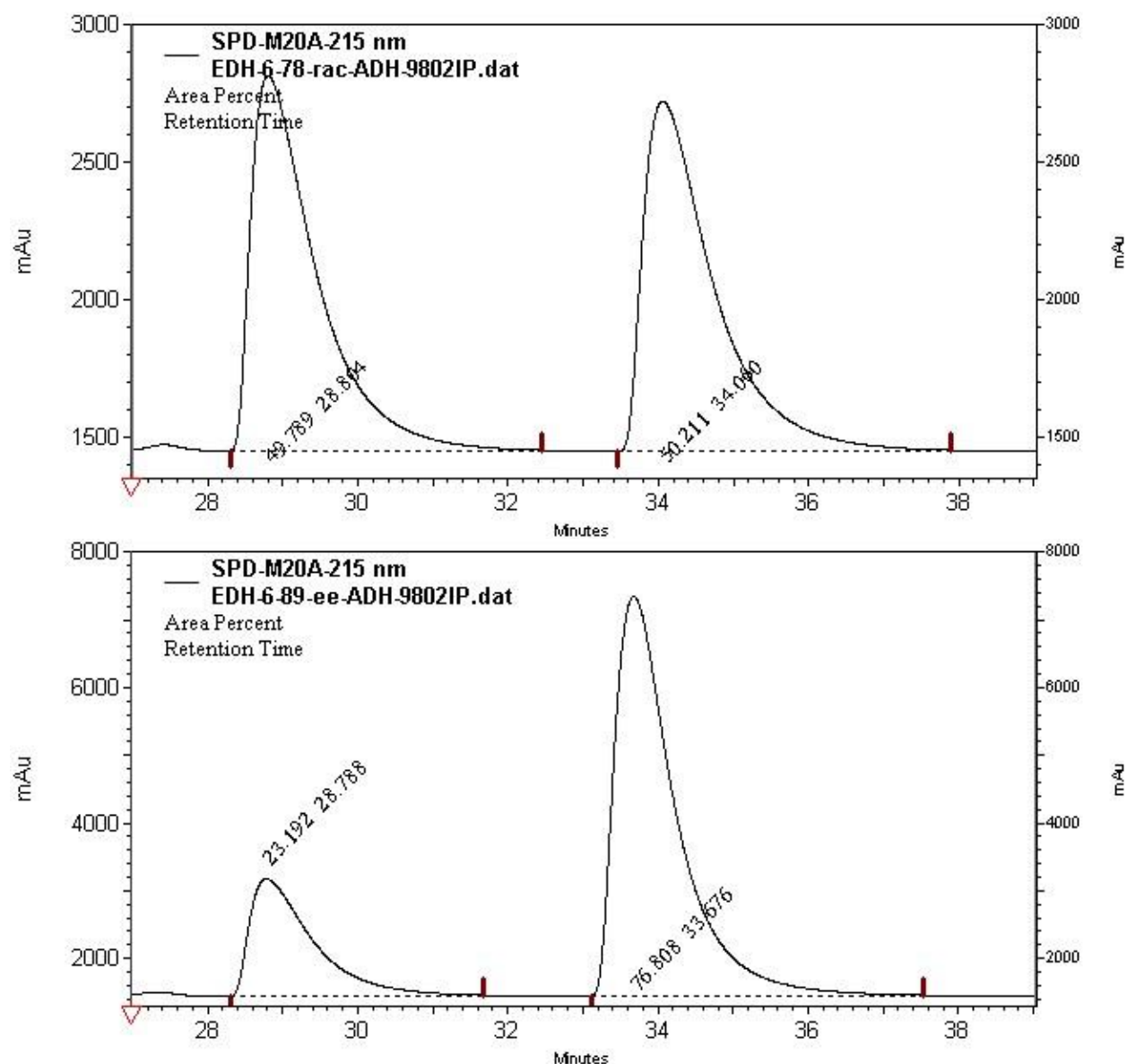


Figure S3.52. Racemic trace (top) and enantioenriched trace (bottom) for hydroxylamine **3z-D**.

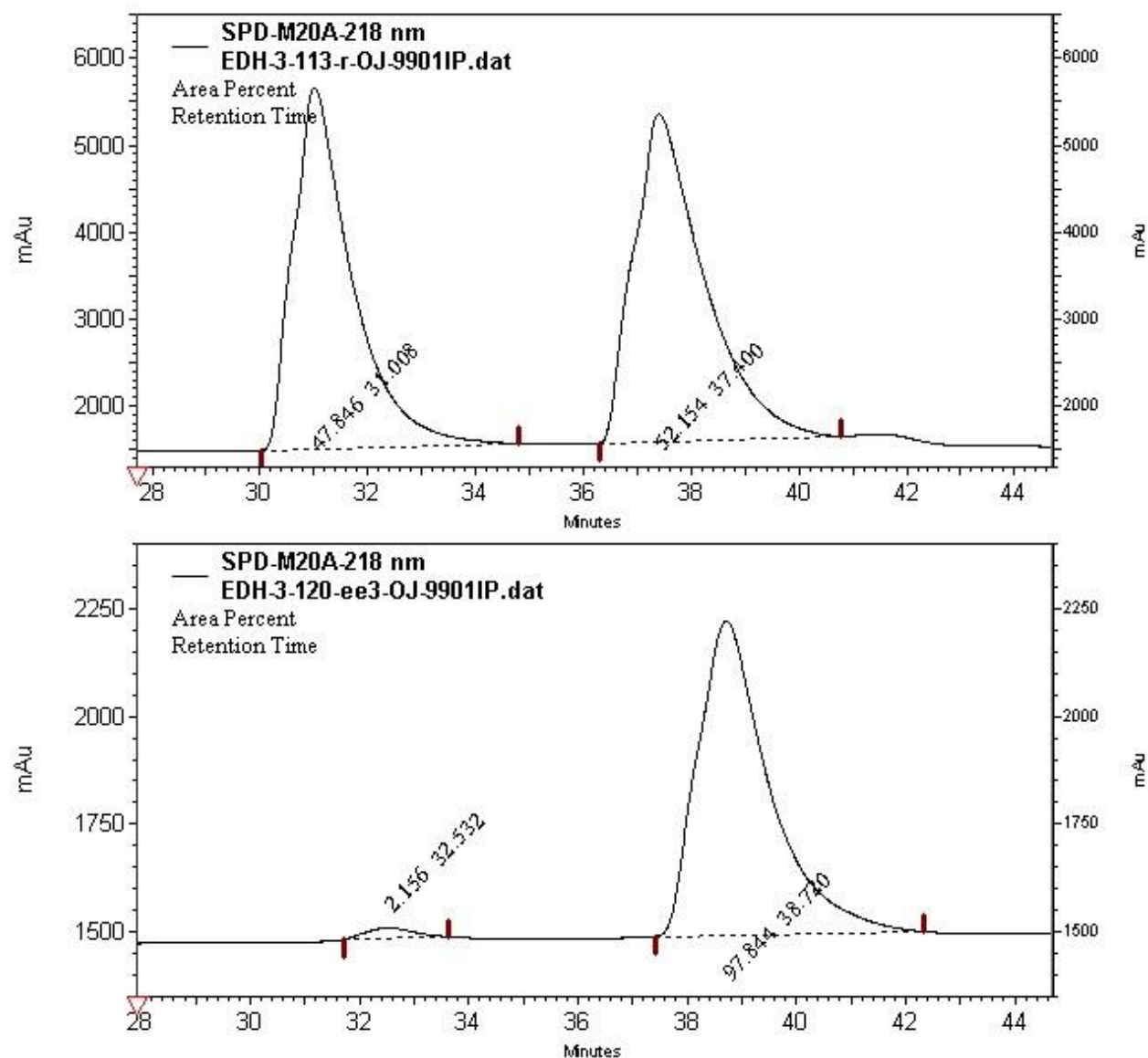


Figure S3.53. Racemic trace (top) and enantioenriched trace (bottom) for hydroxylamine **3aa**.

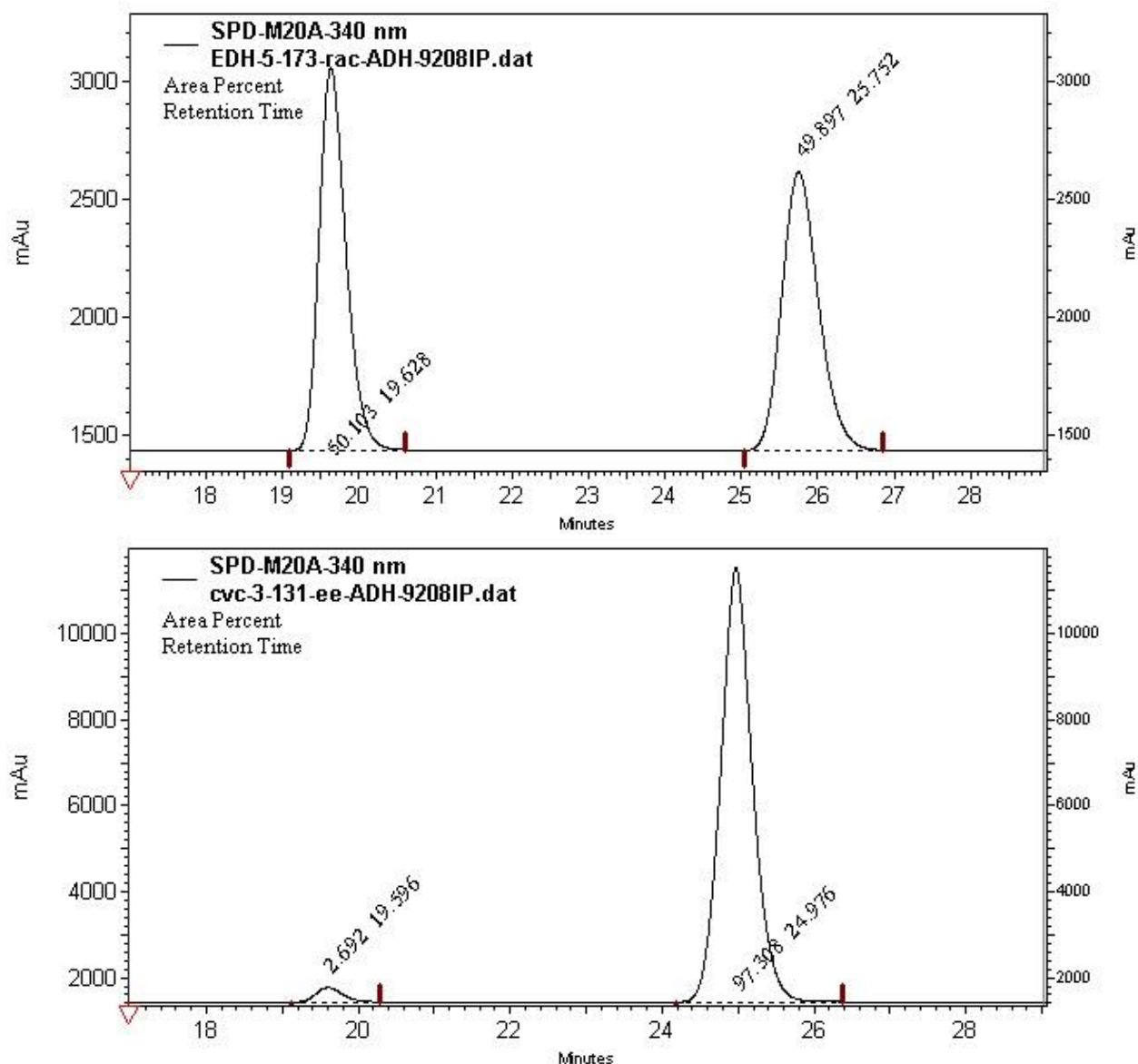


Figure S3.54. Racemic trace (top) and enantioenriched trace (bottom) for functionalized hydroxylamine **3ab**.

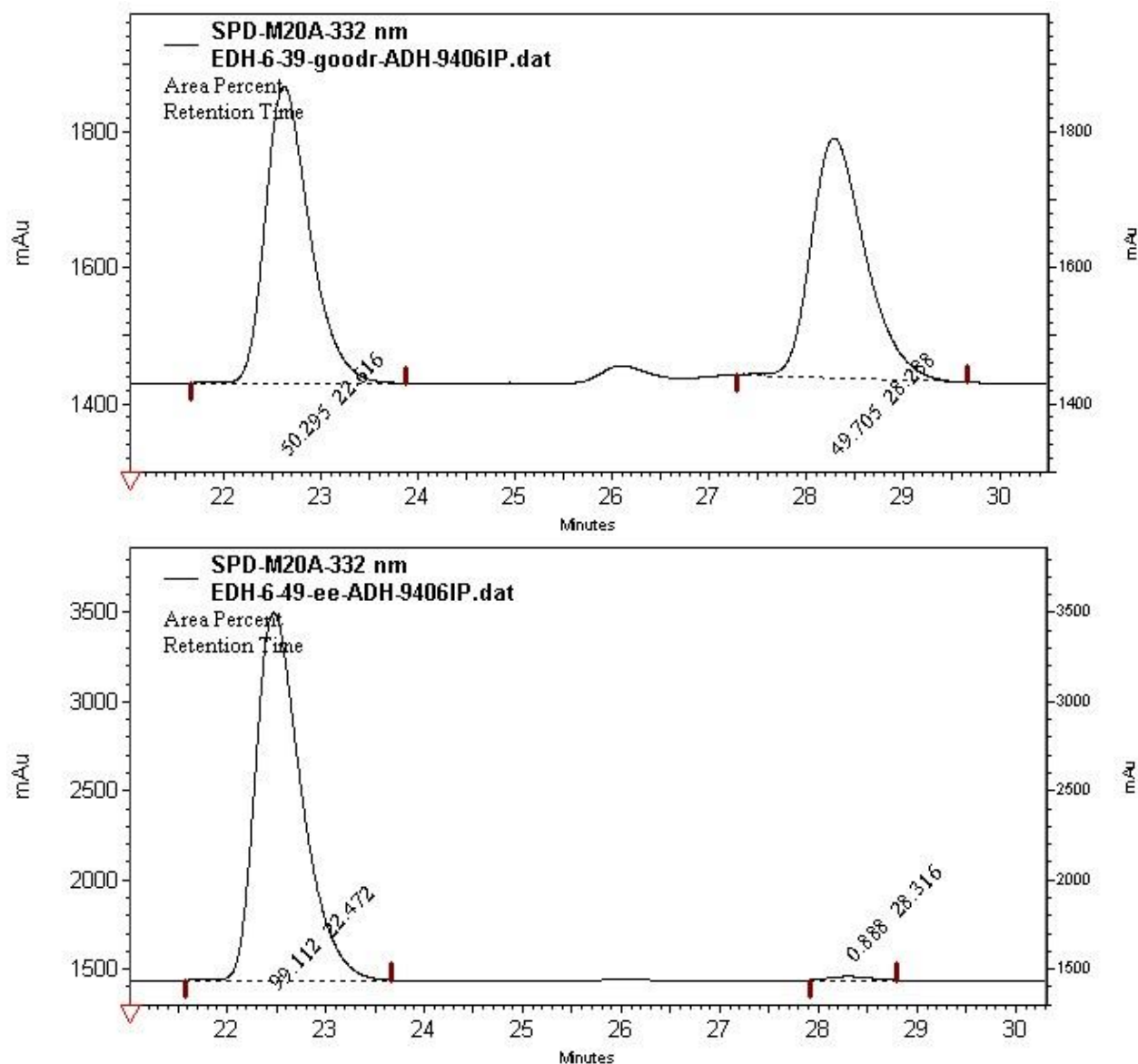


Figure S3.55. Racemic trace (top) and enantioenriched trace (bottom) for functionalized hydroxylamine **3ac**.

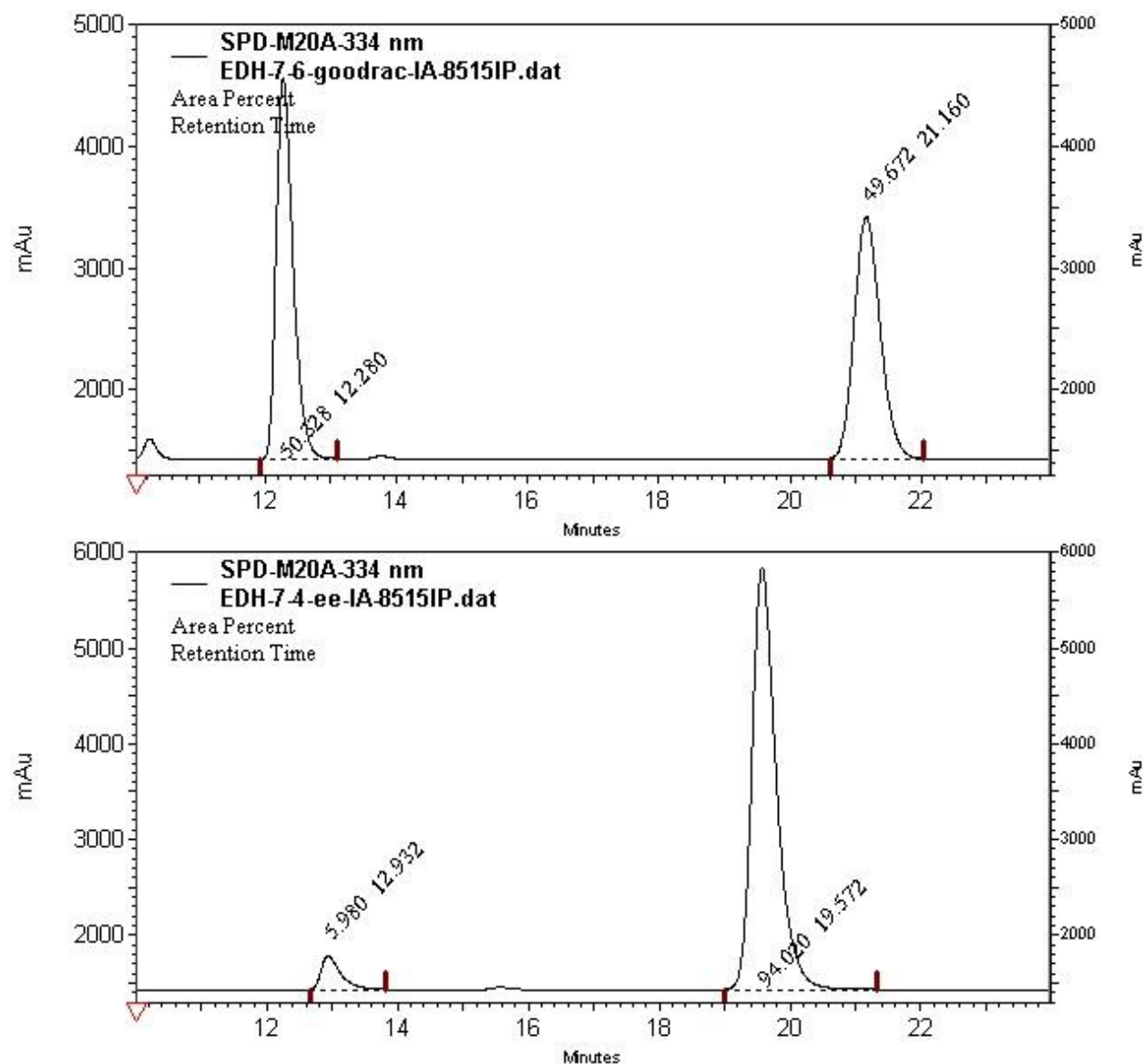


Figure S3.56. Racemic trace (top) and enantioenriched trace (bottom) for functionalized hydroxylamine **3ad**.

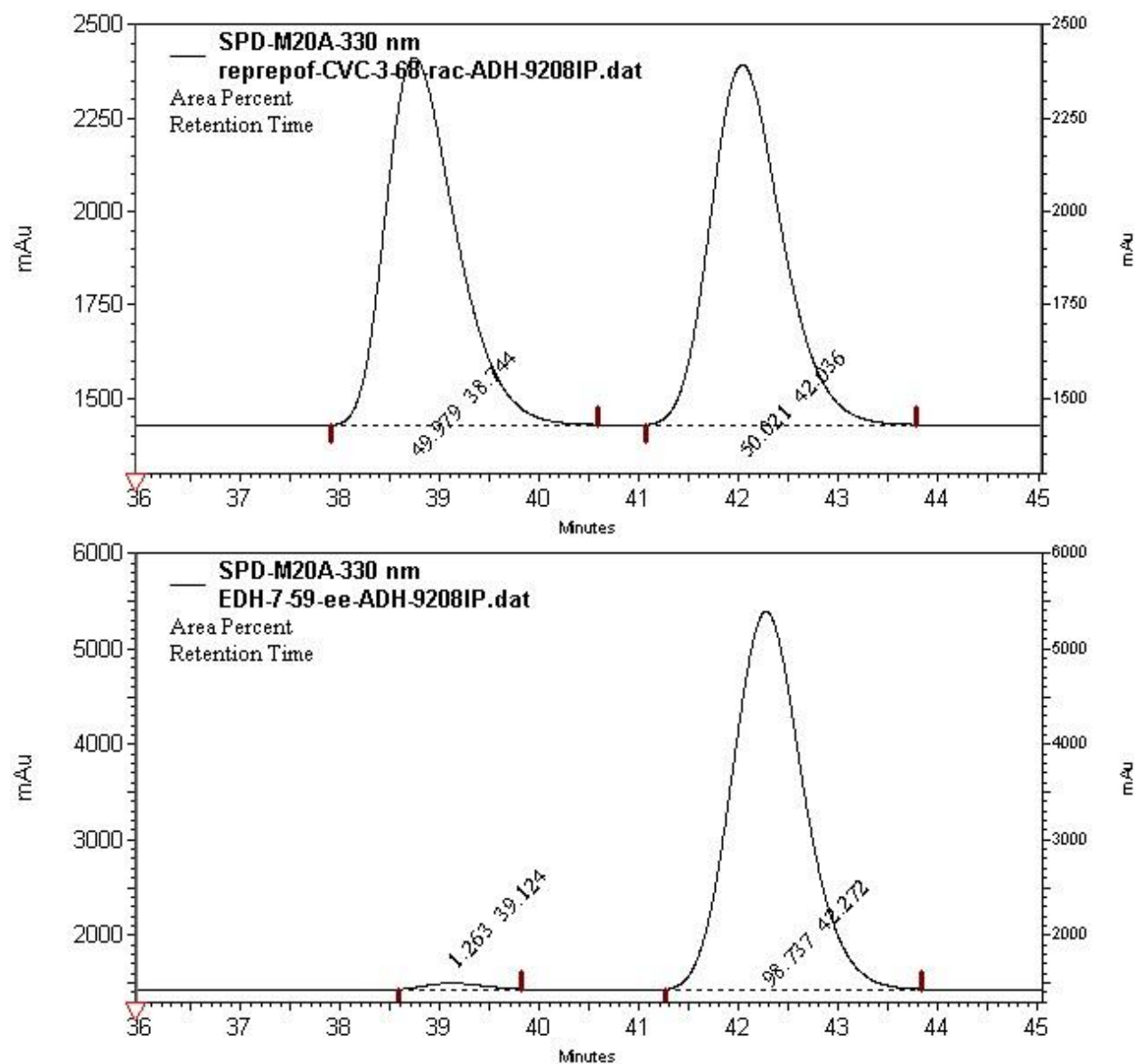


Figure S3.57. Racemic trace (top) and enantioenriched trace (bottom) for functionalized hydroxylamine **3ae**.

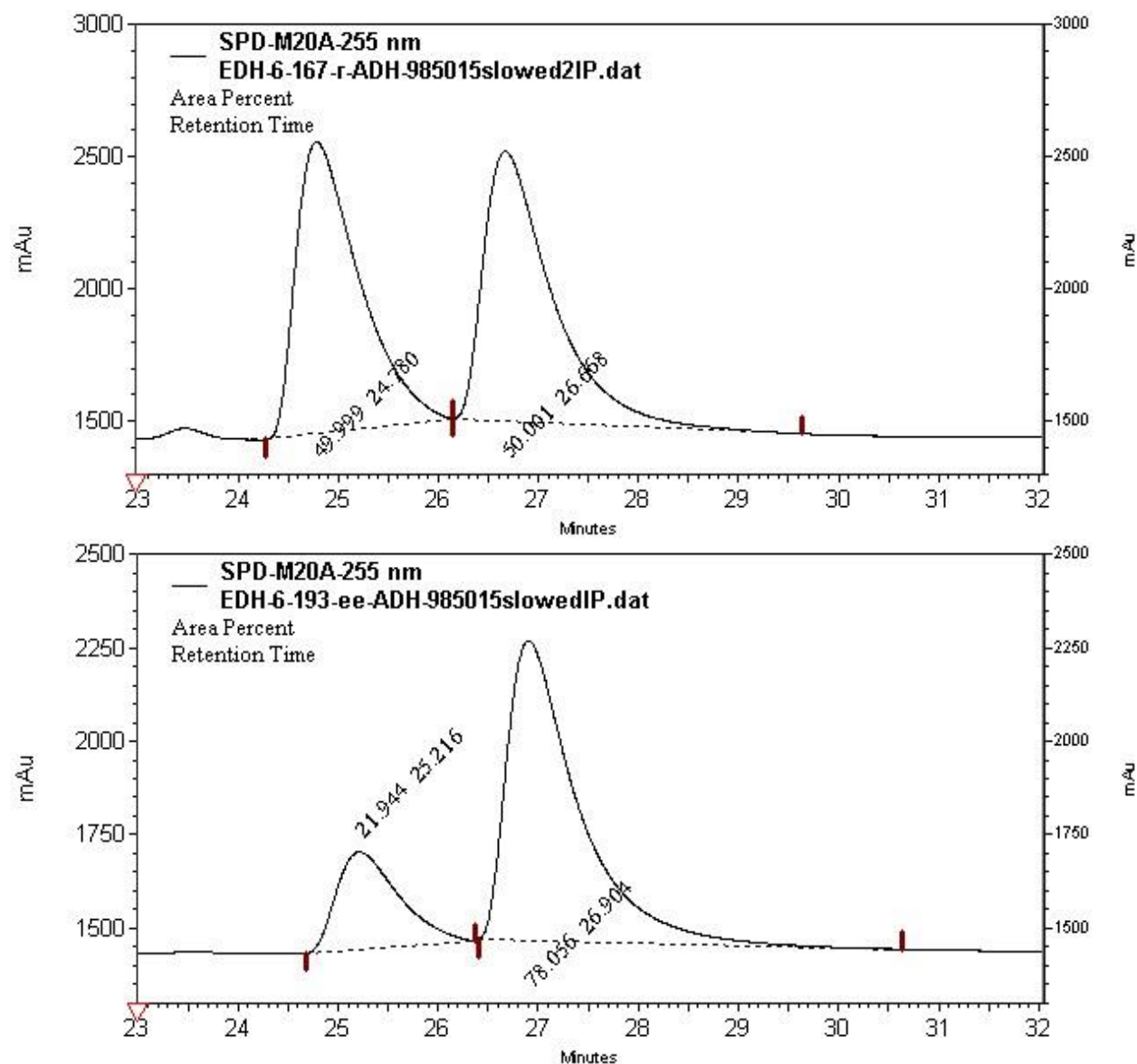


Figure S3.58. Racemic trace (top) and enantioenriched trace (bottom) for hydroxylamine **3af**.

3.7.6 General Calculation Workflows

Calculations were remotely conducted using computing clusters at the Molecular Graphics and Computation Facility (MGCF) at the University of California, Berkeley (NIH S10OD034382). For quantum-level descriptor calculations, semiempirical quantum mechanical method by Grimme's extended tight binding (xtb) package was used (specifically, *xtb* version 6.6.1 was employed for descriptor generation, and the more recent *xtb* version 6.7 was employed for non-covalent interaction coordinate scans). Conformational searching was conducted with Grimme's conformer-rotamer ensemble sampling tool (CREST) which is powered by xTB-based semiempirical quantum mechanical methods (*crest* version 2.12 was employed). In-house Python scripts were

powered by a personal, RDKit conda environment (*Python* == 3.10.12, *rdkit* == 2023.09.2).

Linear correlations were screened using an in-house Python workflow (*mangos.py*), scanning over a set of molecular descriptors (see **Molecular descriptor generation** for full list) against the experimental enantioselectivity (in *kcal/mol*). Both univariate and bivariate correlations to the output are considered. These correlations are scored by (1) Pearson's R^2 metric as measure of goodness-of-fit, and (2) a *leave-one-out* cross-validated R^2 reported as LOO- R^2 (as computed by the *Python* package, *sklearn*). After, an expert-driven analysis invokes chemical intuition to select correlations built from the most *chemically meaningful* feature(s). The selected correlations are reported with the computed R^2 , LOO- R^2 , and the *mean absolute error* (MAE) as a redundant, quantitative measure of error. MAE is computed as the average of the *absolute value of residuals* between the predictions made by the correlation and the true, experimental value. Plots of the linear correlations were generated using *Microsoft Excel*.

Molecular descriptor generation

Overview of calculation workflow

The molecular descriptors are computed and collated via an in-house python script titled *wrangler.py*. The workflow operates by (1) generating an initial conformer for each molecule, (2) optimizing the structure to a local minimum with [Grimme's xTB](#), (3) searching for accessible conformers with [Grimme's CREST](#), (4) extracting descriptors from each conformer collected *within a 1.8 kcal window* (represents >95% of the ensemble population at 298 K), and (5) exporting ensemble-level descriptors for each molecule into csv files. Full Python scripts can be made available upon request.

#1 – Generating initial conformations for each molecule

SMILES strings were processed into 3-D coordinates by using RDKit's *AllChem* module with a preset random seed (*0xf00d*) for reproducibility to generate a reasonable starting conformation.

```
AllChem.EmbedMolecule(this_mol, randomSeed=0xf00d)
```

The atomic coordinates were then rearranged to preserve an organized substructure for later processing. This could be done manually by submitting the desired substructure in a SMILES string to *wrangler.py*, or automatically by (1) solving for the maximum substructure with RDKit's *rdFMCS* module with the settings reported below, and then (2) using RDKit's *GetSubstructMatch()* function to find the atoms of each molecule belonging to the substructure.

```
rdkit_substr = rdFMCS.FindMCS([mol for name, mol in set_mol.items()
                                if this_title in name],
                                atomCompare=rdFMCS.AtomCompare.CompareElements,
                                bondCompare=rdFMCS.BondCompare.CompareAny,
```

```
ringMatchesRingOnly=False,  
completeRingsOnly=True).smartsString
```

The position of the atoms belonging to the conserved substructure are reported into an exported *sdf* file (atomic coordinates reported via RDKit's *Chem.MolToMolBlock(<RDKit molecule object>)* function) for each of the input molecules.

An initial *xyz* file was then prepared by (1) reporting the total number of atoms at the top of the file, (2) writing each atom from the reported substructure at the beginning of the coordinate file, and then (3) filling in the remaining atoms from the molecule below. This file serves as the input to the remaining calculations in the workflow.

```
<number                of                atoms>  
<charge>              <molecule        name>  
<atom symbol> <atom x coord> <atom y coord> <atom z coord>  
...
```

#2 – Local optimization from initial conformation

From the initialized *xyz* file, an *xTB* calculation was conducted (default level of theory at *GFN2-xTB* with implicit solvation via *-alpb water* keyword). The *xTB* job file is specific to syntax at the MGCF computing cluster. For reference, the following generic command line sequence is submitted to initiate the optimization:

```
xtb <Molecule-TITLE>.xyz --opt --chrg 0 --alpb water
```

Manual checks are coded to detect if the local geometry optimization fails. In this work, no RDKit-generated initial conformers led to calculations that would not converge within *xTB*'s default number of cycles (250 iterations). The locally optimized geometry for each molecule is exported to individual directories under the title *xtbopt.xyz*.

#3 – Conformational searching with CREST

From the locally optimized *xtbopt.xyz* files for each molecule considered, a *CREST* calculation was conducted. Because conformational searching is computationally expensive, empirical optimization the following parameters for conformation searching with *CREST* were used.

```
crest xtbopt.xyz -notop -quick -noreftopo -ewin 1.8 -chrg 0 -alpb water -T 8
```

The conformational search uses *CREST*'s built-in *quick* feature which restricts the number of metadynamics (MTD) cycles to search the accessible conformational landscape. Additionally, we restrict the extracted conformers to an energy window of 1.8 *kcal* as it represents approximately 95% of the expected population at 298 K. Like the local geometry optimization, implicit solvation is assigned with *- alpb water*. The unique conformers belonging to the desired energy window are exported to *crest_conformers.xyz* for further processing.

#4 – Descriptor processing and curation

The conformers from the *CREST* calculation are each reported in the *crest_conformers.xyz* file. The in-house python script extracts each conformer, writes the respective xyz file into individual directories, and resubmits an *xTB* calculation to access organized and consistent output. The parameters of this redundant *xTB* calculation are identical to those of the initial, local geometry optimization in *Step #2* (default level of theory at *GFN2-xTB* with implicit solvation via *-alpb water* keyword). This generated *xtbopt.xyz* file is subjected to descriptor processing and curation.

We compute and collate the following descriptors for each conformer calculated.

Table S3.2. List of molecular descriptors computed and curated by *wrangler.py*.

Source	Descriptors
<u>From xTB output</u>	relevant bond lengths, angles, and dihedrals for atoms belonging to the assigned molecular substructure, molecular energy (<i>GFN2/xTB</i>), molecular energies associated with electronic corrections (G_{solv} , G_{sasa} , G_{elec} , G_{hb} , G_{shift}), molecular weight, HOMO, LUMO, molecular dipole, molecular polarizability, xTB-computed atomic charges
	<i>additional processing to compute ...</i>
	$\text{electronegativity} = -(LUMO + HOMO)/2$
	$\text{hardness} = (LUMO - HOMO)/2$
	$\text{softness} = 1/\text{hardness}$
	$\text{electrophilicity} = \frac{\text{electronegativity}^2}{2 * (\text{hardness})}$
<u>From RDKit</u>	occupied molecular volume, van der Waals molecular volume, occupied molecular ovality, van der Waals molecular ovality, total van der Waals molecular surface area, polar van der Waals molecular surface area, apolar van der Waals surface area.
<u>From DBSTEP</u>	buried volumes at the following radii: 2, 2.5, 3, 3.5, 4, 5, 6, and 7 Å for each atom in the assigned molecular substructure; sterimol across the principal axis set by the first two atoms in the assigned molecular substructure: L, Bmin, Bmax.

To access the *xTB output* dataset from the *xtbopt.xyz* file, the following keywords were invoked to identify the location of the corresponding descriptor. Atomistic descriptors were only collected if the atoms belonged to the initial, computed substructure – see *xTB*-computed atomic charges, bond lengths, bond angles, dihedral angles.

Table S3.3. List of keywords used to delimit the *xTB*-derived descriptors.

Keyword	Descriptor(s)
----------------	----------------------

TOTAL ENERGY	molecular energy
-> <i>G_{solv}</i>	electronic energy correction, G_{solv}
-> <i>G_{elec}</i>	electronic energy correction, G_{elec}
-> <i>G_{sasa}</i>	electronic energy correction, G_{sasa}
-> <i>G_{hb}</i>	electronic energy correction, G_{hb}
-> <i>G_{shift}</i>	electronic energy correction, G_{shift}
(HOMO)	HOMO
(LUMO)	LUMO
<i>covCN</i>	<i>xTB</i>-computed atomic charges
<i>molecular mass</i>	molecular weight
<i>molecular dipole</i>	molecular dipole
<i>Mol. $\alpha(0)$</i>	molecular polarizability
<i>Bond Distances</i>	bond lengths
<i>Selected bond angles</i>	bond angles
<i>Selected dihedral angles</i>	dihedral angles

Once all descriptors have been collated and computed, the dataset is exported to a custom *yaml* file as a curated data placeholder (*yaml* available via the package, [PyYAML](https://github.com/yaml/pyyaml), <https://github.com/yaml/pyyaml>).

#5 – Ensemble generation and csv export

Ensembles are generated for each molecule considered in the workflow. In total, *five* ensembles are computed – *ground state*, *Boltzmann averaged*, *minimum value*, *maximum value*,⁷⁸ and *minimum volume conformer*. In this work, all reported descriptor datasets were from the *minimum volume conformer* ensemble because of its (1) chemical relevance to host-guest binding principles, and (2) apparent correlations to experimental outcomes (*yield*, *diastereoselectivity*). In practice, each ensemble is generated in the following manner:

Ground state Accessible conformers calculated from *CREST* are ranked by increasing energy in the *crest_conformers.xyz* output. This relative ranking is preserved upon extraction into individual conformer *xyz* files. Therefore, the *ground state* conformer is denoted with the tag *C_0*. Each *yaml* dataset corresponding to a *ground state* conformer can be collected and exported into a *csv* file marked with the same tag *C_0*.

Boltzmann averaged For each molecule, the entire set of conformers are collected. The rel. energy from the *ground state* (from the lowest energy conformer) is computed in *Hartrees* and then converted into *J/mol* with the factor $2.626 * 10^6$.

$$rel. energy = 2.626 * 10^6 (this energy - gd. state energy)$$

Then, the *Boltzmann weight* is computed with the formula:

$$Boltzmann weight = e^{-rel. energy/(RT)}$$

where $R = 8.314 \text{ J/mol K}$ and $T = 298 \text{ K}$.

The *Boltzmann averaged value* for each descriptor is then computed by (1) converting the *Boltzmann weight* to the proportion of the ensemble populated by this conformer ...

$$this proportion = \frac{this weight}{sum of all weights}$$

... then (2) summing over each conformer's descriptor weighted by its calculated *proportion*. The *csv* file is marked with the tag *AV_XTB* to indicate the *Boltzmann averaged* ensemble was derived from xTB-calculated molecular energies.

Minimum volume The entire set of conformers is collected for each molecule and the molecular volume (as defined by RDKit's *van der Waals molecular volume* descriptor, see #4) is extracted. The *minimum* molecular volume was recorded and the descriptors of the conformer corresponding to this molecule were collected and exported into a *csv* file marked with the tag *MINVOL-N1*.

Non-covalent interaction

The workflow borrows heavily from the technique reported by Orlandi and coworkers. An extended discussion on the theory behind the non-covalent interaction calculation is included in the main text and the supplementary information of Orlandi's report.⁴³ Because the precise nature of the stacked π - π complexes cannot be characterized experimentally, we approximate the nature of the proposed complex using the following probes: **pyridine** is used in place of the reactive, pyridine-borane adducts used as reductants; **oximes** are used as represented by the experimentally supported protonated, (*E*)-oxime intermediates.

The workflow operates by (1) generating geometrically constrained, coordinate scan input files specific to each molecule considered, (2) computing the coordinate scan, and (3) extracting the calculated non-covalent interaction energy. Specific details for each step are described below.

#1a – Generating coordinate scan input files – curating the xyz file

Input files required for each calculation involve (1) an xyz file containing *each* component of the interaction complex under interrogation, (2) a *scan.inp* file containing the specifications for the geometric constraints and the coordinate scan calculation, and (3) a *job* file to submit the *xTB* calculation to the remote computing cluster at the MGCF. The generation of each of these files was automatically completed with an in-house Python script titled *herder*.

The xyz files containing each molecule in the complex (defined as *probe* and *substrate*) were assembled through a series of linear transformations. The following atom assignments are made to each *probe* and *substrate* of the complex: **principal atom**, **secondary atom**, **normal axis**, **secondary axis** (Figure S3.60). The **principal atom** (**C1**, **C2**) refers to the sites that are aligned along the axis scanned during the calculation. The **secondary atom** (**D1**, **D2**) refers to sites adjacent to the **principal atom** that are aligned to create the symmetry of the stacked π - π complex generated. The **normal axis** (**A**) refers to the axis perpendicular to the π -plane of each *probe* and *substrate* (note – these are aligned in the below figure). The **secondary axis** (**B1**, **B2**) refers to the rotation of the π -plane of each *probe* (**B2**) and *substrate* (**B1**) that undergo alignment to create the symmetry of the stacked π - π complex.

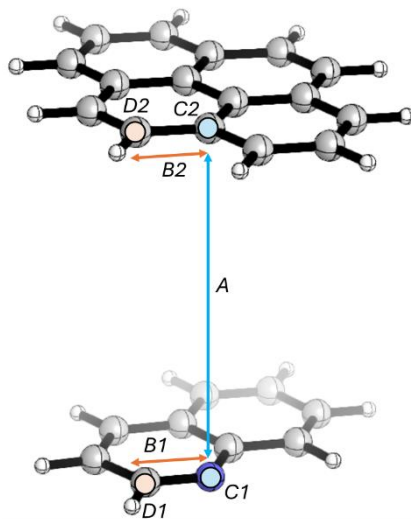


Figure S3.59. General features used to generate the coordinate scan input xyz file. The terms defining *A*, *B1/2*, *C1/2*, and *D1/2* are described in detail above.

The linear transformations involving the following steps. First, **normal axes** defined by the planes surrounding the **principal atoms** of each *probe* and *substrate* were computed. The rotation matrix required to transform the **normal axis** of the *probe* onto the **normal axis** of the *substrate* was computed using a [reported formula](#). The coordinates of the *probe* were transformed by a dot product with the computed rotation matrix. Second, the orientation of the *probe* and *substrate* planes were twisted to achieve the desired symmetry of the stacked π - π complex. From each **principal atom**, an adjacent secondary atom was selected to form a **secondary axis**. The angle between the **secondary axes** of the *substrate* and *probe* molecules was computed and the *probe*

molecule coordinates were transformed with the *apply()* function from the *Rotation* object, instantiated by *from_rotvec()* (*Rotation* is an object accessible from *scipy* in the [spatial.transform package](#)). Finally, the aligned *probe* was centered onto the **principal atom** on the *substrate* by displacing each coordinate by its relative distance to the **principal atom** of the *probe*. Then, the *probe* atoms were displaced along the *substrate* **principal axis** by 7.5 Å, corresponding to the initial distance of the coordinate scan calculation. The aligned *probe* coordinates are then appended to the *substrate* coordinates and exported into an xyz file distinguished by the *substrate*, *probe*, and *non-covalent interaction* computed.

#1b – generating coordinate scan input files – curating the scan.inp specifications

The *scan.inp* file declares to the *xTB path* calculation how to constrain the input xyz file during the coordinate scan. These constraints required specific atomic declarations, so individual *substrate* and *probe* molecules are curated beforehand to maintain common substructures. This allows analogous atomic constraints during the calculation without requiring manual selection of the specific atoms each calculation. The constraints maintain the symmetry of the stacked π - π complex as the π - π complex constricts during the coordinate scan (specific constraints applied to study the oxime-reductant complexes reported herein are described later, see **Specific constrains in non-covalent interaction calculations**). These constraints are assigned to the specific atoms of each *substrate* and *probe* in the xyz input file via the in-house Python script. Altogether, these constraints are specified into a *scan.inp* file which describes to the *xTB* calculation how to proceed with the coordinate scan. As *xTB* computes coordinate scans by a *relaxed fit*, a large *force constant* = 10 was found to be most suitable. The coordinate scan computed varies the *distance* between the *probe* and *substrate* **principal atoms** between the distances of 7.5 Å to 2.5 Å in 200 steps (see *\$scan* declaration).

```
$constrain
force constant = 10
distance: <substrate principal atom>, <probe principal atom>, 7.5
<additional constraints>
$scan
1: 7.5, 2.5, 200
$end
```

#2 – calculating the coordinate scan

With the coordinate scan files generated, the *xTB* job can be completed. This calculation is conducted using *xTB*'s path calculation as declared and specified by the *-input scan.inp* keyword. The energy calculations along each step are computed at the default *GFN2/xTB* level of theory with implicit solvation via *-alpb water* keyword.

```
<complex_calculated>.xyz --opt --chrg <complex_charge> --input scan.inp --alpb water
> scan_out.txt
```

#3 – extracting the non-covalent interaction energy

The calculation produces output to *scan_out.txt* which reports the energies computed at each step in the coordinate scan. These energies are extracted by the in-house Python script, exported to a customized csv file for storage, and analyzed to identify the *minimum* energy along the coordinate scan. This energy corresponds to the *most stable* π - π complex. The distance between the two π systems and the interaction energy of this complex are recorded. A visualization of the computed interaction is shown below, where the *relative energy to the most stable complex* of each scanned coordinate is plotted against the corresponding π - π complex distance.

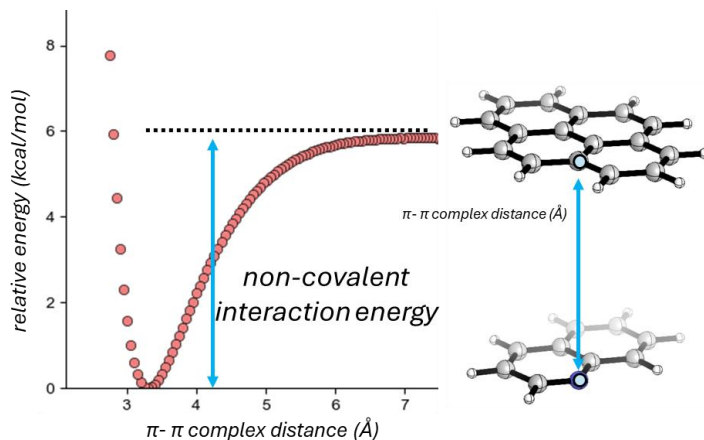


Figure S3.60. An example of the computed interaction energy v. π - π complex distance.

The *non-covalent interaction energy* is computed by taking the difference between the *calculated non-covalent interaction energy* and the total separate energies of both the *probe* and *substrate* molecules (calculated at the same level of theory). For a set of molecules, these calculations are exported into a csv file as a descriptor specified by the *probe* and the specific interaction computed. These descriptors were collated and employed for further analysis.

Unsupervised clustering over chemical space

The clustering algorithm is conducted through an in-house Python workflow titled *bananas.py*. This workflow first reads the csv of the ensemble subjected to analysis, preprocesses the data by (1) normalizing all features with *sklearn's preprocessing.StandardScaler()* object, and (2) dropping features that lack chemical significance like *number of atoms* and *name*, then reduces the dimensionality of the space to a *principal component*-reduced chemical space (corresponding to 90% of the total variance of the original chemical space). This is accomplished with *sklearn's PCA()* object with the *fit_transform()* method.

The resulting *principal component*-reduced space is screened for statistically relevant number of clusters via *sklearn's k-means* clustering object, *cluster.KMeans()*. The *random_state* attribute is set to '1' for reproducible clustering. The workflow then ranks the computed clusters against their relative separation from each other using the

silhouette score metric, as computed by *sklearn's metrics.silhouette_score()*. The numbers of clusters showing the largest separation between each cluster in the *principal component*-reduced chemical space (the largest set of *silhouette scores*) are selected as the most meaningful numbers of clusters.

3.7.7 Expanded Discussion on Data Science Analyses

From *data science analysis informs host-guest interactions*

Oxime identity impacts performance of univariate correlation to observed enantioselectivity

Experimental data supports the expectation that the major oxime species undergoing the host-mediated enantioselective reduction is a *protonated, (E)-oxime*. We prioritize generating models using descriptors calculated from these structures, but also considered other oxime species in solution, namely neutral (*E*)-oxime, neutral (*Z*)-oxime, and protonated (*Z*)-oxime. Below, we show the performance of the reported, best-in-class univariate correlation to experimental enantioselectivity (*kcal/mol*) for each class of oxime species.

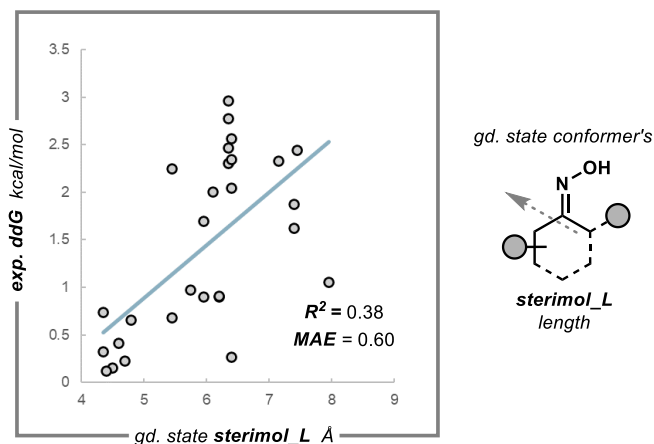


Figure S3.61. Linear correlation between *ground state sterimol_L* of the **neutral (*E*)-oxime** and the experimental enantioselectivity (in *kcal/mol*), $R^2 = 0.38$, $MAE = 0.60$ *kcal/mol*.

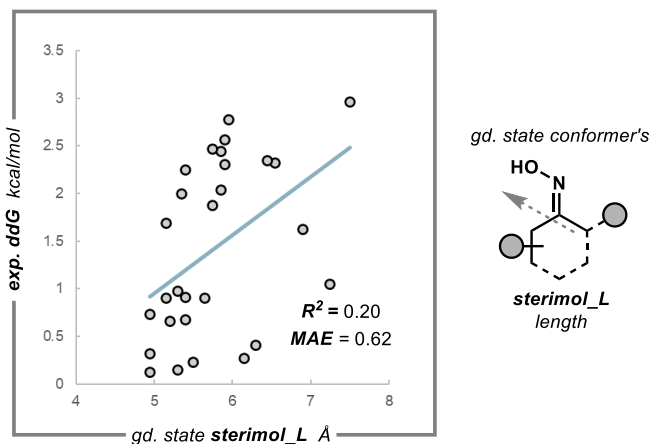


Figure S3.62. Linear correlation between *ground state* sterimol_L of the **neutral (Z)-oxime** and the experimental enantioselectivity (in kcal/mol), $R^2 = 0.20$, MAE = 0.72 kcal/mol.

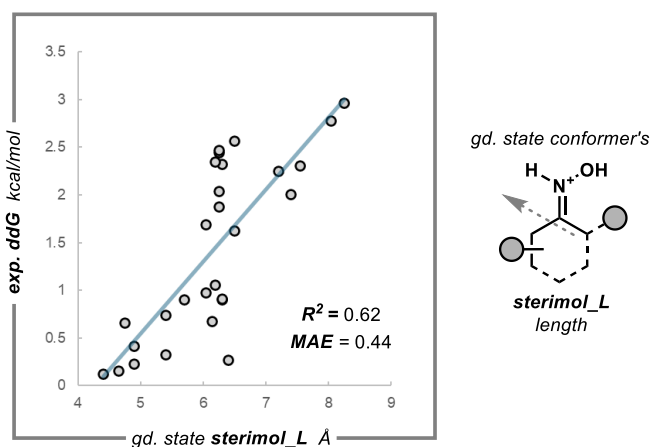


Figure S3.63. Linear correlation between *ground state* sterimol_L of the **protonated (E)-oxime** and the experimental enantioselectivity (in kcal/mol), $R^2 = 0.62$, MAE = 0.44 kcal/mol.

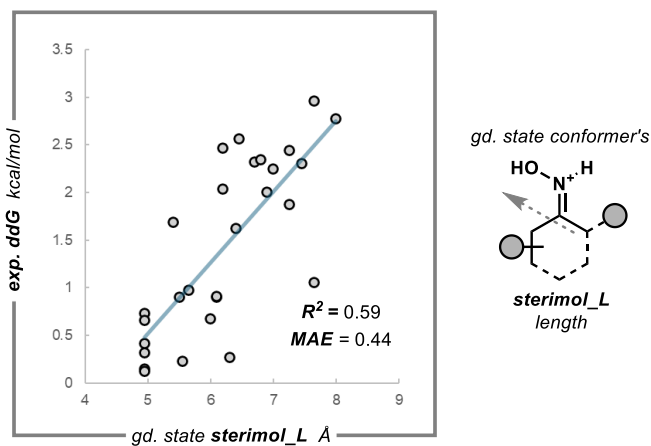


Figure S3.64. Linear correlation between *ground state* *sterimol_L* of the **protonated (Z)-oxime** and the experimental enantioselectivity (in *kcal/mol*), $R^2 = 0.59$, MAE = 0.44 *kcal/mol*.

Besides the identity of the oxime species considered, the molecular descriptor calculation workflow also outputs three separate molecular ensembles: *ground state* (corresponding to the lowest energy conformer found), *Boltzmann average* (corresponding to the Boltzmann averaged value across all conformers found in a 1.8 *kcal/mol* window), and *minimum volume* (corresponding to features of the conformer found with the *minimum molecular volume*). The performance of other ensembles in the univariate correlation were not comparable to the *ground state* ensemble reported. These analyses are included below for reference:

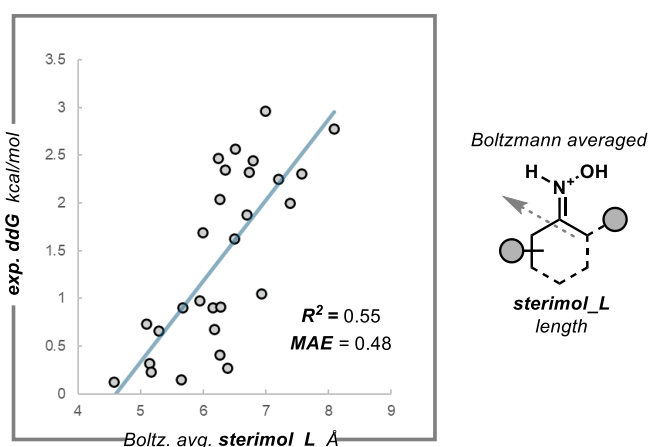


Figure S3.65. Linear correlation between *Boltzmann-averaged* *sterimol_L* of the **protonated (E)-oxime** and the experimental enantioselectivity (in *kcal/mol*), $R^2 = 0.59$, MAE = 0.44 *kcal/mol*.

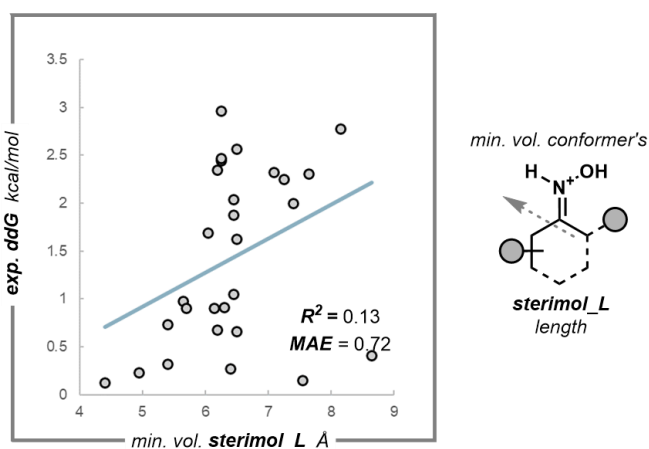


Figure S3.66. Linear correlation between *minimum volume* *sterimol_L* of the **protonated (E)-oxime** and the experimental enantioselectivity (in *kcal/mol*), $R^2 = 0.59$, MAE = 0.44 *kcal/mol*.

From the univariate regression model based on the most chemically meaningful *ground state* *sterimol*_L of the *protonated*, (*E*)-*oxime*, the following predictions were made in *kcal/mol*. The values are converted to % ee for clarity.

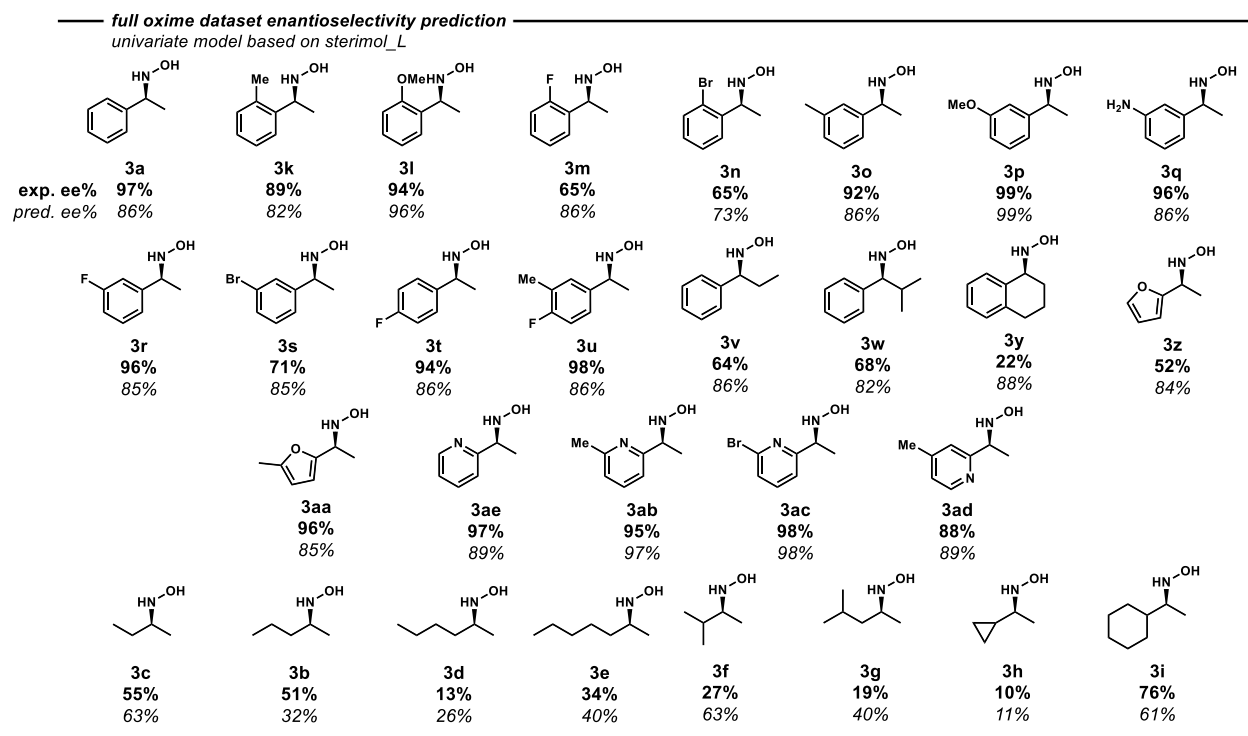


Figure S3.67. Univariate linear regression model based on the *ground state* *sterimol*_L of the *protonated*, (*E*)-*oxime* predictions for the full dataset.

Unsupervised clustering reveals subset of oximes perform better with bivariate correlation

The univariate correlation reported between the *ground state* *sterimol*_L of the *protonated*, (*E*)-*oxime* and the experimental enantioselectivity (*kcal/mol*) displayed a strong correlation, but a subset of oximes dominated error in the regression task. To identify if the subset of oximes were chemically similar, we clustered substrates using the previously described unsupervised, *k-means* clustering algorithm. The clustering was conducted over a *principal component-reduced dataset* comprised of all descriptors calculated for the *protonated*, (*E*)-*oxime* substrates considered in the above correlations. The calculation revealed the dataset cleanly filtered into four separate clusters. The separation can be visualized over the first three principal components. The assignments of each oxime are also shown below.

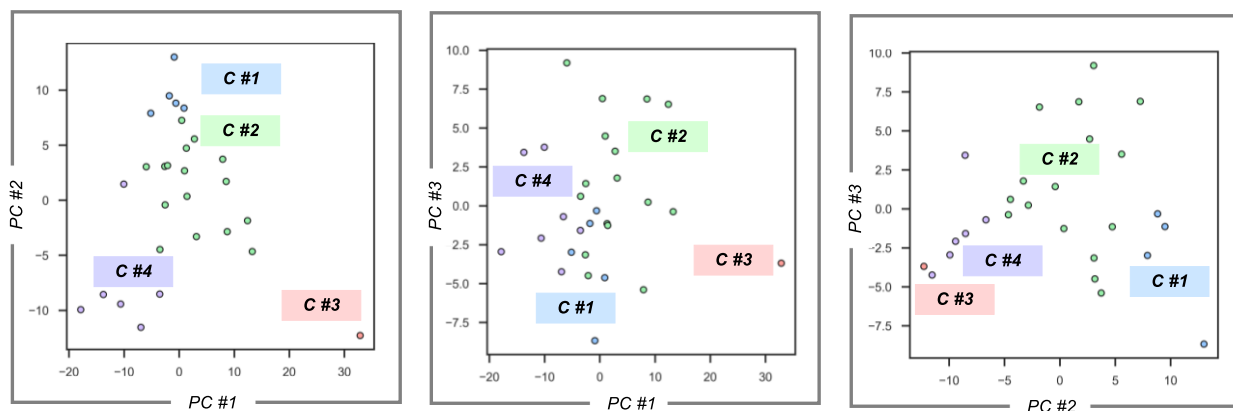


Figure S3.68. Clustered chemical space of the *protonated*, (*E*)-oxime substrates considered in the linear regression tasks reported.

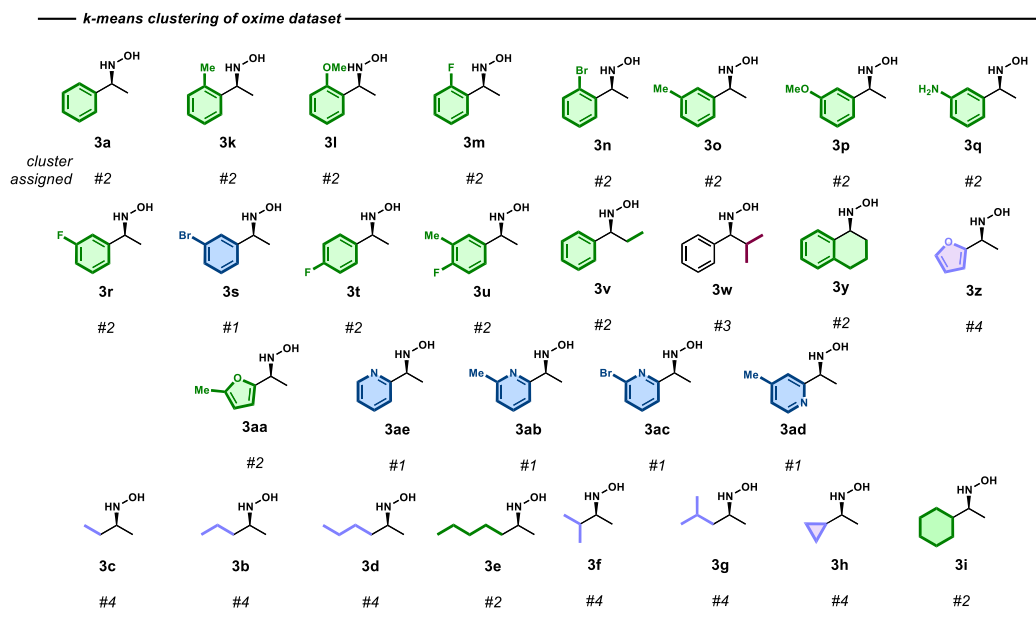


Figure S3.69. Cluster assignments of the *protonated*, (*E*)-oxime substrates considered.

From the clustered dataset, we reconsidered the original univariate regression reported between the *ground state* *sterimol*_L of the *protonated*, (*E*)-oxime and the experimental enantioselectivity (*kcal/mol*). We computed the MAE of each cluster and identified *Cluster* #2, mainly comprised of substituted aryl oximes dominates the error in the correlation measured, see below.

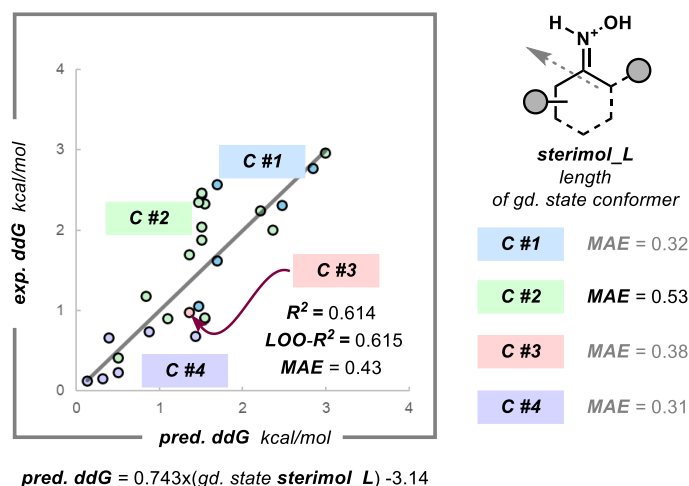


Figure S3.70. Linear correlation between *ground state* sterimol_L of the protonated (*E*)-oxime and the experimental enantioselectivity (in kcal/mol). The MAE of each cluster is recorded showing *Cluster #2* dominates the error in the correlation with an MAE = 0.53 kcal/mol.

The disparate performance of *Cluster #2* is further demonstrated by separate regression analyses of *Clusters #1, 3, and 4* and *Cluster #2*. When *Cluster #2* is removed from the dataset, *ground state* sterimol_L displays excellent correlation to experimental enantioselectivity (kcal/mol). Sole analysis of *Cluster #2* shows *ground state* sterimol_L displays little correlation to experimental enantioselectivity (kcal/mol).

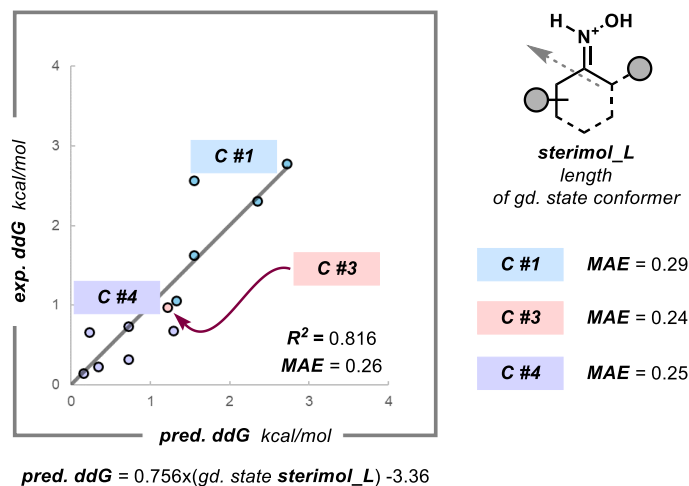


Figure S3.71. Linear correlation between *ground state* sterimol_L of the protonated (*E*)-oximes in *Clusters #1, 3, 4* and the enantioselectivity (in kcal/mol). $R^2 = 0.82$, MAE = 0.26 kcal/mol.

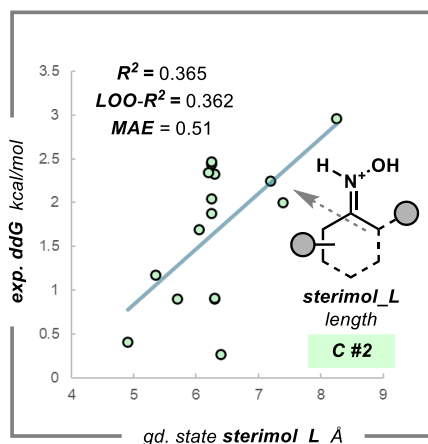


Figure S3.72. Linear correlation between *ground state* sterimol_L of the protonated (*E*)-oximes in *Cluster #2* and the enantioselectivity (in *kcal/mol*). $R^2 = 0.37$, MAE = 0.51 *kcal/mol*.

To improve the performance of the correlation task, specifically for *cluster #2*, additional variables were screened for bivariate linear regression tasks. Here, 4.0 Å buried volume at the α-C of the oxime emerged as one of the most useful features. Specifically, the bivariate linear regression from *ground state* sterimol_L and the buried volume descriptors to the experimental enantioselectivity showed improved performance in *Cluster #2* as well as across the full dataset.

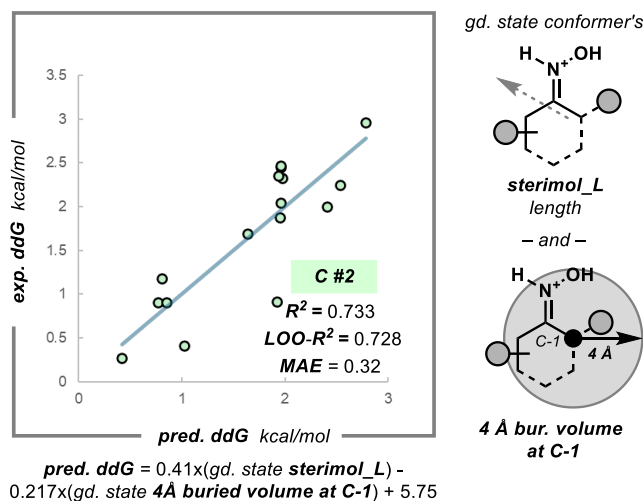


Figure S3.73. Bivariate linear correlation of *ground state* sterimol_L and 4.0 Å buried volume at the α-C of the oxime (C-1) of the protonated (*E*)-oximes in *Cluster #2* and the experimental enantioselectivity (in *kcal/mol*). $R^2 = 0.37$, MAE = 0.51 *kcal/mol*.

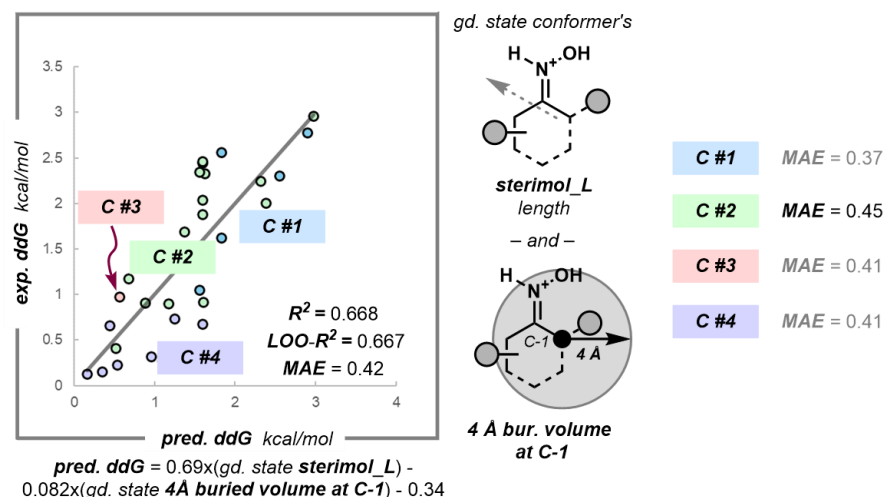


Figure S3.74. Bivariate linear correlation of *ground state* sterimol_L and 4.0 Å buried volume at the α-C of the oxime (C-1) of the protonated (*E*)-oxime and the experimental enantioselectivity (in kcal/mol). $R^2 = 0.37$, MAE = 0.51 kcal/mol.

With the *best-in-class* bivariate linear regression model, the full dataset observes the following enantioselectivity predictions. The model makes the prediction in kcal/mol and these are converted to % ee for clarity in interpretation.

full oxime dataset enantioselectivity prediction

bivariate model based on sterimol_L and 4Å buried volume at C-1

3a	3k	3l	3m	3n	3o	3p	3q
exp. ee% 97%	89%	94%	65%	65%	92%	99%	96%
pred. ee% 88%	82%	97%	88%	64%	88%	99%	88%
3r	3s	3t	3u	3v	3w	3y	3z
96%	71%	94%	98%	64%	68%	22%	52%
xx%	87%	88%	88%	76%	44%	73%	88%
3aa	3ae	3ab	3ac	3ad			
96%	97%	95%	98%	88%			
96%	91%	97%	99%	91%			
3c	3b	3d	3e	3f	3g	3h	3i
55%	51%	13%	34%	27%	19%	10%	76%
79%	36%	29%	42%	67%	43%	14%	52%

Figure S3.75. *Best-in-class* bivariate linear regression model predictions for the full dataset.

From *data science analysis of stereoelectronic effects on enantioselectivity*

Overview of specific constraints used in the non-covalent interaction calculations reported

The non-covalent interaction workflow requires specific constraints to maintain π - π symmetry in the π -stack conformation. These constraints are system specific and are not fully generalizable. In this report, we use the constraints described in detail below. The distance scanned during the coordinate scan calculation is between *P1* (of the oxime) and *P6* (of the pyridine probe). The dihedrals *D1*, *D2*, *D3*, and *D5* comprised of the indicated points are all set to 0°. The dihedrals *D4* and *D6* comprised of the indicated points are set to 180°. The angles *A1*, *A2*, and *A3* are all set to 90°. Again, each of these constraints are specifically invoked to ensure the two π systems remain symmetrically stacked along the coordinate scan.

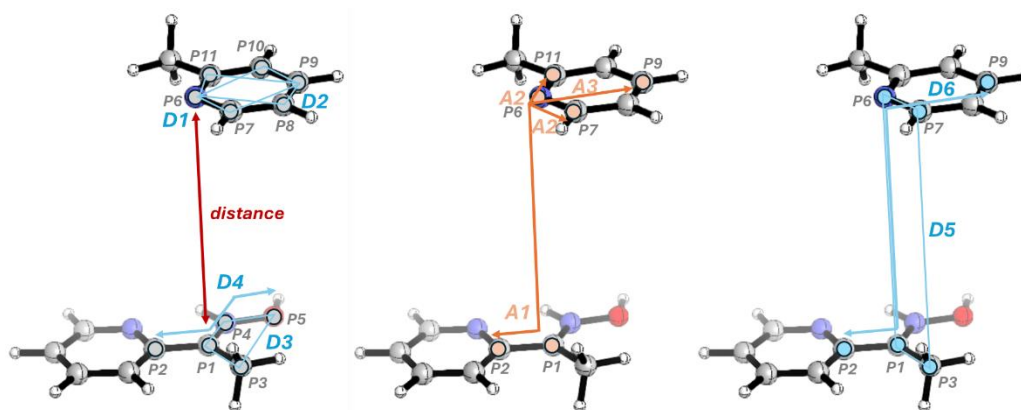


Figure S3.76. Overview of specific constraints used in the non-covalent interaction calculations reported in this work.

The interaction between the oxime and the pyridine probe are not all degenerate. We explicitly consider three chemically meaningful conformations to capture these unique interactions across all substrates. The differences across each conformation are specifically highlighted by the declaration of *D5*, where we can see the points belonging to the dihedral constraint are unique across each conformation. The analogous changes are made to *P1*, *P6*, *D1*, *D2*, *D3*, *D4*, *D6*, *A1*, *A2*, *A3*, and the remaining points to keep the integrity of the constraints declared above.

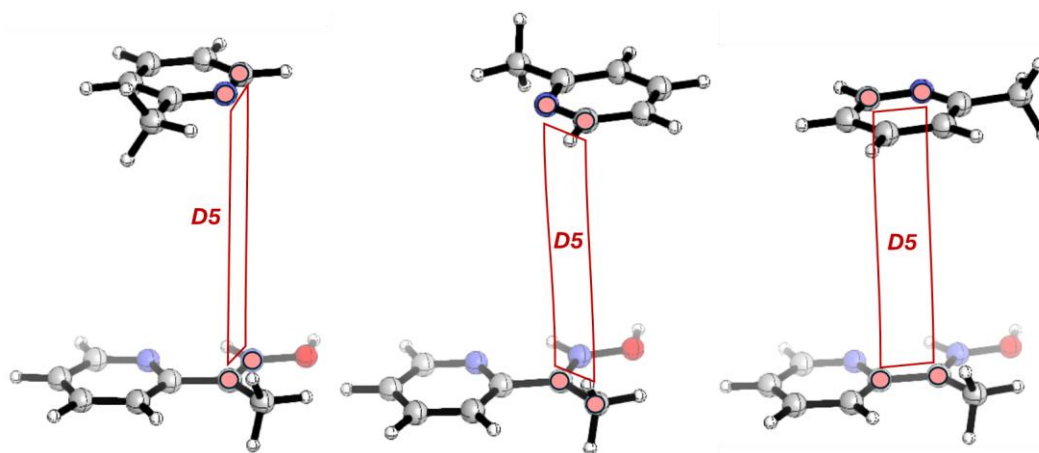


Figure S3.77. Three separate conformations are considered in the non-covalent interaction calculations. The reported interaction energies and distances are a *Boltzmann average* across these three complexes explicitly considered.

Full dataset of non-covalent interaction calculations between oxime and pyridine borane, 1a

Non-covalent interactions between the *protonated, (E)*-oxime and the *pyridine-borane 1a*, simplified as the inert pyridine probe, were calculated. The *Boltzmann averaged* interaction energy (*kcal/mol*) across the three poses described above are recorded below.

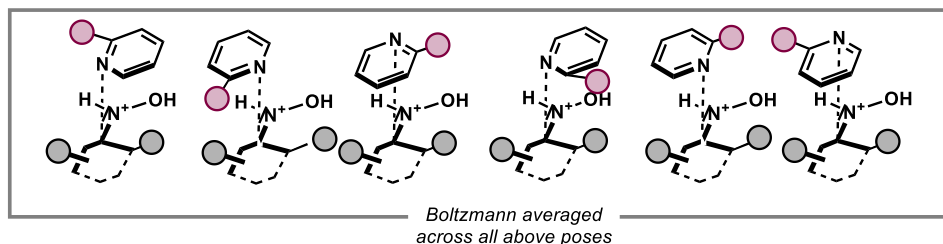
Boltzmann averaged
across all above poses

oxime-pyridine borane probe calculated non-covalent interaction reported as Boltzmann average, from GFN2/xtB (alpb=water) level of theory								
3a	3k	3l	3m	3n	3o	3p	3q	3r
calc. inter. -4.90	-4.42	-5.69	-5.40	-3.50	-4.78	-5.09	-4.93	-4.59
3s	3t	3u	3v	3w	3y	3ae	3ab	3ac
-4.97	-4.42	-4.82	-5.51	-3.68	-5.12	-4.97	-5.19	-5.69
3c	3b	3d	3e	3f	3g	3h	3ad	
-3.45	-3.82	-3.44	-3.47	-4.51	-3.73	-3.47	-4.90	

Figure S3.78. Non-covalent interactions calculated for the *protonated, (E)*-oxime considered, reported as a *Boltzmann average* of the indicated conformations. Individual calculations were conducted at the *GFN2/xtb (alpb=water)* level of theory.

Full dataset of non-covalent interaction calculations between selected oximes and an array of pyridine borane reductants, 1a-e

Over a selected set of oximes, the enantioselectivity of the host-mediated reduction by stereoelectronically diverse pyridine boranes was measured. The calculated non-covalent interaction energies of the corresponding complexes between the indicated *protonated, (E)-oximes* and *pyridine* probes (corresponding to the pyridine borane reductant) are recorded below. Additionally, the distances between the *N* of the pyridine probes and the *C* atom of the oxime substrates at the optimal π -stack complexes are recorded below.



oxime-pyridine borane probe calculated non-covalent interaction reported as Boltzmann average, from GFN2/xtB (alpb=water) level of theory						
	3m	3b	3y	3ae	3n	
calc. inter. (kcal/mol)	-5.40	-3.44	-5.12	-4.97	-4.42	
calc. dist. (Å)	3.23	3.34	3.36	3.19	3.38	
	3m	3b	3y	3ae	3n	
	-6.65	-4.36	-5.98	-6.27	-5.62	
	3.28	3.37	3.37	3.21	3.38	
	3m	3b	3y	3ae	3n	
	-5.53	-3.29	-5.15	-5.23	-4.64	
	3.31	3.38	3.58	3.26	3.40	

...

	3m	3b	3y	3ae	3n
	-7.28 3.18	-5.13 3.31	-6.63 3.33	-6.94 3.17	-5.97 3.35
	3m	3b	3y	3ae	3n
	-4.78 3.32	-2.60 3.35	-4.67 3.41	-4.89 3.24	-3.70 3.44

Figure S3.79. Non-covalent interactions energies (*kcal/mol*) and distances (Å) calculated for the *protonated, (E)-oxime* considered, reported as a *Boltzmann average* of the indicated conformations. Calculations were conducted at the *GFN2/xtb (alpb=water)* level of theory.

Analysis of correlations between non-covalent interactions calculated and enantioselectivity

The non-covalent interactions computed between the *protonated, (E)-oxime* and the *pyridine probe*, serving as a surrogate for the real pyridine borane reductant, display weak correlation to the experimental enantioselectivity (*kcal/mol*).

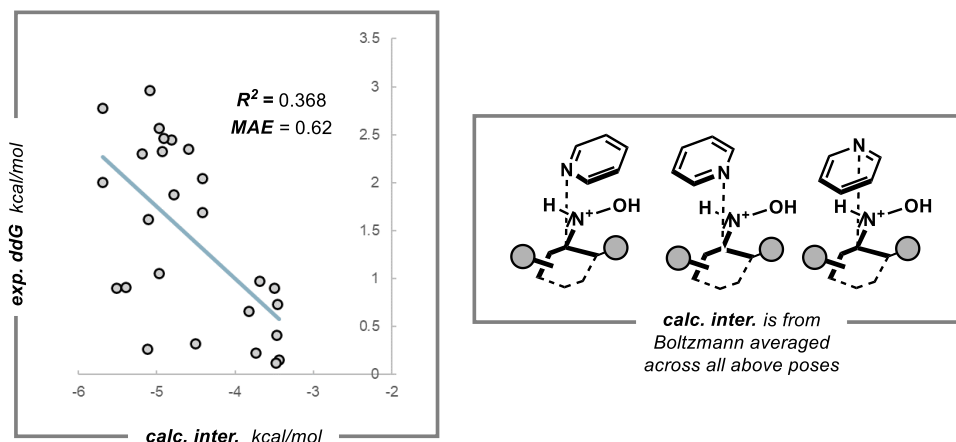


Figure S3.80. Linear correlation between calculated non-covalent interaction energy between protonated (*E*)-oximes and a pyridine probe and the experimental enantioselectivity (in *kcal/mol*). $R^2 = 0.37$, $MAE = 0.62$ *kcal/mol*.

However, the non-covalent interactions computed display a much stronger correlation to the corresponding *ground state* *sterimol_L*. This correlation helps elaborate the chemical significance of *ground state* *sterimol_L* regression models to experimental enantioselectivity. Specifically, it suggests that the *sterimol_L* value is not solely a molecular shape descriptor but may also elaborate the capacity of the oxime substrate to capture energetically favorable non-covalent interactions.

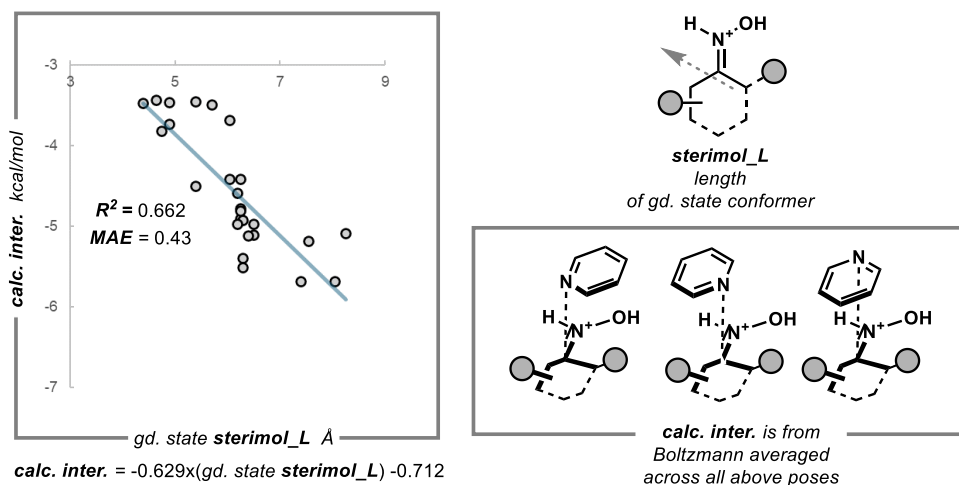


Figure S3.81. Linear correlation between calculated non-covalent interaction of protonated (*E*)-oximes and a pyridine probe and the corresponding *ground state* *sterimol_L*. $R^2 = 0.66$.

To further evaluate how the non-covalent interactions between the reductant and the oxime substrate influence the enantioselectivity in the host-mediated reduction, a series of stereoelectronically distinct pyridine borane reductants were screened. The calculated interaction energies and distances (see *full dataset* above) were compared to the experimental enantioselectivity (*kcal/mol*). While some of the oxime substrates displayed a very strong correlation between computed interaction energies in the proposed π -stack complex and enantioselectivity, others displayed stronger correlations between the computed interaction distances in the proposed π -stack complex and enantioselectivity. Across all substrates, a universal trend could not be identified, supporting the expectation that a complex array of steric and electronic factors in the transient π -stack complex between the reductant and substrate within the host cavity are relevant for enantioselectivity. For reference, the exhaustive set of the correlations measured for each of the oximes considered are reported below. The corresponding hydroxylamine generated from the reduction under analysis is noted on the side for clarity.

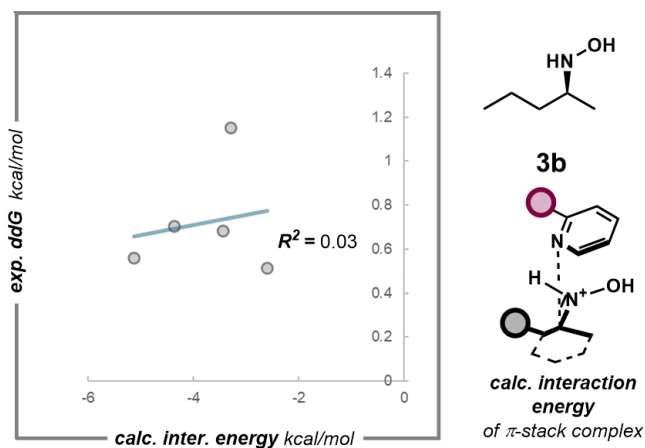


Figure S3.82. Linear correlation between calculated non-covalent interaction energy (kcal/mol) of protonated (*E*)-oxime **2b** and pyridine probes corresponding to **1a-e** to the experimental enantioselectivity of the corresponding host-mediated reduction. $R^2 = 0.03$.

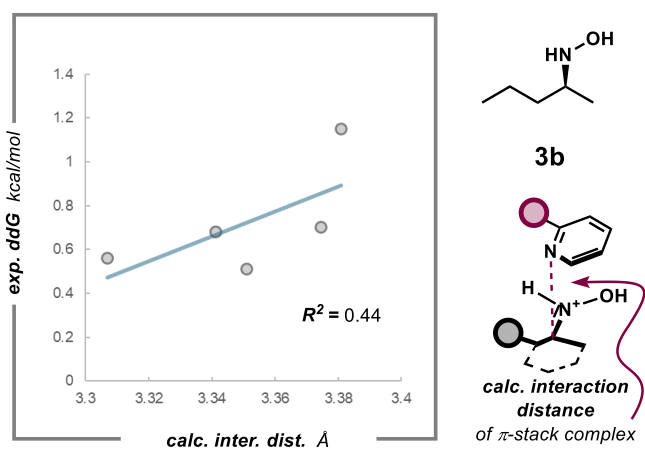


Figure S3.83. Linear correlation between calculated non-covalent interaction distance (Å) of protonated (*E*)-oxime **2b** and pyridine probes corresponding to **1a-e** to the experimental enantioselectivity of the corresponding host-mediated reduction. $R^2 = 0.44$.

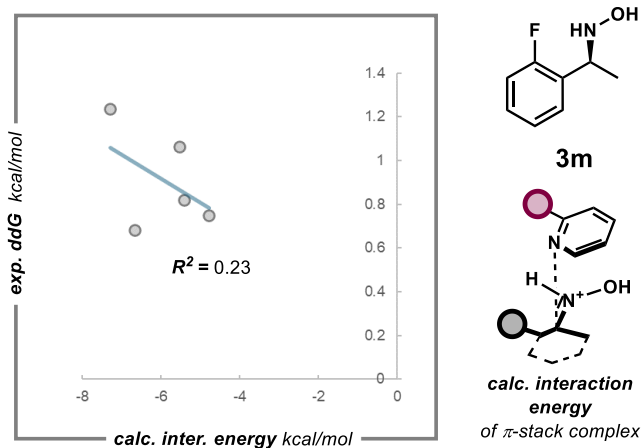


Figure S3.84. Linear correlation between calculated non-covalent interaction energy (kcal/mol) of protonated (*E*)-oxime **2m** and pyridine probes corresponding to **1a-e** to the experimental enantioselectivity of the corresponding host-mediated reduction. $R^2 = 0.23$.

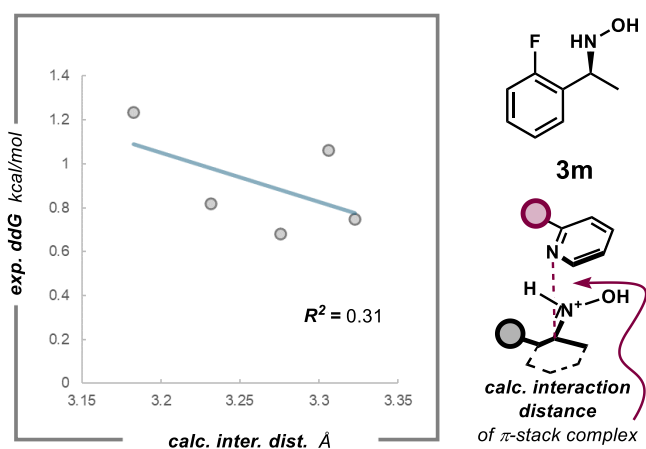


Figure S3.85. Linear correlation between calculated non-covalent interaction distance (Å) of protonated (*E*)-oxime **2m** and pyridine probes corresponding to **1a-e** to the experimental enantioselectivity of the corresponding host-mediated reduction. $R^2 = 0.31$.

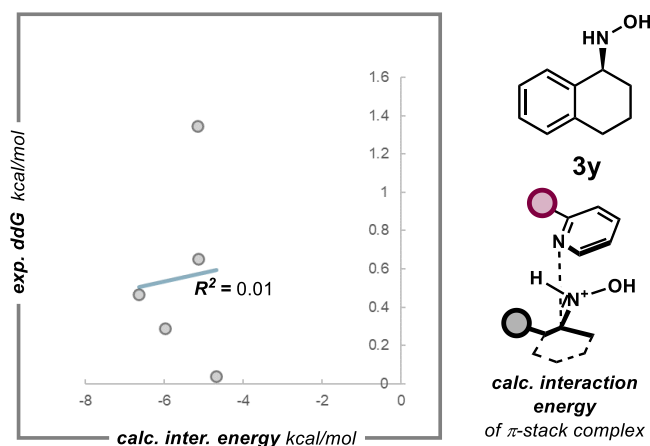


Figure S3.86. Linear correlation between calculated non-covalent interaction energy (kcal/mol) of protonated (*E*)-oxime **2y** and pyridine probes corresponding to **1a-e** to the experimental enantioselectivity of the corresponding host-mediated reduction. $R^2 = 0.01$.

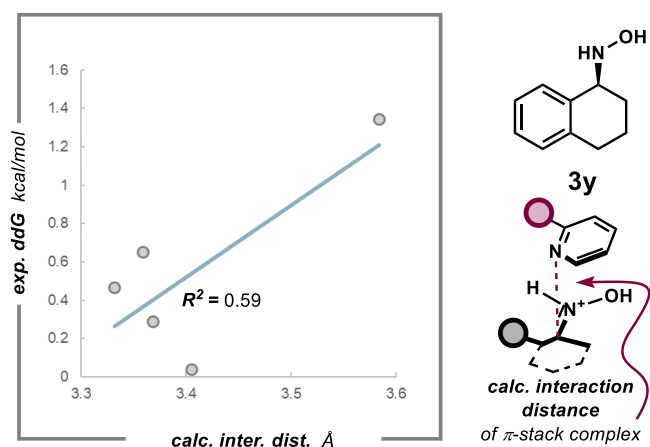


Figure S3.87. Linear correlation between calculated non-covalent interaction distance (Å) of protonated (*E*)-oxime **2y** and pyridine probes corresponding to **1a-e** to the experimental enantioselectivity of the corresponding host-mediated reduction. $R^2 = 0.59$.

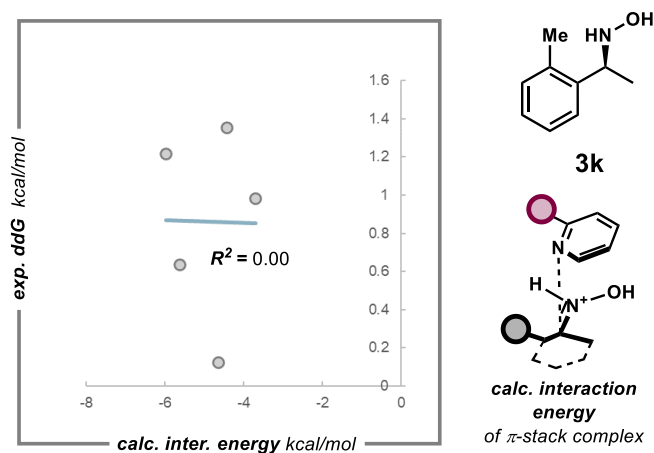


Figure S3.88. Linear correlation between calculated non-covalent interaction energy (kcal/mol) of protonated (*E*)-oxime **2k** and pyridine probes corresponding to **1a-e** to the experimental enantioselectivity of the corresponding host-mediated reduction. $R^2 = 0.00$.

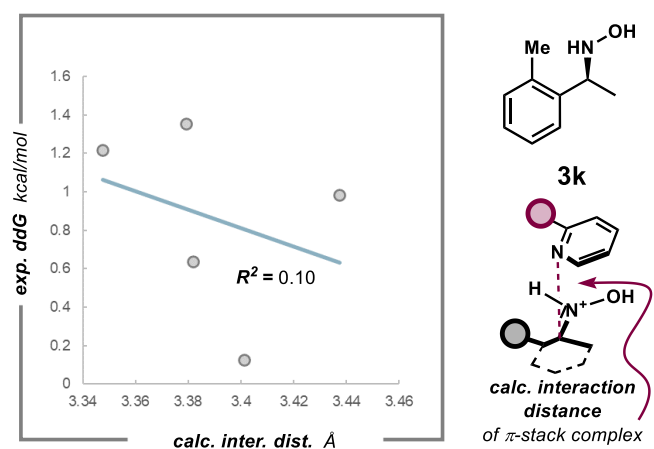


Figure S3.89. Linear correlation between calculated non-covalent interaction distance (Å) of protonated (*E*)-oxime **2k** and pyridine probes corresponding to **1a-e** to the experimental enantioselectivity of the corresponding host-mediated reduction. $R^2 = 0.10$.

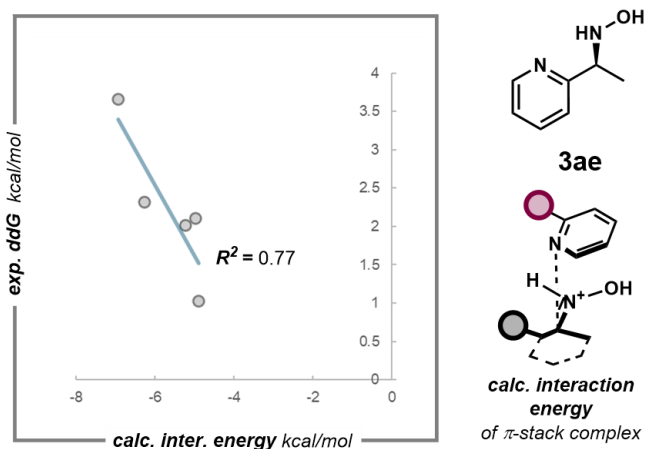


Figure S3.90. Linear correlation between calculated non-covalent interaction energy (kcal/mol) of protonated (*E*)-oxime **2ae** and pyridine probes corresponding to **1a-e** to the experimental enantioselectivity of the corresponding host-mediated reduction. $R^2 = 0.77$.

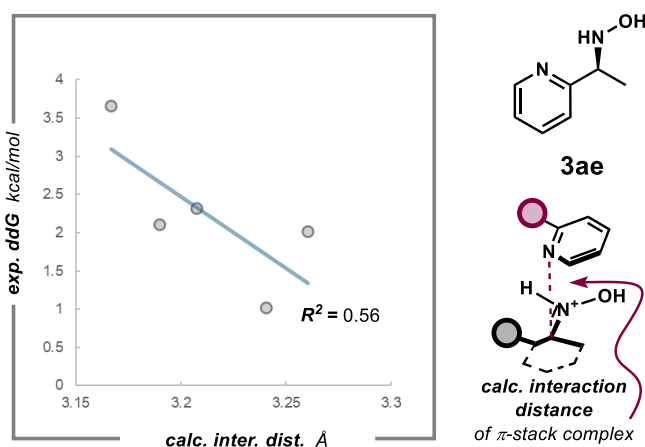


Figure S3.91. Linear correlation between calculated non-covalent interaction distance (Å) of protonated (*E*)-oxime **2ae** and pyridine probes corresponding to **1a-e** to the experimental enantioselectivity of the corresponding host-mediated reduction. $R^2 = 0.56$.

Analysis of correlations between pyridine borane features and enantioselectivity

The non-covalent interaction calculations may not provide a complete picture of the stereoelectronic features at play in the host-mediated enantiodetermining reduction step. Additional evidence for the complex array of stereoelectronic interactions at this step across each oxime substrate could be further gleaned by separate linear regression analyses of calculated pyridine borane features to the experimental enantioselectivities (*kcal/mol*) measured for the subset of oximes selected. The features of the pyridine borane molecules were computed using the general molecular feature calculation workflow. The *ground state* conformer was extracted and features of this molecule were considered in the regression analyses. After screening correlations, two features emerged as the most relevant: *calculated electrophilicity* (a function of the calculated HOMO and LUMO energies), and *6.0Å buried volume at the N-atom*. Again, no universal trend emerges across all the oximes considered. For reference, an exhaustive set of these correlations are included below.

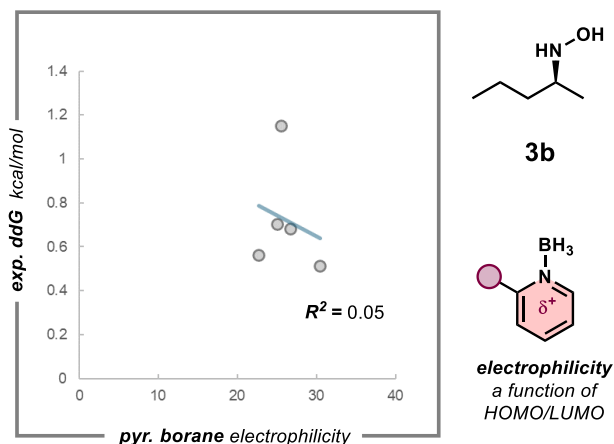


Figure S3.92. Linear correlation between the *calculated electrophilicity* of pyridine boranes **1a-e** to the experimental enantioselectivity of host-mediated reduction of oxime **2b**. $R^2 = 0.05$.

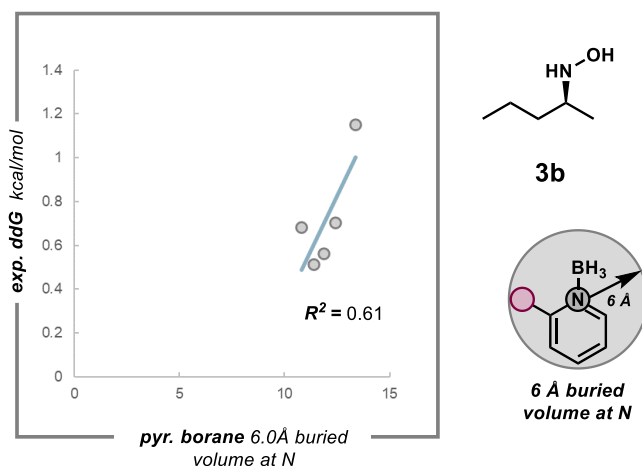


Figure S3.93. Linear correlation between the $6.0\text{\AA}$ buried volume at *N* of pyridine boranes **1a-e** to the experimental enantioselectivity of host-mediated reduction of oxime **2b**. $R^2 = 0.61$.

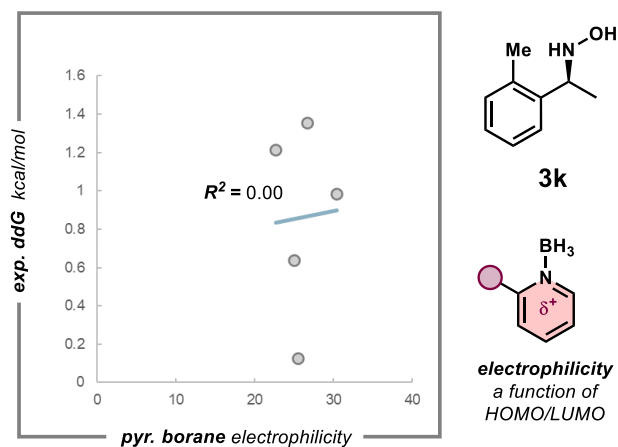


Figure S3.94. Linear correlation between the *calculated electrophilicity* of pyridine boranes **1a-e** to the experimental enantioselectivity of host-mediated reduction of oxime **2k**. $R^2 = 0.00$.

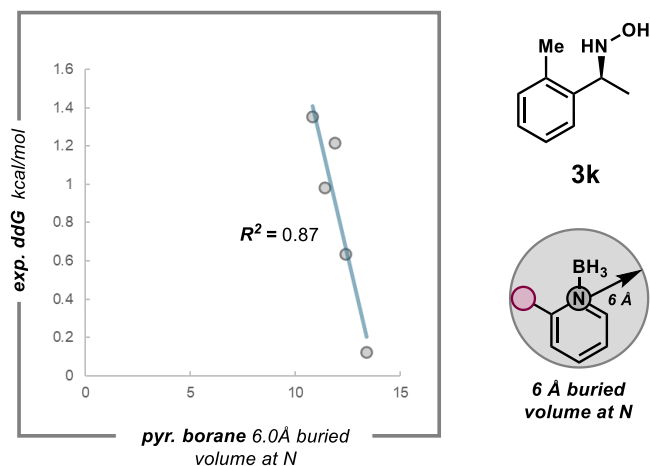


Figure S3.95. Linear correlation between the $6.0\text{\AA}$ buried volume at *N* of pyridine boranes **1a-e** to the experimental enantioselectivity of host-mediated reduction of oxime **2k**. $R^2 = 0.87$.

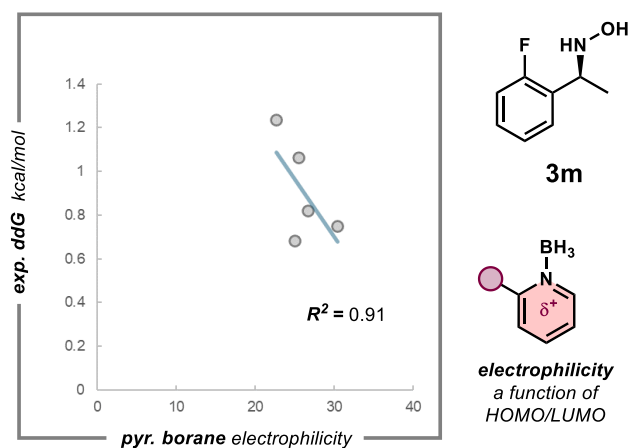


Figure S3.96. Linear correlation between the *calculated electrophilicity* of pyridine boranes **1a-e** to the experimental enantioselectivity of host-mediated reduction of oxime **2m**. $R^2 = 0.91$.

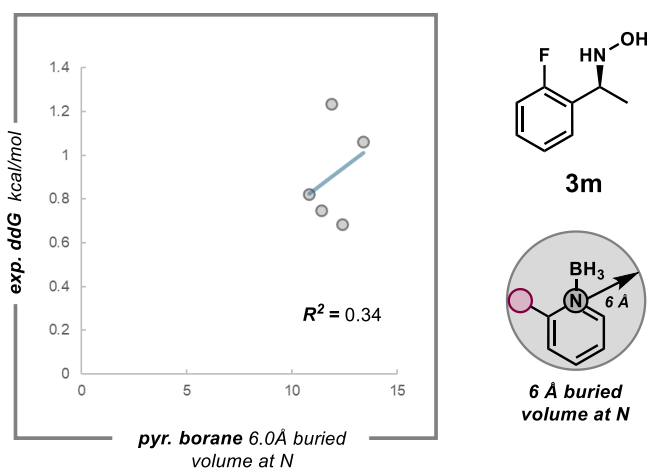


Figure S3.97. Linear correlation between the *6.0 Å buried volume at N* of pyridine boranes **1a-e** to the experimental enantioselectivity of host-mediated reduction of oxime **2m**. $R^2 = 0.34$.

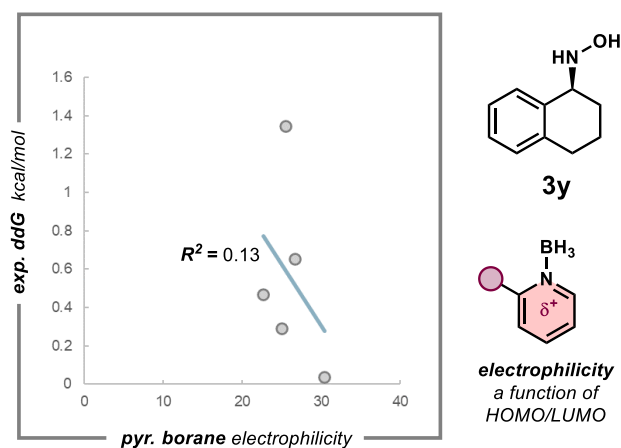


Figure S3.98. Linear correlation between the *calculated electrophilicity* of pyridine boranes **1a-e** to the experimental enantioselectivity of host-mediated reduction of oxime **2y**. $R^2 = 0.13$.

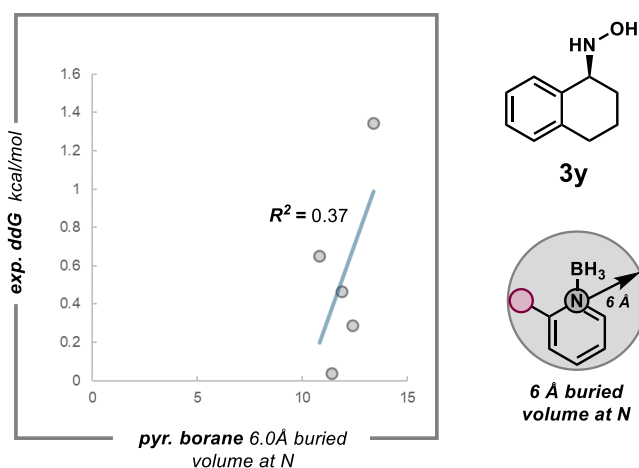


Figure S3.99. Linear correlation between the *6.0 Å buried volume at N* of pyridine boranes **1a-e** to the experimental enantioselectivity of host-mediated reduction of oxime **2y**. $R^2 = 0.37$.

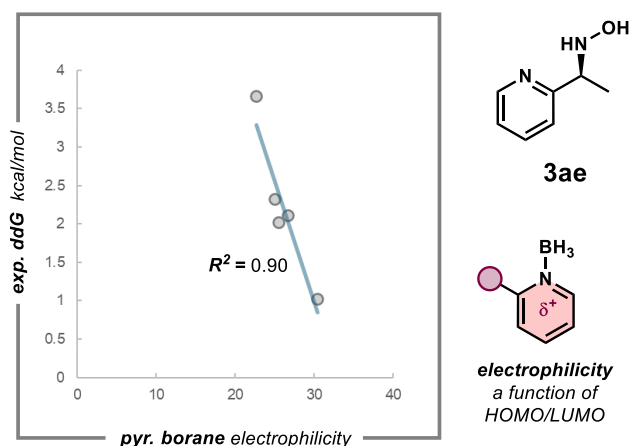


Figure S3.100. Linear correlation between the *calculated electrophilicity* of pyridine boranes **1a-e** to the experimental enantioselectivity of host-mediated reduction of oxime **2ae**. $R^2 = 0.90$.

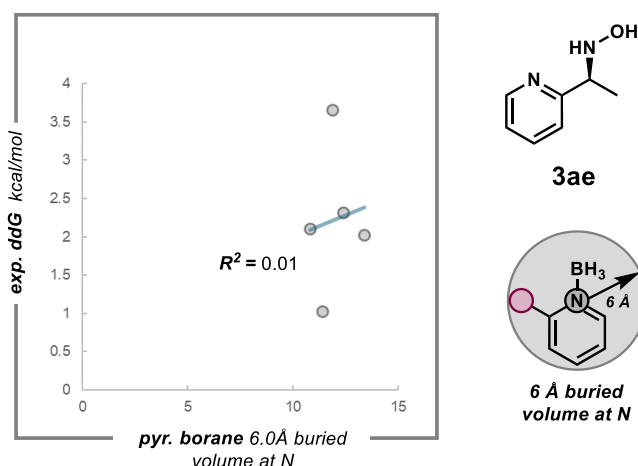


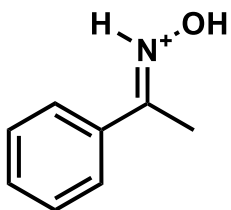
Figure S3.101. Linear correlation between the *6.0 Å buried volume at N* of pyridine boranes **1a-e** to the experimental enantioselectivity of host-mediated reduction of oxime **2ae**. $R^2 = 0.01$.

3.7.8 XYZ Coordinates for Non-Covalent Interaction Calculations

The non-covalent interaction workflow relies on a preoptimized structure for both the substrate and the probe molecule considered. The xyz coordinates selected in our report correspond to the *ground state* conformer of the oxime and analogous pyridine molecules generated during the molecular descriptor calculation workflow. For the calculations reported herein, the xyz coordinate files are included for reference.

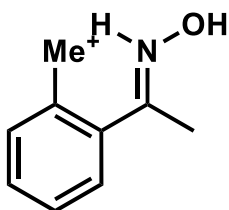
For the *protonated, (E)-oxime* substrates

Protonated, (E)-oxime 2a



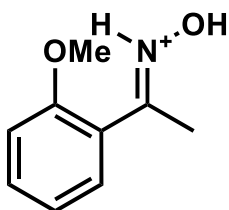
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N	1.9714478316	-0.7080702523	0.2403598799
C	1.1985065916	0.2762088908	-0.0869482163
C	-0.2431080720	0.0889346771	-0.0409652815
C	-0.8247208588	-1.1636452345	-0.2743789434
C	-2.1970380383	-1.3118997920	-0.2302013548
C	-3.0087954350	-0.2254178074	0.0616946791
C	-2.4421624786	1.0184909735	0.2954006115
C	-1.0718616302	1.1818364132	0.2345416014
C	1.8042455285	1.5568955675	-0.4873918826
H	2.7557164578	1.3769651436	-0.9853862081
H	2.0299548369	2.1438277832	0.4042813116
H	1.1436708847	2.1329633701	-1.1255874849
H	-0.2194885498	-2.0141723791	-0.5449878746
H	-2.6399186608	-2.2759681385	-0.4252899116
H	-4.0800062265	-0.3471514873	0.1006785202
H	-3.0732965550	1.8634416834	0.5216851855
H	-0.6438565252	2.1502961702	0.4341970286
H	1.6013318711	-1.5941713844	0.5807856854
H	3.7587184839	-1.4480853919	0.2537712204

Protonated, (E)-oxime 2k



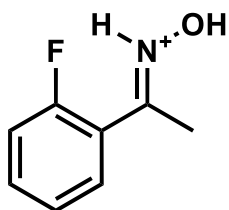
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N	-1.9938688709	-0.4229147659	0.4380031761
C	-1.2073502709	0.4446992099	-0.1103067898
C	0.2354032192	0.2686271726	-0.0355356367
C	0.8732672657	-0.9810686343	-0.1443610178
C	2.2586839160	-1.0217907639	-0.0359538309
C	3.0069019952	0.1196615078	0.1849148464
C	2.3759662047	1.3516041162	0.2777731054
C	1.0055663265	1.4248541977	0.1530081583
C	-1.8097327915	1.6136914759	-0.7755245763
C	0.1420972213	-2.2574400691	-0.4318035993
H	-2.1542454926	2.3261059101	-0.0245553302
H	-2.7003191147	1.3010230208	-1.3201870719
H	-1.1126464182	2.1053512657	-1.4437311559
H	-0.7395024788	-2.0956373677	-1.0444984454
H	0.8012369739	-2.9367836765	-0.9671448757
H	-0.1365195380	-2.7617826480	0.4929545140
H	2.7611328486	-1.9728410337	-0.1283687349
H	4.0800754722	0.0516308729	0.2734295763
H	2.9533160849	2.2475835693	0.4414451220
H	0.5176857275	2.3815166072	0.2422498383
H	-1.6375821791	-1.2197731769	0.9621880994
H	-3.7985614612	-1.0673996457	0.6992555453

Protonated, (E)-oxime 2l



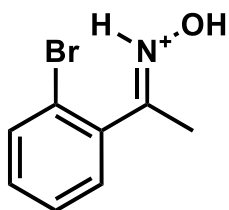
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N	2.0328452372	-0.4254624198	0.1189322217
C	1.3425142218	0.6602521000	-0.0352267395
C	-0.1055416462	0.6160538419	-0.0011640169
C	-0.8575335393	-0.5893807851	-0.0037519396
C	-2.2476809099	-0.5302109145	0.0164748580
C	-2.9074579627	0.6831607200	0.0524430547
C	-2.1877684780	1.8689304665	0.0680726747
C	-0.8122329241	1.8291667332	0.0376832840
C	2.0702482841	1.9322139791	-0.2408451273
O	-0.1770725645	-1.7618700656	-0.0378948685
C	-0.8856008639	-2.9921655416	-0.1140908735
H	2.0196625495	2.5389201726	0.6620854799
H	1.6360668632	2.5029871892	-1.0562865252
H	3.1177245956	1.7323072993	-0.4503931596
H	-1.5087554094	-3.0332179381	-1.0084507385
H	-1.4962033469	-3.1513815684	0.7761954994
H	-0.1206554401	-3.7627170009	-0.1713988841
H	-2.8279315433	-1.4373870319	0.0093516631
H	-3.9856432297	0.7001545066	0.0713516111
H	-2.7018911948	2.8153315769	0.1036718448
H	-0.2691303221	2.7576913938	0.0604744516
H	1.5643650485	-1.3182518314	0.2898200489
H	3.7362418755	-1.3099487860	-0.0492033097

Protonated, (E)-oxime 2m



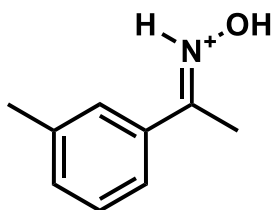
O	-3.3629054158	-0.2965850083	-0.2606409681
N	-2.0131913539	-0.4595161113	-0.2773815514
C	-1.2254350712	0.5103765365	0.0583303240
C	0.2198585974	0.3410080761	-0.0022855218
C	0.8599706886	-0.9017666587	0.0886676686
C	2.2299674899	-1.0407894113	0.0575372345
C	3.0169560837	0.0906305961	-0.0915144339
C	2.4204437413	1.3383724723	-0.1969132868
C	1.0464706817	1.4645138276	-0.1430885551
C	-1.8199331705	1.7870937978	0.4895578164
F	0.1062521970	-2.0230424554	0.2430039371
H	-2.8021142796	1.6098658942	0.9239403391
H	-1.1831425594	2.3103675386	1.1941724991
H	-1.9747558376	2.4264378903	-0.3807280881
H	2.6631106908	-2.0234783158	0.1479525131
H	4.0897604340	-0.0068489126	-0.1238463358
H	3.0326807232	2.2171098439	-0.3172834386
H	0.6029763181	2.4409979048	-0.2388616595
H	-1.6756788717	-1.3597074017	-0.6152951164
H	-3.8142566752	-1.1624162213	-0.2802430653

Protonated, (E)-oxime 2n



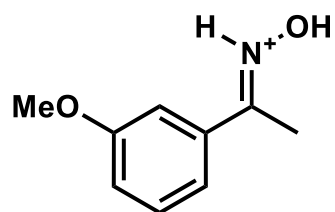
O	-3.7203051274	-0.6849240350	0.4211266578
N	-2.6154091929	0.0871863626	0.5573686215
C	-1.6118656551	-0.0652594374	-0.2387698813
C	-0.4863982750	0.8652476995	-0.1115453504
C	0.8456753412	0.4490040492	-0.0258606639
C	1.8747246394	1.3721164816	0.0423050379
C	1.5927408553	2.7279350313	0.0140771435
C	0.2785675694	3.1610000271	-0.0608545522
C	-0.7494400319	2.2395571011	-0.1149646732
C	-1.6862435336	-1.0919913875	-1.2863569724
Br	1.3032598289	-1.4237066980	0.1149522266
H	-1.8035658036	-2.0791174354	-0.8366407803
H	-0.8220259860	-1.0845741579	-1.9399416748
H	-2.5948924560	-0.9281319889	-1.8688517646
H	2.8947048411	1.0300988072	0.1194646102
H	2.4024722976	3.4380212746	0.0564510994
H	0.0570318074	4.2154436127	-0.0768950429
H	-1.7668392242	2.5840245258	-0.2075891213
H	-2.6224073333	0.7945346679	1.2936529615
H	-4.3500321244	-0.5295890290	1.1520145416

Protonated, (E)-oxime 2o



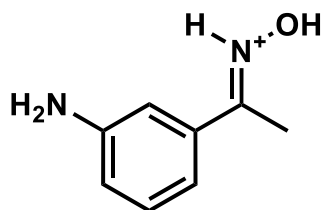
O	-3.7176763600	-0.1216986404	0.3316618935
N	-2.4055343617	-0.4930268785	0.3074480439
C	-1.4853461194	0.3147968836	-0.1110107600
C	-0.0992850279	-0.1216631871	-0.0886789944
C	0.9164153805	0.8270756328	0.0684814717
C	2.2488595213	0.4495977661	0.1090202793
C	2.5675865261	-0.8991470018	-0.0328808574
C	1.5734378384	-1.8471919300	-0.2082441323
C	0.2441953946	-1.4715922649	-0.2286137990
C	-1.8731059052	1.6534880782	-0.5867058786
C	3.3288460795	1.4631788289	0.3119821691
H	-1.9286715163	2.3357272895	0.2627676610
H	-1.1596629446	2.0471439324	-1.3020550944
H	-2.8706588653	1.6186584782	-1.0212553593
H	0.6654207247	1.8678569768	0.1942966615
H	3.7320063559	1.3780398008	1.3205169063
H	2.9539394043	2.4735652943	0.1773847931
H	4.1477167329	1.2947616842	-0.3838587752
H	3.6030306638	-1.2036497376	-0.0123591721
H	1.8402609319	-2.8851749078	-0.3316021897
H	-0.5069660488	-2.2231787140	-0.4103089096
H	-2.1817603386	-1.4050906947	0.7019447142
H	-4.2929610798	-0.9071352763	0.4032145064

Protonated, (E)-oxime 2p



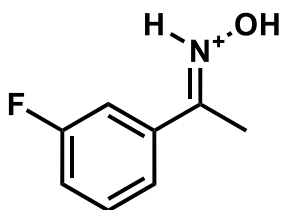
O	-3.6976598712	-1.3633321201	-0.2349916321
N	-2.3759662516	-1.0366938954	-0.2754614643
C	-1.9600123634	0.1266785138	0.1054789758
C	-0.5404674903	0.4344269951	0.0155115651
C	0.4224760113	-0.5692442233	0.1196662897
C	1.7797215170	-0.2638847719	0.0359661746
C	2.1738765739	1.0569892378	-0.1727082763
C	1.2137517533	2.0503053250	-0.2816846221
C	-0.1315026226	1.7587263384	-0.1793366296
C	-2.9377879529	1.1074628727	0.6042641109
O	2.6205778934	-1.3196786244	0.1690381243
C	4.0162106264	-1.0985417853	0.0994053569
H	-2.4806408461	1.8235802768	1.2776588617
H	-3.7620119577	0.5925047123	1.0949328354
H	-3.3693300489	1.6476456125	-0.2396679507
H	0.1708982198	-1.5968625487	0.3253058370
H	4.4706764425	-2.0775308978	0.2329707610
H	4.3513492415	-0.4299114202	0.8961318550
H	4.3046522476	-0.6926462181	-0.8733807300
H	3.2165994648	1.3184764886	-0.2441679864
H	1.5299330552	3.0686617994	-0.4432950323
H	-0.8572892630	2.5467982594	-0.2829796906
H	-1.7435018286	-1.7275565097	-0.6764525827
H	-3.8147454502	-2.3285337388	-0.3219871089

Protonated, (E)-oxime 2q



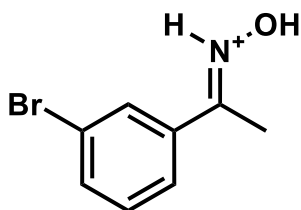
O	3.7295370857	0.1444511416	-0.3222527802
N	2.4129837173	0.5066084593	-0.2921697803
C	1.4938650671	-0.3137069990	0.1066978487
C	0.1084708626	0.1176371828	0.0859989492
C	-0.8987938756	-0.8356169718	-0.0609564944
C	-2.2451054291	-0.4610068950	-0.1027505958
C	-2.5615100331	0.8996154017	0.0356626490
C	-1.5657477010	1.8402396430	0.2029057096
C	-0.2326728861	1.4712035734	0.2195279958
C	1.8882763180	-1.6591821402	0.5600108502
N	-3.2143878620	-1.3846797662	-0.3144577675
H	1.1874967521	-2.0569969869	1.2854761884
H	1.9216091469	-2.3315227746	-0.2981980210
H	2.8941742442	-1.6327167796	0.9747543376
H	-0.6491812781	-1.8761630173	-0.1869877050
H	-4.1759499317	-1.1204080717	-0.2021120498
H	-2.9870626431	-2.3609408349	-0.2616358355
H	-3.5965778746	1.2048904784	0.0149458321
H	-1.8338536654	2.8787215372	0.3228076695
H	0.5157796844	2.2245967951	0.3996665665
H	2.1841930845	1.4208291746	-0.6779595555
H	4.2987030752	0.9370457604	-0.3031711699

Protonated, (E)-oxime 2r



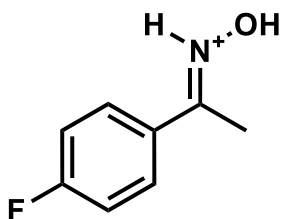
O	3.7745097687	-0.1195901483	-0.3324506301
N	2.4678215591	-0.4901914053	-0.3292541803
C	1.5524480382	0.3066624997	0.1134251071
C	0.1611159603	-0.1327617930	0.0900640581
C	-0.8497387866	0.8173395056	-0.0764027871
C	-2.1607849721	0.3896484674	-0.1065900568
C	-2.5171668926	-0.9389391707	0.0422851331
C	-1.5088905268	-1.8717628750	0.2269779405
C	-0.1827616919	-1.4803027907	0.2440405253
C	1.9414082649	1.6309599895	0.6209339958
F	-3.1368064731	1.3157575700	-0.2868623660
H	2.9073369835	1.5647284313	1.1202611657
H	2.0811673011	2.3140417600	-0.2187155478
H	1.1959818608	2.0450804687	1.2899579620
H	-0.6343862703	1.8639771826	-0.2119911162
H	-3.5565250765	-1.2220513010	0.0188235556
H	-1.7667573664	-2.9099854537	0.3577613359
H	0.5722155084	-2.2265265645	0.4299789736
H	2.2432089013	-1.3988147579	-0.7341050739
H	4.3493958472	-0.8777652932	-0.5526240498

Protonated, (E)-oxime 2s



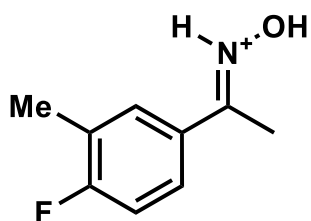
O	4.8058455642	0.6266639424	-0.4253642365
N	3.6382860623	-0.0648590428	-0.4109640183
C	2.5793305915	0.4358291966	0.1329828723
C	1.3437175183	-0.3429940658	0.1206397768
C	0.1195365758	0.3265054544	0.0459706374
C	-1.0535508378	-0.4046903308	0.0277269512
C	-1.0438854772	-1.7890312477	0.1022896994
C	0.1719208387	-2.4480709595	0.1936643976
C	1.3590170318	-1.7392786528	0.1961122938
C	2.6517624576	1.7707952735	0.7441096642
Br	-2.7458501701	0.5318945486	-0.0985561439
H	3.6210952740	1.9026202566	1.2238440816
H	2.5974401630	2.5310527701	-0.0370334632
H	1.8508010666	1.9378705581	1.4548018858
H	0.0783549445	1.4008444190	-0.0278689460
H	-1.9705610635	-2.3397228098	0.0947341447
H	0.1836208762	-3.5235609753	0.2633861363
H	2.2847263192	-2.2794555271	0.3089368948
H	3.6277052841	-0.9680119772	-0.8849619189
H	5.5379039123	0.0674399169	-0.7511335537

Protonated, (E)-oxime 2t



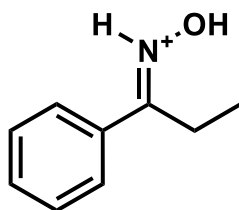
O	3.8089776286	-0.6524653404	-0.2504809451
N	2.4523337082	-0.7446446957	-0.2577397269
C	1.7150351425	0.2600212910	0.0850604261
C	0.2644935779	0.1207746485	0.0487949986
C	-0.5249355621	1.2415105120	-0.2297216290
C	-1.9007920433	1.1365843283	-0.2792599144
C	-2.4822240042	-0.0937439334	-0.0266098684
C	-1.7319681886	-1.2190016004	0.2696781044
C	-0.3559234381	-1.1093558542	0.2988552695
C	2.3626333418	1.5159505178	0.4939548220
F	-3.8319778860	-0.2004636778	-0.0633060209
H	1.7184980797	2.1167775323	1.1254162641
H	2.6241195995	2.0943407746	-0.3934965425
H	3.3009873671	1.2990065128	1.0022326144
H	-0.0661124988	2.1931301664	-0.4397498322
H	-2.5237913778	1.9862862782	-0.5046366616
H	-2.2290698434	-2.1530286934	0.4736605901
H	0.2189359525	-1.9795856139	0.5706377641
H	2.0517644419	-1.6181994393	-0.5974436398
H	4.2154669992	-1.5334304548	-0.3595035858

Protonated, (E)-oxime 2u



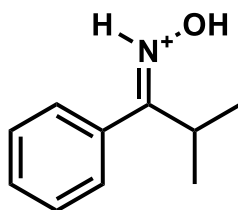
O	-4.1088486323	-0.3821241851	-0.3312746619
N	-2.7701230907	-0.6248816560	-0.3201701773
C	-1.9341846543	0.2614359194	0.1124462846
C	-0.5089889539	-0.0382512637	0.0872228520
C	0.4056409695	1.0069295894	-0.0749837923
C	1.7712991777	0.7777897866	-0.1175900010
C	2.1957152646	-0.5405714006	0.0310723851
C	1.3217686310	-1.5963643227	0.2132152157
C	-0.0362487381	-1.3473096335	0.2326389361
C	-2.4488729879	1.5477574057	0.6078695234
C	2.7574085375	1.8803639450	-0.3167670565
F	3.5264722093	-0.8035133010	0.0057009021
H	-1.7650728921	2.0129475145	1.3085762670
H	-3.4259666685	1.4031158694	1.0662820919
H	-2.6030135989	2.2241776568	-0.2342740076
H	0.0536773073	2.0174861266	-0.2026518909
H	2.2751151357	2.8508178051	-0.2644209512
H	3.5414707935	1.8274400835	0.4367122010
H	3.2390177444	1.7777141519	-1.2886521588
H	1.7154102238	-2.5917798037	0.3381601970
H	-0.7058977496	-2.1708327390	0.4171306119
H	-2.4592723830	-1.5081437835	-0.7223039387
H	-4.6071482201	-1.2064464161	-0.4910333734

Protonated, (E)-oxime 2v



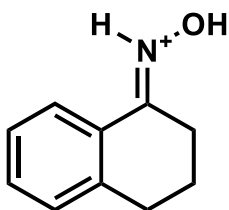
O	-2.9525127669	-1.2497421754	0.1495660408
N	-1.5967421116	-1.1618412915	0.2149836936
C	-0.9666558214	-0.1097506927	-0.1942460303
C	0.4817320067	-0.0674515020	-0.0918171275
C	1.2483054601	-1.2402511528	-0.1443927468
C	2.6241525103	-1.1781193249	-0.0499003321
C	3.2598604648	0.0444847660	0.1132858685
C	2.5116761768	1.2106884851	0.1652404488
C	1.1358099532	1.1614171515	0.0524271379
C	-1.7563125671	1.0243484186	-0.7379105641
C	-2.4176185316	1.8157376474	0.4036037844
H	-3.2412160854	-2.1784637957	0.2398011767
H	-1.1110974560	-1.9372845590	0.6651932191
H	-2.5518029624	0.6198271621	-1.3676966546
H	-1.1267402412	1.6792042221	-1.3355079001
H	-2.9651460737	2.6537746630	-0.0158878966
H	-1.6739362066	2.2007613592	1.0958159041
H	-3.1170115390	1.1908981549	0.9508604369
H	0.7848849802	-2.1988899936	-0.3145544820
H	3.2078611526	-2.0834700689	-0.1057227762
H	4.3348225933	0.0879144240	0.1920806924
H	3.0051006266	2.1618402209	0.2893901149
H	0.5697631332	2.0763057980	0.1087051225

Protonated, (E)-oxime 2w



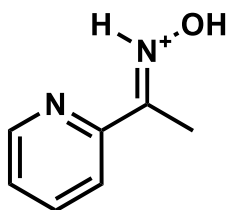
O	-2.5763512063	1.5174197420	-0.5038908268
N	-1.2442858305	1.2597430917	-0.4777647663
C	-0.7333665426	0.1445308113	-0.0783949797
C	0.7217535899	0.0555961262	-0.0392825519
C	1.4925731878	1.1506863671	0.3703339025
C	2.8698914954	1.0548930202	0.4126235533
C	3.5002068585	-0.1196929140	0.0297816260
C	2.7452263895	-1.2064798481	-0.3846567356
C	1.3661107520	-1.1285780245	-0.4096088341
C	-1.5801603155	-1.0105140359	0.3537632893
C	-2.5208378312	-1.4653183361	-0.7689760775
C	-2.3737675070	-0.6162545450	1.6091477001
H	-2.7565149756	2.3417401168	-0.9964685775
H	-0.6310852688	2.0285389128	-0.7541951274
H	-0.9210197759	-1.8383790771	0.6219284392
H	-3.0345054061	-2.3687351177	-0.4539968593
H	-3.2687274926	-0.7095391456	-0.9856743100
H	-1.9633235838	-1.6877091001	-1.6751732623
H	-3.0874816088	0.1719534598	1.3913217922
H	-2.9215242210	-1.4832860963	1.9655138188
H	-1.7041104731	-0.2874534906	2.3996519618
H	1.0207799078	2.0575057919	0.7152888706
H	3.4566846947	1.8960209963	0.7465655217
H	4.5762280026	-0.1898516435	0.0592823157
H	3.2349229184	-2.1190233883	-0.6857851085
H	0.7930962514	-1.9734252285	-0.7557940540

Protonated, (E)-oxime 2y



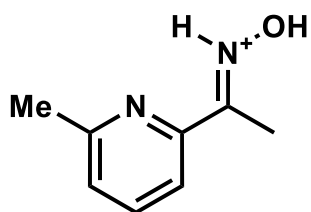
O	-3.2797391727	1.0965287936	0.1986266358
N	-1.9237907207	1.2449930384	0.1368497091
C	-1.1583164975	0.2108552220	-0.0217034959
C	0.2788665938	0.3490980694	-0.0346564441
C	0.9083429357	1.5881425403	-0.2368232917
C	2.2816726688	1.6885144267	-0.2036104598
C	3.0542028900	0.5593624149	0.0406173271
C	2.4468375456	-0.6700235194	0.2221333478
C	1.0661498481	-0.7993545152	0.1765699695
C	-1.8046463523	-1.1162830375	-0.1395204479
C	-0.8271912888	-2.2136067688	-0.5377552409
C	0.4082502138	-2.1306657847	0.3533358559
H	-3.7218127701	1.9549589579	0.0545564460
H	-1.5575648759	2.1786547546	0.3093543919
H	-2.6382963774	-1.0453866258	-0.8429612335
H	-2.2554515427	-1.3466393485	0.8327439359
H	-1.3025688954	-3.1877509992	-0.4367971821
H	-0.5290334516	-2.0896349886	-1.5801917830
H	0.1172287335	-2.2548984548	1.4006972785
H	1.1128956908	-2.9265329910	0.1139428986
H	3.0522884696	-1.5466754274	0.3944619476
H	4.1296092054	0.6387117786	0.0738709067
H	2.7588508472	2.6414906531	-0.3682461551
H	0.3344005253	2.4726978571	-0.4609757658

Protonated, (E)-oxime 2ae



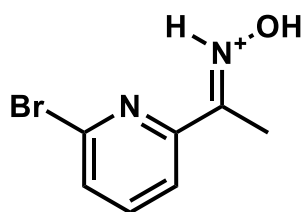
C	1.8174119883	1.7109491807	0.0028751654
C	1.1901072665	0.3808306982	0.0005222729
C	-0.2620874609	0.1851470694	-0.0001580779
N	-0.6538874755	-1.0975299186	0.0012708261
C	-1.9402073310	-1.3685637049	0.0016520661
C	-2.9230119561	-0.3804346428	0.0003010277
C	-2.5235750643	0.9452773480	-0.0017083404
C	-1.1669114332	1.2429704390	-0.0018341641
N	1.8897411811	-0.7009308231	-0.0014043240
O	3.2405553547	-0.7096148678	-0.0012410738
H	1.4991372165	2.2747938867	0.8779971318
H	1.5054736671	2.2749077102	-0.8745258375
H	2.8999471441	1.6204905324	0.0064252264
H	-2.2018716629	-2.4172286297	0.0026657048
H	-3.9661104537	-0.6500698136	0.0005060865
H	-3.2545075038	1.7385715933	-0.0031528425
H	-0.8335949404	2.2666975547	-0.0033623652
H	1.3764504860	-1.5915700752	-0.0032193174
H	3.5763315905	-1.6273997887	-0.0014399933

Protonated, (E)-oxime 2ab



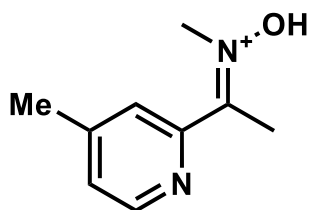
C	2.4134762607	1.5104330501	0.0025047567
C	1.5137028460	0.3466831848	-0.0003843176
C	0.0545040411	0.4645996339	-0.0009286725
N	-0.5966788216	-0.7090326179	-0.0002535148
C	-1.9149611143	-0.7253293776	0.0005015899
C	-2.6595299551	0.4642998443	0.0006056329
C	-1.9961855151	1.6744144446	-0.0006483096
C	-0.6049909397	1.6873741811	-0.0014924043
N	1.9626070233	-0.8610038963	-0.0017031985
O	3.2794469001	-1.1664802978	0.0006576274
C	-2.5915178171	-2.0534497174	0.0011600454
H	2.2252881109	2.1328977424	-0.8704124464
H	2.2291263829	2.1245793720	0.8822147929
H	3.4508981212	1.1881941540	-0.0009864542
H	-3.2172308891	-2.1526916823	-0.8835071219
H	-3.2367474655	-2.1428424535	0.8726123270
H	-1.8603393977	-2.8544397206	0.0132458607
H	-3.7367854439	0.4202587882	0.0017718593
H	-2.5477728579	2.6016096279	-0.0009514484
H	-0.0668686904	2.6193914400	-0.0025619175
H	1.2621190458	-1.6139256658	-0.0026306808
H	3.4032020308	-2.1358571633	-0.0077519089

Protonated, (E)-oxime 2ac



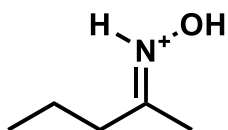
C	3.9024358876	-0.6260215438	0.0081978291
C	2.5966300882	0.0472747976	0.0011614464
C	1.3310944523	-0.6938944587	-0.0000997517
N	0.2291316533	0.0700530353	0.0002218338
C	-0.9413846413	-0.5098054712	-0.0007332324
C	-1.1283747526	-1.8894991180	-0.0026442575
C	0.0074204632	-2.6806624136	-0.0032603954
C	1.2630568220	-2.0829193144	-0.0017590354
N	2.4947192295	1.3314021678	-0.0041935822
O	3.5642884520	2.1494251538	-0.0023741498
Br	-2.4685917044	0.6721216271	0.0010876196
H	4.0002046442	-1.2675799088	-0.8658590089
H	3.9922383868	-1.2639211275	0.8858247667
H	4.7065121167	0.1043750031	0.0102392752
H	-2.1192880967	-2.3118112425	-0.0033562373
H	-0.0866188277	-3.7546845430	-0.0049145129
H	2.1524919497	-2.6891208885	-0.0021555849
H	1.5533732131	1.7405917314	-0.0070716041
H	3.2867828462	3.0869958739	-0.0163283108

Protonated, (E)-oxime 2ad



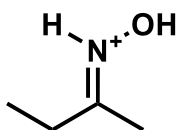
C	-1.8492403298	1.8672621797	-0.0030637675
C	-1.4671422205	0.4469721889	-0.0001992750
C	-0.0739859440	-0.0048801554	-0.0001558835
N	0.0807053882	-1.3389703913	-0.0014980877
C	1.3026998982	-1.8246867912	-0.0017727752
C	2.4409790306	-1.0242608711	-0.0001414726
C	2.2989099112	0.3578710077	0.0017506410
C	1.0010729533	0.8736270517	0.0014654553
N	-2.3468024963	-0.4942429213	0.0017157903
O	-3.6793034189	-0.2655265556	0.0012130839
C	3.4726735694	1.2754415214	0.0009104576
H	-2.9306507263	1.9695692509	-0.0055719055
H	-1.4372685843	2.3647739029	-0.8793921791
H	-1.4411391961	2.3670935848	0.8735611220
H	1.3819725994	-2.9026749652	-0.0028868818
H	3.4190909694	-1.4775990376	-0.0003705575
H	3.4262700110	1.9470008784	0.8559899080
H	4.4055930951	0.7208332393	0.0396661298
H	3.4672170893	1.8880727416	-0.8989683816
H	0.8521389800	1.9405543877	0.0030871366
H	-1.9958261628	-1.4604809316	0.0025721372
H	-4.1695218694	-1.1107494690	0.0044107067

Protonated, (E)-oxime 2b



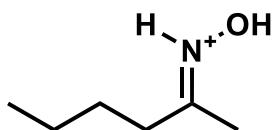
C	0.7564772122	1.4737524151	0.6919245626
C	0.3822397986	0.4187184720	-0.2583523184
N	1.1802971691	-0.5716380349	-0.4505250042
O	2.3489592472	-0.6794030027	0.2468476601
C	-0.9086786563	0.4503038707	-0.9792693251
C	-2.0845744601	0.2731366850	0.0026826436
C	-2.0815678999	-1.1059721516	0.6510807910
H	0.1049808159	2.3366326492	0.6196881348
H	0.7148251124	1.0772217008	1.7079688703
H	1.7950303856	1.7655315635	0.5351979054
H	-1.0126917683	1.4223377489	-1.4630377386
H	-0.9627920844	-0.3284531931	-1.7396763361
H	-3.0115207703	0.4070672954	-0.5544542974
H	-2.0469528539	1.0417193921	0.7736758472
H	-2.9534532922	-1.2158382816	1.2910275269
H	-2.1242314460	-1.8892577006	-0.1018778439
H	-1.1981376755	-1.2551685694	1.2666796640
H	0.9439147959	-1.3478343758	-1.0687347021
H	2.9671596178	-1.2788435968	-0.2118195181

Protonated, (E)-oxime 2c



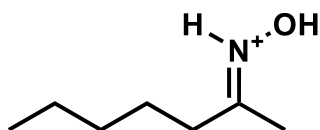
C	-0.8735401647	-1.6300269293	-0.0010209800
C	-0.0210686599	-0.4311392546	-0.0074308102
N	-0.5717164147	0.7308831148	-0.0127903631
O	-1.9308756086	0.8636222087	0.0259670148
C	1.4512087220	-0.5585586665	-0.0053066390
C	2.2404671670	0.7463921024	0.0086945733
H	-1.6224874960	-1.5584431708	-0.7897971769
H	-0.2969232778	-2.5407880638	-0.1119579792
H	-1.4355117521	-1.6681002660	0.9330924511
H	1.7280799516	-1.1511091728	-0.8819719154
H	1.7243587156	-1.1696048750	0.8597714486
H	2.0443260998	1.3424875251	-0.8787648138
H	2.0323239715	1.3304764299	0.9016217731
H	3.3028453041	0.5194303668	0.0143890251
H	-0.0221853060	1.5886034530	0.0189893491
H	-2.1912693030	1.7651308619	-0.2394806098

Protonated, (E)-oxime 2d



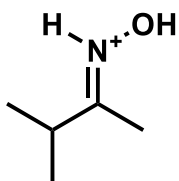
C	-1.2538327529	1.0181861274	-1.2301516097
C	-0.9447827311	0.4882665694	0.1039208742
N	-1.6324948198	-0.4939844876	0.5701767626
O	-2.6135190512	-1.0839456962	-0.1737172395
C	0.1545708167	1.0472456322	0.9207234532
C	1.5172993675	0.8310973995	0.2354811977
C	1.8826105901	-0.6483989882	0.1302480409
C	3.2619219678	-0.8289785424	-0.4937344859
H	-2.3329196533	1.0911998226	-1.3635999760
H	-0.9114911499	0.3111798040	-1.9876912693
H	-0.7822223737	1.9778110505	-1.4053230609
H	0.1814768773	0.6022294256	1.9151279313
H	-0.0054309853	2.1218299344	1.0221709356
H	1.5137948454	1.2751115692	-0.7593834668
H	2.2789245663	1.3441114534	0.8229603268
H	1.8851771378	-1.0999061020	1.1241713452
H	1.1498936875	-1.1755967452	-0.4834136161
H	3.5150631054	-1.8838926063	-0.5678393569
H	4.0251123439	-0.3398688774	0.1078681724
H	3.2934022110	-0.4014512101	-1.4934547111
H	-1.4273001192	-0.9205875954	1.4737333708
H	-3.2393599036	-1.5611903417	0.4029834590

Protonated, (E)-oxime 2e



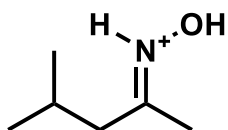
C	-1.8227240162	0.6767857148	-1.3778270356
C	-1.4805152276	0.4301170644	0.0285938146
N	-1.9514854646	-0.6094021103	0.6223467299
O	-2.7273744428	-1.5124773483	-0.0453470223
C	-0.5879609252	1.3421463562	0.7769663556
C	0.8237090187	1.3611937260	0.1605765885
C	1.5218097774	0.0085723003	0.2838901711
C	2.9393954044	0.0574098275	-0.2836154044
C	3.6420800803	-1.2898605717	-0.1587432135
H	-1.2779564007	-0.0262176795	-2.0101501816
H	-2.8785639912	0.4686785977	-1.5489325378
H	-1.5783917939	1.6871202887	-1.6840435579
H	-0.5143461424	1.0590626435	1.8266887604
H	-0.9977867407	2.3514743745	0.7145762926
H	1.4131034033	2.1156012271	0.6819578463
H	0.7730597134	1.6499367844	-0.8886768950
H	0.9611615022	-0.7578096424	-0.2547567707
H	1.5786037732	-0.2847673682	1.3340817172
H	2.9037599880	0.3471427954	-1.3360165507
H	3.5202360986	0.8157983877	0.2460411673
H	3.0995794241	-2.0600708501	-0.7025967361
H	3.7139231346	-1.5914671117	0.8840486404
H	4.6495720228	-1.2351788609	-0.5644783011
H	-1.7077129111	-0.8419106436	1.5852119453
H	-3.2551226768	-2.0408599479	0.5826842496

Protonated, (E)-oxime 2f



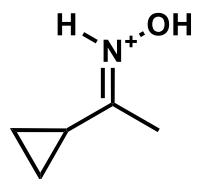
C	0.8228415590	-1.6090248667	-0.4608590129
C	0.2386999596	-0.2814639675	-0.2198089314
N	1.0104173170	0.6824339416	0.1348048830
O	2.3463970281	0.4793804192	0.3224095643
C	-1.2284965597	-0.0544319567	-0.3509931193
C	-1.6440093054	1.4155750782	-0.3455906030
C	-1.9291379167	-0.8167256267	0.7875178850
H	1.2051984795	-2.0137076760	0.4772194082
H	0.1077966126	-2.3012182154	-0.8888918441
H	1.6914486396	-1.5145072661	-1.1128219861
H	-1.5389287469	-0.5090769642	-1.2970527662
H	-1.4785953464	1.8763657845	0.6253664958
H	-1.1306405327	1.9780803027	-1.1210360881
H	-2.7093559040	1.4817052906	-0.5493204253
H	-1.6425689129	-0.4090480341	1.7531136791
H	-3.0044896997	-0.7122292031	0.6799293712
H	-1.6873315588	-1.8744438595	0.7685923246
H	0.6505392218	1.6134432588	0.3430764087
H	2.8188122972	1.3321673769	0.3582985956

Protonated, (E)-oxime 2g



C	-1.1660685454	1.4430000701	-0.7808272084
C	-0.7595354460	0.4296271559	0.2014849065
N	-1.5898445869	-0.4947141152	0.5364624295
O	-2.8227480419	-0.5774637381	-0.0440741131
C	0.5926231080	0.4271845277	0.7951577809
C	1.6697521367	0.0913188216	-0.2657176869
C	3.0515993723	0.2448445498	0.3621597795
C	1.4754092371	-1.3267471197	-0.7954803541
H	-0.4552103887	2.2580772258	-0.8427393858
H	-1.2657557154	0.9777067589	-1.7625514163
H	-2.1582523331	1.8217035193	-0.5360393333
H	0.6745263126	-0.2908306754	1.6111242165
H	0.8045304714	1.4243578588	1.1832696013
H	1.5859941138	0.7955782212	-1.0969884361
H	3.8230523264	0.0226015844	-0.3708357448
H	3.1754628403	-0.4392627003	1.1984388193
H	3.2104932246	1.2589469249	0.7199609885
H	0.5175379712	-1.4392165406	-1.2963525693
H	2.2546432813	-1.5621050133	-1.5161025111
H	1.5435090130	-2.0521298638	0.0118247842
H	-1.3377317269	-1.2436401988	1.1814464649
H	-3.4315440416	-1.0920133571	0.5185010609

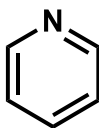
Protonated, (E)-oxime 2h



C	-0.4259295374	-1.4929592659	-0.0357666476
C	-0.2797374951	-0.0291345991	-0.0027586731
N	-1.3556939290	0.6935484941	-0.0005968087
O	-2.5918947479	0.1070694590	0.0346329692
C	0.9979439814	0.6478756059	0.0381507097
C	2.1786017444	0.0895514892	-0.7456952472
C	2.1810363220	-0.0158913481	0.7290479367
H	-0.8027890237	-1.8298163065	0.9314616139
H	-1.1881890038	-1.7716828130	-0.7629221597
H	0.5031087688	-2.0056608261	-0.2505408580
H	0.9484827307	1.7264219194	0.1092702853
H	2.0185106170	-0.7961319693	-1.3384005353
H	2.8165925062	0.8184948512	-1.2190343087
H	2.8229426407	0.6363581896	1.2990649782
H	2.0205043943	-0.9779011780	1.1871562507
H	-1.3362672223	1.7085342149	0.0802096907
H	-3.2554137846	0.6937162539	-0.3748869499

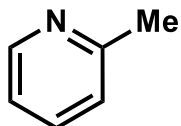
For the pyridine probe analogs to pyridine borane reductants

Pyridine probe corresponding to 1a



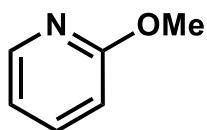
N	1.3748666514	-0.0003236518	0.0000080474
C	0.6905473498	-1.1342172230	0.0000149379
C	-0.6949378688	-1.1918345581	-0.0000330744
C	-1.4020050354	0.0003452543	-0.0000330656
C	-0.6942997109	1.1921647404	0.0000097178
C	0.6910998602	1.1338635108	-0.0000276945
H	1.2883051834	-2.0358573451	0.0000448878
H	-1.2026643411	-2.1429616019	0.0002945401
H	-2.4817879897	0.0007002806	0.0000504610
H	-1.2016555467	2.1435351224	0.0003167161
H	1.2893451935	2.0352473613	0.0000059560

Pyridine probe corresponding to 1c



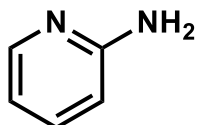
N	-0.2963715434	-1.1582135539	-0.0001982020
C	-0.8991899916	0.0256042312	-0.0002834960
C	-0.1785228275	1.2200062873	-0.0001593031
C	1.2028824737	1.1718709057	0.0000846904
C	1.8276333770	-0.0675309396	0.0001412686
C	1.0273577013	-1.1969724847	0.0000719088
C	-2.3950060916	0.0293149055	0.0001734393
H	-2.7634080289	-0.9910304181	-0.0127674682
H	-2.7684584458	0.5596361640	-0.8732828777
H	-2.7672441433	0.5358545046	0.8882505174
H	1.4590076960	-2.1895851243	0.0002680077
H	2.9022847875	-0.1536255731	0.0000393468
H	1.7853370238	2.0815126741	0.0000371799
H	-0.7020730111	2.1636170740	-0.0001300350

Pyridine probe corresponding to 1e



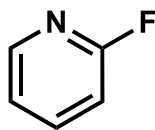
N	0.1247722341	-1.0039678530	0.0002359914
C	0.4401928528	0.2822797927	0.0001557871
C	-0.5170719581	1.3064343877	0.0000402888
C	-1.8466532152	0.9494785347	-0.0001800310
C	-2.1859938779	-0.4014595660	-0.0001603898
C	-1.1643979210	-1.3282076254	0.0001181302
C	2.6959707003	-0.4067823075	-0.0004458483
O	1.7353102815	0.6427829466	0.0003371380
H	3.6632347241	0.0879966499	-0.0007435883
H	2.5794414871	-1.0292187369	0.8874512140
H	2.5785758594	-1.0284724744	-0.8887445422
H	-1.3625596145	-2.3911157451	0.0000774630
H	-3.2155479324	-0.7179907953	-0.0004371861
H	-2.6144385862	1.7079147787	-0.0005909976
H	-0.1878606657	2.3318916624	-0.0000181351

Pyridine probe corresponding to 1d



N	-0.3017330148	-1.1636444092	0.0100945939
C	-0.9016105207	0.0317847631	0.0090667711
C	-0.1689520609	1.2336273433	0.0067936415
C	1.2044466395	1.1692313074	-0.0014080155
C	1.8272223081	-0.0767909111	-0.0064198427
C	1.0224015031	-1.1993775358	-0.0005572446
N	-2.2560385783	0.0318928138	-0.0369836872
H	-2.7163743844	-0.8489879523	0.1100889931
H	-2.7511423523	0.8779430721	0.1793372617
H	1.4507999033	-2.1939745239	0.0001065469
H	2.9012723186	-0.1662766133	-0.0123011478
H	1.7943822855	2.0744350875	-0.0025283540
H	-0.6878410766	2.1793356230	0.0098899301

Pyridine probe corresponding to 1b



N	-0.2474441143	-1.1648931975	-0.0003343332
C	-0.8066991341	0.0198070998	-0.0002698573
C	-0.1404719578	1.2333573614	-0.0002136441
C	1.2437323690	1.1768585641	-0.0001026102
C	1.8675301878	-0.0637367840	0.0003632332
C	1.0795982523	-1.2023024575	0.0000711674
F	-2.1644087660	0.0217515115	0.0003294782
H	1.5073908398	-2.1937725003	-0.0003685630
H	2.9412715822	-0.1452102520	0.0007534629
H	1.8226775485	2.0865884694	0.0000414079
H	-0.6892169599	2.1597823232	-0.0001826852

3.8 References

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Chapter 4

Optimization of Asymmetric Reductions as a Probe to Understand Enantioinduction in Supramolecular Hosts

4.1 Preface

Informed by the findings of the previous chapter, this chapter describes ongoing work investigating specific substrate and host features important for enantioinduction in enantiopure $M_4L_6^{12-}$ supramolecular hosts. Previously studied but poorly selective oximes, as well as other reducible functional groups such as ketones and indoles are examined. Oximes are reduced in higher enantioselectivities than ketones and indoles under previously reported reaction conditions, but modulating the host scaffold through changing the metal center and tuning borane identity can improve enantioselectivity. There is currently no model for enantiodetermining interactions within these $M_4L_6^{12-}$ host systems, which makes rational reaction optimization and host design inaccessible. Reaction optimization and computational modeling of transition states is expected to provide insight into substrate-reductant and host-guest interactions involved in enantioinduction within these hosts. This work is done in collaboration with Cristina Craescu, a fellow graduate student, who has also contributed to the experimental work.

4.2 Introduction to Stereoselective Reductions as a Probe to Understand Enantioinduction in Supramolecular Hosts

The importance and ubiquity of chirality in natural and medically relevant compounds cannot be overstated,¹⁻³ so the ability to synthesize products in a highly enantioselective fashion is of interest from both a practical and fundamental standpoint. While still few, there are a growing number of reports of asymmetric catalysis within supramolecular hosts. However, many of these reports display only low to moderate enantioselectivities (generally 75% ee or below), noticeably below that generally achieved using other state-of-the-art transition metal or organocatalysts. In this sense, the field is far from achieving its overarching goal of designing highly enantioselective supramolecular catalysts which can complement existing catalytic scaffolds.

Beyond the inherent challenges of host design, namely the limited range of scaffolds accessible to covalent cages and the requirement for clean self-assembly of coordination cages, developing highly selective catalysts poses another layer of difficulty. There is little known about the specific interactions utilized for enantiodetermination in most asymmetric supramolecular catalysis systems, rendering efforts towards improving enantioinduction extremely challenging and labor intensive. These shortcomings highlight the need for further study of the nature of enantiodetermining interactions in these systems, however, capturing these interactions to elucidate mechanisms of enantioinduction is also intrinsically challenging. While x-ray crystallography can point to potential host-guest interactions, obtaining crystal structures of hosts with encapsulated guests can be challenging, and solid-state behavior may not be indicative of solution state behavior. *In situ* spectroscopic analyses such as ROESY NMR have been used in cyclodextrins to study guest orientation within the host cavity,⁴ but these techniques can only inform behavior of strongly binding, rather than rapidly exchanging, guests on the spectroscopic time scale. Similarly, these techniques cannot adequately capture enantiodetermining interactions during the transition state due to their inherently transient nature. In light of these limitations, further experimental work, combined with computational analysis, is necessary to better understand enantioinduction in

supramolecular hosts. For transition-state analysis, large differences in enantioselectivities which translate to larger energy differences (>1 kcal/mol) are required for accurate analysis. For data science analysis to probe for underlying trends, clever, systematic scope design encompassing diverse chemical space is needed to draw meaningful conclusions. The large range of enantioselectivities for varying oxime classes demonstrated in Chapter 3 position these reductions as a suitable model reaction for such computational analysis. Continued efforts toward developing and improving examples of enantioselective reductions, and more broadly of catalysis, in these hosts is therefore expected to be of significant value.

Although some oximes examined in Chapter 3 were found to give high enantioselectivity with the $\text{Ga}_4\text{L}_6^{12-}$ host, aliphatic oximes and some aryl oximes were reduced in only low to moderate selectivity. The previously described experimental and computational work points to the importance of optimizing interactions between host, oxime, and pyridine borane reductant within the host cavity for successful enantioinduction but fails to recognize specific interactions at play or how to rationally optimize them. Previous work by Raymond, Bergman, and Toste has demonstrated that host identity can impact enantioselectivity. A reported aza-Darzens condensation described the ability to modulate enantioselectivity of substrates through changing the chiral amide, and, more importantly, metal identity.⁵ Crystal structure overlays across different chiral amides within one metal and across different metal identities within a single chiral amide demonstrate a very high degree of similarities between the host cavities (**Figure 4.1**). However, overlap in the solid state may not translate to the solution state, where more dynamic behavior can be observed which may be impacted by different properties within Group 13 metals. For example, ionic radii and electronegativities are expected to impact M–O bond strength, which might impact host behavior such as the ability for the ligands to distort around the metal center for encapsulation. Consistent with this, differing guest exchange rates were observed across hosts featuring different chiral amide and metal combinations. Perhaps due to increased M–O bond strength, Al-based host **IIa** was previously found to have a slower rate of guest exchange for benzylammonium salts than Ga-based host **Ia**, which had a slower guest exchange rate than In-based host **IIIa**. An observed correlation between guest exchange rates and enantioselectivity led to the hypothesis that hosts with improved guest exchange may enable more facile access to favorable non-covalent interactions within the host.⁵ However, this hypothesis is specific to aza-Darzens reactions of aryl substrates and was not tested on a wide range of substrates or other reactions, therefore this principle may not be generalizable.

The use of other $\text{M}_4\text{L}_6^{12-}$ hosts towards enantioselective oxime reductions was therefore of interest to test this hypothesis and, hopefully, improve enantioselectivity for poorly selective substrates. Additionally, previous work in this dissertation has demonstrated the ability to improve enantioselectivity of some oximes by tuning pyridine borane identity and was likewise of interest in this context. While of some synthetic value, the ability to greatly improve enantioselectivity might, more importantly, lend insight to the requirements for successful enantioinduction. Although Chapter 3 focuses on the reductions of oximes, we expected that study of other reducible functional groups, such

as ketones and indoles, would broaden our understanding of the system and provide a more holistic picture of enantioinduction in these hosts.

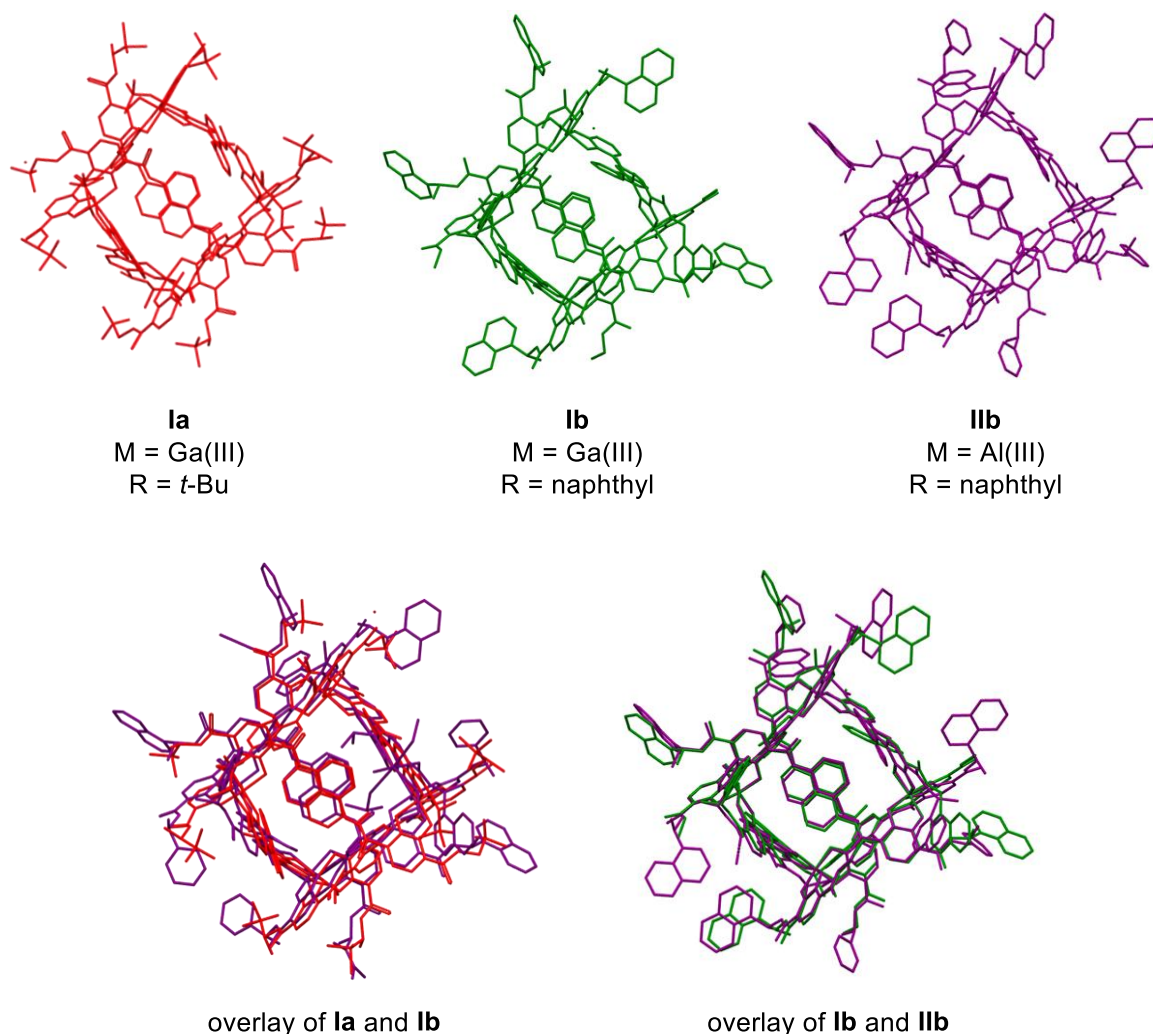


Figure 4.1. Crystal structures of hosts **1a**, **1b**, and **11b** shown individually and overlaid to compare cavity size and shape.

4.3 Improved and Enantiodivergent Selectivities Based on Pyridine Borane Identity

In light of the previously noted ability to modulate enantioselectivity using pyridine borane identity (see **Chapter 3**), the ability to sizably improve enantioselectivity of less selective oximes was of particular interest. Using host **1a**, oxime **2a** was subjected to four 2-substituted pyridine boranes (**1b-1e**) with differing stereoelectronic profiles and compared to those of the parent, **1a**. Very sizeable differences in enantioselectivity were observed across the range of boranes. Notably, enantioselectivity was improved using borane **1a** compared to previous reaction conditions with the use of a moderate amount of MeOD-*d*₆ as co-solvent under gentle heating (22% ee to 49% ee). More electron-

deficient borane **1b** displayed nearly racemic reactivity, while electronically similar but more sterically hindered 2-methylpyridine borane **1c** displayed low levels of selectivity. These results suggest that both borane electronic and steric effects play a role in enantioinduction for this substrate with host **1a**. Very surprisingly, however, 2-amino (**1d**) and 2-methoxypyridine (**1e**) boranes produced the other enantiomer of product. Furthermore, while **1d** displayed comparatively lower enantioselectivity, **1e** afforded hydroxylamine in noticeably improved enantioselectivity compared to **1a** (**Figure 4.6**).

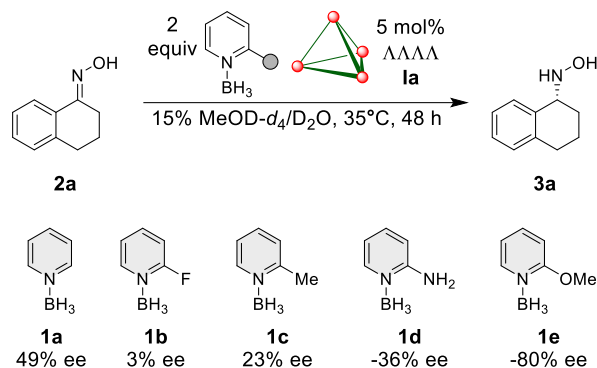


Figure 4.2. Effects of pyridine borane identity on enantioselective reductions of tetralone oxime **2a** with naphthalene-based Ga host **1a**.

While varying structure of the achiral co-catalyst have been reported to afford different enantiomers in organocatalytic systems,^{6,7} this type of enantiodivergent behavior has not been reported in a supramolecular system to date to the best of our knowledge. Beyond the interesting mechanistic questions they provoke regarding the change in mechanism observed between boranes, these results serve as proof-of-concept that enantioselectivity can indeed be dramatically improved by optimizing steric and electronic interactions within the host, and can enable selectivities more akin to those reported with state-of-the-art catalysts.⁸ Previously reported pyridine borane screens did not show sizable energy differences between the pyridine boranes or over initially optimized conditions (97% ee to >99% ee, 89% ee to 80% ee, 65% ee to 77% ee, 51% ee to 73% ee, see **Chapter 3** for details), prompting the question of what substrate features enabled the substantial improvements in selectivity and enantiodivergent behavior. More specifically, we wondered if this was due to the bicyclic structure and might be occur using other cyclic oximes such as indanone oxime. Alternatively, enantiodivergence may be due to the longer alkyl side chain length, whether cyclic or acyclic, and may also be possible with the acyclic congeners. Lastly, we wondered whether the oxime moiety is even required, in addition to either of these criteria, for enantiodivergence, or if similar behavior may be observed in, for example, the parent ketones. These questions are the subject of ongoing work.

4.4 Effects of Host Structure on Enantioselectivity in Oxime Reductions

Encouraged by this success in improving enantioselectivity through pyridine borane identity, work was also directed towards the optimization of reactivity and enantioselectivity of aliphatic oxime **2b** with pyridine borane (**1a**) with Ga₄L₆¹²⁻ host (**1a**).

In contrast to that observed with the enantioselective aza-Darzens,⁵ Al-based host **IIa**, featuring stronger M–O bonds, imparted improved enantioselectivity compared to Ga-based host **Ia**, while In-based host **IIIa**, featuring weaker M–O bonds led to diminished enantioselectivity (**Figure 4.2A, Entries 1, 3, and 5**). This trend was also observed using naphthalene-based amide ligands (**Ib, IIb**) (**Figure 4.2A, Entries 2 and 4**). Although host **IIa** showed decreased reactivity compared to **Ia**, reactivity and enantioselectivity were further improved with extended reaction times at 5°C and *in situ* yield analysis (**Entries 7–9**). A control experiment performed with pyridine borane (**1a**) and host whose cavity was blocked by very strongly binding tetraethylphosphonium bromide (PEt₄Br) showed trace conversion in D₂O using oxime **2b** under reaction conditions. Thus, the observed selectivities are due to reactivity within the cavity rather than a mixture of enantioenriched, host-catalyzed and racemic, background catalyzed products. To corroborate results of oxime **2b** with hosts **Ia, IIa**, and **IIIa**, oxime **2e** was similarly subjected with each host. Much like the results of oxime **2b**, Al-based host **IIa** was found to exhibit an increase in selectivity relative to Ga-based host **Ia** for **2e** and was selected for further use. Surprisingly, although In-based host **IIIa** likewise afforded hydroxylamine **3e** in decreased selectivity compared to **Ia**, the opposite enantiomer of product was preferentially formed, suggesting a break in mechanism of enantioinduction (**Figure 4.3B**).

With these newly optimized conditions, the reductions of additional aliphatic oximes catalyzed by host **Ia** were explored (**Figure 4.4**). When reactivity and selectivity are compared between host **Ia** conditions and newly optimized host **IIa** conditions, substrates were less reactive but were reduced with a higher degree of enantioselectivity under modified conditions with host **IIa**. The highest enantioselectivity (78% ee) was observed in the reduction of oxime **2b**, a remarkable result given the subtle difference in steric bulk between a methyl and an ethyl group. As length of the alkyl chain in the oxime increased (**2a, 2c** and **2d**), the observed reactivity and enantioselectivity diminished, suggesting smaller oximes are potentially better able to capture favorable interactions or minimize disfavorable interactions within the host cavity. Much like with host **Ia**, linear aliphatic oximes were reduced in higher enantioselectivity than their bulkier counterparts, with small, branched oxime **2e** giving modest enantioselectivity and larger branched and cyclic oximes giving poor enantioselectivities (**2f, 2g**). Interestingly, 1-cyclohexylethanone oxime, which was reactive with host **Ia**, was repeatedly found to be unreactive under these conditions.

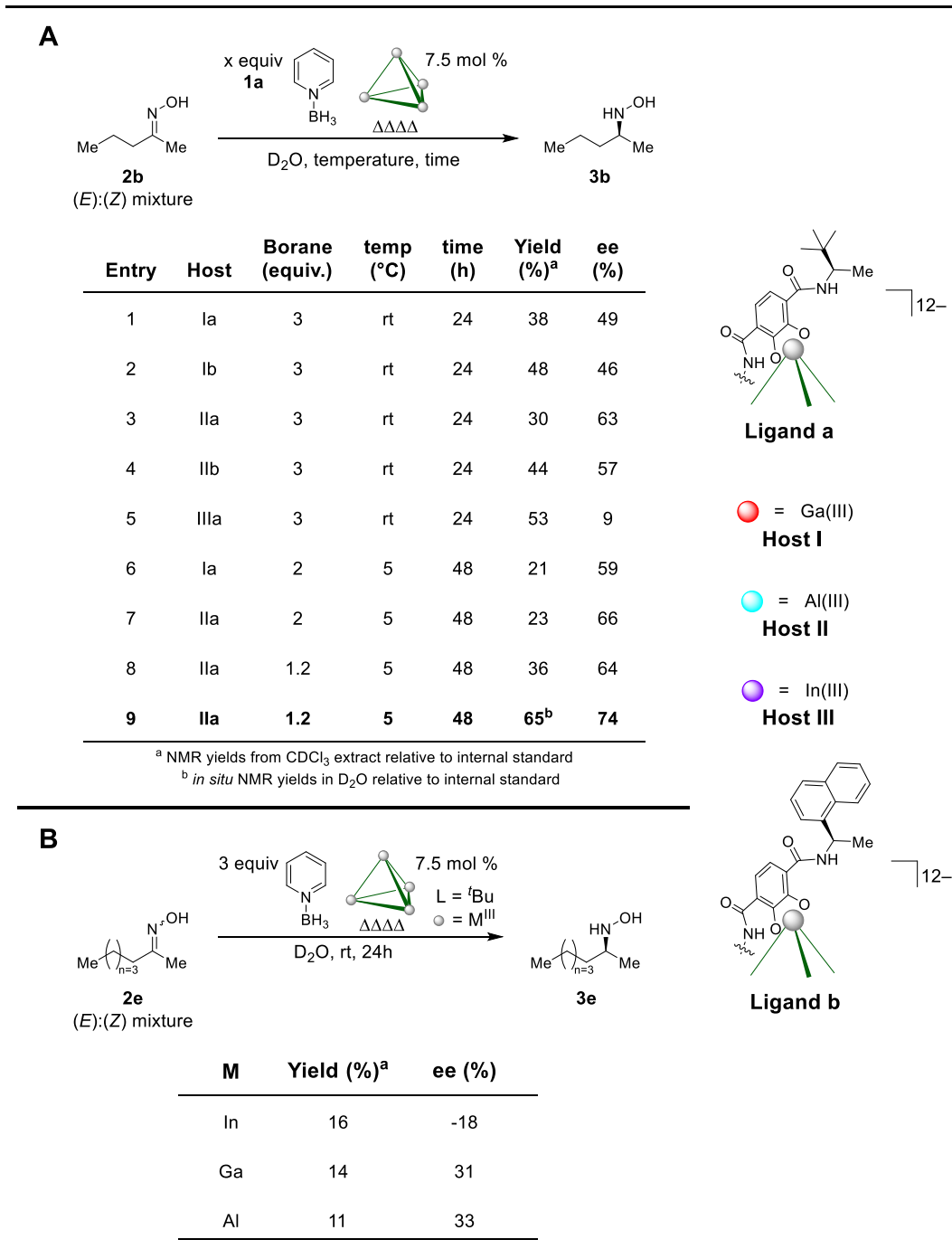


Figure 4.3. A) Optimization of enantioselectivity of aliphatic oxime **2b** with pyridine borane (**1a**) based on host metal and chiral amide identity. **B)** Effects of host metal identity on enantioselectivity of aliphatic oxime **2e**.

It is possible that the previously reported increased barrier to guest exchange with Al host **IIa** also decreases the number of conformations easily accessible to substrates within the host, leading to increased enantioselectivity. This type of behavior is akin to constrictive binding regimes,⁹ which have been hypothesized to promote enantioselectivity in unimolecular cyclizations of aliphatic substrates in these hosts¹⁰ and

could also be applicable in other host-catalyzed reactions, particularly of less rigid aliphatic substrates. Indeed, the decrease in reactivity and increase in selectivity of these aliphatic oximes are generally consistent with increased constrictive binding in Al-based hosts versus Ga-based hosts. Across reactive substrates, enantioselectivity was improved by an average of 1.4x fold, suggesting a similar mechanism is at play with both hosts. Oxime **2d**, however, appears to be a notable exception to this and was over 3x more selective when subjected to host **IIa**, further highlighting the complexity of this system. It is possible this substrate may have unique interactions within the host cavity due to its structure, leading to this deviation in the selectivity trend. However, host **IIIa**'s apparent preference for the transition state favoring the other enantiomer of **3d** does not appear consistent with the idea that **IIIa** engages substrates through a similar mechanism. Although the metal is typically viewed as a catalytically innocent lynchpin which holds the ligand scaffold together, these at times conflicting results merely within aliphatic oximes point to a more complicated picture of reactivity in which the metal influences the number of possible conformations within the host and nature of the non-covalent interactions accessible to substrates. More work is certainly needed to better understand the nuances of metal effects on the nature of host-guest interactions.

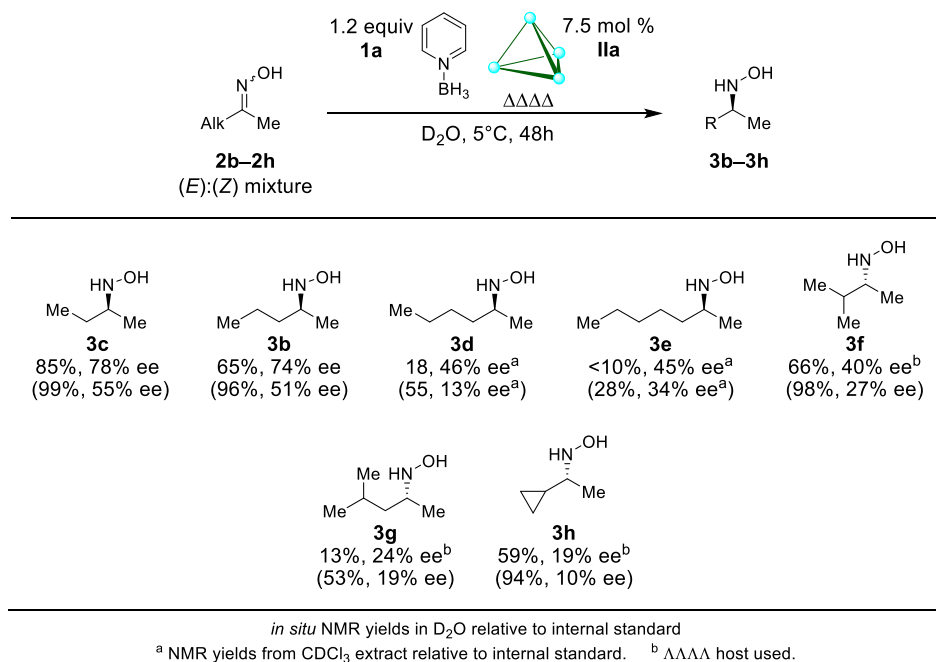


Figure 4.4. Reactivity of aliphatic oximes (**2b–2h**) under optimized reaction conditions with Al-based host **IIa** and pyridine borane (**1a**).

Encouraged by the ability to improve selectivity of aliphatic oximes by changing host metal, similar experiments were undertaken with a small number of aryl oximes which showed poor to moderate selectivity under previous host **Ia** conditions. Unlike aliphatic oximes, however, no clear trends were observed based on the metal or chiral amide identity. When oxime **2i** was subjected to additional hosts, host **IIa** afforded slightly diminished reactivity while enantioselectivity remained approximately constant when compared to **Ia**. Both reactivity and selectivity were more noticeably negatively impacted using host **IIIa** (**Figure 4.5A**). When oxime **2a** was similarly subjected to host **IIIa**,

reactivity remained constant and enantioselectivity improved. Oxime **2j** similarly showed a slight increase in enantioselectivity and slight decrease in reactivity with host **IIIa**, while a decrease in both reactivity and selectivity was noted with **IIa**. This data, particularly in light of the ability to improve ee with aliphatic oximes by changing metal identity, is generally consistent with the previous hypothesis in Chapter 3 that the host interacts with each oxime slightly differently on a substrate-by-substrate basis. Although replacement of the metal identity had a more substantial impact on enantioselectivity in the aza-Darzens condensation, modifications to the chiral amide were also reported to have some impact.⁵ However, much like changing the metal identity in this system, substitutions of the chiral amide had only very slight impact on oxime **2i**. In contrast to that previously observed,⁵ hosts with faster guest exchange rates (those featuring aliphatic amides), afforded products in decreased enantioselectivities compared to those with slower guest exchange rates (those featuring aryl-based chiral amides) (**Figure 4.5B**).

When considered as a whole, these results strongly suggest that utilizing hosts with faster guest exchange rates in an attempt to better capture favorable non-covalent interactions by increasing the number of conformations easily accessed is not a generalizable strategy for improving enantioselectivity in these hosts. Furthermore, the use of hosts which demonstrate a decrease in possible substrate conformations to enforce enantioselectivity is also not a reliable approach for optimized enantioinduction. Instead, a more comprehensive model is needed which can account for the multiple modes of enantioinduction which seem to occur in these hosts. The substrate scope and the resulting data science analysis of Chapter 3 point to the importance of steric effects and guest size and shape for host-guest interactions. Meanwhile, the pyridine borane reductant screens and data science analysis of Chapter 3 implicate both steric and electronic effects are important for interactions between substrates within the host. We therefore wondered whether electronic effects may likewise be important for host-guest interactions and might better explain the observed selectivities. Previous work on the racemic Ga₄L₆ host (**IV**), which is structurally analogous to the enantiopure hosts but lacks chiral amides, has studied the electron density throughout the scaffold of the assembled host using electrostatic potential maps.¹¹ The naphthalene spacer groups were found to be the most electron-rich portion of the host scaffold. Furthermore, when ligands were detached from the host but overall charge of the system maintained, a more electron-withdrawing metal (As) led to a decrease in electron density on the naphthalene groups compared to Ga. Additional computations are needed to further probe this finding. However, similar behavior is certainly possible in the enantiopure host systems. Under this regime, the In-based host **IIIa** would be expected to have increased electron density on the naphthalene groups, while Al-based host **IIa** would be expected to have decreased electron density on the naphthalene groups, when compared to Ga-based host **Ia**. Such a hypothesis implies that oximes which are dominated by electronic interactions could be favorably impacted by the use of host **IIIa**, while those dominated by steric interactions could be reduced in greater selectivity with host **IIa** if encapsulation is possible.

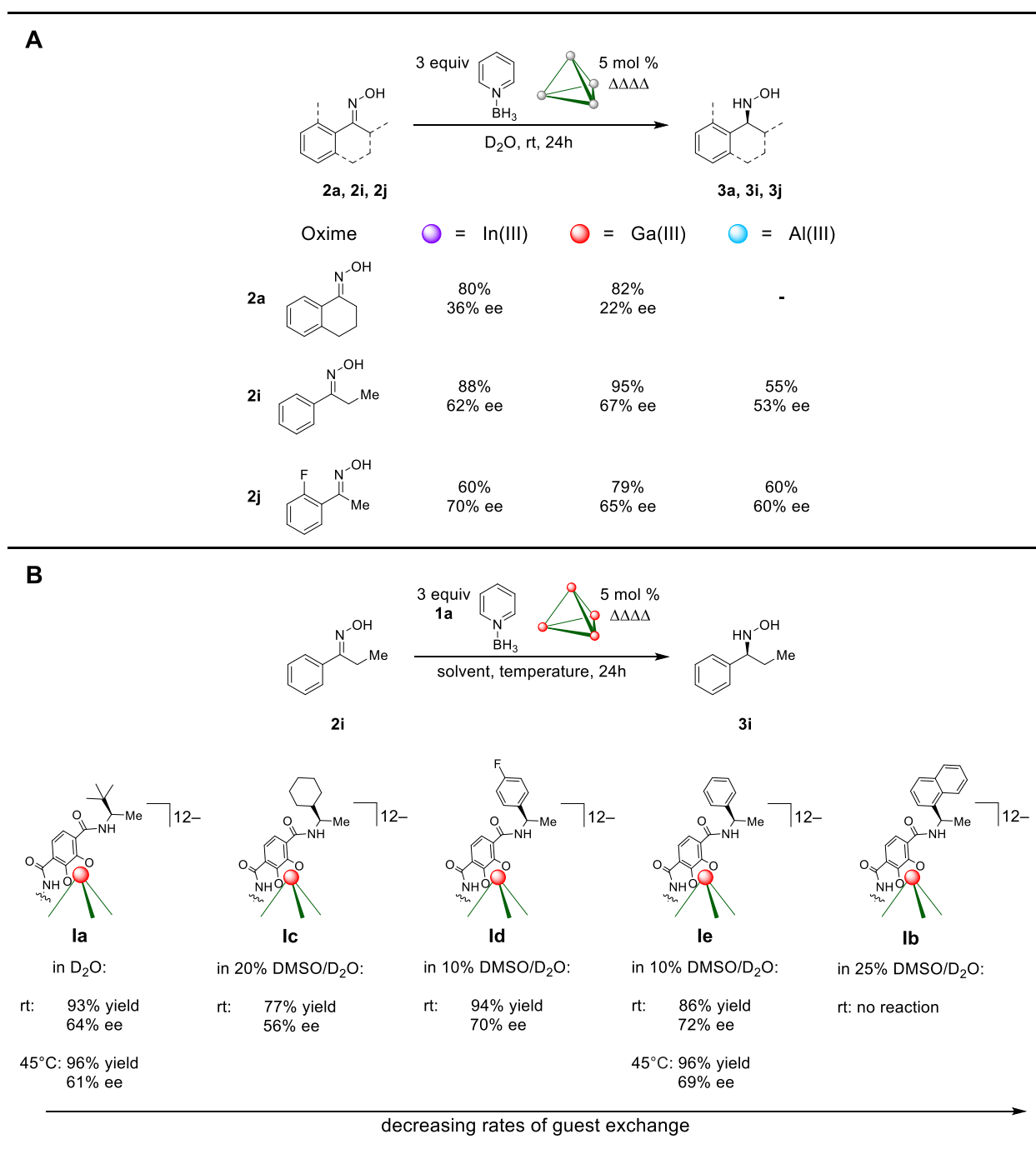


Figure 4.5. A) Effects of host metal identity on enantioselectivities of aryl ketones. **B)** Effects of chiral amide identity on enantioselectivity of aryl ketone **2i**.

Although modification to the host electronics through changing metal and/or amide identity may be possible, substitutions to the aryl spacer group may more easily affect the electronic environment experienced by substrates. Although the bulk of work using an enantiopure $\text{Ga}_4\text{L}_6^{12-}$ host has employed hosts featuring a naphthalene-based spacer, a related host featuring a pyrene-based spacer (host **Va**) (**Figure 4.5**) has been previously reported for a Prins cyclization.¹⁰ Decreased enantioselectivity was observed, which was

attributed to the loss of constrictive binding with a larger cavity volume. Much like the effects of chiral amide and metal identity on enantioselectivity, the effects of a pyrene spacer on a wider range of substrates or reactions have not yet been studied. We were therefore interested in the effects of a pyrene-based host to modulate enantioselectivity of oxime reductions. Aryl oximes may be reduced in increased enantioselectivity due to an increase in π -type interactions with the pyrene group but could also demonstrate decreased selectivity due to a loss of constrictive binding. Host **Va** was applied under previously utilized borane screen reaction conditions with oxime **2a**, which previously demonstrated poor enantioselectivity with host **1a**, using pyridine borane **1a** and 2-substituted boranes **1c–1e**. Enantioselectivity was minimally affected by borane identity, with the desired hydroxylamine being afforded in good enantioselectivity (**Figure 4.5**), suggesting that selectivity is largely influenced by the host rather than substrate-substrate interactions. Unlike that previously observed with oximes in Chapter 3, borane **1c** afforded the product in highest selectivity, though only slightly higher than other boranes. The observed selectivities are a dramatic improvement compared to the initially reported results in Chapter 3 (22% ee at room temperature in D₂O). However, the enantiomer of hydroxylamine was opposite to that which might be expected. The structures of hosts **1a** and **Va** are highly related; both feature the same chiral amide and should differ only in cavity size due to **Va**'s larger spacer group, so both hosts are expected to display the same helical chirality inside their cavity. Nevertheless, the same enantiomer of product was formed using $\Delta\Delta\Delta\Delta$ -**Va** as was formed with $\Delta\Delta\Delta\Delta$ -**1a**. This highly unexpected result is the subject of current investigations. The improved selectivities found using oxime **2a** with In-based host **IIIa**, pyrene spacer-based host **Va**, and more electron-rich borane **1e** could be due to the dominance of electronic effects in enantiodetermining interactions for this substrate, but additional work is needed to probe this.

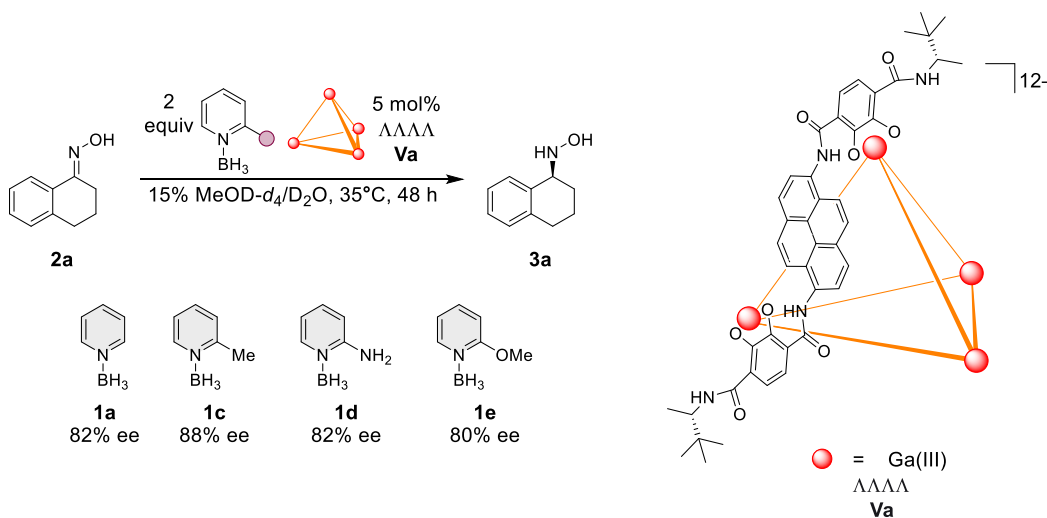


Figure 4.6. Effects of pyridine borane identity on enantioselective reductions of tetralone oxime **2a** with pyrene-based host **Va**.

4.5 Employing Borane and Host Optimization to Improve Selectivity Beyond Oxime Reductions

Encouraged by the improved enantioselectivities observed by modification of host scaffold and borane identity, attention has also been directed towards the ability to enantioselectively reduce functional groups beyond oximes, such as ketones and indoles. Although comparatively less challenging reductions for state-of-the-art transition metal and organocatalysts and generally solved challenges,¹² reductions of these functional groups are expected to provide insight into enantioinduction in these hosts, specifically with respect to substrate requirements for good enantioselectivity. The enantioselective reduction of ketones has been the focus of a large portion of work in the larger field of asymmetric catalysis. Not only can ketones and alcohols be found in a number of drug molecules, they also have a wide range of synthetic utility for incorporation of other functional groups.^{13,14} Indoles and the reduced indoline product can also be found in a number of medically relevant compounds.^{12,15}

Initial work focused on the enantioselective reduction of acetophenone, **4a**, under optimized conditions for aryl oximes using pyridine borane **1a**. However, while reasonable reactivity was observed, the resulting alcohol, 1-phenylethanol, **5a**, was nearly racemic. More bulky ketones **4b** and **4c** were less reactive, and only **4b** showed a degree of selectivity (**Figure 4.7A**). A blocked host control experiment using ketone **4a** showed no reactivity, indicating that the poor selectivities observed are due to host-catalyzed reactivity within the confines of the host cavity. Although certainly less than desirable, these poor enantioselectivities allow for a large amount of potential optimization. Towards this aim, ketones **4a** and **4b** were screened with Al-based host **IIa** and In-based host **IIIa** for comparison against host **Ia**. Ketone **4b** saw no noticeable improvement in enantioselectivity, with both **IIa** and **IIIa** showing decreased enantioselectivity. However, ketone **4a** showed a very slight improvement in selectivity with both hosts. Host **IIa** improved selectivity to the same enantiomer of product as afforded by **Ia**, while **IIIa** led to formation of the other enantiomer of product (**Figure 4.7A**). While the ability to slightly improve enantioselectivity by changing the host metal identity is somewhat encouraging, these results are still far below useful levels of selectivity. Consistent with work with oximes, chiral amide identity also had no discernable effect on enantioselectivity of ketone **4b**. No difference in enantioselectivity was observed between hosts **Ia** and **Ie** (37% vs 39% ee), which was the most selective host for oxime **2i**. A pyridine borane screen using pyridine borane **1a** and 2-substituted boranes **1c–1e** also attempted to improve improved selectivity but was largely unsuccessful (**Figure 4.7B**). Much like oxime **2a**, the use of a small amount of MeOD-*d*₆ as co-solvent and increased temperature appeared to give a very slight improvement in selectivity. Furthermore, each of the functionalized boranes gave an improvement in enantioselectivity over the parent **1a**, with more electron-rich boranes **1d** and **1e** giving the highest selectivities. Borane **1d**, which also features a potential hydrogen bonding donor group, gave the highest enantioselectivity, but these levels of selectivity are far below useful levels. A combination of modulating borane and host metal identities is expected to provide further improved enantioselectivities but may not provide the product in useful levels given the small changes observed by changing each component individually. Given the success in improving enantioselectivity of oxime **2a** using host **Va**, ketone **4a** was then subjected to host **Va** using **1a** as reductant, MeOD-

d_6 as co-solvent, and increased temperature. Under these conditions, selectivity was improved to a modest 56% ee (**Figure 4.7B**). This increase in enantioselectivity serves as proof-of-concept for the ability to engineer enantioselectivity in substrates which may show poor enantioenrichment in the initial system. Screening additional pyridine boranes is likely to further improve enantioselectivity, particularly given the ability to further functionalize the pyridine borane while preserving the ability for encapsulation due to the host's expanded cavity.

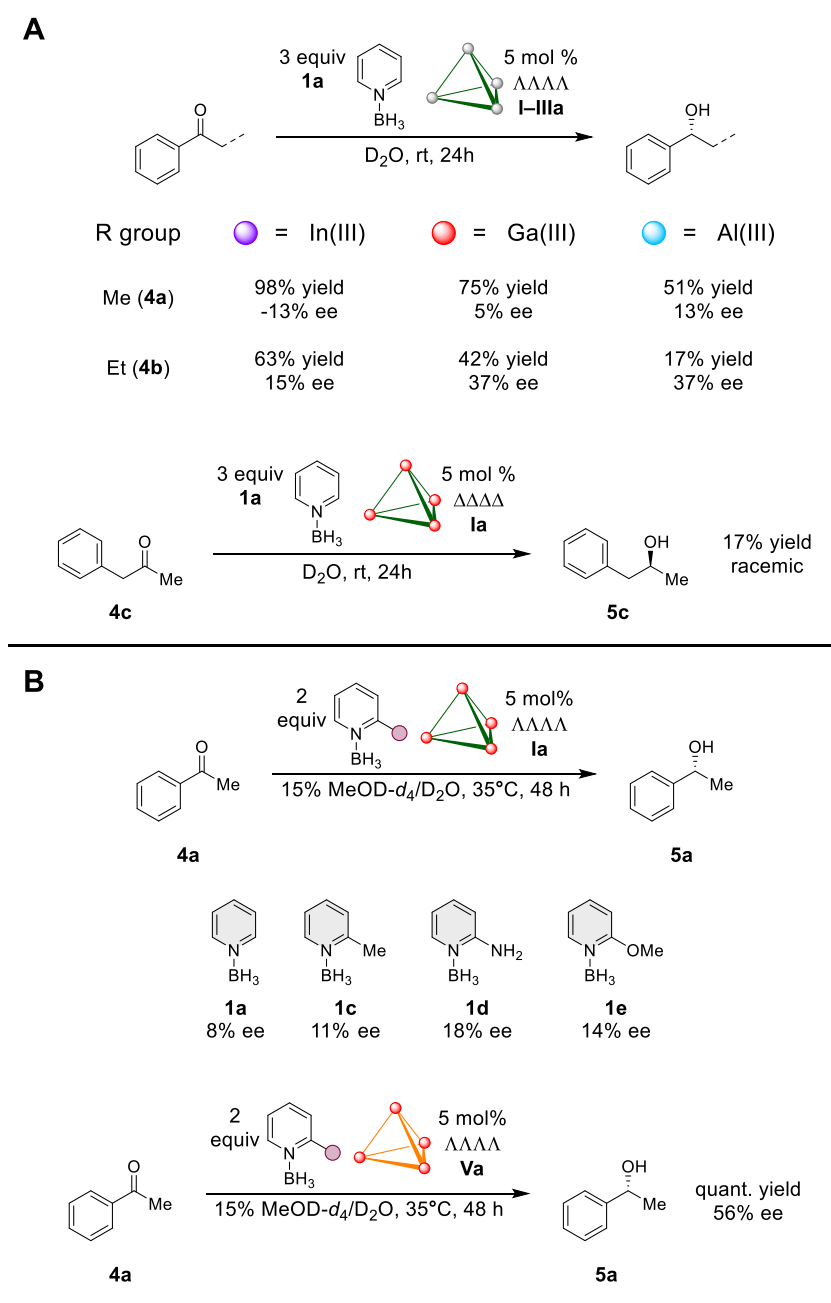


Figure 4.7. A) Initial reactivity of ketones with hosts **Ia**, **Ila**, and **IIla**. **B)** Attempts at optimization of ketone **4a** by modulating pyridine borane identity and host spacer group.

Initial investigation of indoles was then undertaken using slightly modified conditions (**Figure 4.8**). Though modestly reactive with racemic host **IV** and pyridine borane (**1a**), 2- and 3-methylindoles (**6a** and **6b**, respectively), showed only trace reactivity with host **1a**. 2,3-disubstituted indoles (**6c**, **6d**) displayed good diastereoselectivity to the trans indoline with the racemic host **IV** and enantiopure host **1a**, but no enantioselectivity was observed (see **Supporting Information** for Optimization of Reactivity with **6c**). However, sluggish reactivity was still observed. The poor solubility of indoles in D₂O was noted, so co-solvents and gentle heating may be required to improve reactivity through increasing the amount of indole present in solution. Interestingly, deuterium incorporation was noticed at the 3-position of the indoline product in each case. Subsequent deuterium labelling studies on 3-methylindole (**6b**) in the absence of pyridine borane with blocked and empty host **IV** showed substantial amounts of deuterium incorporation after 40h (see **Supporting Information**). Although the deuterium incorporation process is reversible, this highlights the potential for the stereocenter at the 3 position to be set outside of the host, which might make highly enantioselective reductions of 3-substituted indoles challenging in this system. Protonation with D₂O may also be more challenging than with H₂O, which could also contribute to sluggish reactivity. A blocked host control with indole **6c** and blocked racemic host **IV** showed no reactivity, and reactivity is likewise assumed to only occur within the cavity using enantiopure hosts. Thus, the poor selectivity observed with **6c** is again due to host cavity-promoted catalysis. Considering these challenges, In-based host **IIIa** was applied to the reduction of **6a** in H₂O an attempt to increase enantioselectivity. While reactivity was improved, enantioselectivity was not. Given the success in improving enantioselectivities of oxime **2a** using functionalized pyridine boranes or host **Va** and of ketone **4a** with host **Va**, the ability to improve selectivities of these mono- and disubstituted indoles is likely possible but will likely require a combination of structural changes to the host scaffold.

When taken together, results with ketones and indoles suggest that oximes are in some way a privileged scaffold for enantioselective reductions in these enantiopure host systems, and that optimization of enantioselectivity for these alternate substrates will be challenging. When comparing the structures for potential sources of these differences, the free hydroxyl group of the oxime is a notable difference. The ketone **O** lacks a hydrogen bond donating ability, and the imine-type structure of the indole features a hydrogen bonding motif but is attached to the rest of the molecule and may be more structurally analogous to the methyl ether oximes which showed poor selectivity (see **Chapter 3, Figure 3.3**). Work interrogating the reactivity of nitrones and hydrazones may lend more insight into the importance of hydrogen bond donors on these reductions. If a requirement, the addition of an –OH group or similar moiety to the substrate to serve as a directing group is possible but would severely limit potential substrate scopes and is therefore ideally avoided.

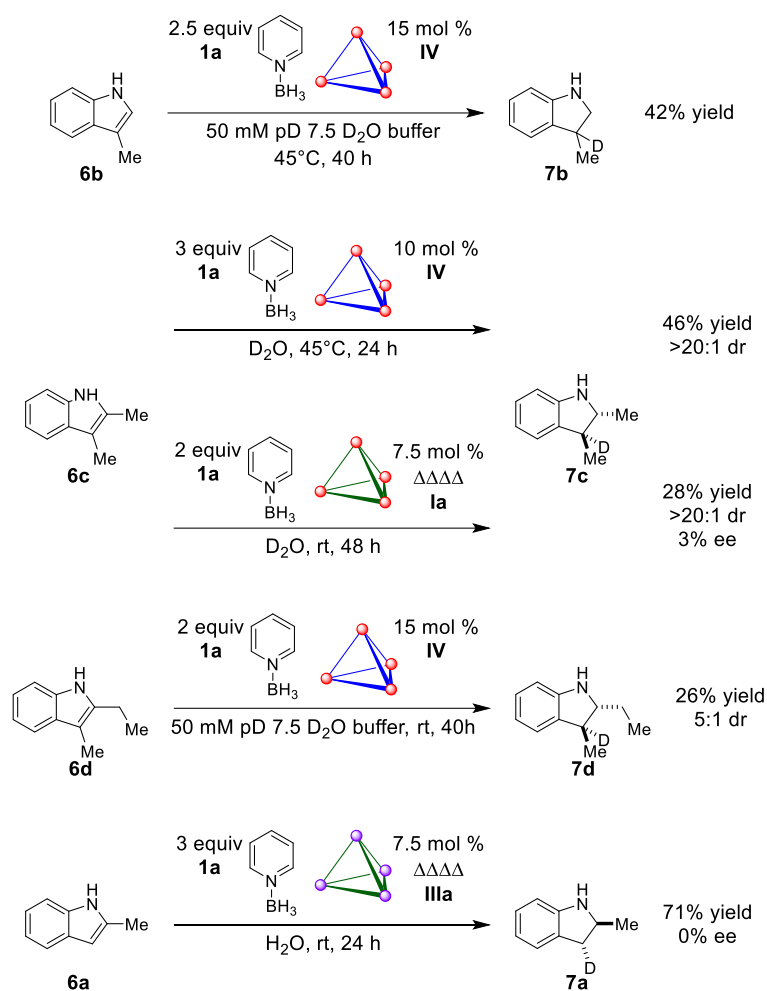


Figure 4.8. Reactivity of substituted indoles (**6a–6d**) using $M_4L_6^{12-}$ hosts and pyridine borane (**1a**).

4.6 Conclusions

Ongoing work investigating the role of host structure, particularly with respect to metal identity and spacer group, is underway. Work to optimize enantioselectivity of aliphatic oximes highlights the potential for constrictive binding in this system, in which hosts with more rigid M–O bonds confer a higher degree of enantioselectivity. However, similar work with aryl oximes showed little improvement with this approach. Application of an enantiopure host featuring a pyrene, rather than naphthalene, spacer group improved enantioselectivity for both ketones and oximes that were poorly selective in initial work. Furthermore, modulating pyridine borane identity emerges as a promising tool to tune steric and electronic interactions between guests for optimal reactivity of otherwise poorly selective substrates. Alternative substrate classes, particularly ketones, show some potential as viable substrates for enantioselective reductions but much additional work is needed.

Despite these promising initial results, many outstanding challenges and questions remain. Although guest exchange rates do not appear to consistently correlate with hosts found to be optimal for enantioselectivity, it is not clear what the role of the host metal identity plays in guiding enantiodetermining interactions. Furthermore, the observed enantiodivergence observed with some substrates using an In-based enantiopure host suggests that, while the metal does not directly bind or engage the substrate, it plays some role in catalysis beyond that of a lynchpin holding the host together. Similarly, the role of spacer in enantioinduction is likewise of interest. The pyrene-based host, which should have decreased constrictive binding relative to the naphthalene-based host, has demonstrated notable improvements in selectivity among some substrates found poorly selective with the naphthalene-based host. Additional work is needed to test the abilities of this host to improve enantioselectivity across a range of aryl and aliphatic substrates to probe the role of constrictive binding with this host. Moreover, the enantiodivergence observed with this host using some oximes prompts questions about the interactions used by the host to guide interactions between substrates. Beyond questions regarding host structure, many questions remain as to the features of substrates that are beneficial for enantioselectivity. For example, it is notable that oximes are thus far much more selective than their ketone counterparts. Given the need for size and shape complementarity more broadly in supramolecular catalysis, the ability to find specific features which aid or hinder enantioinduction or a potential size threshold above which selectivity decreases is of interest. Woven into the aforementioned questions lies bigger questions regarding the types of interactions utilized for enantioinduction. Although the ability to identify specific interactions applicable to one substrate is an important starting point, identifying underlying trends should be the overarching goal. The ability to answer these questions is expected to constitute substantial progress towards the goal of rational employment of these supramolecular hosts towards enantioselective catalysis.

4.7 Supporting Information

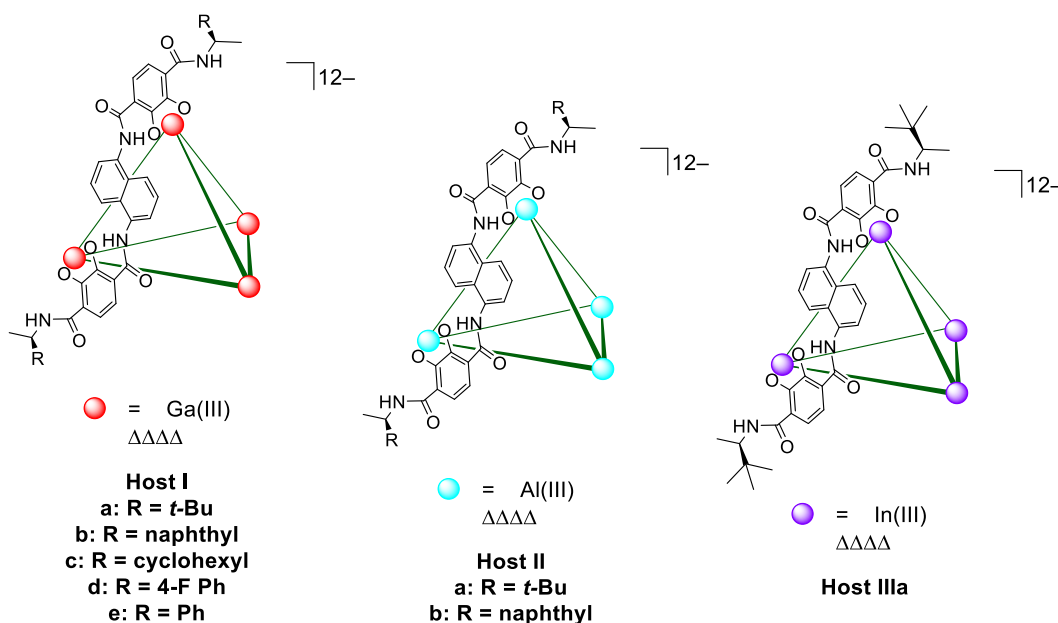
4.7.1 General Methods and Instrumentation:

All reactions were capped and performed at room temperature under ambient atmosphere with Teflon-coated magnetic stir bars unless otherwise specified. Air sensitive materials were prepared using standard Schlenk technique and handled in a wet glovebox under a nitrogen (N_2) atmosphere. All solvents were degassed for 0.5 hours by sparging before introduction into the glovebox. Flash column chromatography was performed on a Teledyne Isco CombiFlash Rf instrument using pre-packed silica gel columns unless otherwise stated. Thin layer chromatography (TLC) analysis was performed using Merck 60 pre-coated silica gel plates with F254 indicator and visualized using UV light (254 nm) or potassium permanganate ($KMnO_4$). Commercial grade solvents were used without further purification except as indicated. Dichloromethane (CH_2Cl_2), diethyl ether (Et_2O), tetrahydrofuran (THF), and triethylamine (Et_3N) were dried by passing the previously degassed solvents through activated alumina columns under argon. All other reagents were used directly as received without further purification. All deuterated solvents were used as received from Cambridge Isotope Laboratories, Inc. Proton nuclear magnetic resonance (^1H NMR), carbon nuclear magnetic resonance (^{13}C

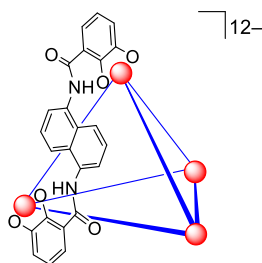
NMR), and fluorine nuclear magnetic resonance (^{19}F NMR) spectra were taken with Bruker AVB-400, AVQ-400, NEO-500, NEO-501, AV-600, or AV-700 and JEOL-400 NMR spectrometers operating at 300 MHz, 400 MHz, 500 MHz, 600, or 700 MHz. Chemical shifts are reported in parts per million (ppm) with reference to the appropriate residual solvent signal. ^1H NMR: CDCl_3 : δ : 7.26 ppm, CD_2Cl_2 : δ : 5.32 ppm, $\text{DMSO}-d_6$: δ : 2.50 ppm, $\text{MeOD}-d_4$: δ : 3.31 ppm, D_2O : δ : 4.79 ppm. ^{13}C NMR: CDCl_3 : δ : 77.16 ppm, CD_2Cl_2 : δ : 53.84 ppm, $\text{DMSO}-d_6$: δ : 39.52 ppm, $\text{MeOD}-d_4$: δ : 49.00 ppm. ^1H NMR multiplicities are reported as (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, hept = heptet, oct = octet, m = multiplet; coupling constant(s) in Hz; integration). High resolution mass spectra were recorded by an Agilent 6230 ESI-TOF LC/MS and are given in m/z . The determination of enantiomeric excess was performed by chiral phase high performance liquid chromatography (HPLC) using Shimadzu Prominence HPLC and Diacel ChiralCel OJ-H, AD-H and IA columns. Samples for chiral HPLC analysis were prepared in 95% hexanes/isopropanol (IPA) solutions unless otherwise stated. Oximes, hydroxylamines, and pyridine boranes were stored in a -20°C freezer when not in use. M_4L_6 hosts were stored in a wet glovebox to avoid oxidative decomposition.

4.7.2 Synthesis and Characterization of Compounds:

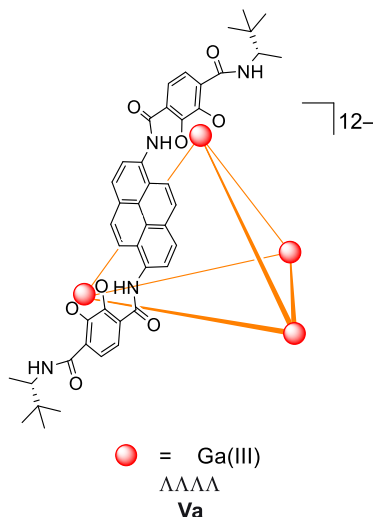
Host Synthesis



$\text{K}^{12}[\text{Ga}_4\text{L}^*_6]$ Hosts **Ia–IIIa** were synthesized according to their respective reported procedures.¹⁶



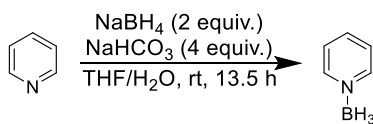
K¹²[Ga₄L₆] Host IV was synthesized according to a previously reported procedure.¹⁷



K¹²[Ga₄L₆] Host Va** was synthesized according to a modified procedure.¹⁶ Ligand precursor¹⁸ (30 mg, 0.040 mmol, 6 equiv.) and Ga(acac)₃ (9.8 mg, 0.05 mmol, 4 equiv.) were suspended in degassed wet ethanol (95% EtOH by volume) (2 mL) and the oil bath was heated to 72°C. After 15 minutes, KOH (4.5 mg, 0.080 mmol, 12 equiv.) as a solution in wet ethanol (0.7 mL) was added slowly at 0.010 mL/min via syringe pump to the heterogeneous reaction. Upon complete addition of KOH, the yellow reaction mixture became a homogeneous solution, and the reaction was stirred for an additional 2.5h. The solution was not allowed to fully cool to rt but was partially cooled for 2–3 minutes before the host was precipitated via addition of diethyl ether (15 mL) to the stirring solution. The yellow solid was then collected by filtration and washed with diethyl ether (15 mL) to give the desired supramolecular complex, which was dried under vacuum before use (40 mg, near quant. yield). Analytical data were consistent with the literature.¹⁸

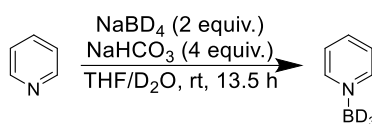
Pyridine Borane Synthesis:

2-methylpyridine (picoline) **borane (1c)** was used as received from Thermo Fisher Scientific.



Pyridine borane (1a) was synthesized according to a modified procedure.¹⁷ To a flame-dried 25 mL round bottom flask equipped with a magnetic stir bar was added sodium borohydride (207 mg, 5.46 mmol, 2 equiv.), sodium bicarbonate (888 mg, 10.57 mmol, 3.9 equiv.) and THF (4 mL). Then, pyridine (0.22 mL, 2.73 mmol, 1 equiv.) was added in a single portion, followed by a slow, dropwise addition of DI water (0.2 mL) and additional THF (0.8 mL). The heterogeneous mixture was vigorously stirred for 4 hours at room temperature. The solids were removed by vacuum filtration, and the filtrate was concentrated *in vacuo*. Purification of the crude product by column chromatography eluting with CH₂Cl₂/MeOH (0–5% MeOH) yielded the title compound as a hazy liquid. Analytical data were consistent with the literature.¹⁷

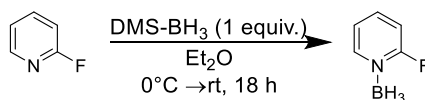
¹H NMR (300 MHz, Chloroform-*d*) δ 8.65 (d, *J* = 5.6 Hz, 2H), 8.06 – 7.88 (m, 1H), 7.64 – 7.48 (m, 2H), 2.54 (dt, *J* = 163.6, 66.0 Hz, 3H).



Pyridine BD₃ (1a-D) was synthesized under an analogous procedure as used to synthesized pyridine borane-H₃. To a flame-dried 25 mL round bottom flask equipped with a magnetic stir bar was added sodium borodeuteride (284 mg, 6.75 mmol, 2 equiv.), sodium bicarbonate (1155 mg, 13.5 mmol, 4 equiv.) and THF (5 mL). Then, pyridine (275 μ L, 3.375 mmol, 1 equiv.) was added in a single portion, followed by a slow, dropwise addition of D₂O (0.25 mL) and additional THF (1 mL). The heterogeneous mixture was vigorously stirred for 13.5 hours at room temperature. The solids were removed by vacuum filtration, and the filtrate was concentrated *in vacuo*. Purification of the crude product by column chromatography eluting with CH₂Cl₂/MeOH (0–5% MeOH) yielded the title compound as a clear liquid.

¹H NMR (500 MHz, CDCl₃) δ 8.60 (d, *J* = 6.4 Hz, 2H), 7.93 (tt, *J* = 7.8, 1.6 Hz, 1H), 7.55 – 7.48 (m, 2H).

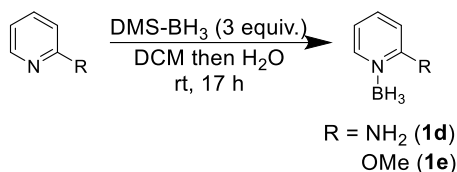
¹³C NMR (126 MHz, CDCl₃) δ 147.64, 139.19, 125.45.



2-fluoropyridine borane (1b) was synthesized according to a modified procedure.¹⁹ To a flame-dried 25 mL round bottom flask equipped with a magnetic stir bar was added Et₂O (6 mL) and 2-fluoropyridine (515 μ L, 6.00 mmol, 1.0 equiv.) under N₂. The reaction was cooled to 0°C before dimethyl sulfide borane (DMS-BH₃) (570 μ L, 6.00 mmol, 1.0 equiv.) was slowly added and kept at 0°C for 1h before being allowed to slowly warm to room temperature and stopped after 17h, after which time the reaction was filtered. The reaction flask was washed with Et₂O and the rinse also filtered. To the filtrate was added a large excess of hexanes to precipitate out a white solid, which was filtered off and washed twice with H₂O (2x15 mL). The solid was allowed to dry on the fritted glass funnel briefly before drying on high vacuum overnight and isolation in 95% purity. The solid was found to be poorly stable, particularly in protic solvents.

¹H NMR (600 MHz, CDCl₃) δ 8.51 (s, 1H), 8.12 – 8.00 (m, 1H), 7.36 (t, *J* = 6.1 Hz, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 2.91 – 2.04 (m, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 161.01 (d), 148.14 (d), 144.50 (d), 121.55 (d), 112.39 (d).
 ^{19}F NMR (565 MHz, CDCl_3) δ -68.45.



2-NH₂ pyridine borane (1d) and 2-OMe pyridine borane (1e) were synthesized according to a modified procedure.²⁰ To a flame-dried 25 mL round bottom flask equipped with a magnetic stir bar was added CH_2Cl_2 (5 mL) and pyridine (2.8 mmol, 1.0 equiv.) under N_2 before slow addition of DMS-BH₃ (8.4 mmol, 3.0 equiv.). The reaction was allowed to stir at room temperature for 13h, after which H_2O (10 mL) was slowly added. A vent needle was also added to the flask. The reaction was then allowed to stir another 4h before it was further diluted with H_2O (5 mL) and extracted three times with CH_2Cl_2 (3x10 mL). The organic layers were backwashed once with NaHCO_3 (1x15 mL). The resulting organic layers were combined and dried over MgSO_4 , filtered, and concentrated *via* rotary evaporation. Purification of the crude product by column chromatography eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (0–30% MeOH) yielded the title compound.

2-aminopyridine borane (1d): Prepared according to the general procedure and isolated as a white solid.

^1H NMR (600 MHz, CDCl_3) δ 8.15 (s, 1H), 7.60 – 7.52 (t, J = 7.7 Hz, 1H), 6.65 (d, J = 8.0 Hz, 2H), 5.57 (s, 2H), 2.60 – 1.79 (m, 3H).

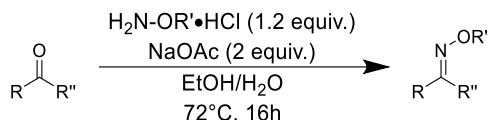
^{13}C NMR (151 MHz, CDCl_3) δ 155.38, 146.05, 139.99, 113.11, 111.43.

2-methoxypyridine borane (1e): Prepared according to the general procedure and isolated as a white solid. Analytical data were consistent with literature reports.^{20,21}

^1H NMR (600 MHz, CDCl_3) δ 8.51 (d, J = 5.2 Hz, 1H), 7.96 – 7.89 (m, 1H), 7.06 – 7.01 (m, 1H), 6.96 (d, J = 8.5 Hz, 1H), 4.10 (s, 3H), 2.82 – 2.02 (m, 3H).

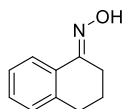
^{13}C NMR (151 MHz, CDCl_3) δ 163.15, 148.65, 142.76, 116.98, 107.65, 57.06.

General Procedure A for the Synthesis of Aryl and Heteroaryl Oximes:



Synthesized based on a modified procedure.¹⁷ To a 100 mL round bottomed flask equipped with a stir bar was added hydroxylamine HCl (4.8 mmol, 1.2 equiv.) and NaOAc (8 mmol, 2 equiv.), followed by EtOH (28 mL) and H_2O (12 mL). The ketone was then added, and the solution was brought to reflux. After overnight reflux, the solution was cooled and concentrated *via* rotary evaporation to remove most of the EtOH. The remaining residue was diluted with H_2O (15 mL) and transferred to a separatory funnel and extracted twice with EtOAc (2x20 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated *via* rotary evaporation. Purification of the crude product

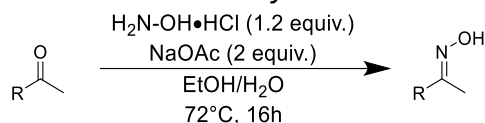
by column chromatography eluting with hexanes/EtOAc (0–50% EtOAc) yielded the title compound.



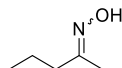
(E)-3,4-dihydronaphthalen-1(2H)-one oxime (2a): Prepared according to General Procedure A and isolated as an off-white solid. Analytical data were consistent with literature reports.^{22,23}

¹H NMR (500 MHz, CDCl₃) δ 8.38 (br s, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.34 – 7.22 (m, 2H), 7.19 (d, J = 7.5 Hz, 1H), 2.87 (t, J = 6.7 Hz, 2H), 2.81 (t, J = 6.0 Hz, 2H), 1.92 (q, J = 6.5 Hz, 2H).

General Procedure B for the Synthesis of Aliphatic Oximes: A modified version of General Procedure A due to substrate volatility.



To a 100 mL round bottomed flask equipped with a stir bar was added hydroxylamine HCl (2.4 mmol, 1.2 equiv.) and NaOAc (4 mmol, 2 equiv.), followed by EtOH (14 mL) and H₂O (6 mL). The ketone (2 mmol, 1 equiv.) was then added, and the solution was brought to reflux. After overnight reflux, the solution was cooled and partially concentrated *via* rotary evaporation. To minimize product loss but remove as much EtOH as possible, the rotovap bath temperature was kept below 14°C. The remaining residue was diluted with H₂O (15 mL) and transferred to a separatory funnel and washed with DCM (20 mL) x2. The combined organic layers were dried over MgSO₄, filtered, and concentrated *via* rotary evaporation. To minimize product loss, the rotovap bath temperature was kept below 7°C. The resulting crude product still generally contained small amounts of acetic acid, so the product was diluted with DCM (20 mL), returned to the separatory funnel and washed with H₂O (20 mL) x2. The organic layer was dried over MgSO₄, filtered, concentrated *via* rotary evaporation below 10°C, and then briefly dried on high vacuum to remove any remaining residual solvent.



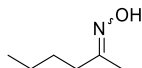
(E)- and -(Z)-pentan-2-one oxime (2b): Prepared according to General Procedure B with slight modification. Rather than repeated washing with H₂O, the crude product was purified *via* Hickman distillation and isolated as a colorless oil in a 3:1 (*E*):(*Z*) isomer mixture. Analytical data were consistent with literature reports.^{17,24}

¹H NMR (600 MHz, CDCl₃) δ 8.67 (br s, 1H), 2.38 – 2.32 (m, 2H, minor), 2.19 – 2.13 (m, 2H, major), 1.87 (s, 3H, major), 1.86 (s, 3H, minor), 1.54 (m, 4H, major and minor), 0.96 (t, J = 7.4 Hz, 3H, minor), 0.92 (t, J = 22.4, 7.4 Hz, 3H, major).



(E)- and-(Z)-butan-2-one oxime (2c): Prepared according to General Procedure B with slight modification. Rather than repeated washing with H₂O, the crude product was purified *via* Hickman distillation and isolated as a colorless oil in a 3.4:1 (*E*):(*Z*) isomer mixture. Analytical data were consistent with literature reports.^{25,26}

¹H NMR (500 MHz, CDCl₃) δ 8.62 (br s, 1H), major: 2.22 (q, *J* = 7.5 Hz, 2H), 1.88 (s, 3H, major), 1.09 (t, *J* = 7.5 Hz, 3H, major), minor: 2.39 (q, *J* = 7.7 Hz, 2H), 1.86 (s, 3H), 1.08 (t, *J* = 7.7 Hz, 3H).

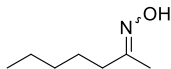


(E)- and-(Z)-hexan-2-one oxime (2d): Prepared according to General Procedure B and isolated as a colorless oil in a 2.5:1 (*E*):(*Z*) isomer ratio (64% yield).

¹H NMR (600 MHz, CDCl₃) δ 8.29 (br s, 1H), 2.40 – 2.34 (m, 2H, minor), 2.21 – 2.16 (m, 2H, major), 1.88 (s, 3H, major), 1.86 (s, 3H, minor), 1.53 – 1.45 (m, 2H, major and minor), 1.41 – 1.33 (m, 2H, minor), 1.36 – 1.28 (m, 2H, major), 0.93 (t, *J* = 7.3 Hz, 3H, minor), 0.91 (t, *J* = 7.4 Hz, 3H, major).

¹³C NMR (151 MHz, CDCl₃) δ 159.37 (minor), 158.93 (minor), 35.66 (major), 28.48 (major), 28.43, 27.79, 22.96, 22.42 (major), 19.98, 13.98, 13.94 (major), 13.45.

HRMS (ESI⁺): *m/z* calcd for C₆H₁₃NO [*M*+H]⁺ 116.1070, found 116.1075.



(E)- and-(Z)-heptan-2-one oxime (2e): Prepared according to General Procedure B and isolated as a light yellow oil in a 10.1:1 (*E*):(*Z*) isomer ratio (78% yield).

¹H NMR (600 MHz, CDCl₃) δ 7.75 (br s, 1H), 2.39 – 2.32 (m, 2H, minor), 2.20 – 2.15 (m, 2H, major), 1.88 (s, 3H, major), 1.86 (s, 3H, minor), 1.55 – 1.47 (m, 2H, major and minor), 1.37 – 1.24 (m, 4H, major and minor), 0.93 (t, *J* = 7.5 Hz, 3H, minor) 0.89 (t, *J* = 7.1 Hz, 3H, major).

¹³C NMR (151 MHz, CDCl₃) δ major: 158.95, 35.91, 31.48, 26.04, 22.53, 14.09, 13.49, minor: 31.99, 28.68, 25.30, 20.97, 19.96.

HRMS (ESI⁺): *m/z* calcd for C₇H₁₅NO [*M*+H]⁺ 130.1226, found 130.1232.

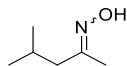


(E)- and (Z)-3-methylbutan-2-one oxime (2f): Prepared according to General Procedure B and isolated as a colorless liquid in a 6.6:1 (*E*):(*Z*) isomer ratio (62% yield).

¹H NMR (600 MHz, CDCl₃) δ 8.69 (br s, 1H), major: 2.49 (hept, *J* = 6.9 Hz, 1H), 1.85 (s, 3H), 1.09 (d, *J* = 6.9 Hz, 6H), minor: 3.47 (sept, *J* = 6.9 Hz, 1H), 1.78 (s, 3H), 1.05 (d, *J* = 6.9 Hz, 6H).

¹³C NMR (151 MHz, CDCl₃) δ 163.39, 162.78, 34.62, 25.86, 19.83, 18.98, 15.52, 11.20.

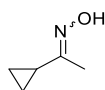
HRMS (ESI⁺): *m/z* calcd for C₅H₁₁NO [*M*+H]⁺ 102.0913, found 102.0915.



(E)- and (Z)-4-methyl-pentan-2-one oxime (2g): Prepared according to General Procedure B with some modifications. Rather than repeated washing with H₂O, the crude product was purified *via* column chromatography and isolated as a very pale yellow liquid in a 3.5:1 (*E*):(*Z*) isomer ratio (98% yield).

¹H NMR (600 MHz, CDCl₃) δ 7.81 (br s, 1H), 2.28 (d, *J* = 7.5 Hz, 2H, minor), 2.05 (d, *J* = 7.3 Hz, 2H, major), 2.03 – 1.96 (m, 1H, minor), 1.94 – 1.87 (m, 1H, major), 1.87 (s, 3H, major), 1.86 (s, 3H, minor), 0.94 (d, *J* = 6.6 Hz, 6H, minor), 0.91 (d, *J* = 6.6 Hz, 6H, major).
¹³C NMR (151 MHz, CDCl₃) δ 158.53, 158.25, 44.93, 37.62, 25.94, 25.89, 22.84, 22.51, 20.59, 13.62.

HRMS (ESI⁺): *m/z* calcd for C₆H₁₃NO [M+H]⁺ 116.1070, found 116.1072.

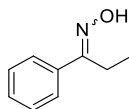


(E)- and (Z)-1-cyclopropylethan-1-one oxime (2h): Prepared according to General Procedure B with some modifications. Rather than repeated washing with H₂O, the crude product was purified *via* column chromatography and isolated as a light yellow liquid in a 10:1 (*E*):(*Z*) isomer ratio (99% yield).

¹H NMR (600 MHz, CDCl₃) δ 6.29 (s, 1H), 2.46 (tt, *J* = 8.6, 5.2 Hz, 1H, minor), 1.72 (s, 3H, major), 1.61 (tt, *J* = 8.4, 5.2 Hz, 1H, major), 1.57 (s, 3H, minor), 0.89 (dd, *J* = 8.7, 2.2 Hz, 1H), 0.0.78 – 0.66 (m, 4H, major and minor).

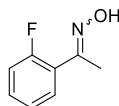
¹³C NMR (151 MHz, CDCl₃) δ 159.76, 15.21 (major), 14.61 (minor), 10.83 (major), 8.91 (minor), 5.16 (minor), 4.64 (major).

HRMS (ESI⁺): *m/z* calcd for C₅H₉NO [M+H]⁺ 100.07569, found 100.07564.



(E)-1-phenyl-1-propanone oxime (2i): Prepared according to General Procedure A and isolated as a white solid. Analytical data were consistent with literature reports.^{27,28}

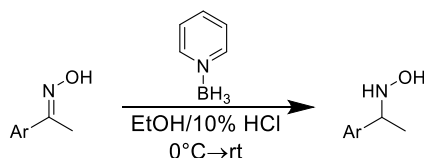
¹H NMR (500 MHz, CDCl₃) δ 7.65 – 7.58 (m, 2H), 7.38 (dd, *J* = 5.2, 1.9 Hz, 3H), 2.82 (q, *J* = 7.6 Hz, 2H), 1.18 (t, *J* = 7.6 Hz, 3H).



(E)- and (Z)-1-(2-fluorophenyl)ethanone oxime (2j): Prepared according to General Procedure A and isolated as a white solid as a mixture of isomers 14:1 (*E*):(*Z*). Analytical data were consistent with literature reports of the (*E*) isomer.²⁹

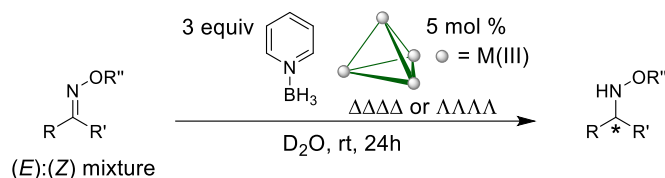
¹H NMR (500 MHz, CDCl₃) δ 9.17 (br, 1H), 7.46 (td, *J* = 7.6, 1.8 Hz, 1H, major), 7.35 (dddd, *J* = 8.2, 7.1, 5.1, 1.8 Hz, 1H, major), 7.30 (td, *J* = 7.6, 1.8 Hz, 1H minor), 7.20 – 7.06 (m, 2H major, 3H minor), 2.30 (d, *J* = 2.4 Hz, 3H, major), 2.23 (s, 3H, minor).

General Procedure C for the Racemic Synthesis of Aryl Hydroxylamines:



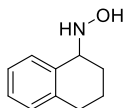
Synthesized based on a modified procedure.¹⁷ To a 25 mL round bottomed flask equipped with a stir bar containing oxime (0.62 mmol, 1 equiv.) was added EtOH (5 mL) and pyridine borane (**1a**) (1.90 mmol, 3.05 equiv.). The flask was cooled to 0°C before dropwise addition of 10% HCl (10 mL). The reaction was allowed to slowly warm to rt until stopped. The resulting solution was transferred to a separatory funnel and washed twice with Et₂O (2x15 mL). To the aqueous layer was added 5M KOH until the aqueous solution pH was between 12 and 14. The basic aqueous layer was then washed three times with EtOAc (3x15 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated *via* rotary evaporation. The resulting crude product was purified by prep TLC in 2.5% MeOH/DCM.

General Procedure D for M₄L₆¹²⁻ Host-Catalyzed Reductions of Aryl Oximes



To a 1 dr vial containing host (5 mol%) was added D₂O *via* Eppendorf pipette. The host solution was transferred to a second 1 dr vial equipped with a magnetic stir bar containing oxime (1.0 equiv.). The 1 dr vial containing host was rinsed with D₂O and the rinse was also transferred to the 1 dr vial containing oxime. The final concentration of solution was 55 mM in oxime. The heterogeneous solution was allowed to stir at rt for 5 minutes before addition of pyridine borane (**1a**) (3.0 equiv.) *via* Hamilton syringe. The reaction was then stirred at rt until the reaction time was complete, at which point the reaction was stopped by adding a large unmeasured excess of tetraethylphosphonium iodide (PEt₄I) or bromide (PEt₄Br). The stir bar was removed using a stir bar magnet and rinsed with CDCl₃. Additional CDCl₃ was added to the vial to extract the product and the CDCl₃ rinse was transferred to a 2 dr vial. The reaction solution was washed at least 3 times with CDCl₃. Solvent in the 2 dr vial from the combined rinses was removed *via* rotary evaporation to be less than 500 µL, but not to full dryness. Internal standard, 1,3,5-trimethoxybenzene (2.00 mg, 0.0119 mmol), as a stock solution in CDCl₃ (594.5 mM) was added *via* Hamilton syringe to the 2 dr vial and the solution was transferred to an NMR tube for ¹H NMR analysis to determine yield.

Following NMR analysis of the crude reaction mixture extract, the product was returned to the 2 dr vial and the NMR tube was rinsed with EtOAc and CH₂Cl₂. Solvent in the vial was removed to near-dryness *via* rotary evaporation. The crude product was purified and isolated *via* prep TLC.



1,2,3,4-Tetrahydro-*N*-hydroxy-1-naphthalenamine (3a): Racemic material was prepared from oxime **2a** according to General Procedure C. The reaction was run for 3h before workup. The crude product was purified by prep TLC in 2.0% MeOH/DCM and isolated as a white solid. Analytical data were consistent with literature reports.⁸

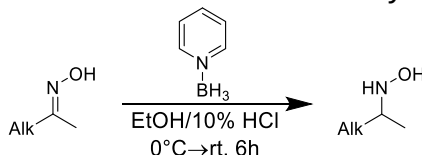
¹H NMR (600 MHz, CDCl₃) δ 7.34 (dd, *J* = 7.2, 1.9 Hz, 1H), 7.21 – 7.14 (m, 2H), 7.13 – 7.09 (m, 1H), 5.30 (s, 1H), 4.11 (t, *J* = 4.3 Hz, 1H), 2.85 – 2.69 (m, 2H), 2.26 – 2.18 (m, 1H), 2.01 – 1.71 (m, 3H).

Although the purified product was found to exhibit moderate solubility in 95% hexanes/IPA, the addition of small amounts of THF to improve solubility was found to lead to rapid product decomposition. To avoid product decomposition before analysis, co-solvents were avoided and prepared HPLC samples were immediately run on chiral HPLC.

ChiralCel OJ-H column (98:2 hexanes/*i*PrOH, 1 mL/min), *t_r* = 26.3 min (major with $\Delta\Delta\Delta\Delta$ -**Va**), *t_r* = 34.0 min (minor).

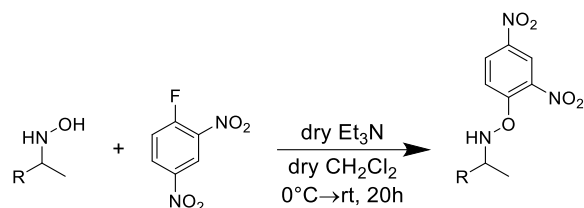
Enantioenriched material was prepared from oxime **2a** (4.42 mg, 0.0274 mmol) according to General Procedure D. The reaction was stopped with PEt₄I after 24h. Following extraction, the crude extract solution was analyzed by ¹H NMR (82% NMR yield), then the product was purified by prep TLC in 2% MeOH/DCM and isolated as a white solid for HPLC analysis (24% ee).

General Procedure E for the Synthesis of Aliphatic Hydroxylamines: Modified version of General Procedure C due to substrate volatility.



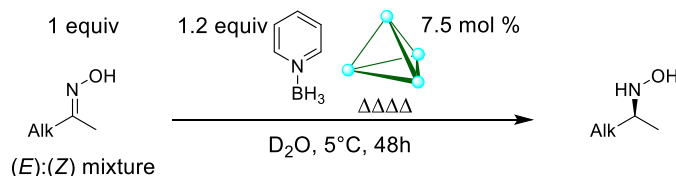
To a 25 mL round bottomed flask equipped with a stir bar containing oxime (0.62 mmol, 1 equiv.) was added EtOH (5 mL) and pyridine borane (**1a**) (1.85 mmol, 3.00 equiv.). The flask was cooled to 0°C before dropwise addition of 10% HCl (10 mL). The reaction was kept at 0°C for 2h, after which it was allowed to slowly warm to rt overnight and was stopped after 16h. The resulting solution was transferred to a separatory funnel and washed with Et₂O (15 mL) x2. To the aqueous layer was added 2k KOH until the solution pH was 12–13. The aqueous layer was then washed with DCM (15 mL) x3. The combined organic layers were dried over MgSO₄, filtered, and concentrated *via* rotary evaporation. To minimize product loss, the rotovap bath temperature was kept below 8°C. Characterized products were purified by prep TLC in 2.5% MeOH/DCM with 0.5% Et₃N and visualized using KMnO₄.

General Procedure F for Hydroxylamine Protection for HPLC Analysis



Based on a modified procedure.³⁰ To a 1 or 2 dr vial containing crude hydroxylamine was added dry CH_2Cl_2 (0.09 mM). The vial was cooled to 0°C before addition of 2,4-dinitrofluorobenzene (1.05 equiv.) and dry Et_3N (1.0 equiv.). The reaction was allowed to slowly warm to room temperature overnight. After approximately 20h, the reaction was stopped and the organic layer diluted with CH_2Cl_2 . The organic layer was washed with H_2O , and the aqueous layer was then back extracted with EtOAc . The combined organic layers were dried with MgSO_4 and solvent removed *via* rotary evaporator. The hydroxylamine was purified and isolated by prep TLC in 30% EtOAc /hexanes before being dissolved in 5% hexanes/IPA for chiral HPLC analysis.

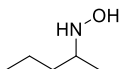
General Procedure G for Enantiopure Host Catalyzed Reactions Optimized for Aliphatic Oximes



To a 1 dr vial containing $\Delta\Delta\Delta\Delta$ host **IIa** (7.5 mol%) was added D_2O *via* Eppendorf pipette. The host solution was transferred to an NMR tube. The 1 dr vial was rinsed with D_2O and the rinse was also transferred to the NMR tube. Oxime (1 equiv.) was then added *via* Hamilton syringe to the NMR tube and capped with a septa cap before being added to a cold bath kept at 5°C . The final concentration of solution was 55 mM in oxime. After 5 mins in the cold bath, the NMR tube was quickly removed to add pyridine borane (**1a**) (1.2 equiv.) *via* Hamilton syringe. The tube was electrical taped and inverted two or three times to mix the solution thoroughly before being returned to the cold bath. After 48h, the NMR tube was removed from the cold bath and the reaction was stopped by adding tetraethylphosphonium iodide (PEt_4I) or bromide (PEt_4Br) ($3.15\ \mu\text{mol}$, 7.5 mol%) as a stock solution in D_2O . Internal standard, 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt (2 mg, $9.16\ \mu\text{mol}$), as a stock solution in D_2O was added *via* Hamilton syringe for NMR analysis.

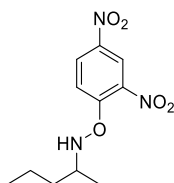
Following ^1H NMR analysis, the reaction mixture was transferred to a 1 dr vial. The NMR tube was rinsed with CH_2Cl_2 . Additional CH_2Cl_2 was added to the vial to extract the product and the CH_2Cl_2 rinse was transferred to a 1 dr vial. The reaction solution was washed at least 3 times with CH_2Cl_2 . Organic solvent in the 1 dr vial from the combined rinses was removed to dryness *via* rotary evaporation below 7°C . Then a small portion of NaCl was added to the host solution in the 1 dr vial and aqueous layer was again washed at least 3 times with CH_2Cl_2 . Again the rinses were transferred to the 1 dr vial and solvent was removed to dryness *via* rotary evaporation. The crude product was assumed to be

extracted quantitatively and subjected to General Procedure F with a slight modification, through the use of increased amounts of 2,4,-dinitrofluorobenzene (1.4 equiv.) and dry Et₃N (1.4 equiv.).



N-hydroxy-2-pentanamine (3b): Racemic material was prepared from oxime **2b** according to General Procedure E and isolated as white solid. Analytical data were consistent with literature reports.¹⁷

¹H NMR (600 MHz, CDCl₃) δ 5.00 (br s, 2H), 2.98 (dq, J = 12.6, 6.3 Hz, 1H), 1.52 (ddt, J = 13.0, 9.6, 5.7 Hz, 1H), 1.41 – 1.20 (m, 3H), 1.08 (d, J = 6.4 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H).



A portion of the purified product (6.7 mg, 0.065 mmol) was functionalized for chiral HPLC analysis using General Procedure F with a slight modification. Increased 2,4-dinitrofluorobenzene (1.5 equiv.) was used. After workup the product was isolated as a yellow solid.

ChiralPak IA column (98.5:1.5 hexanes/*i*PrOH, 1mL/min), t_r = 15.4 min (major), t_r = 17.0 min (minor).

Enantioenriched material was prepared from oxime **2b** (4.65 mg, 0.0460 mmol) according to General Procedure G and allowed to react at 5°C for 48h before quenching with PEt₄. Following *in situ* ¹H NMR analysis (65% NMR yield), the product was extracted and subjected to a modified version of General Procedure F using dry CH₂Cl₂ (350 μ L), 2,4,-dinitrofluorobenzene (4.50 μ L, 0.0358 mmol, 1.2 equiv.), and dry Et₃N (5.00 μ L, 0.0358 mmol, 1.2 equiv.). The crude functionalized product was purified by prep TLC in 30% EtOAc/hexanes and isolated as yellow solid for HPLC analysis (74% ee).

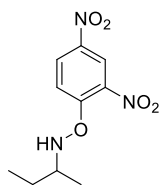


N-hydroxy-2-butanamine (3c): Racemic material was prepared from oxime **2c** according to General Procedure E and isolated as white solid.

¹H NMR (600 MHz, CDCl₃) δ 4.71 (br s, 2H), 2.91 (dq, J = 12.7, 6.3 Hz, 1H), 1.59 (dq, J = 12.9, 7.5, 5.4 Hz, 1H), 1.36 – 1.27 (m, 1H), 1.07 (d, J = 6.3 Hz, 3H), 0.92 (t, J = 7.5 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 58.83, 26.57, 17.36, 10.33.

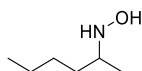
HRMS (ESI⁺): m/z calcd for C₄H₁₁NO [M+H]⁺ 90.0913, found 90.0921.



A portion of the purified product (5.35 mg, 0.60 mmol) was functionalized for chiral HPLC analysis using General Procedure F and isolated as a yellow solid.

ChiralPak AD-H column (99:1 hexanes/*i*-PrOH, 1 mL/min), t_r = 26.8 min (major), t_r = 30.0 min (minor).

Enantioenriched material was prepared from oxime **2c** (3.74 mg, 0.0429 mmol) according to General Procedure G and allowed to react at 5°C for 48h before quenching with PEt_4Br . Following *in situ* ^1H NMR analysis (85% NMR yield), the product was extracted and subjected to a modified version of General Procedure F using dry CH_2Cl_2 (400 μL), 2,4-dinitrofluorobenzene (5.60 μL , 0.0443 mmol, 1.21 equiv.), and dry Et_3N (6.20 μL , 0.0443 mmol, 1.21 equiv.). The crude functionalized product was purified by prep TLC in 30% EtOAc/hexanes and isolated as yellow solid for HPLC analysis (78% ee).

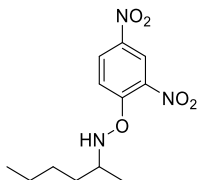


N-hydroxy-2-hexanamine (3d): Racemic material was prepared from oxime **2d** according to General Procedure E and isolated as white solid.

^1H NMR (500 MHz, CDCl_3) δ 4.11 (br s, 2H), 2.97 (h, J = 6.4 Hz, 1H), 1.54 (m, 1H), 1.29 (m, 5H), 1.08 (d, J = 6.3 Hz, 3H), 0.90 (t, J = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 57.47, 33.61, 28.31, 23.03, 23.03, 17.94, 14.18.

HRMS (ESI⁺): m/z calcd for $\text{C}_6\text{H}_{15}\text{NO}$ [$\text{M}+\text{H}$]⁺ 118.1226, found 118.1230.



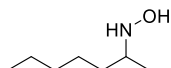
A portion of the purified product (23 mg, 0.200 mmol) was functionalized for chiral HPLC analysis using General Procedure F and isolated as a yellow solid.

ChiralPak AD-H column (99.6:0.4 hexanes/*i*-PrOH, 1 mL/min), t_r = 50.4 min (major), t_r = 57.3 min (minor).

Enantioenriched material was prepared from oxime **2d** according to General Procedure D with some modifications. To a 1 dr vial equipped with a magnetic stir bar containing $\Delta\Delta\Delta\Delta$ host **IIa** (15.04 mg, 3.226 μmol , 7.5 mol%) was added D_2O (775 μL) *via* Eppendorf pipette. Oxime was added to the solution *via* Hamilton syringe (4.94 mg, 0.0429 mmol). The solution was cooled to 5°C before pyridine borane (**1a**) (4.78 mg, 5.15 μL , 0.0515 mmol, 1.2 equiv.) was added *via* Hamilton syringe to the cooled vial. The reaction was then stirred at 5°C for 48h, then the reaction was stopped by adding an unmeasured excess of PEt_4Br . The stir bar was removed using a stir bar magnet and rinsed with CDCl_3 . Additional CDCl_3 was added to the vial to extract the product and the CDCl_3 rinse was

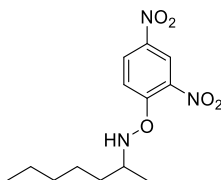
transferred to a 2 dr vial. The reaction solution was washed at least 3 times with CDCl_3 . Solvent in the 2 dr vial from the combined rinses was removed *via* rotary evaporation to be less than 500 μL , but not to full dryness. To minimize product loss, the rotovap bath temperature was kept below 7°C . To the 1 dr reaction vial was added a small, unmeasured amount of NaCl . The extraction process was repeated once more and the resulting solution from rinses partially removed *via* rotary evaporation. Internal standard was added, and the solution was transferred to an NMR tube for ^1H NMR analysis (18% NMR yield).

Following NMR analysis of the crude reaction mixture extract, the product was returned to the 2 dr vial and the NMR tube was rinsed with CH_2Cl_2 . Solvent in the vial was removed to near-dryness ($<50\ \mu\text{L}$ solution) *via* rotary evaporation, still below 7°C . Dry CH_2Cl_2 (200 μL) was added to the 2 dr vial and the solution transferred to a new 1 dr vial equipped with a magnetic stir bar. The 2 dr vial was rinsed with additional CH_2Cl_2 (350 μL) and the rinse transferred to the 1 dr vial. The crude product was assumed to be transferred quantitatively and subjected to General Procedure F with a slight modification, through the use of increased amounts of 2,4,-dinitrofluorobenzene (4.15 μL , 0.330 mmol, 4.28 equiv.), and dry Et_3N (4.60 μL , 0.033 mmol, 4.28 equiv.). The crude functionalized product was purified by prep TLC in 30% EtOAc /hexanes and isolated as yellow solid for HPLC analysis (46% ee).



N-hydroxy-2-heptanamine (3e): Racemic material was prepared from oxime **2e** according to General Procedure E and isolated as a white solid. Analytical data were consistent with literature reports.³¹

^1H NMR (600 MHz, CDCl_3) δ 5.13 (s, 2H), 2.96 (h, $J = 6.3\ \text{Hz}$, 1H), 1.52 (ddd, $J = 12.6, 9.7, 5.7\ \text{Hz}$, 1H), 1.35 – 1.22 (m, 7H), 1.08 (d, $J = 6.3\ \text{Hz}$, 3H), 0.89 (t, $J = 7.2\ \text{Hz}$, 3H).



A portion of the purified product (28.8 mg, 0.219 mmol) was functionalized for chiral HPLC analysis using General Procedure F and isolated as a yellow solid.

ChiralPak AD-H column (99.4:0.6 hexanes/ i PrOH, 1 mL/min), $t_r = 23.9\ \text{min}$ (major), $t_r = 25.9\ \text{min}$ (minor).

Enantioenriched material was prepared from oxime **2e** according to General Procedure D with some modifications. To a 1 dr equipped with a magnetic stir bar vial containing $\Delta\Delta\Delta\Delta$ host **IIa** (14.45 mg, 3.100 μmol , 7.5 mol%) was added D_2O (750 μL) *via* Eppendorf pipette. Oxime was added to the solution *via* Hamilton syringe (5.33 mg, 0.0413 mmol). The solution was cooled to 5°C before pyridine borane (**1a**) (4.60 mg, 4.95 μL , 0.0495 mmol, 1.2 equiv.) was added *via* Hamilton syringe to the cooled vial. The reaction was then stirred at 5°C for 48h, then the reaction was stopped by adding an unmeasured excess of PEt_4Br . The stir bar was removed using a stir bar magnet and rinsed with CDCl_3 .

Additional CDCl₃ was added to the vial to extract the product and the CDCl₃ rinse was transferred to a 2 dr vial. The reaction solution was washed at least 3 times with CDCl₃. Solvent in the 2 dr vial from the combined rinses was removed *via* rotary evaporation to be less than 500 μ L, but not to full dryness. To minimize product loss, the rotovap bath temperature was kept below 7°C. To the 1 dr reaction vial was added a small, unmeasured amount of NaCl. The extraction process was repeated once more and the resulting solution from rinses partially removed *via* rotary evaporation. Internal standard was added, and the solution was transferred to an NMR tube for ¹H NMR analysis (<10% NMR yield).

Following NMR analysis of the crude reaction mixture extract, the product was returned to the 2 dr vial and the NMR tube was rinsed with CH₂Cl₂. Solvent in the vial was removed to near-dryness (<50 μ L solution) *via* rotary evaporation, still below 7°C. Dry CH₂Cl₂ (200 μ L) was added to the 2 dr vial and the solution transferred to a new 1 dr vial equipped with a magnetic stir bar. The 2 dr vial was rinsed with additional CH₂Cl₂ (400 μ L) and the rinse transferred to the 1 dr vial. The crude product was assumed to be transferred quantitatively and subjected to General Procedure F with a slight modification, through the use of increased amounts of 2,4-dinitrofluorobenzene (5.2 μ L, 0.0414 mmol) and dry Et₃N (5.75 μ L, 0.0413 mmol). The crude functionalized product was purified by prep TLC in 30% EtOAc/hexanes and isolated as yellow solid for HPLC analysis (45% ee).

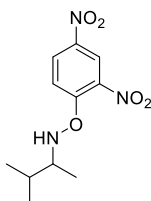


N-Hydroxy-3-methyl-2-butanamine (3f): Racemic material was prepared from oxime **2f** according to General Procedure E and isolated as a white solid.

¹H NMR (600 MHz, CDCl₃) δ 2.83 (qd, *J* = 6.5, 5.1 Hz, 1H), 1.84 (hept, *J* = 6.9, 5.0 Hz, 1H), 1.01 (d, *J* = 6.5 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 62.44, 29.75, 19.61, 17.35, 13.64.

HRMS (ESI⁺): *m/z* calcd for C₅H₁₃NO [M+H]⁺ 104.1070, found 104.1068.

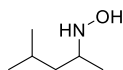


A portion of the purified product (12.0 mg, 0.116 mmol) was functionalized for chiral HPLC analysis using General Procedure F with a slight modification. Increased 2,4-dinitrofluorobenzene (1.2 equiv.) and Et₃N (1.2 equiv.) were used. After workup the product was isolated as a yellow solid.

ChiralPak AD-H column (99:1 hexanes/*i*PrOH, 1 mL/min), *t_r* = 22.1 min (minor), *t_r* = 25.4 min (major).

Enantioenriched material was prepared from oxime **2f** (3.41 mg, 0.0337 mmol) according to General Procedure G using $\Delta\Delta\Delta\Delta$ host **IIa** (11.79 mg, 2.529 μ mol, 7.5 mol%) and allowed to react at 5°C for 48h before quenching with PEt₄Br. Following *in situ* ¹H NMR

analysis (65% NMR yield), the product was extracted and subjected to a modified version of General Procedure F using dry CH_2Cl_2 (300 μL), 2,4,-dinitrofluorobenzene (4.05 μL , 0.0323 mmol, 1.47 equiv.), and dry Et_3N (4.50 μL , 0.0323 mmol, 1.47 equiv.). The crude functionalized product was purified by prep TLC in 30% EtOAc/hexanes and isolated as yellow solid for HPLC analysis (40% ee).

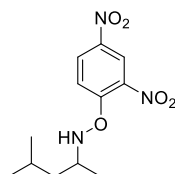


N-Hydroxy-4-methyl-2-pentanamine (3g): Racemic material was prepared from oxime **2g** according to General Procedure E and isolated as a white solid.

^1H NMR (600 MHz, CDCl_3) δ 4.94 (br s, 2H), 3.05 (dp, J = 7.6, 6.2 Hz, 1H), 1.66 (dh, J = 7.9, 6.5 Hz, 1H), 1.38 (ddd, J = 13.7, 7.9, 6.0 Hz, 1H), 1.13 (ddd, J = 13.8, 7.6, 6.5 Hz, 1H), 1.09 (d, J = 6.3 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 55.49, 43.19, 25.12, 23.38, 22.60, 18.26.

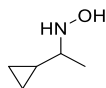
HRMS (ESI⁺): m/z calcd for $\text{C}_6\text{H}_{15}\text{NO}$ [$\text{M}+\text{H}$]⁺ 118.1226, found 118.1228.



A portion of the purified product (14.6 mg, 0.125 mmol) was functionalized for chiral HPLC analysis using General Procedure F with a slight modification. Increased 2,4-dinitrofluorobenzene (1.1 equiv.) and Et_3N (1.1 equiv.) were used. After workup the product was isolated as a yellow solid.

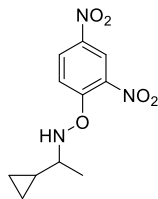
ChiralPak AD-H column (98.5:1.5 hexanes/ i PrOH, 1 mL/min), t_r = 10.5 min (minor), t_r = 11.9 min (major).

Enantioenriched material was prepared from oxime **2g** (6.99 mg, 0.0607 mmol) according to General Procedure G using $\Delta\Delta\Delta\Delta$ host **IIa** (22.01 mg, 4.721 μmol , 7.5 mol%) and allowed to react at 5°C for 48h before quenching with PET_4Br . Following *in situ* ^1H NMR analysis (13% NMR yield), the product was extracted and subjected to a modified version of General Procedure F using dry CH_2Cl_2 (150 μL), 2,4,-dinitrofluorobenzene (2.00 μL , 0.0159 mmol, 2.02 equiv.), and dry Et_3N (2.20 μL , 0.0158 mmol, 2.00 equiv.). The crude functionalized product was purified by prep TLC in 30% EtOAc/hexanes and isolated as yellow solid for HPLC analysis (23% ee).



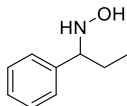
N-Hydroxy- α -methylcyclopropanemethanamine (3h): Racemic material was prepared from oxime **2h** according to General Procedure E and isolated as a white solid. Analytical data were consistent with literature reports.³²

^1H NMR (600 MHz, CDCl_3) δ 5.29 (s, 2H), 2.26 – 2.16 (m, 1H), 1.20 (d, J = 6.4 Hz, 3H), 0.76 – 0.68 (m, 1H), 0.49 (d, J = 8.8 Hz, 2H), 0.31 – 0.23 (m, 1H), 0.19 – 0.10 (m, 1H).



A portion of the purified product (17.3 mg, 0.171 mmol) was functionalized for chiral HPLC analysis using General Procedure F and isolated as a yellow solid. ChiralPak IA column (96:4 hexanes/*i*PrOH, 1 mL/min), t_r = 12.4 min (major), t_r = 14.0 min (minor).

Enantioenriched material was prepared from oxime **2h** (4.89 mg, 0.0493 mmol) according to General Procedure G using $\Lambda\Lambda\Lambda$ host **IIa** (17.30 mg, 3.711 μ mol, 7.5 mol%) and allowed to react at 5°C for 48h before quenching with PET_4Br . Following *in situ* ^1H NMR analysis (59% NMR yield), the product was extracted and subjected to a modified version of General Procedure F using dry CH_2Cl_2 (500 μL), 2,4,-dinitrofluorobenzene (5.15 μL , 0.0410 mmol, 1.41 equiv.), and dry Et_3N (5.70 μL , 0.0409 mmol, 1.41 equiv.). The crude functionalized product was purified by prep TLC in 30% EtOAc/hexanes and isolated as yellow solid for HPLC analysis (19% ee).

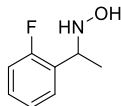


α -Ethyl-*N*-hydroxybenzenemethanamine (3i): Racemic material was prepared from oxime **2i** according to General Procedure C. The reaction was run for 2h before workup. The crude product was purified by prep TLC in 2% MeOH/DCM and isolated as a white solid. Analytical data were consistent with literature reports.³³

^1H NMR (600 MHz, CDCl_3) δ 7.37 – 7.31 (m, 2H), 7.31 – 7.25 (m, 3H), 5.61 (br, 1H), 3.83 (dd, J = 8.7, 5.4 Hz, 1H), 1.88 (dtd, J = 13.1, 7.5, 5.6 Hz, 1H), 1.68 – 1.55 (m, 1H), 0.82 (t, J = 7.4 Hz, 3H).

ChiralCel OJ-H column (97:3 hexanes/*i*PrOH, 1 mL/min), t_r = 14.5 min (minor), t_r = 19.0 min (major).

Enantioenriched material was prepared from oxime **2i** (4.03 mg, 0.0270 mmol) according to General Procedure D. The reaction was stopped with PET_4I after 24h. Following extraction, the crude extract solution was analyzed by ^1H NMR (93% NMR yield), then the product was purified by prep TLC in 2% MeOH/DCM and isolated as a white solid for HPLC analysis (64% ee).



2-Fluoro-*N*-hydroxy- α -methylbenzenemethanamine (3j): Racemic material was prepared from oxime **2j** according to General Procedure C. The reaction was run for 5h and the product was isolated as a white solid. Analytical data were consistent with literature reports.³⁴

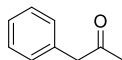
^1H NMR (600 MHz, CDCl_3) δ 7.37 (td, $J = 7.5, 1.8$ Hz, 1H), 7.28 – 7.21 (m, 1H), 7.13 (td, $J = 7.5, 1.2$ Hz, 1H), 7.04 (ddd, $J = 10.6, 8.2, 1.2$ Hz, 1H), 5.84 (br, 2H), 4.46 (q, $J = 6.8$ Hz, 1H), 1.40 (d, $J = 6.8$ Hz, 3H).

ChiralCel OJ-H column (98:2 hexanes/ i PrOH, 1 mL/min), $t_r = 19.9$ min (major), $t_r = 23.3$ min (minor).

Enantioenriched material was prepared from oxime **2j** (3.98 mg, 0.0260 mmol) according to General Procedure D using $\Delta\Delta\Delta\Delta$ host **I** (6.29 mg, 1.30 μmol , 5.0 mol%). The reaction was stopped with PET_4Br after 24h. Following extraction, the crude extract solution was analyzed by ^1H NMR (79% NMR yield), then the product was purified by prep TLC in 2.25% MeOH/DCM and isolated as a white solid for HPLC analysis (65% ee).

Ketone Synthesis

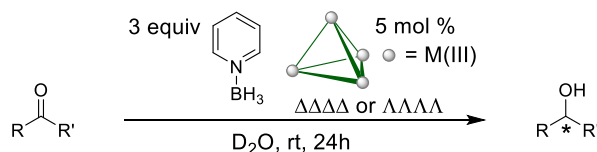
1-Phenylethanone (4a) and **1-phenyl-1-propanone (4b)** were used as received from commercial sources.



1-Phenyl-2-propanone (4c): The title compound was prepared according to a reported procedure from α -Methylstyrene.³⁵ Purification by column chromatography eluting with hexanes/EtOAc (0–30% EtOAc) yielded the title compound as a clear oil. Analytical data were consistent with literature reports.³⁶

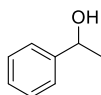
Alcohol Synthesis

General Procedure H for the Enantioenriched Synthesis of Aryl Alcohols: A slightly modified version of General Procedure D to account for the use of ketones.



To a 1 dr vial equipped with a magnetic stir bar containing host (5 mol%) was added D_2O *via* Eppendorf pipette. To this 1 dr vial was added ketone (1.0 equiv.) *via* Hamilton syringe. The final concentration of solution was 55 mM in ketone. The heterogeneous solution was allowed to stir at rt for 5 minutes before addition of pyridine borane (**1a**) (3.0 equiv.) *via* Hamilton syringe. The reaction was then stirred at rt until the reaction time was complete, at which point the reaction was stopped by adding a large unmeasured excess of tetraethylphosphonium iodide (PET_4I) or bromide (PET_4Br). The stir bar was removed using a stir bar magnet and rinsed with CDCl_3 . Additional CDCl_3 was added to the vial to extract the product and the CDCl_3 rinse was transferred to a 2 dr vial. The reaction solution was washed at least 3 times with CDCl_3 . Solvent in the 2 dr vial from the combined rinses was removed *via* rotary evaporation to be less than 500 μL , but not to full dryness. Internal standard, 1,3,5-trimethoxybenzene (2.00 mg, 0.0119 mmol), as a stock solution in CDCl_3 (594.5 mM) was added *via* Hamilton syringe to the 2 dr vial and the solution was transferred to an NMR tube for ^1H NMR analysis to determine yield.

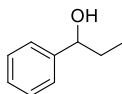
Following NMR analysis of the crude reaction mixture extract, the product was returned to the 2 dr vial and the NMR tube was rinsed with EtOAc and CH₂Cl₂. Solvent in the vial was removed to near-dryness *via* rotary evaporation. The crude product was isolated *via* prep TLC in 2% MeOH/DCM.



1-Phenylethanol (5a) was used as received from commercial sources for a racemic chiral HPLC trace.

ChiralCel OJ-H column (97:3 hexanes/*i*PrOH, 1 mL/min), *t_r* = 12.0 min (minor when ΔΔΔΔ host used), *t_r* = 14.1 min (major).

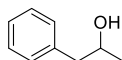
Enantioenriched material was prepared from **4a** using General Procedure H for each respective synthesis using ΔΔΔΔ **1a**, ΔΔΔΔ **1la**, or ΔΔΔΔ **1lla**.



1-Phenyl-1-propanol (5b) was used as received from commercial sources for racemic chiral HPLC traces.

ChiralCel OJ-H column (90:1 hexanes/*i*PrOH, 1 mL/min), *t_r* = 25.8 min (minor when ΔΔΔΔ host used), *t_r* = 28.6 min (major).

Enantioenriched material was prepared from **4b** using General Procedure H for each respective synthesis using ΔΔΔΔ **1a**, ΔΔΔΔ **1la**, or ΔΔΔΔ **1lla**.



1-Phenyl-2-propanol (5c): The title compound was prepared according to a reported procedure from the parent ketone (**4c**).³⁷ The crude product was purified by prep TLC in 2.0% MeOH/DCM and isolated as a clear oil. Analytical data were consistent with literature reports.³⁸

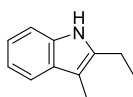
ChiralCel OJ-H column (99:1 hexanes/*i*PrOH, 1 mL/min), *t_r* = 18.7 min, *t_r* = 21.0 min.

Enantioenriched material was prepared from ketone **4c** (5.88 mg, 0.0438 mmol) according to a slightly modified version of General Procedure H. To a 1 dr vial containing ΔΔΔΔ host **1a** (10.58 mg, 2.19 μmol, 5 mol%) was added D₂O (600 μL) *via* Eppendorf pipette. The host solution was transferred to a second 1 dr vial equipped with a magnetic stir bar containing ketone. The 1 dr vial containing host was rinsed with D₂O (195 μL) and the rinse was also transferred to the 1 dr vial containing oxime. The final concentration of solution was 55 mM in oxime. The heterogeneous solution was allowed to stir at rt for 5 minutes before addition of pyridine borane (**1a**) (13.25 μL, 12.31 mg, 0.132 mmol, 3.0 equiv.) *via* Hamilton syringe. The reaction was stopped with PEt₄I after 24h. Following

extraction, the crude extract solution was analyzed by ^1H NMR (17% NMR yield), then the product was purified by prep TLC in 2% MeOH/DCM and isolated as a white solid for HPLC analysis (0% ee).

Synthesis of Indoles:

2-Methylindole (6a), **3-Methylindole (6b)**, and **2,3-Dimethylindole (6c)** were used as received from commercial sources.

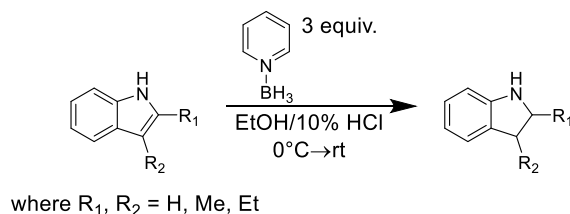


2-ethyl-3-methylindole (6d): The title compound was prepared according to a reported procedure from phenylhydrazine hydrochloride and 3-pentanone.³⁹ After cooling, the reaction vessel was covered with foil and solution largely kept in the dark during workup. Purification by column chromatography eluting with hexanes/EtOAc (0–10% EtOAc) yielded the title compound as a white solid. Analytical data were consistent with literature reports.⁴⁰

^1H NMR (400 MHz, CDCl_3) δ 7.83 – 7.62 (br s, 1H), 7.52 – 7.45 (m, 1H), 7.30 – 7.26 (m, 1H), 7.10 (pd, J = 7.1, 1.4 Hz, 2H), 2.77 (q, J = 7.6 Hz, 2H), 2.24 (s, 3H), 1.28 (t, J = 7.6 Hz, 3H).

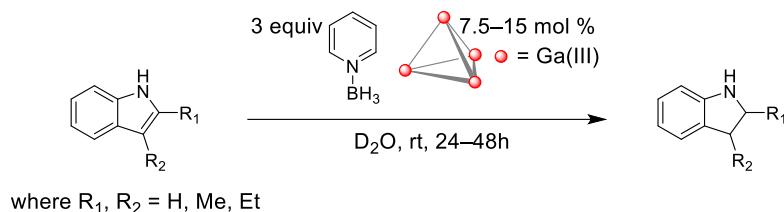
Indoline Synthesis

General Procedure I for Racemic Synthesis of Indolines: A modified version of General Procedure C to account for the use of indoles.



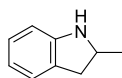
Synthesized based on a modified procedure.¹⁷ To a 25 mL round bottomed flask equipped with a stir bar containing indole (0.31 mmol, 1 equiv.) was added EtOH (2.5 mL) and pyridine borane (**1a**) (0.95 mmol, 3.06 equiv.). The flask was covered with foil and kept in the dark to limit indole decomp. The flask was cooled to 0°C before dropwise addition of 10% HCl (5 mL). The reaction was allowed to slowly warm to rt until stopped. The resulting solution was transferred to a separatory funnel and washed twice with Et_2O (2x15 mL). To the aqueous layer was added 5M KOH until the aqueous solution pH was between 12 and 14. The basic aqueous layer was then washed three times with EtOAc (3x15 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated *via* rotary evaporation. The resulting crude product was purified and quickly isolated by prep TLC in 1.5% MeOH/ CH_2Cl_2 to avoid decomposition.

General Procedure J for the Host-Catalyzed Synthesis of Indolines: A slightly modified version of General Procedure D to account for the use of indoles.



To a 1 dr vial containing host (7.5 mol% for enantiopure host, 15 mol% host for racemic host **IV** unless otherwise noted) was added D₂O (for enantiopure hosts unless otherwise noted)/50 mM K₃PO₄ pD 7.5 D₂O buffer (for host **IV** unless otherwise noted) *via* Eppendorf pipette. The host solution was transferred to a second, amber 1 dr vial equipped with a magnetic stir bar containing indole (1.0 equiv.) and covered in foil. The 1 dr vial containing host was rinsed with D₂O and the rinse was also transferred to the 1 dr vial containing indole. The final concentration of solution was 55 mM in indole. The heterogeneous solution was allowed to stir at rt for 5 minutes before addition of pyridine borane (**1a**) (2.0–3.0 equiv.) *via* Hamilton syringe. The reaction was then stirred at rt until the reaction time was complete, at which point the reaction was stopped by adding a large unmeasured excess of tetraethylphosphonium bromide (PEt₄Br). The stir bar was removed using a stir bar magnet and rinsed with CDCl₃. Additional CDCl₃ was added to the vial to extract the product and the CDCl₃ rinse was transferred to a 2 dr vial. The reaction solution was washed at least 3 times with CDCl₃. Solvent in the 2 dr vial from the combined rinses was removed *via* rotary evaporation to be less than 500 μ L, but not to full dryness. Internal standard, 1,3,5-trimethoxybenzene (2.00 mg, 0.0119 mmol), as a stock solution in CDCl₃ (594.5 mM) was added *via* Hamilton syringe to the 2 dr vial and the solution was transferred to an NMR tube for ¹H NMR analysis to determine yield.

Following NMR analysis of the crude reaction mixture extract, the product was returned to the 2 dr vial and the NMR tube was rinsed with EtOAc and CH₂Cl₂. Solvent in the vial was removed to near-dryness *via* rotary evaporation. The crude product was purified and quickly isolated *via* prep TLC in 1.5% MeOH/CH₂Cl₂ to avoid decomposition.



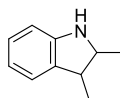
2-Methylindoline (7a): Racemic material was prepared from indole **6a** (82 mg, 0.625 mmol) and scaled up according to General Procedure I. The reaction was run for 16h before workup. The resulting product was purified by prep TLC in 1.5% MeOH/DCM and quickly isolated as a white solid. Analytical data were consistent with literature reports.⁴¹ ¹H NMR (400 MHz, CDCl₃) δ 7.07 (d, *J* = 7.3 Hz, 1H), 7.04 – 6.97 (m, 1H), 6.69 (td, *J* = 7.3, 1.1 Hz, 1H), 6.61 (d, *J* = 7.7 Hz, 1H), 3.99 (dtt, *J* = 12.4, 8.1, 4.1 Hz, 1H), 3.14 (dd, *J* = 15.4, 8.5 Hz, 1H), 2.63 (dd, *J* = 15.4, 7.8 Hz, 1H), 1.29 (d, *J* = 6.3 Hz, 3H).

Host-catalyzed reactions employed indole **6a** using General Procedure H for each respective synthesis using host **la**, **IIla**, or **IV**.



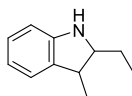
3-Methylindoline (7b): Racemic material was prepared from indole **6b** (81.5 mg, 0.62 mmol) and scaled up according to General Procedure I. The reaction was stirred for 2h before workup. The resulting product was purified by prep TLC in 1.5% MeOH/DCM and quickly isolated as a white solid. Analytical data were consistent with literature reports.⁴¹ ¹H NMR (400 MHz, CDCl₃) δ 7.09 (d, *J* = 7.2 Hz, 1H), 7.06 – 6.99 (m, 1H), 6.79 – 6.70 (m, 1H), 6.65 (d, *J* = 7.7 Hz, 1H), 3.70 (t, *J* = 8.6 Hz, 1H), 3.37 (h, *J* = 7.7 Hz, 1H), 3.11 (t, *J* = 8.6 Hz, 1H), 1.33 (d, *J* = 6.8 Hz, 3H).

Host-catalyzed reactions employed indole **6b** using General Procedure H for each respective synthesis using host **la** or **IV**.



2,3-Dihydro-2,3-dimethyl-1H-indole (7c): Racemic material was prepared from indole **6c** (95 mg, 0.654 mmol) and scaled up according to General Procedure I. The reaction was stirred for 4h before workup. The resulting product was purified by prep TLC in 1.5% MeOH/DCM and quickly isolated as a white solid. Analytical data were consistent with literature reports.⁴² ¹H NMR (400 MHz, CDCl₃) δ 7.09 – 6.98 (m, 4H), 6.72 (td, *J* = 7.4, 1.0 Hz, 2H), 6.61 (dt, *J* = 7.6, 0.9 Hz, 2H), 3.94 (dq, *J* = 8.2, 6.6 Hz, 1H, cis), 3.80 (br s, 1H), 3.46 (dt, *J* = 9.3, 6.2 Hz, 1H, trans), 3.31 – 3.22 (m, 1H, cis), 2.82 (dddd, *J* = 9.3, 7.8, 6.8, 5.7 Hz, 1H), 1.31 (t, *J* = 6.6 Hz, 6H, trans), 1.16 (dd, *J* = 17.3, 6.9 Hz, 6H, cis).

Host-catalyzed reactions employed indole **6c** using General Procedure H for each respective synthesis using host **la** or **IV**.



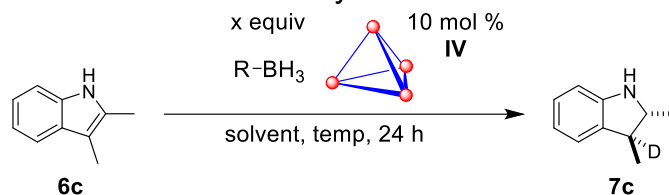
2-ethyl-3-methyl-2,3-dihydroindole (7d): Material was prepared from indole **6d** (4.38 mg, 0.0275 mmol) according to a General Procedure J. In an air-free wet box, to a 1 dr vial containing host **IV** (15.0 mg, 4.11 μmol, 15 mol%) was added 50 mM pD 7.5 D₂O buffer (540 μL) via Eppendorf pipette. The host solution was transferred to the 1 dr amber vial equipped with a magnetic stir bar containing indole. The 1 dr vial containing host was rinsed with D₂O buffer (110 μL) and the rinse was also transferred to the 1 dr vial containing indole. The reaction mixture vial was capped with a Teflon coated vial septa cap and sealed with electrical tape, removed from the wet box, and allowed to stir for 2–3 minutes before addition of pyridine borane (5.5 μL, 5.11 mg, 0.055 mmol, 2.00 equiv) via Hamilton syringe. The reaction was allowed to stir at rt and stopped with an unmeasured excess of PEt₄Br after 40h. Following extraction, the crude extract solution was analyzed by ¹H NMR (12% NMR yield, 5:1 dr). Spectral data were consistent with the literature.⁴³

4.7.3 Reactivity in the M₄L₆¹²⁻ Host System

Optimization of Reaction Conditions:

Reactions for substrate optimization were performed according to the respective general procedures for each substrate.

Table S4.1. Optimization Table for Reactivity of Indole **6c**



Entry	Solvent	Temp (°C)	Borane R	Borane Equiv	% Yield (% Conv.) ^a	trans:cis ratio
1	D ₂ O	rt	pyridine	3	9 (9)	>20:1
2	D ₂ O	rt	pyridine	2	6 (6)	>20:1
3	D ₂ O	45	pyridine	3	46 (56)	>20:1
4	D ₂ O	rt	NMe ₃	3	nr	nd
5	100 mM pD 8 D ₂ O buffer	rt	pyridine	3	10 (10)	>20:1

^a NMR yields from CDCl₃ extract relative to internal standard

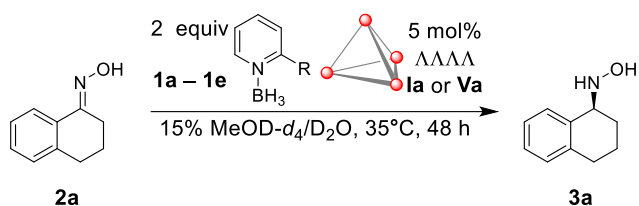
Blocked Host Control Reactions:

To probe background reactivity, blocked host controls were performed in a manner nearly identical to that of the General Procedures applicable for the respective substrate, with the addition of PEt₄I or PEt₄Br before addition of pyridine borane. A representative example is provided:

To a 1 dr vial containing host **1a** (5 mol%) was added D₂O *via* Eppendorf pipette. A portion from a second 1 dr vial containing PEt₄I or PEt₄Br (6 mol%) as a stock solution in D₂O was added to the vial containing host. The blocked host solution was transferred to a third 1 dr vial equipped with a magnetic stir bar containing oxime (1 equiv.). The 1 dr vial containing blocked host was rinsed with D₂O and the rinse was also transferred to the 1 dr vial containing oxime before addition of pyridine borane (3 equiv.) and subsequent workup 24h later.

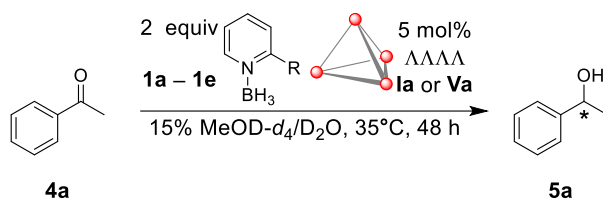
Blocked host controls in D₂O for oximes **2a** and **2i** ketone **4a** each found <5% NMR yield vs. internal standard (1,3,5-trimethoxybenzene) in CDCl₃ extracts. Similar blocked host controls in D₂O using oxime **2b** with increased amounts of host **1** (7.5 mol%) and PEt₄Br (8–9 mol%) likewise found only trace *in situ* NMR yield vs. internal standard (3-(trimethylsilyl)-1-propanesulfonic acid sodium salt). A similar blocked host control using indole **6c** and racemic host **IV** likewise showed no NMR yield vs. internal standard (1,3,5-trimethoxybenzene) in a CDCl₃ extract.

Procedure for Pyridine Borane Reductant Screens



Reductant screens using oxime **2a** were performed using a modified version of General Procedure D. To a 1 dr vial containing host **1a** or **Va** (5 mol%) was added D_2O *via* Eppendorf pipette. The host solution was transferred to a second 1 dr vial equipped with a magnetic stir bar containing oxime (1 equiv.) and $MeOD-d_6$ (15% by volume). The 1 dr vial containing host was rinsed with D_2O and the rinse was also transferred to the 1 dr vial containing oxime. The final concentration of solution was 55 mM in oxime. The heterogeneous solution was allowed to sit at rt for 5 minutes before addition of borane (2.0 equiv.). The reaction was then capped, sealed with electrical tape, and heated at $35^\circ C$ for 48h, after which point the reaction was stopped by adding an excess of tetraethylphosphonium bromide (PEt_4Br). Internal standard, 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt (2.50 mg, 0.01145 mmol), as a stock solution in D_2O (176 mM) was added *via* Hamilton syringe to the 1 dr reaction vial. If the quenched reaction solution was found to be partially heterogenous, minimal amounts of $MeOD-d_6$ were added to make the solution homogenous. The solution was mixed briefly by pipetting and an aliquot taken for ^1H NMR analysis.

Following NMR analysis of the crude reaction mixture, the product was returned to the 1 dr vial and the NMR tube was rinsed with CH_2Cl_2 . Solvent in the vial was removed to near-dryness *via* rotary evaporation. The crude product was then extracted repeatedly with CH_2Cl_2 . Hydroxylamine **3a** was purified and isolated *via* prep TLC.



Pyridine borane reductant screen and test with pyrene-based host **Va** were performed using a modified version of General Procedure H.

To a 1 dr vial equipped with a magnetic stir bar containing host (5 mol%) was added D_2O *via* Eppendorf pipette. To this 1 dr vial was added ketone (1.0 equiv.) *via* Hamilton syringe. The final concentration of solution was 55 mM in ketone. The heterogeneous solution was allowed to sit at rt for 5 minutes before addition of borane (2.0 equiv.). The reaction was then capped, sealed with electrical tape, and heated at $35^\circ C$ for 48h, after which point the reaction was stopped by adding an excess of tetraethylphosphonium bromide (PEt_4Br). Internal standard, 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt (2.50 mg, 0.01145 mmol), as a stock solution in D_2O (176 mM) was added *via* Hamilton syringe to the 1 dr reaction vial. If the quenched reaction solution was found to be partially heterogenous, minimal amounts of $MeOD-d_6$ were added to make the solution

homogenous. The solution was mixed briefly by pipetting and an aliquot taken for ^1H NMR analysis.

Following NMR analysis of the crude reaction mixture, the product was returned to the 1 dr vial and the NMR tube was rinsed with CH_2Cl_2 . Solvent in the vial was removed to near-dryness *via* rotary evaporation. The crude product was then extracted repeatedly with CH_2Cl_2 . Alcohol **5a** was purified and isolated via prep TLC.

Representative ^1H NMR Spectra for Yield Determination

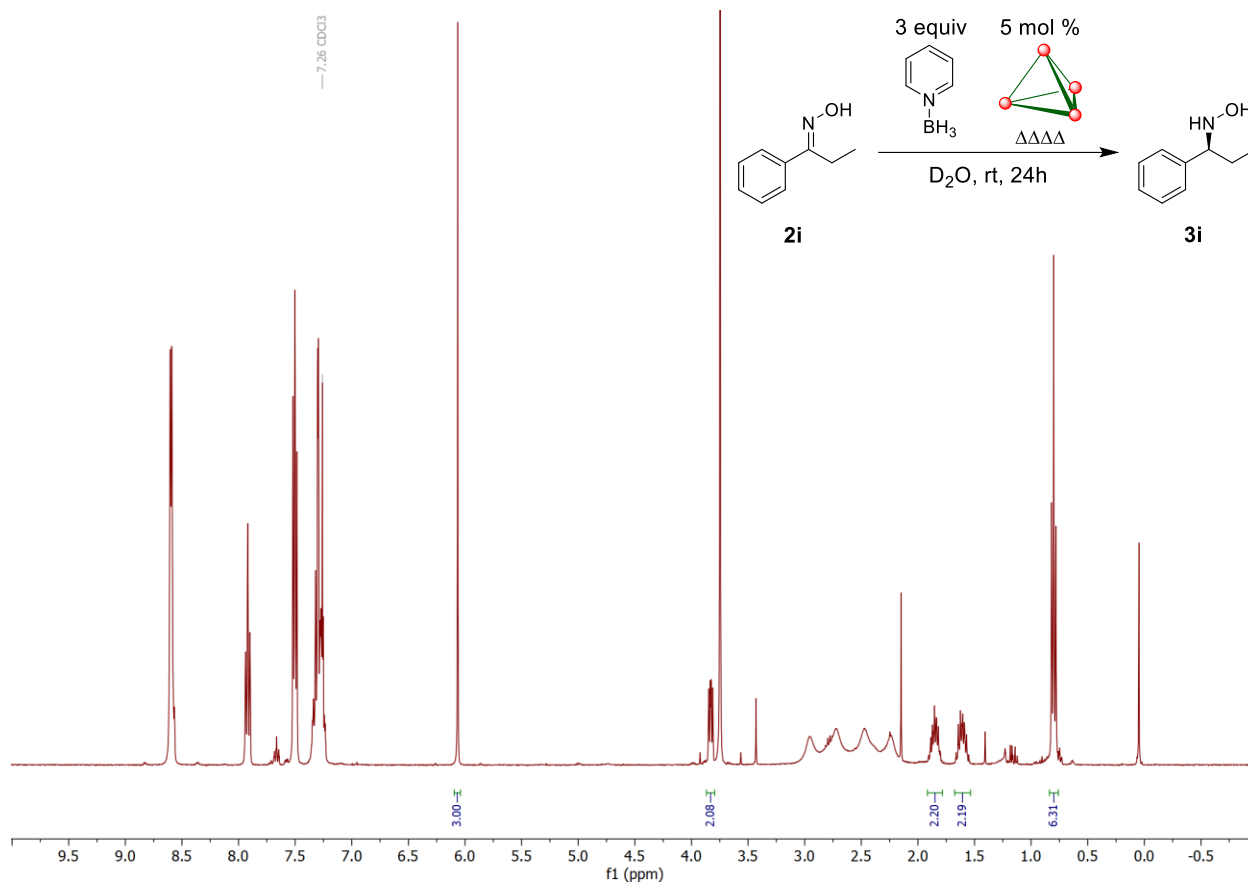


Figure S4.1. Representative crude ^1H NMR spectrum in CDCl_3 extract after enantiopure host **1a**-catalyzed reduction of oxime **2i**. Contains 1,3,5-trimethoxybenzene as internal standard, used to determine extract NMR yields.

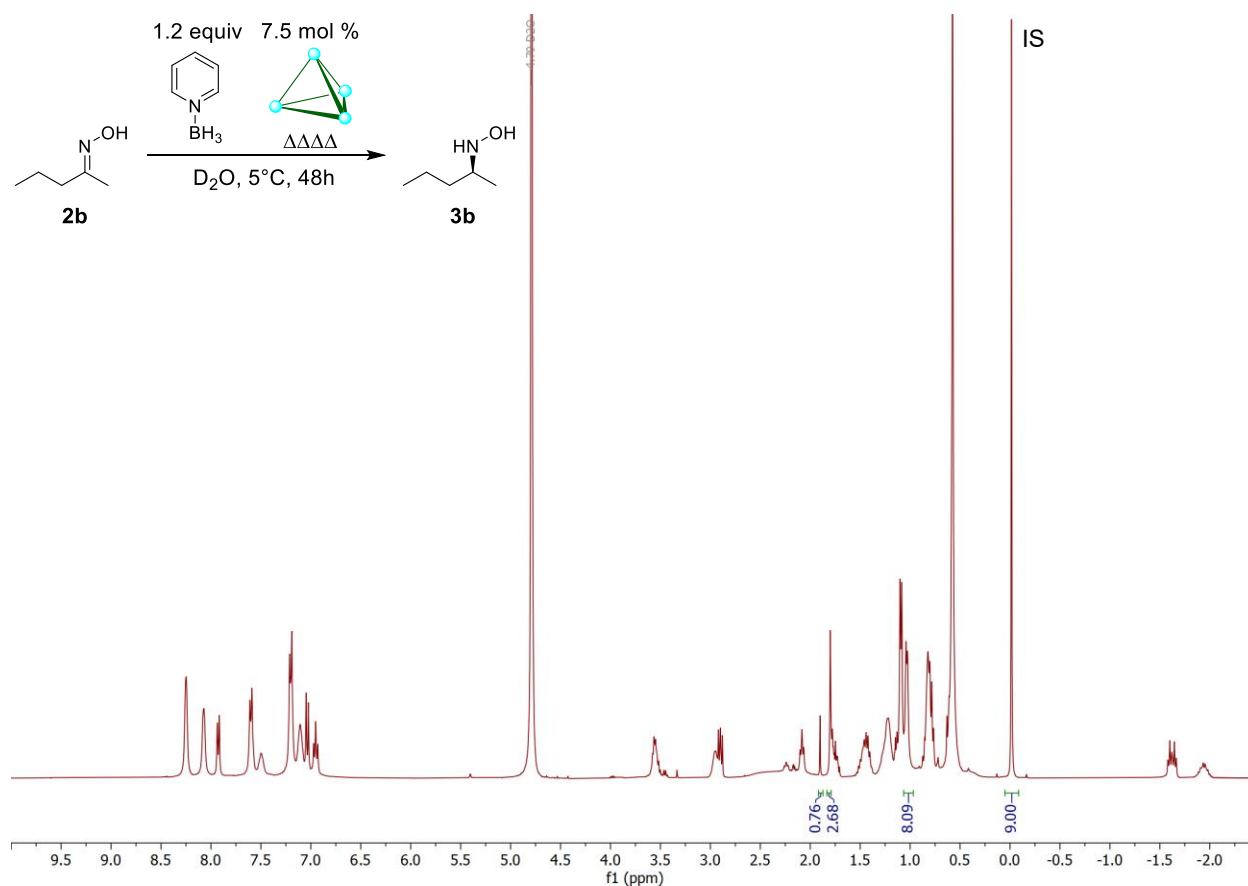


Figure S4.2. Representative crude ^1H NMR spectrum in D_2O of enantiopure host I-catalyzed reduction of oxime **2b** after quenching with PEt_4Br and with 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt as internal standard, used to determine *in situ* yields.

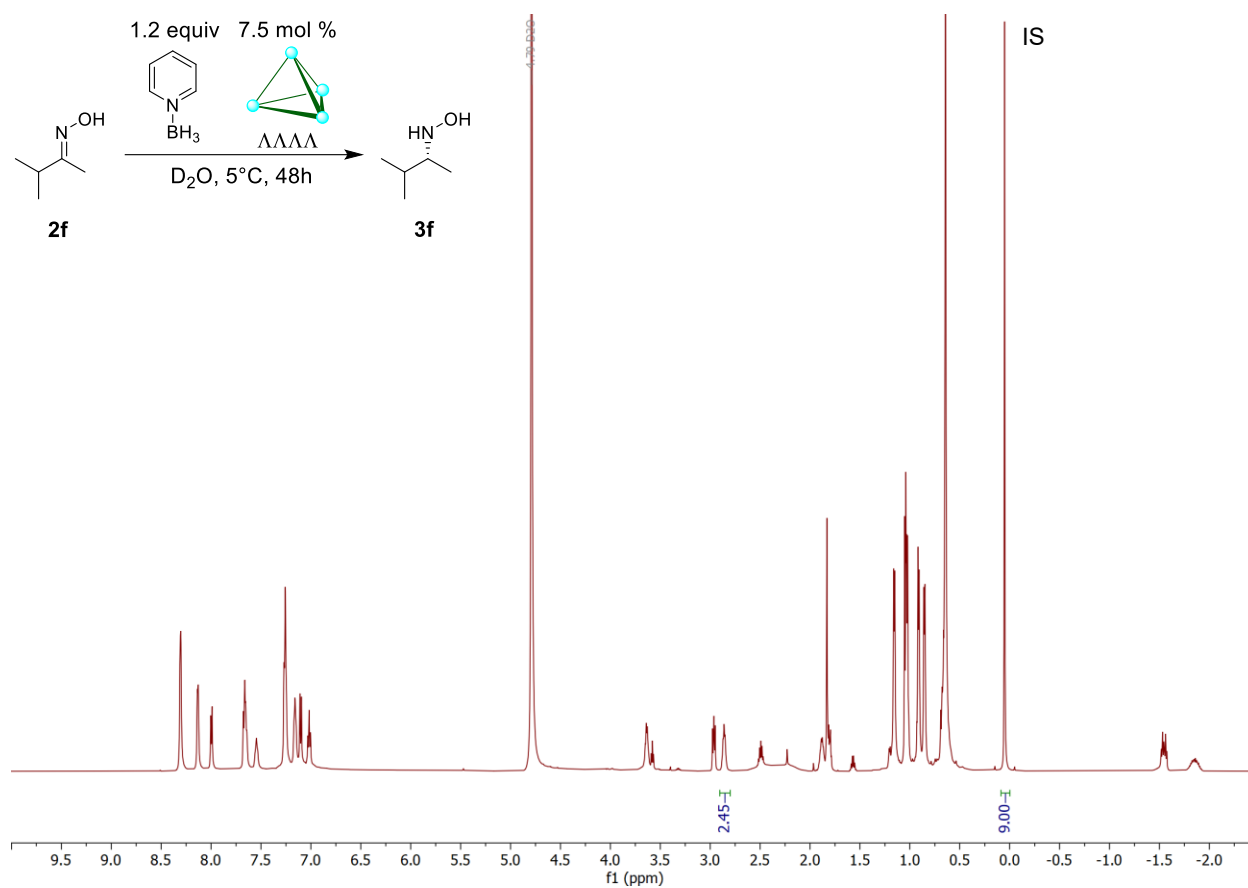


Figure S4.3. Representative crude ^1H NMR spectrum in D_2O of enantiopure host **Ila**-catalyzed reduction of oxime **2f** after quenching with PEt_4Br and with 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt as internal standard, used to determine *in situ* yields.

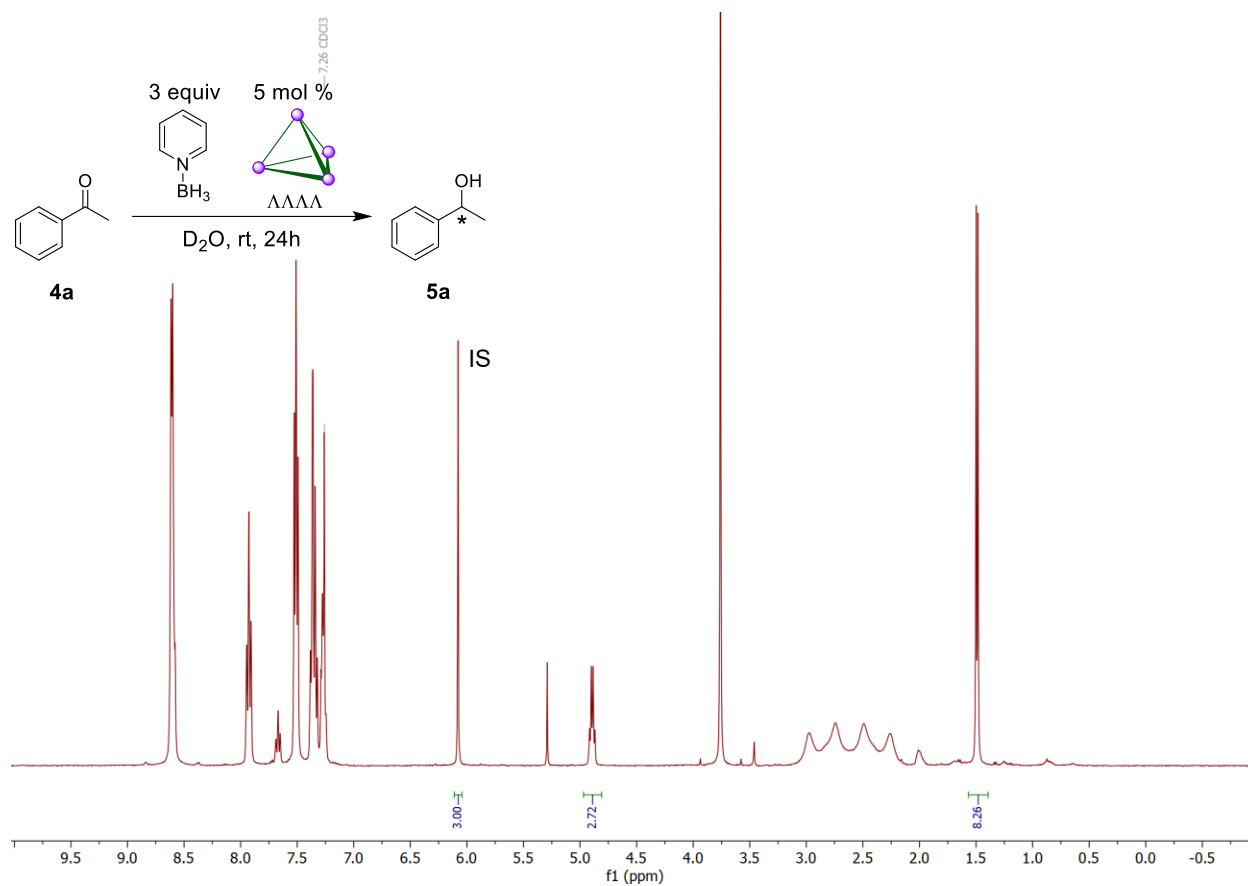


Figure S4.4. Representative crude ^1H NMR spectrum in CDCl_3 extract after enantiopure host **IIIa**-catalyzed reduction of ketone **4a**. Contains 1,3,5-trimethoxybenzene as internal standard, used to determine extract NMR yields.

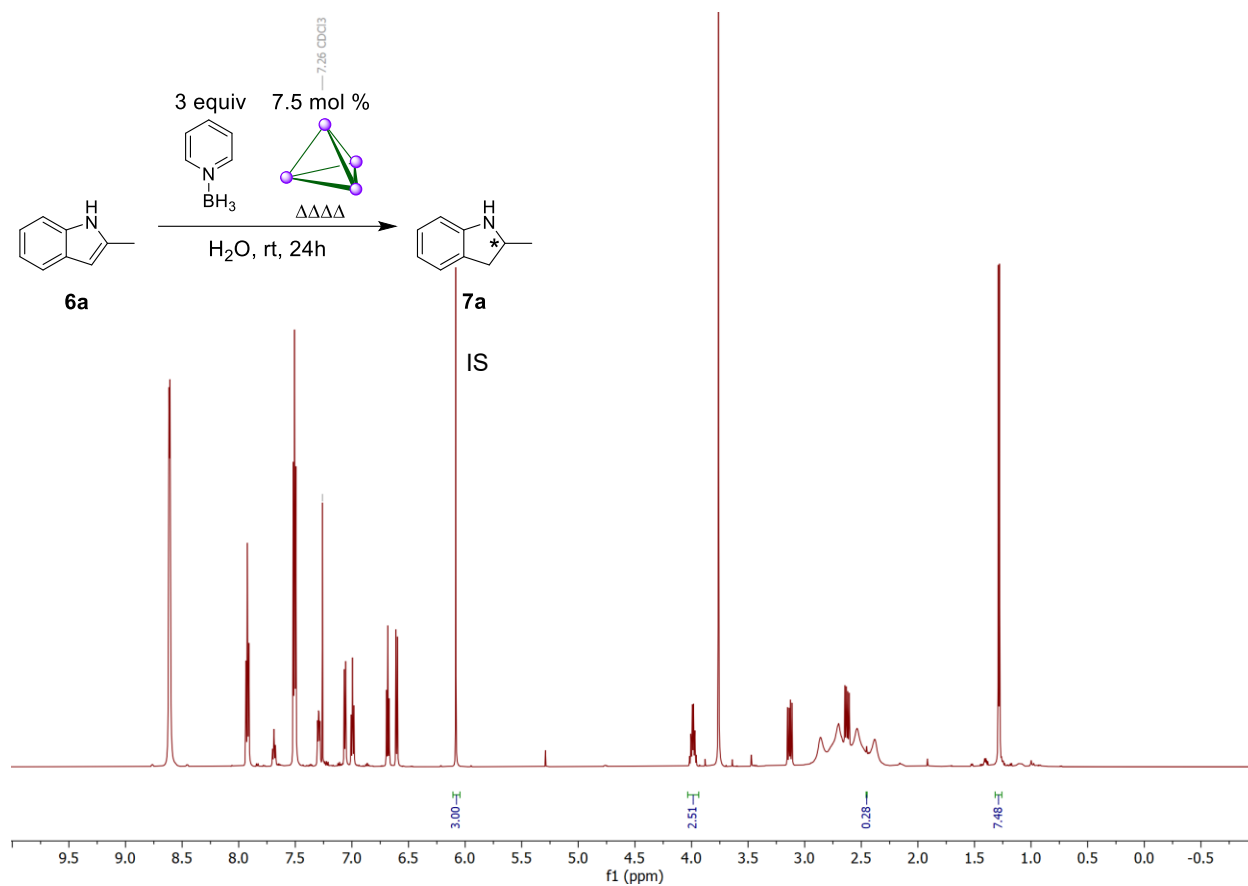


Figure S4.5. Representative crude ^1H NMR spectrum in CDCl_3 extract after enantiopure host **IIIa**-catalyzed reduction of indole **6a**. Contains 1,3,5-trimethoxybenzene as internal standard, used to determine extract NMR yields.

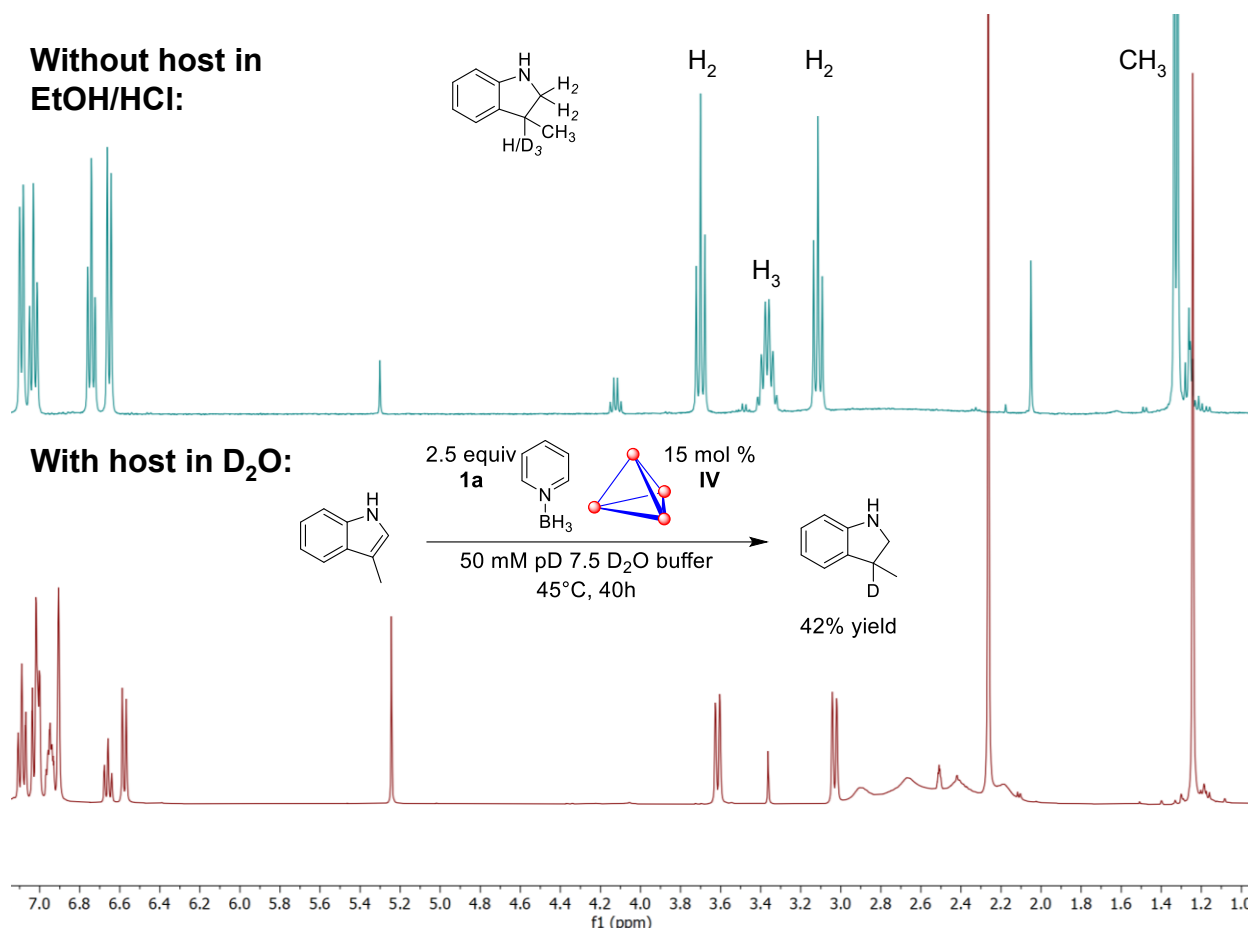
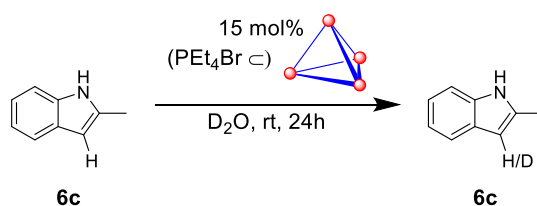


Figure S4.6. ¹H NMR spectra showcasing deuterium incorporation at the 3-position of indole **6b**. **Top:** NMR spectrum in CDCl₃ of isolated racemic product formed using General Procedure I. **Bottom:** CDCl₃ NMR extract after racemic host **IV**-catalyzed reduction of indole **6b** in D₂O.

Deuterium Incorporation Studies on Indoles



Based on a modified version of General Procedure J which excluded pyridine borane. To a 1 dr vial containing host **IV** (20 mg, 5.48 μmol, 15 mol%) was added D₂O via Eppendorf pipette. The host solution was transferred to a second, amber 1 dr vial equipped with a magnetic stir bar containing indole (1.0 equiv.) and covered in foil. The 1 dr vial containing host was rinsed with D₂O and the rinse was also transferred to the 1 dr vial containing indole. The final concentration of solution was 42 mM in indole. The reaction was then stirred at rt for 24h, after which point the reaction was stopped by adding a large unmeasured excess of tetraethylphosphonium bromide (PEt₄Br). The stir bar was removed using a stir bar magnet and rinsed with CDCl₃. Additional CDCl₃ was added to

the vial to extract the product and the CDCl₃ rinse was transferred to a 2 dr vial. The reaction solution was washed at least 3 times with CDCl₃. Solvent in the 2 dr vial from the combined rinses was removed *via* rotary evaporation to be less than 500 μ L, but not to full dryness. Internal standard, 1,3,5-trimethoxybenzene (2.00 mg, 0.0119 mmol), as a stock solution in CDCl₃ (594.5 mM) was added *via* Hamilton syringe to the 2 dr vial and the solution was transferred to an NMR tube for ¹H NMR analysis. A very similar experiment was also performed with the addition of PEt₄Br (1.33 mg, 5.85 μ mol, 16 mol%) to host before it was added to the vial containing indole. At the end of 24h, the reaction was not quenched but was instead immediately transferred to an NMR tube for ¹H NMR analysis. The resulting ¹H NMR spectra were compared to literature reports⁴⁴ and found to showcase a high degree of deuterium incorporation at the 3-position. Nearly identical levels of deuterium incorporation were observed with empty and blocked host **IV**.

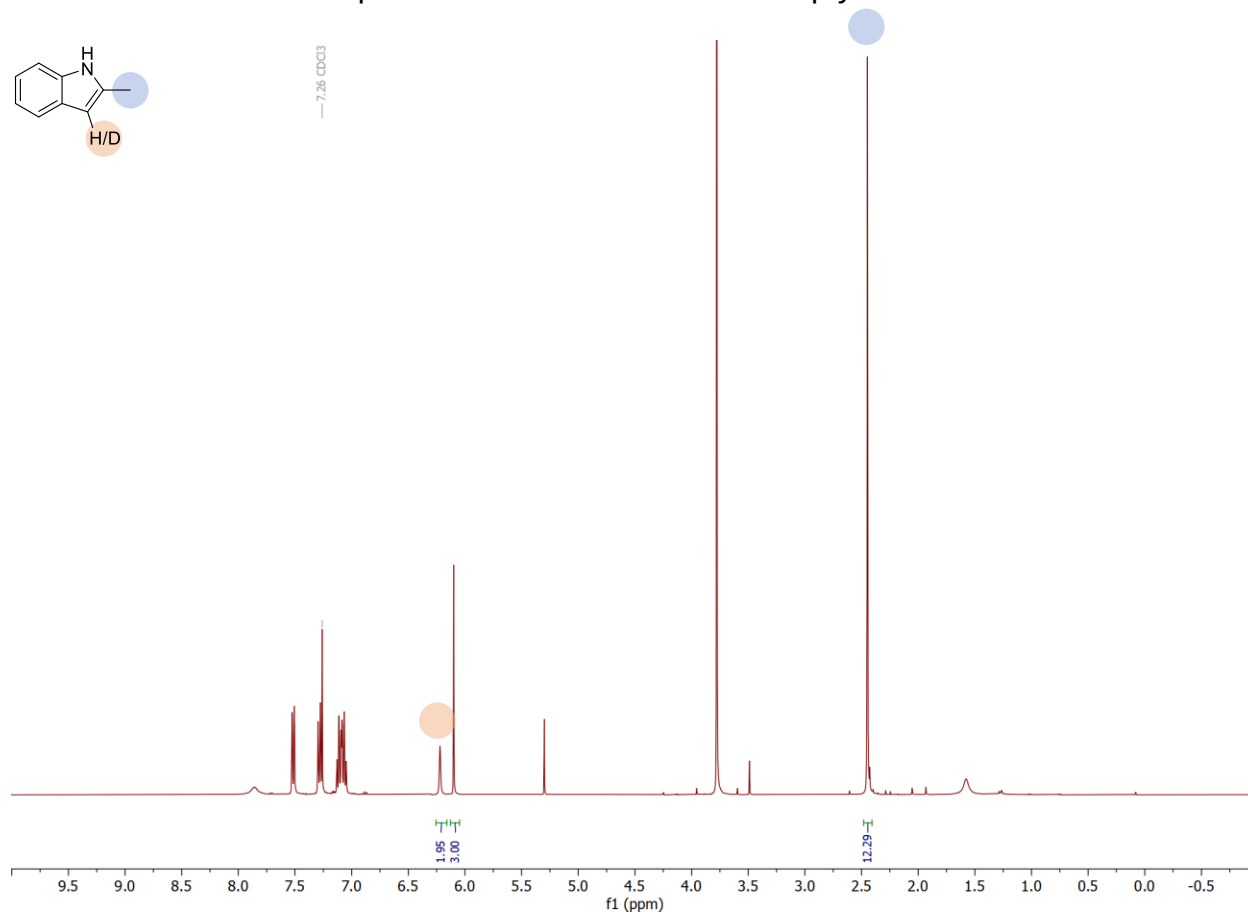
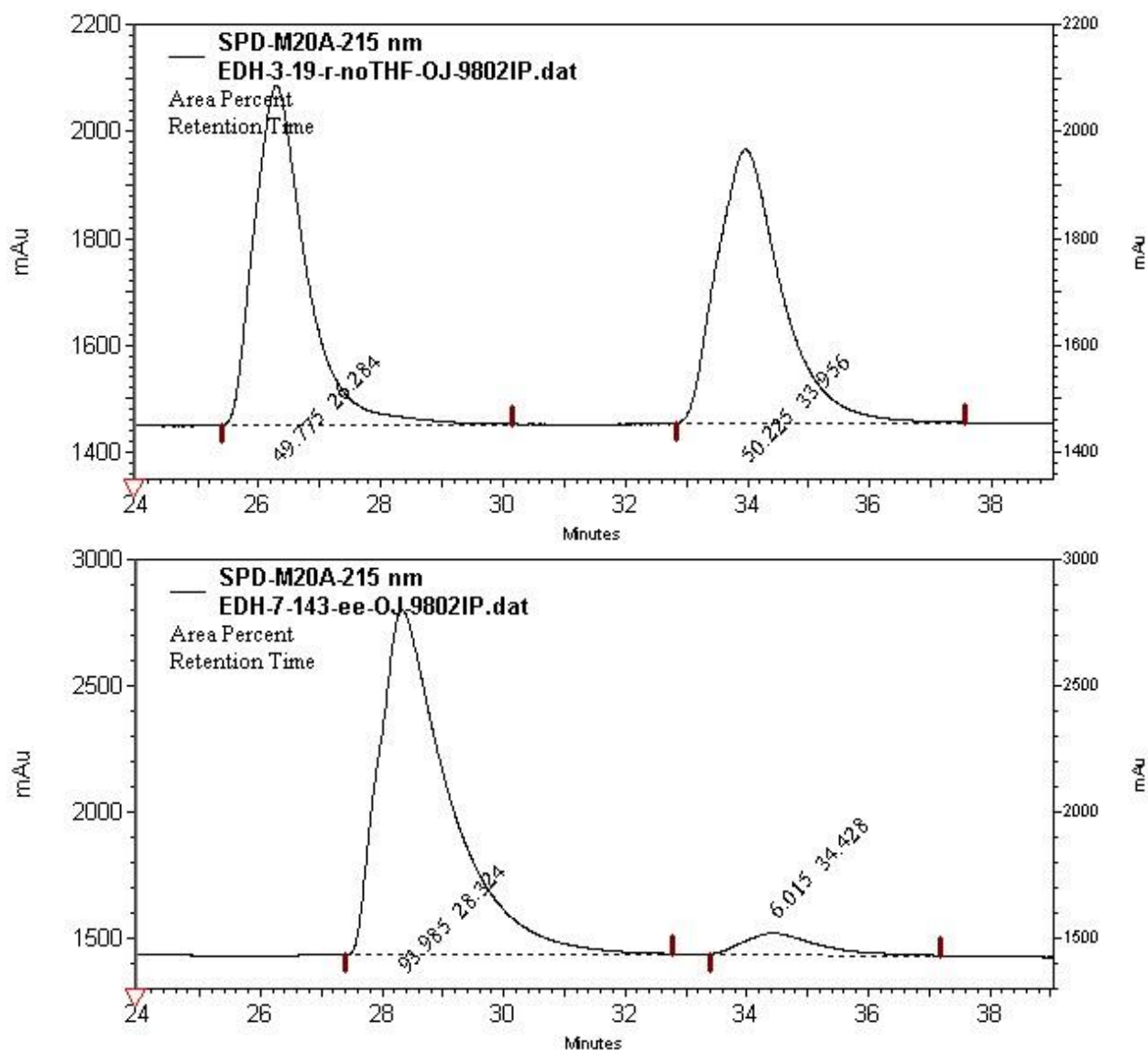


Figure S4.7. ¹H NMR spectra showcasing deuterium incorporation at the 3-position of indole **6a** in D₂O in the presence of host **IV** alone.

4.7.4 Chiral HPLC Traces



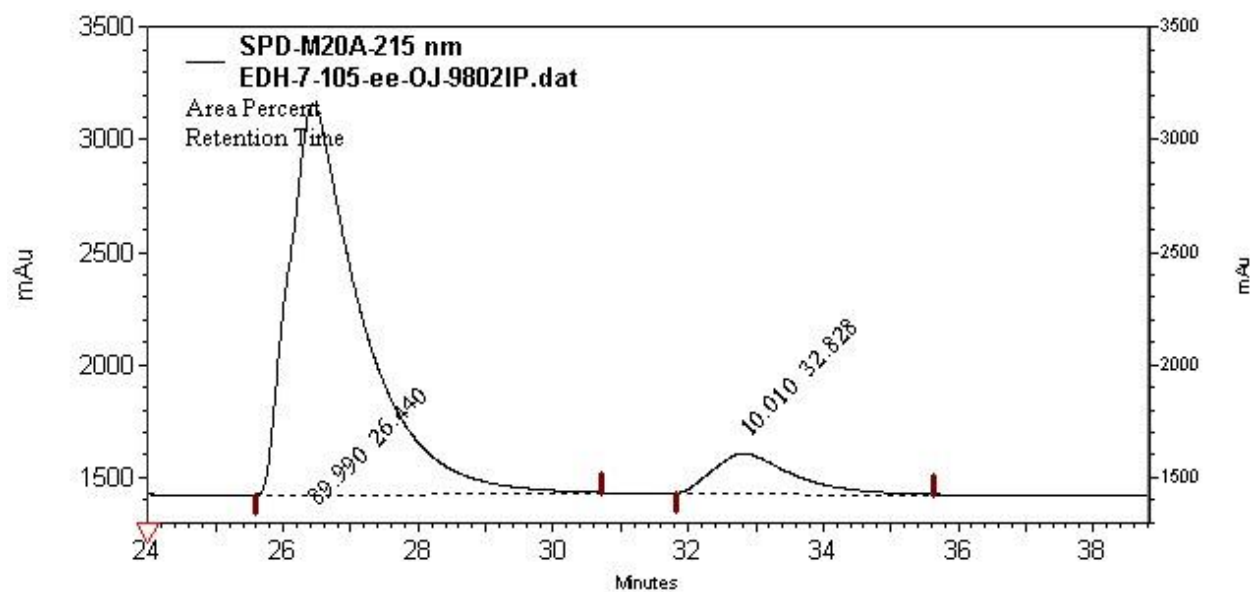


Figure S4.8. Racemic trace (top) and enantioenriched trace from host $\Lambda\Lambda\Lambda$ -**Va** (middle) and symbol $\Lambda\Lambda\Lambda$ -**Ia** with borane **1e** (bottom) of hydroxylamine **3a**.

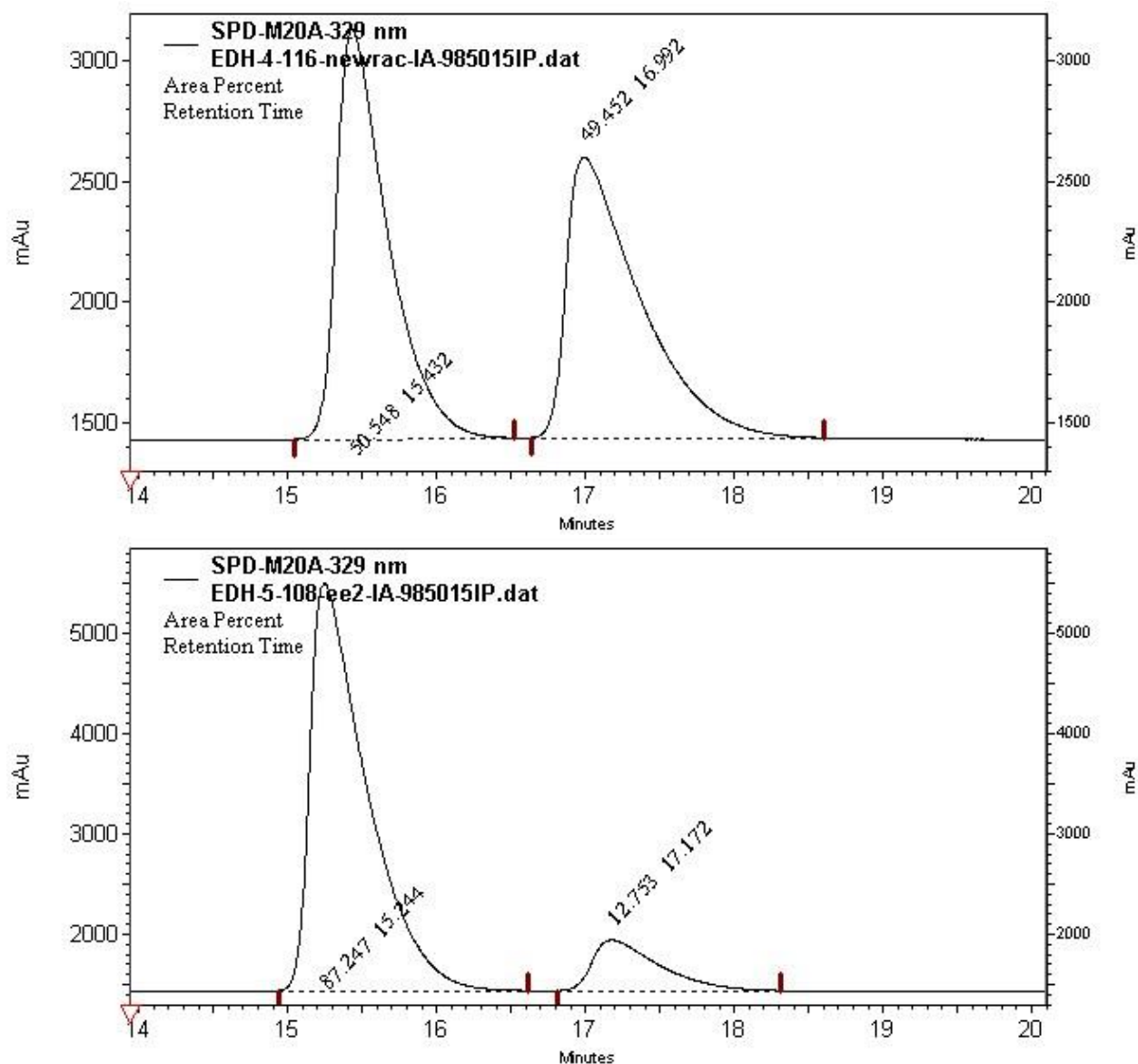


Figure S4.9. Racemic trace (top) and enantioenriched trace (bottom) of hydroxylamine **3b**.

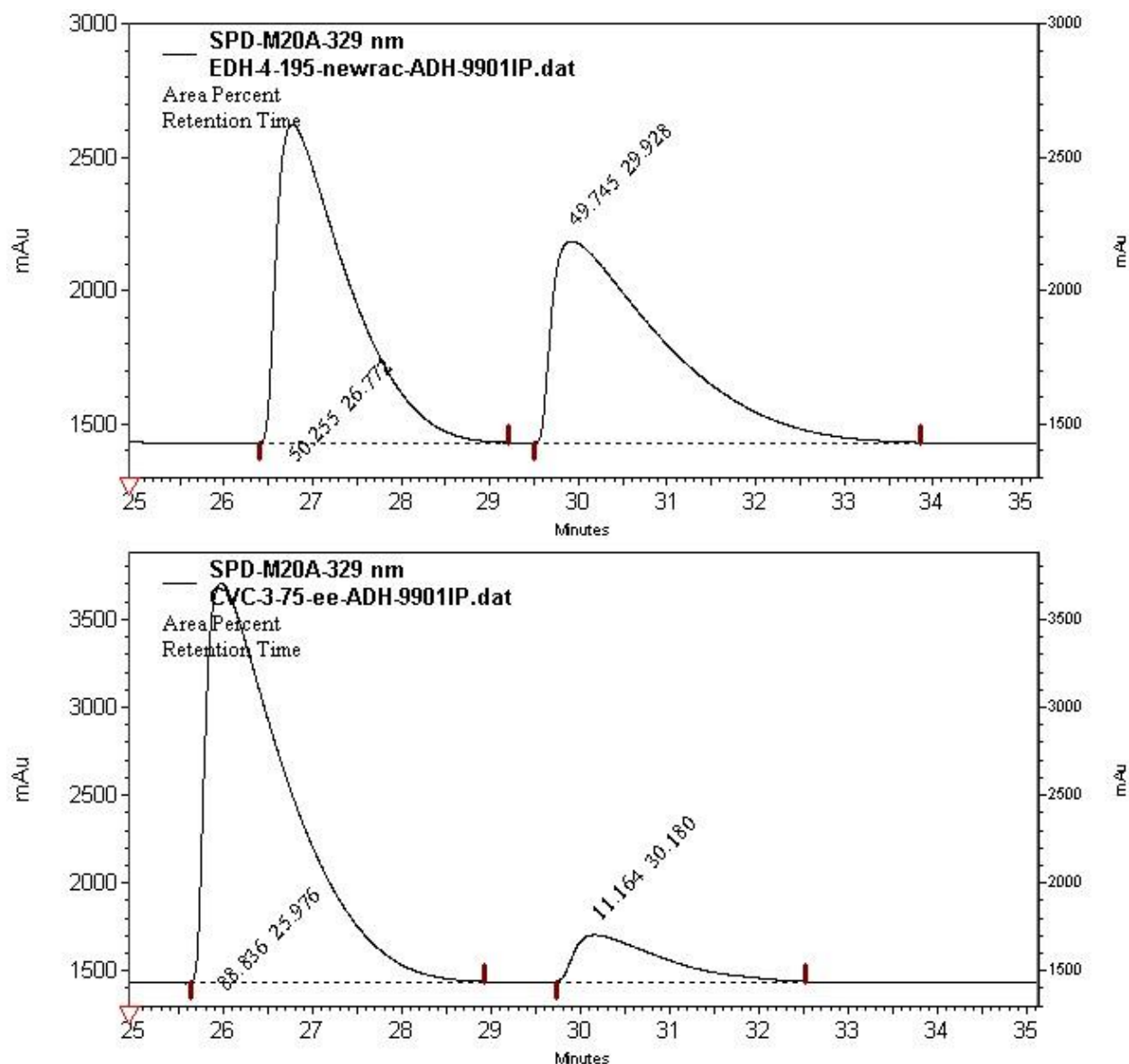


Figure S4.10. Racemic trace (top) and enantioenriched trace (bottom) of hydroxylamine **3c**.

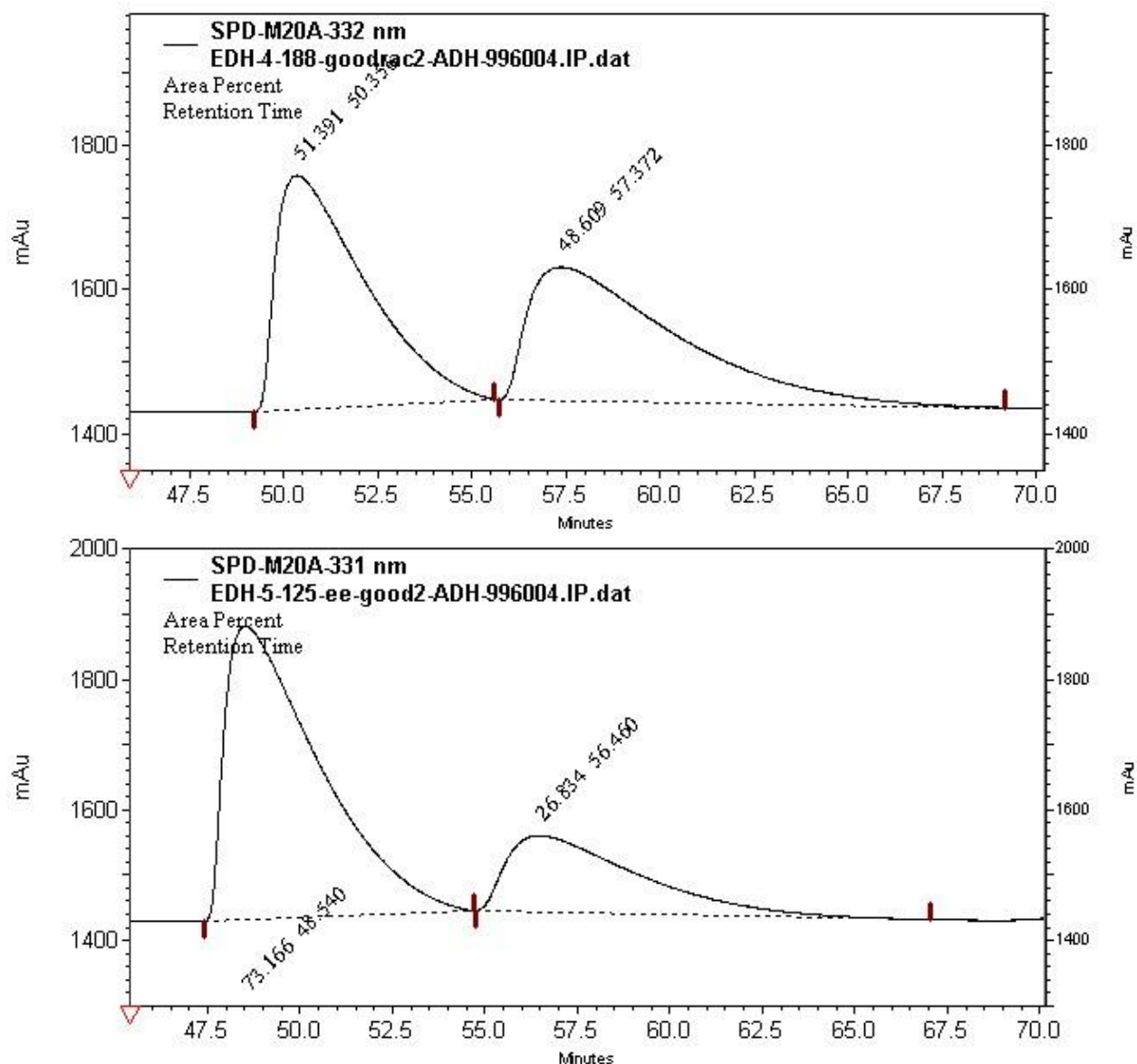


Figure S4.11. Racemic trace (top) and enantioenriched trace (bottom) of hydroxylamine 3d.

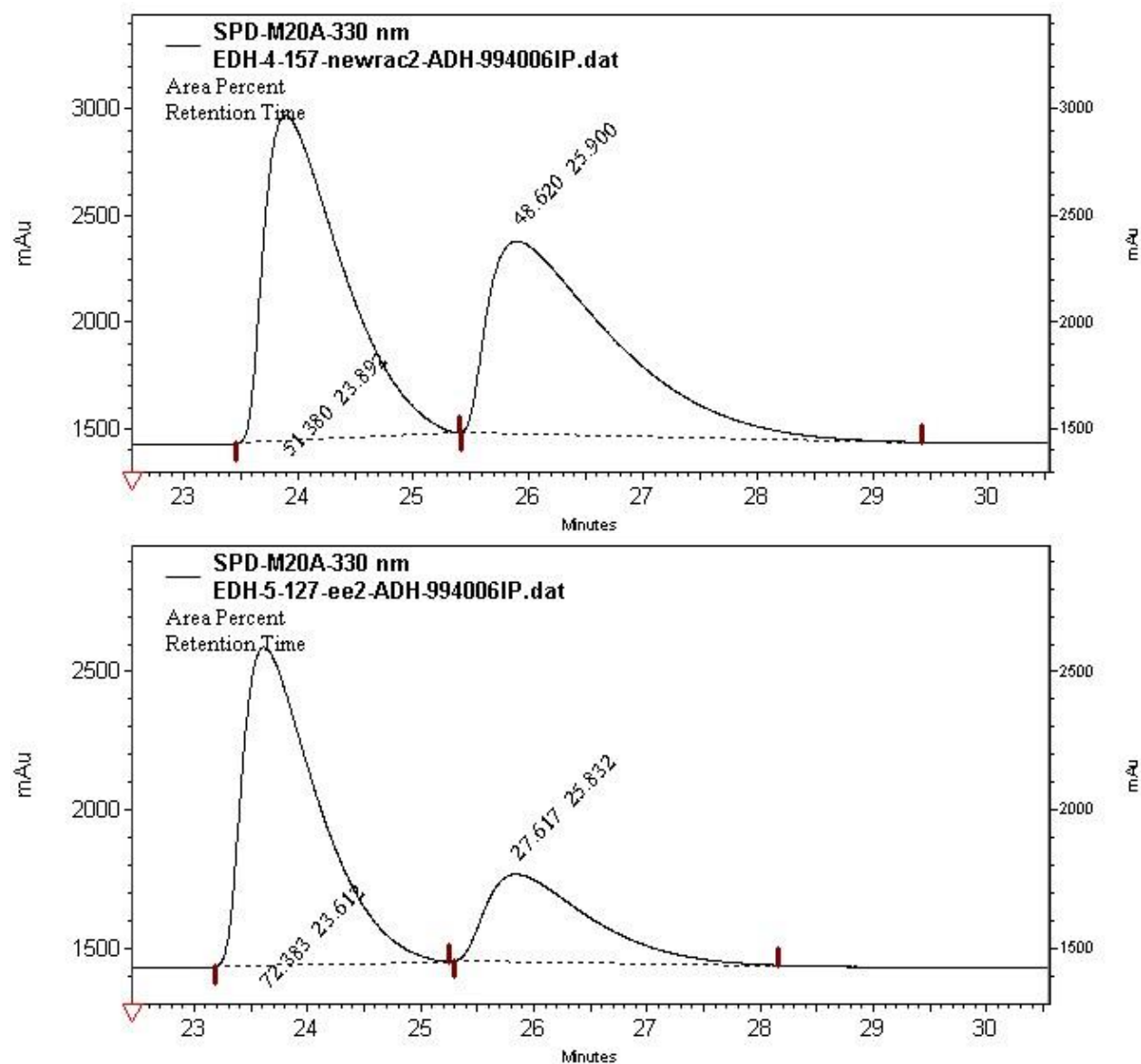


Figure S4.12. Racemic trace (top) and enantioenriched trace (bottom) of hydroxylamine **3e**.

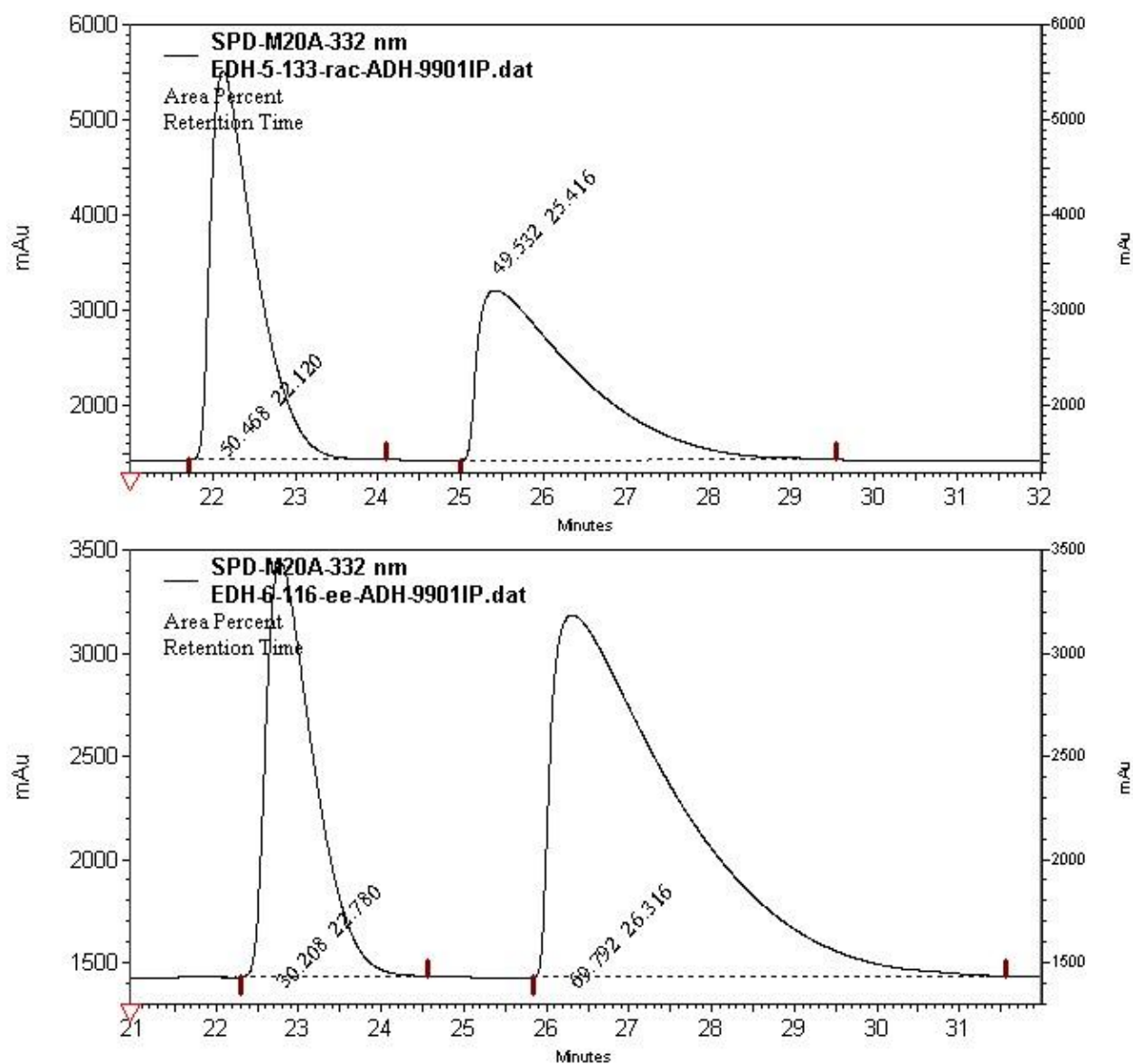


Figure S4.13. Racemic trace (top) and enantioenriched trace (bottom) of hydroxylamine 3f.

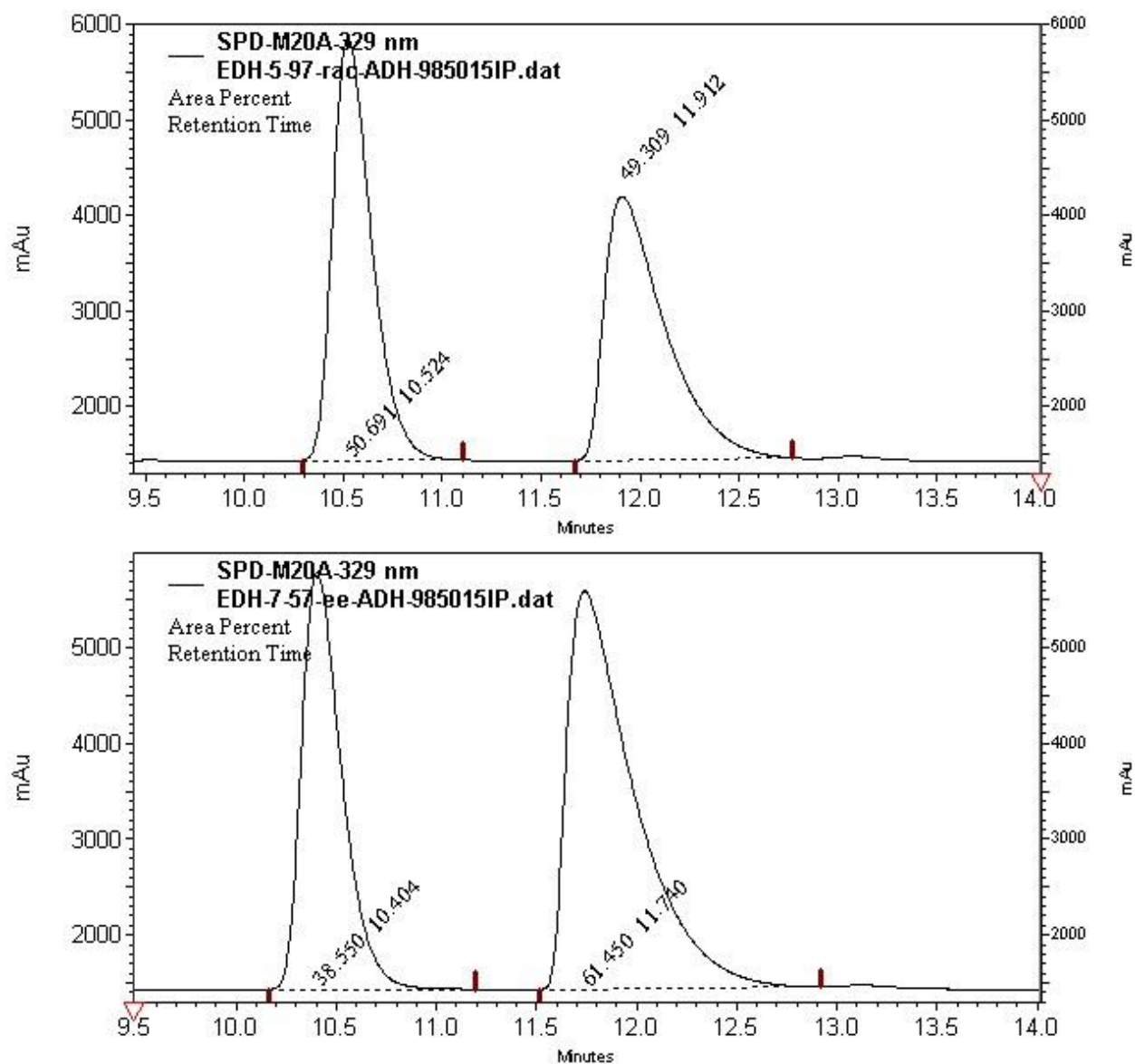


Figure S4.14. Racemic trace (top) and enantioenriched trace (bottom) of hydroxylamine 3g.

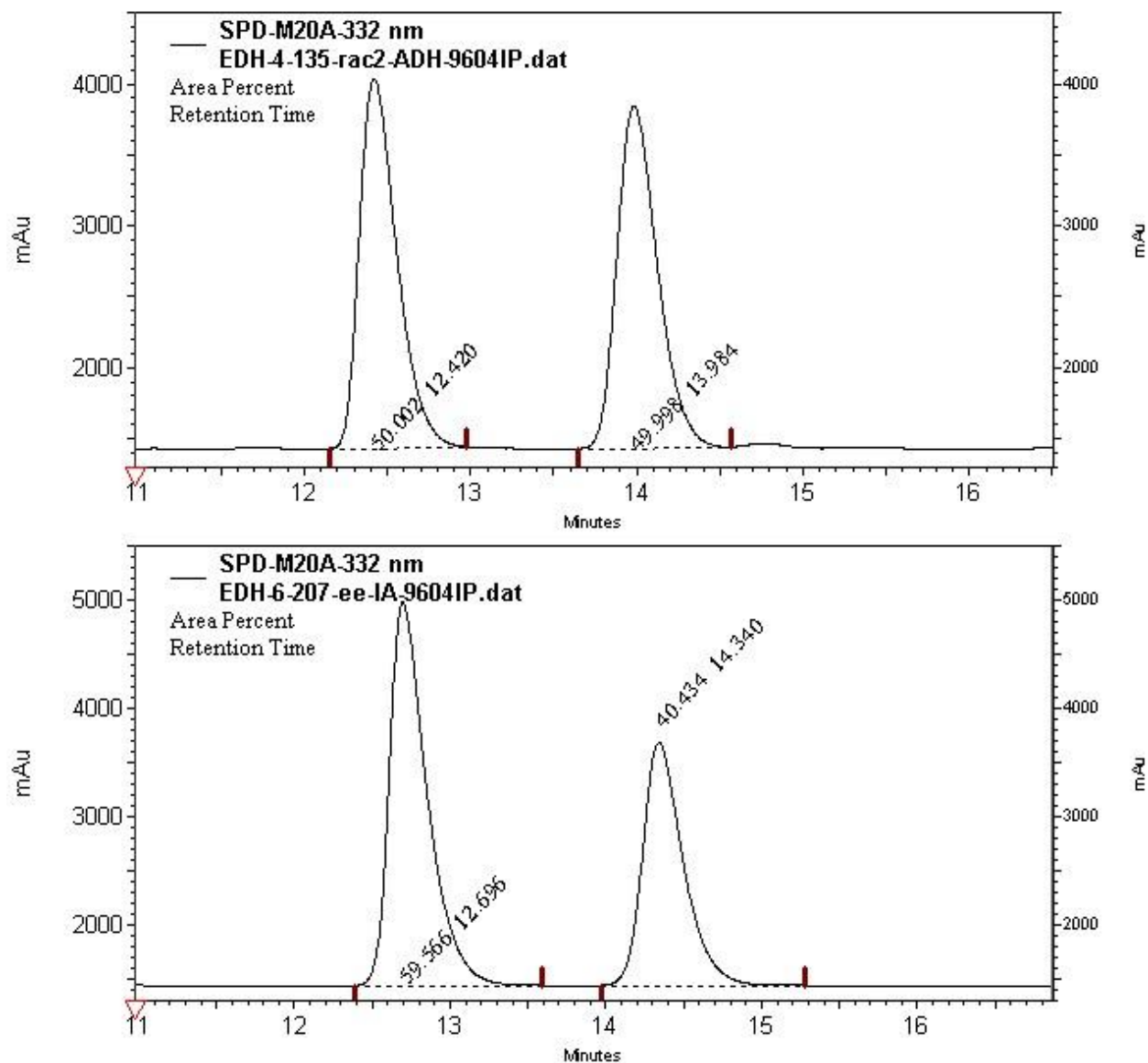


Figure S4.15. Racemic trace (top) and enantioenriched trace (bottom) of hydroxylamine 3h.

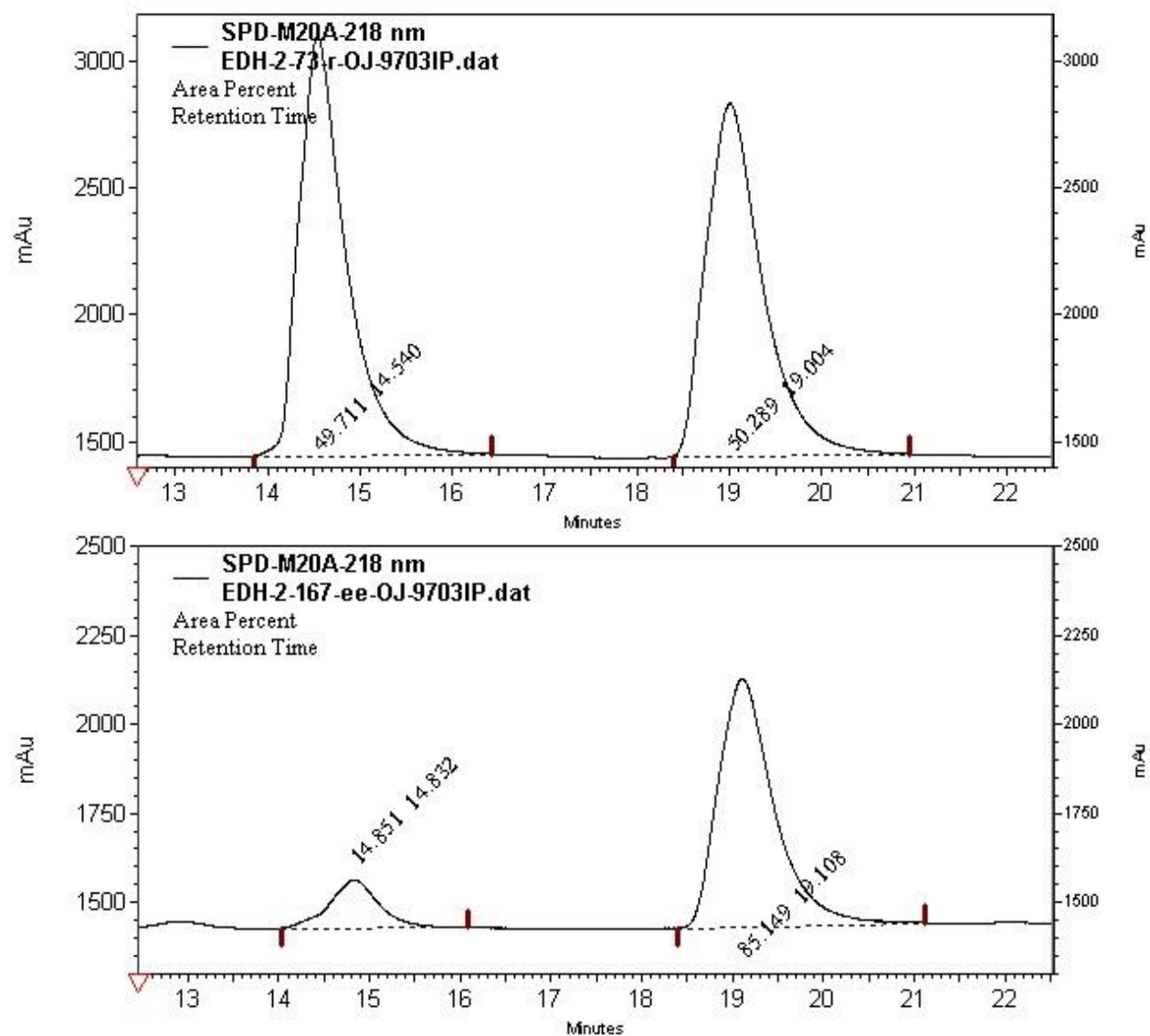


Figure S4.16. Racemic trace (top) and enantioenriched trace from host $\Delta\Delta\Delta$ -IIIa (bottom) of hydroxylamine **3i**.

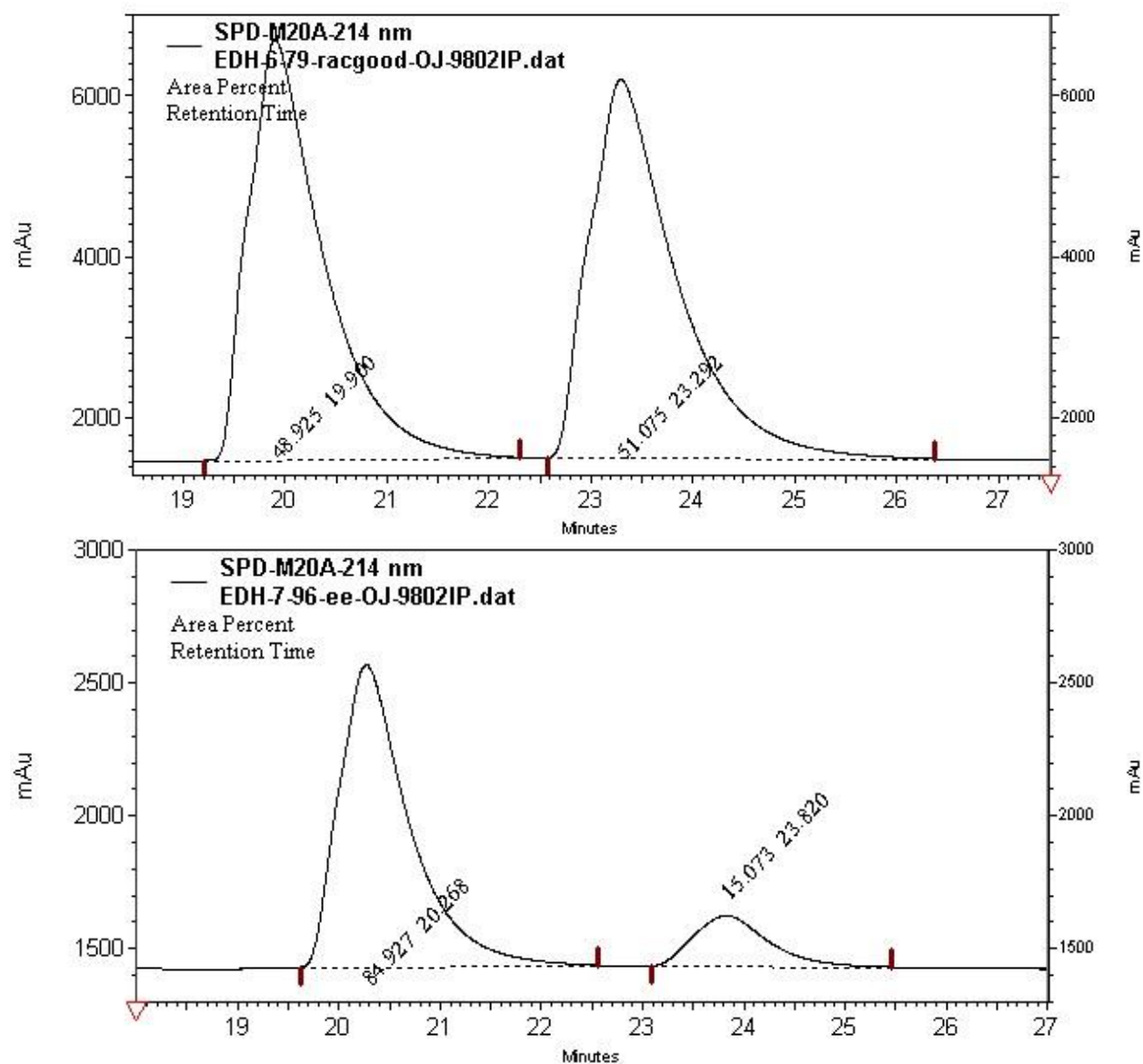


Figure S4.17. Racemic trace (top) and enantioenriched trace from host $\Delta\Delta\Delta\Delta$ -IIIa (bottom) of hydroxylamine **3j**.

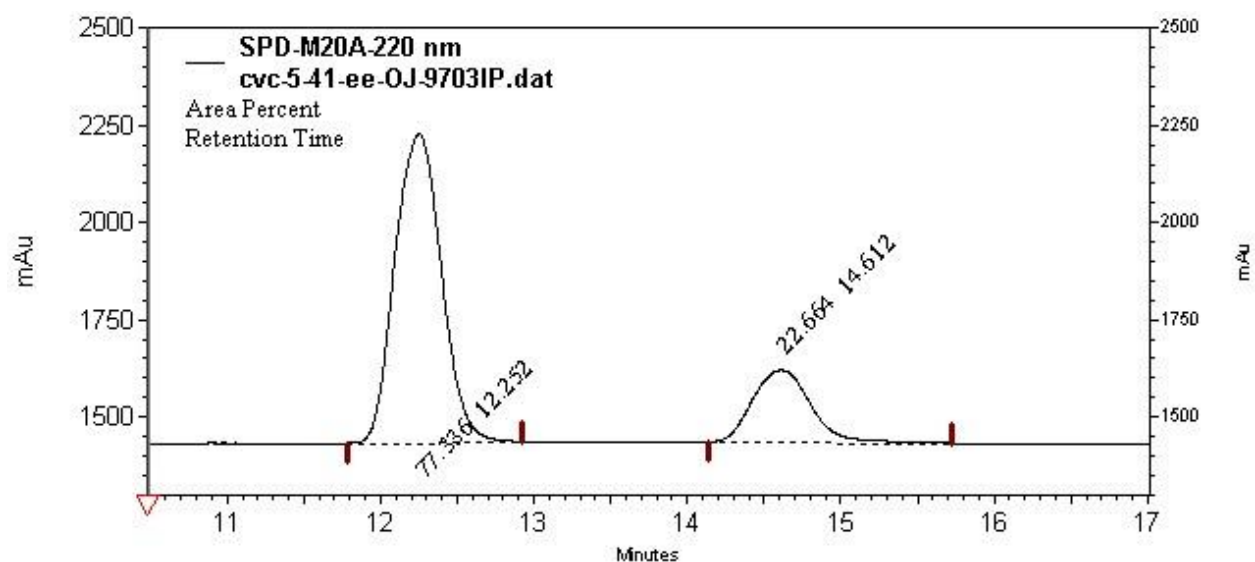
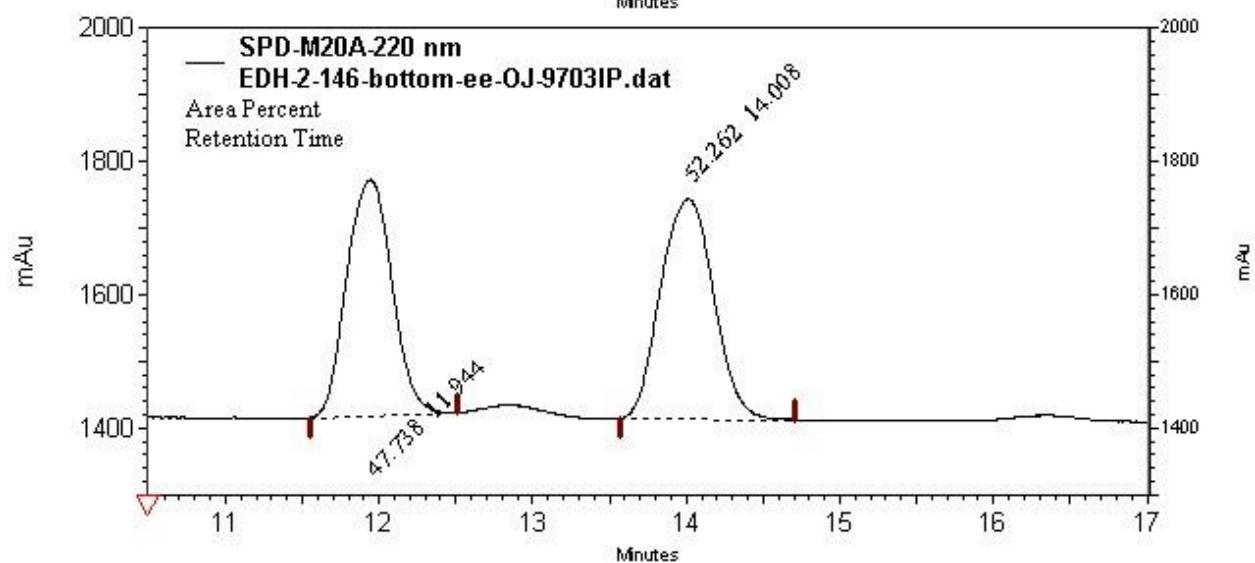
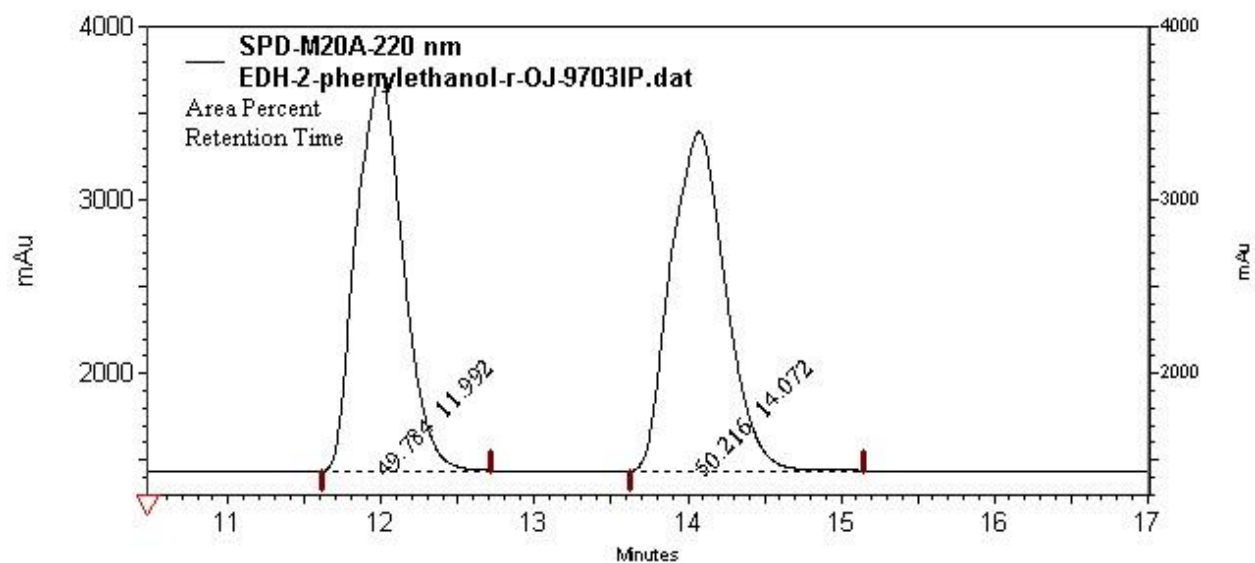


Figure S4.18. Racemic trace (top) and enantioenriched trace from host $\Delta\Delta\Delta\Delta$ -**1a** (middle) and symbol $\Delta\Delta\Delta\Delta$ -**Va** (bottom) of alcohol **5a**.

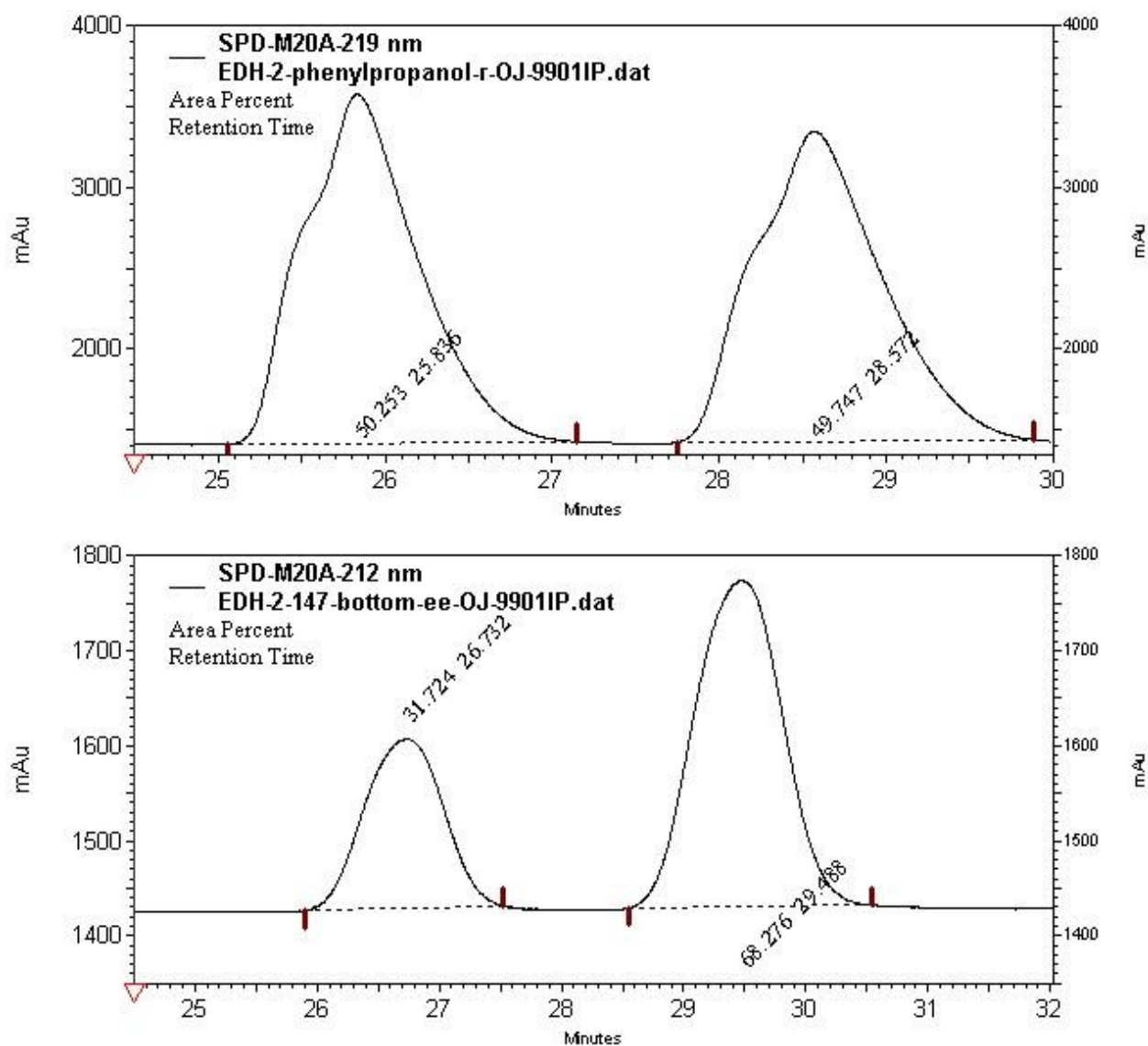


Figure S4.19. Racemic trace (top) and enantioenriched trace from host $\Delta\Delta\Delta\Delta$ -**1a** (bottom) of alcohol **5b**.

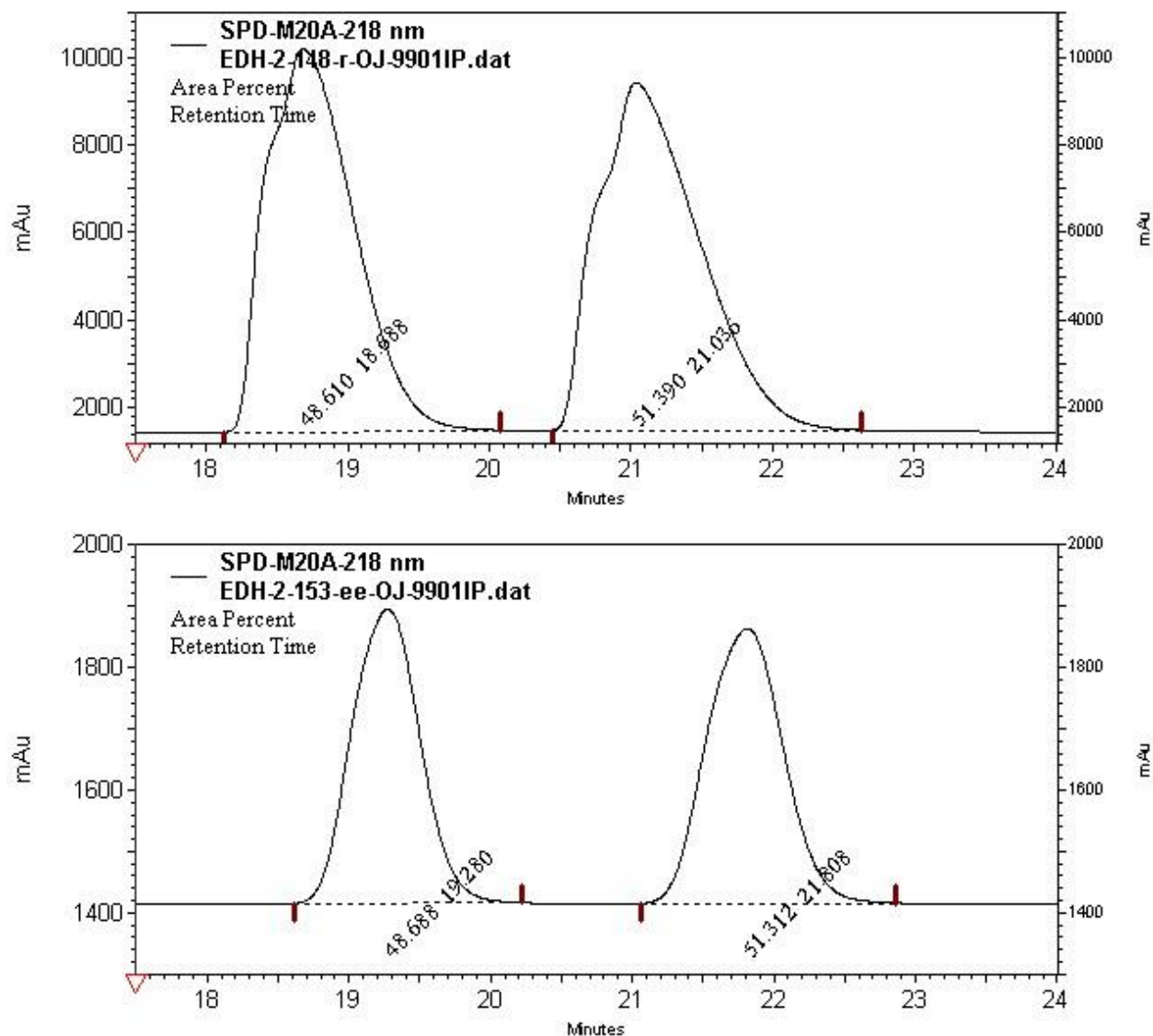


Figure S4.20. Racemic trace (top) and enantioenriched trace (bottom) of alcohol **5c**.

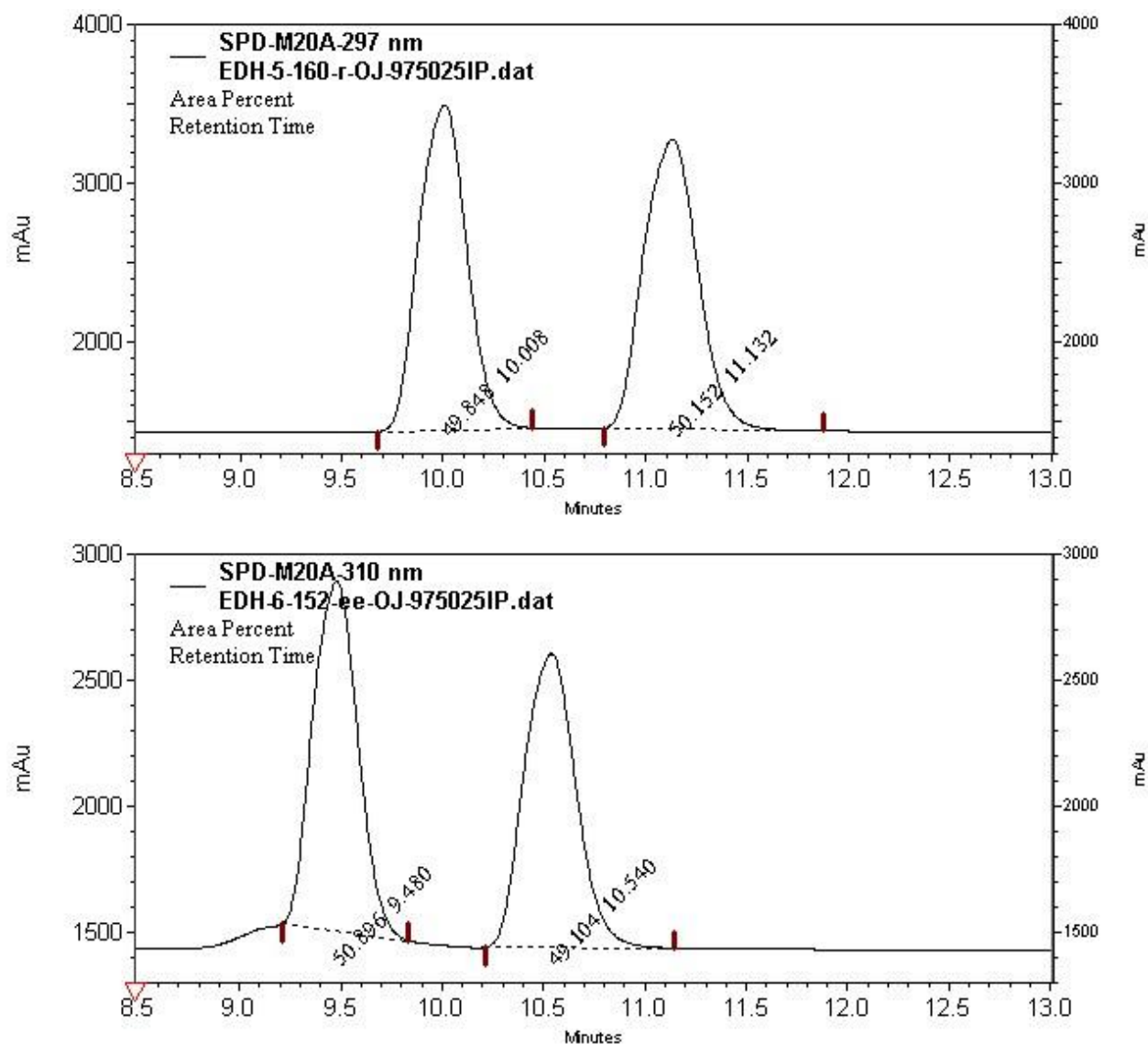


Figure S4.21. Racemic trace (top) and enantioenriched trace (bottom) of indoline **7a**.

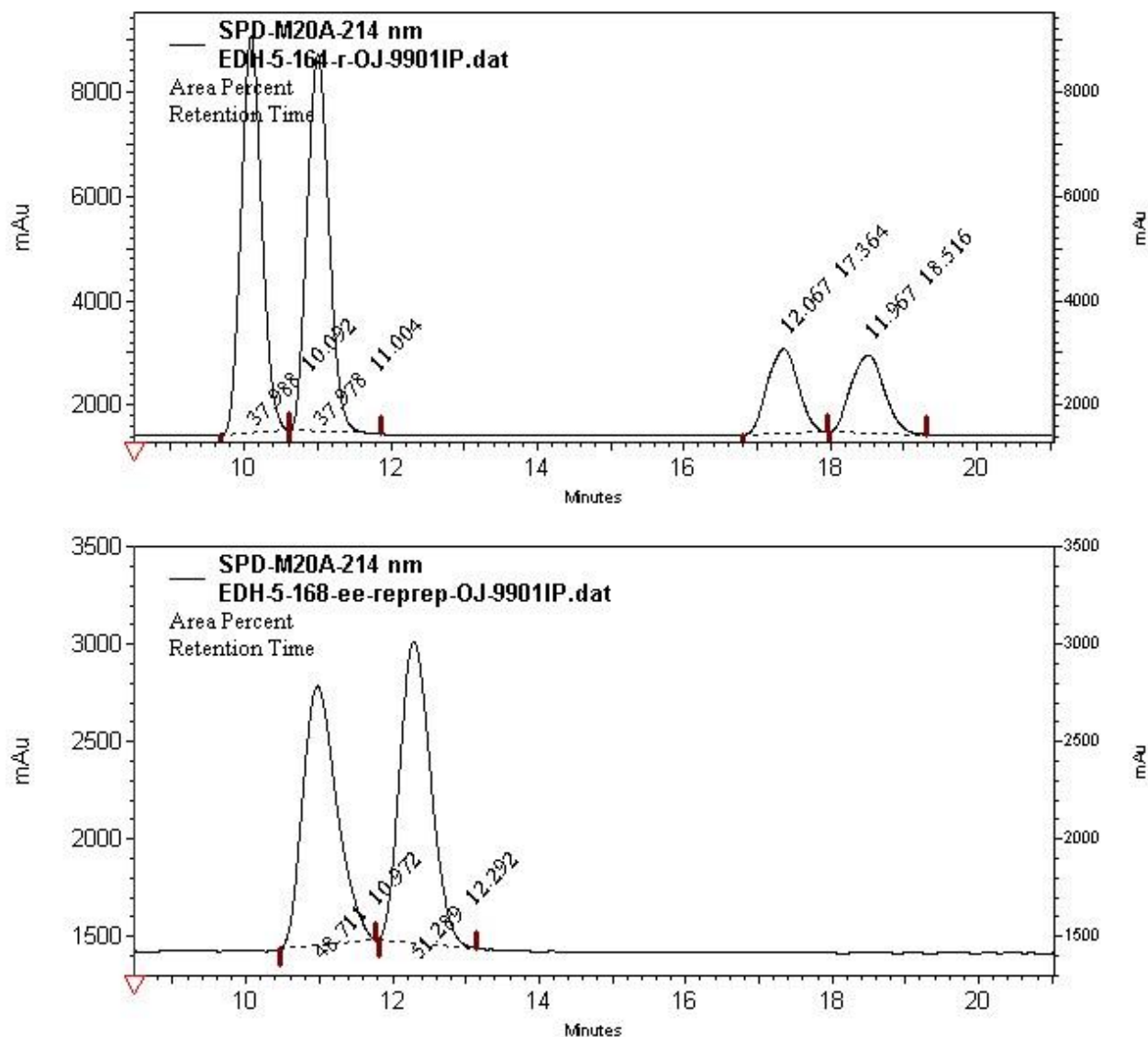


Figure S4.22. Racemic trace (top) and enantioenriched trace (bottom) of indoline **7c**.

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