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Hydroamination of Dihapto-Coordinated Benzene and Diene Complexes of Tungsten: Fundamental Studies and the Synthesis of γ-Lycorane

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Dedicated to Prof. *E. Peter Kündig* on the occasion of his 75th birthday

Abstract: Reactions are described for complexes of the form WTp(NO)(PMe_3)(η^2-arene) and various amines, where the arene is benzene or benzene with an electron-withdrawing substituent (CF_3, SO_2Ph, SO_2Me). The arene complex is first protonated to form an η^2-arenium species, which then selectively adds the amine. The resulting η^2-5-amino-1,3-cyclohexadiene complexes can then be subjected to the same sequence with a second nucleophile to form 3-aminocyclohexene complexes, where up to three stereocenters originate from the arene carbons. Alternatively, 1,3-cyclohexadiene complexes containing an ester group at the 5 position (also prepared from an arene) can be treated with acid followed by an amine to form trisubstituted 3-aminocyclohexenes. When the amine is primary, ring closure can occur to form a cis-fused bicyclic γ lactam. Highly functionalized cyclohexenes can be liberated from the tungsten through oxidative decomplexation. The potential utility of this methodology is demonstrated in the synthesis of the alkaloid γ-lycorane. An enantioenriched synthesis of a lactam precursor to γ-lycorane is also described. This compound is prepared from an enantioenriched version of the tungsten benzene complex. Regio- and stereochemical assignments for the reported compounds are supported by detailed 2D NMR analysis and 13 molecular structure determinations (SC-XRD).

keywords: tungsten, hydroamination, lycorane, dearomatization, diene, arene, nitrosyl, cyclohexene

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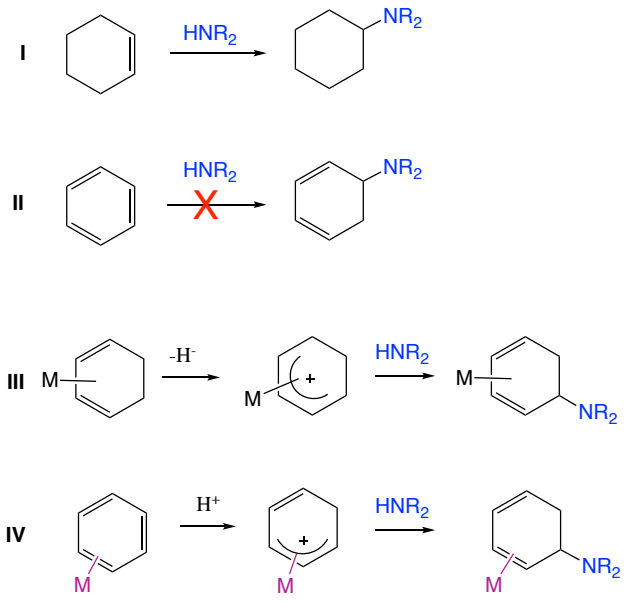
Introduction

Hydroamination is among the most powerful tools available for the synthesis of amines (reaction **I**, Scheme 1).[1-4] While numerous methods have been developed for the addition of amines to alkenes and alkynes, such a reaction for benzene itself (reaction **II**) is highly endergonic. For more than half a century, chemists have exploited the properties of transition metals to promote the nucleophilic addition to benzenes.[5-6] However, the majority of this work has been limited to carbon nucleophiles, typically stabilized enolates, dithianes, Grignards or other organometallics.[7] Amines have been widely demonstrated to undergo nucleophilic substitution with arene ligands containing suitable leaving groups in complexes such as $Cr(CO)_3$, $[Mn(CO)_3]^+$, and $[RuCp]^{+}$.[8] However, examples of nitrogen nucleophiles undergoing addition to benzene complexes are far less common. Still, pioneering work by Birch, Pearson and those that followed demonstrated that cyclohexadiene complexes can be subjected to hydride abstraction to form electrophilic cyclohexadienyl species such as the venerable $[Fe(CO)_3(C_6H_7)]^+$ system,[9-10] which readily adds amines to form complexed aminodienes (reaction **III**). Research in our laboratories has focused on the ability of π-basic transition metal complexes to promote addition reactions to η^2-bound arenes.[11-13] In this case, the metal activates the aromatic ligand toward protonation to form an η^3- or η^2-arenium intermediate (reaction **IV**).[14] Our previous work has demonstrated that this intermediate reacts with carbon nucleophiles to generate substituted cyclohexadienes. [15-16] Strikingly, we found that addition of methylamine resulted in the hydroamination of the benzene ring to form the aminodiene (reaction **IV**).[15] This result was surprising because not only was addition of the amine competitive with deprotonation of the arenium ligand, but the resulting complex was kinetically stable with respect to elimination, provided that it was kept in a basic environment. The results outlined below are a systematic examination of the ability of {WTp(NO)PMe_3} (Tp = tripyrazolylborate) to promote the hydroamination of η^2-coordinated arenes and cyclohexadienes to form highly substituted, three dimensional cyclohexenes.



Scheme 1. Hydroamination of alkenes and arenes via cyclohexadienyl intermediates.

Hydroaminations are typically carried out through the use of transition metal or lanthanide catalysts, or by strong bases.[1-4] However, if the amine is suitably protected by a strong withdrawing group, acid catalyzed hydroaminations can also be realized, especially intramolecular variations.[17-19] The main obstacle in carrying out such a reaction is the incompatibility of the acid and the amine, as well as the negative entropy associated with the intermolecular reaction.[2] In the case of benzene dihapto-coordinated to {WTp(NO)(PMe_3)}, we have previously demonstrated that the strong tungsten-benzene backbonding interaction promotes the protonation of the aromatic ligand to form an arenium species.[14] The question remained, however, whether the addition of the amine could pre-empt deprotonation of the η^2-arenium (i.e. η^2-cyclohexadienyl) complex at reduced temperatures. Our study commenced by preparing the arenium complex in situ from its benzene precursor (**1**) followed by addition of an amine. Even with benzene, several regio- and stereochemical issues come into play. The benzene ligand is competitively protonated at two different carbons,[14] resulting in two different arenium species, **2** and **3**. Each of these exists as two different conformational isomers in which two carbons are tightly bound by the tungsten but a third is loosely associated.[20] Herein, we indicate this weakly bound carbon as a carbocation in order to differentiate the two conformations. We note however, that much like

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conformations of chiral amines that differ only by inversion of the nitrogen (invertomers), allyl-shift isomers can be represented by the same bond structure (i.e., bonds from the metal to all three allyl carbons) but they differ in torsion and bond angles.[14] For the η^2-benzenium system, this equilibrium in solution is approximately 10:1 (^{1}H NMR), favoring isomer **2** in its distal conformer (**2D**)**.** Under Curtin–Hammett conditions, addition of the amine is not necessarily dictated by the dominant species in solution, but in the case of methylamine, addition occurs smoothly at the anticipated carbon providing the distal aminodiene **4D** with a >96:4 selectivity.[15] As is typical for these arenium species,[13] nucleophilic addition occurs strictly anti to the ring face bound by the metal.[15] The selectivity becomes even more impressive when the arene contains an electron-withdrawing group. Protonation of the trifluorotoluene ligand of **5** generates the arenium in >20:1 selectivity,[16] and subsequent addition of methylamine generates aminodiene **6** (Scheme 3), exclusively. In this case, protonation occurs ortho to the CF_3 group, and amine addition occurs at the adjacent carbon. Analogous reactions are achieved with p-chlorobenzylamine, 2-(aminomethyl)pyridine, and even with the secondary amine, morpholine. In all cases (**6**-**9**), both regio- and stereoselectivity is >98:2. Structural assignments were confirmed with a combination of NOE interactions between the diene and the PMe_3 and Tp ligands of the complex (Figure 1), and when possible, SC-XRD data (Figure 2). When the diphenylsulfone complex **10** was subjected to similar reaction conditions, the selective formation of 5-aminodiene complexes was also realized, this time with either morpholine (**11**) or piperidine (**12**). In all cases, the corresponding aminodiene complexes were found to be kinetically stable in solution, *provided* that they were kept away from acid. Even under weakly acidic conditions, elimination to re-form the η^2-arene starting materials was rapid.

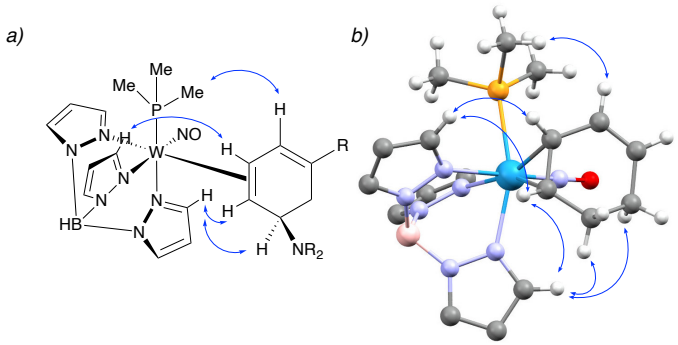
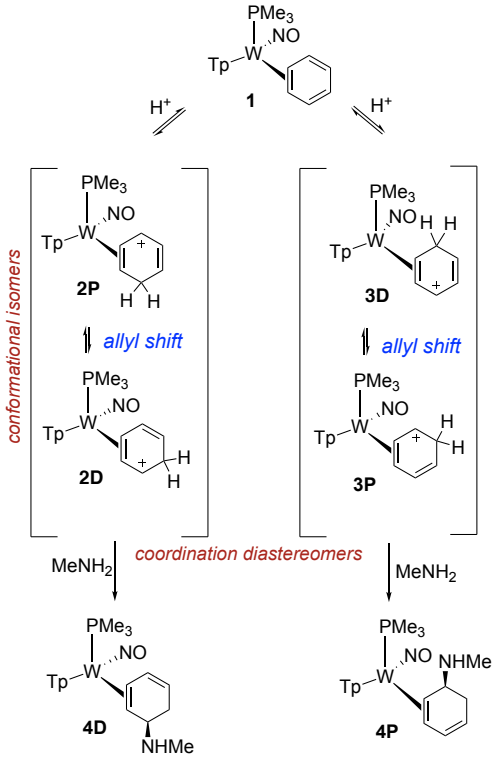


Figure 1. Key NOE interactions with a generic η^2-1,3-diene complex (a), and the WTp(NO)(PMe_3)(η^2-1,3-cyclohexadiene complex) (b); structure of the parent η^2-1,3-cyclohexadiene from SC-XRD analysis)[14]



Scheme 2. Dihapto-coordinated η^2-benzenium isomers and their reaction with methylamine.

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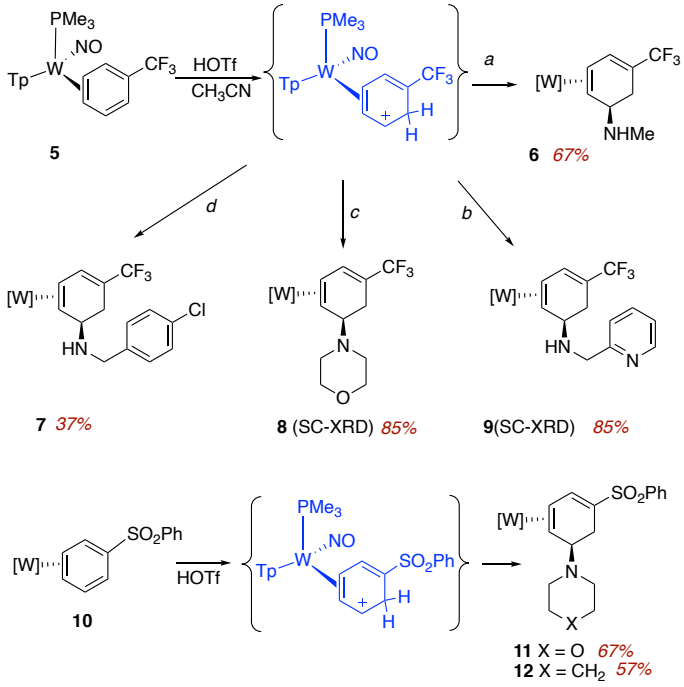

Scheme 3. Preparation of 5-amino-1,3-cyclohexadiene complexes from trifluorotoluene and diphenyl sulfone precursors.

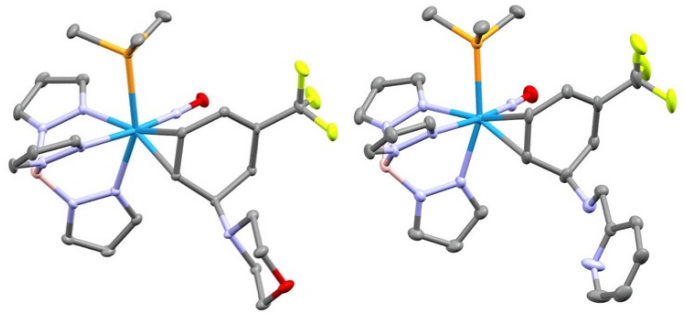

Figure 2. SC-XRD molecular structures (50% ellipsoids) of **8** (left) and **9** (right): products of hydroamination of the trifluorotoluene complex (**5**) using morpholine or 2-methylaminopyridine.

Our next objective was to carry out a second hydroamination reaction with the diene derived from the arene complexes **1** and **5**. We began this phase of the research with an exploration of the aminodiene complex **6**, derived from methylamine and trifluorotoluene. While we speculate that subjecting this compound to an excess of strong acid first results in the protonation of the amino group, a second protonation can occur to form the allyl dication (**I**, Scheme 4).[20] Gratifyingly, the addition of acid followed by the addition of the methoxide source Bu_4NOH/MeOH at low temperature (–30 °C) provides the trisubstituted cyclohexene **13**.

Significantly, in the absence of an added nucleophile, a different outcome was observed: When **6** was allowed to stand in a solution of acetone, an isomerization occurred over a period of 12 hours to form a new diene complex (**14**). From 2D NMR data and an SC-XRD study, the new diene now has an amino group adjacent to the CF_3 group. This suggests that protonation from adventitious water momentarily forms an allyl *monocation* (**II**; Scheme 4) that can undergo intramolecular addition of the amino group to form the azabicyclic intermediate **III**. We postulate further that this species then evolved into a new allyl intermediate, **IV**, which upon deprotonation delivers the new diene (**14**). We note that in both **13** and **14** the CF_3 group is trans to the tungsten. This suggests that protonation at the carbon bearing this substituent occurs syn to the metal, similar to that seen in the protonation of η^2-arene complexes of TpW(NO)(PMe_3).[14] Protonation anti to the metal is disfavored owing to a steric interaction between the CF_3 group and the nitrosyl ligand.

A third reactivity type for **6** was observed in an attempt to add the silyl ketene acetal ((1-methoxy-2-methylprop-1-en-1-yl)oxy)trimethylsilane (MMTP) to the allyl intermediate (**I**, Scheme 4). The product generated (**15**) did not show any incorporation of the enolate, but rather the acetonitrile solvent appears to have acted as the initial nucleophile (**V**), analogous to the Ritter reaction. Subsequent ring closure with the pendent amine group (exposed upon addition of triethylamine base) results in the benzimidazolium derivative **15**. Detailed 2D NMR data and a SC-XRD study confirm the assigned structure. When the reaction was repeated in the absence of the MMTP, no reaction occurred. This observation suggests that the TMS group of the MMTP plays an important role in this reaction. We speculate that interaction of the TMS with the nitrosyl may enhance the electrophilicity of the allyl cation (via the tungsten), which would enhance its reactivity with the nitrile solvent. Previously we have shown that the nitrosyl ligand of WTp(NO)(PMe_3)(cyclohexene) can be methylated with MeOTf,[14] and independently the Legzdins group has demonstrated this reactivity with similar tungsten-nitrosyl systems and Lewis acids.[21] In absence of the TMS group, a purported protonation of the nitrosyl is apparently reversed by the addition of triethylamine and cyclization does not occur. Again, we find that the CF_3

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substituent in **15** is trans to the tungsten, as is the cis-fused amidine ring (Figure 3).

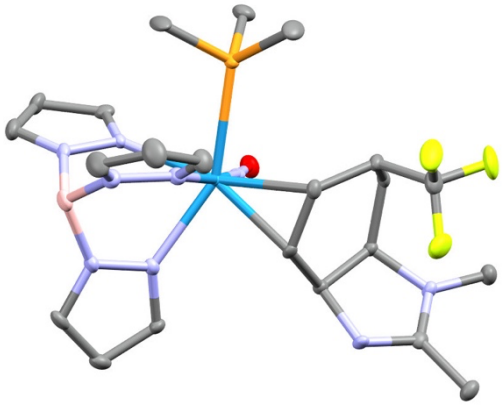
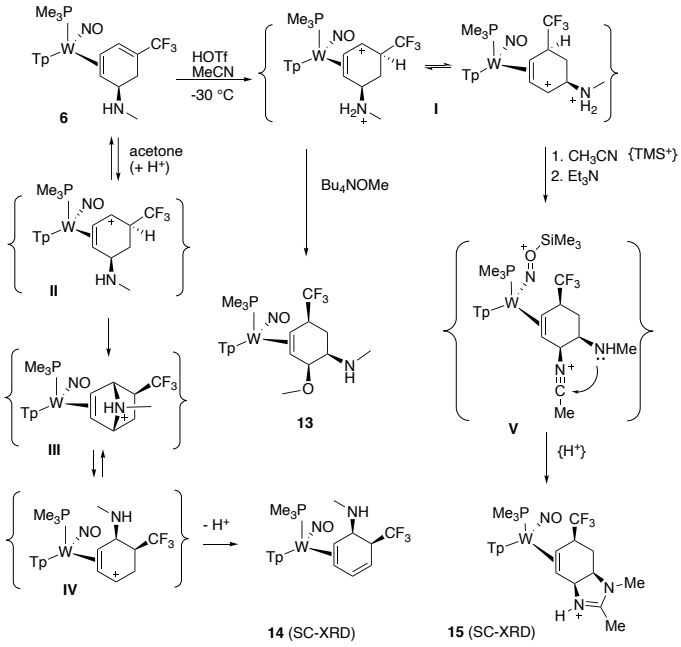
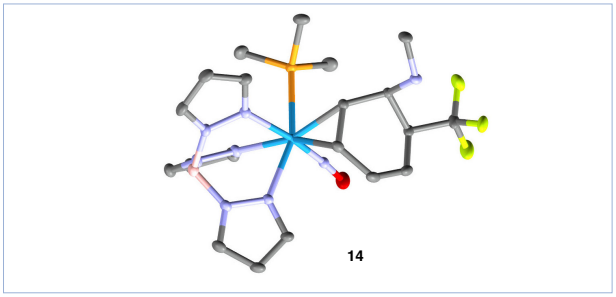


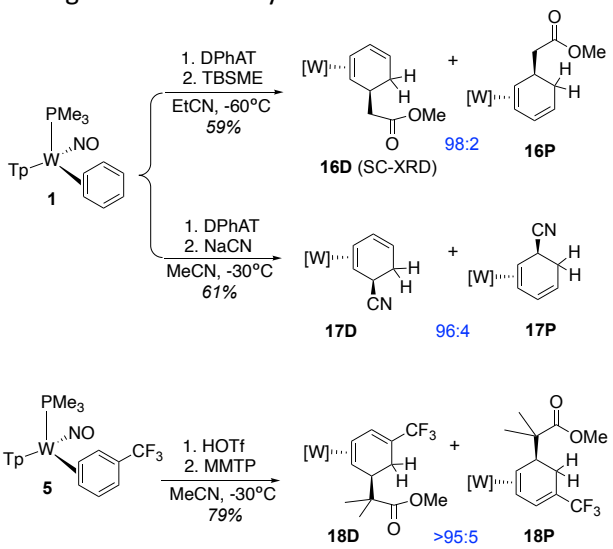
Figure 3. SC-XRD molecular structure of **15** (50% ellipsoids).

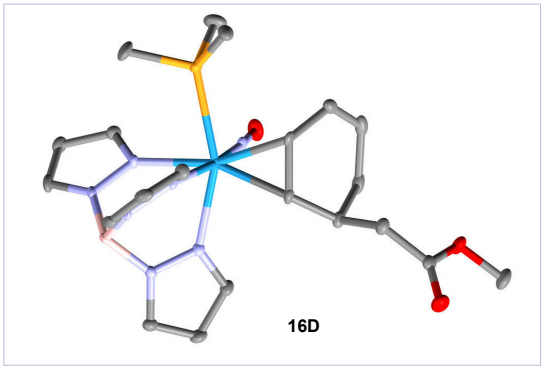




Scheme 4. Rearrangement, elimination, and nucleophilic addition reactions observed for the aminodiene complex **6**. Bottom: SC-XRD molecular structure of **14** (50% ellipsoids)

Although addition reactions similar to the formation of the aminomethoxycyclohexene **13** from **6** were also successful with other amine and cyanide nucleophiles, these reactions were plagued by significant amounts of elimination. Hence, we decided on a new tack in which a carbon nucleophile was first employed in the preparation of the diene, and then the amine would be incorporated in the second step. Three diene complexes were prepared as test cases (**16**-**18**). Two were derived from the benzene complex **1**, and the third was derived from the trifluorotoluene analog **5** (Scheme 5). High stereoselectivity was observed (95:5 or greater) in all three examples, with the dominant isomer having the carbon substituent distal to the PMe_3 and trans to the tungsten. 2D NMR data was used to assign all three structures (**16**-**18D**) and that of **16D** was confirmed through a SC-XRD analysis.





Scheme 5. Protonation and addition of carbon nucleophiles to dihapto-coordinated arene complexes. Bottom: SC-XRD molecular structure of **16D** (50% ellipsoids). (DPhAT = diphenylammonium

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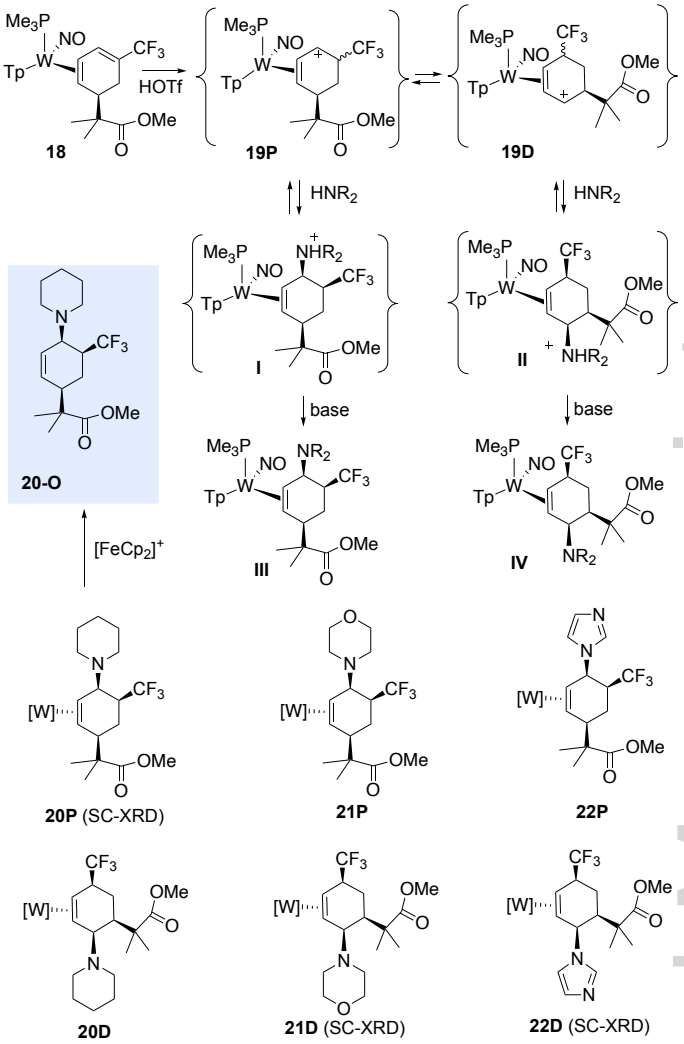
triflate; TBSME = *tert*-butyl((1-methoxyvinyl)oxy)dimethylsilane; MMTP = ((1-methoxy-2-methylprop-1-en-1-yl)oxy)trimethylsilane).

The addition of amines to the diene complexes **16**-**18** follow a general pattern. Here we will focus on the trifluorotoluene examples, which lead to cyclohexene complexes with three stereocenters in the ring. Protonation of the diene occurs at the terminal position of the η^2-diene ligand, which in this case is the carbon bearing a CF_3 substituent. While we speculate that initial protonation is trans to the metal,[14] this process is likely reversible and protonation ultimately occurs cis to the tungsten in order to avoid a CF_3-nitrosyl steric interaction (vide supra). The purported allyl intermediate exists as four conformations, including two different distortions of the allyl framework (**19P** and **19D**). DFT calculations indicate that the boat form of **19D** is favored over the chair-like form by 15.0 kcal/mol, while proximal conformations (**19P**) are energetically uncompetitive. Correspondingly, amines appear to first add to **19D** to form **II** (Scheme 6). Subsequent deprotonation of the amine results in compounds of the type **IV**, which can be isolated provided that they are kept in a basic environment. In several cases (**20**-**22**), one of the isomers spontaneously crystallized from CH_3CN solution in pure form. However, even in the presence of an excess of amine, the ammonium salt byproduct resulting from the reaction of HOTf and the amine was sufficient to allow the re-protonation of **IV** to form **II**. Rearrangement of the latter to type **I** and its deprotonation to **III** resulted in the species **20**-**22P**. SC-XRD analysis was performed on three examples, (**20P**, **21D**, **22D**; e.g., as shown in Figure 4) confirming the structures of these 3,4,6-trisubstituted cyclohexene complexes. Proton NMR data confirmed that these complexes in solution were often mixtures of the **D** and **P** isomers, even when starting with crystalline material. However, these allyl amine ligands were much more stable once the metal was removed. An example is shown for **20P**, which upon oxidation by $[FeCp_2]PF_6$ yields the organic compound, **20-O** (Scheme 6).



Scheme 6. The stereoselective preparation of 3,4,6-trisubstituted cyclohexene complexes.

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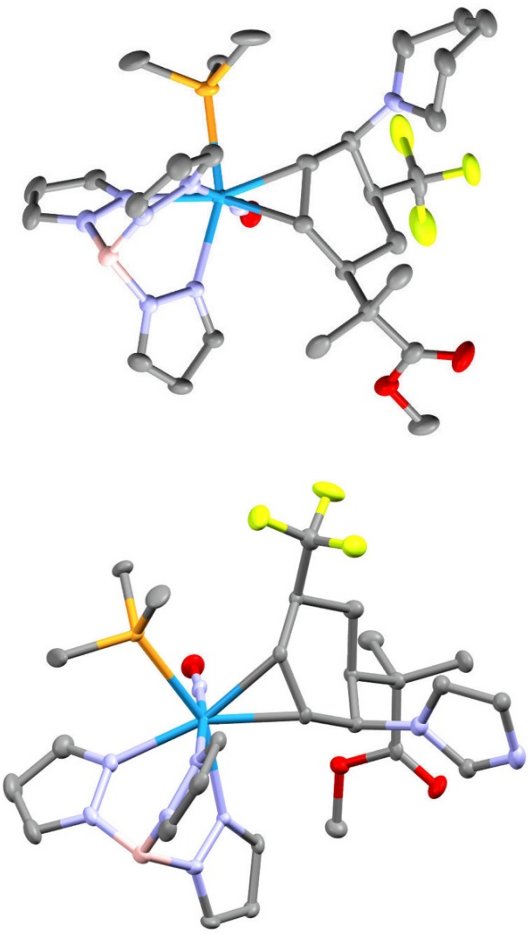
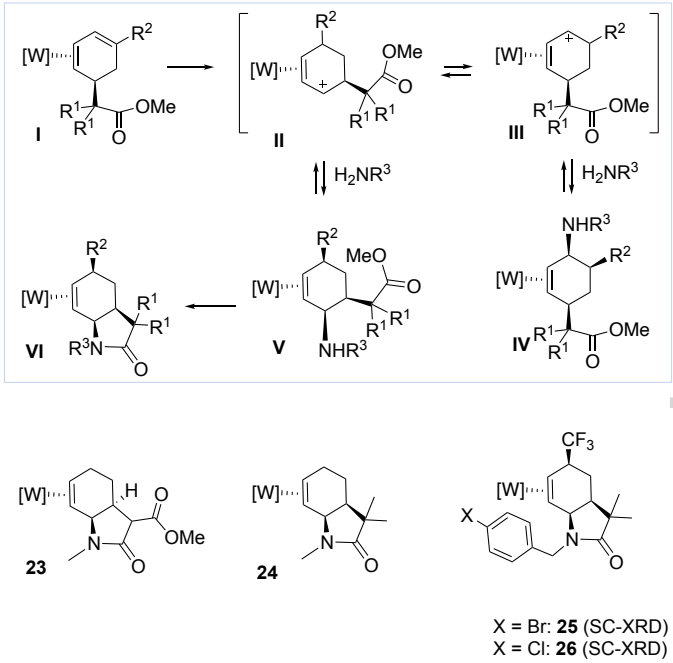


Figure 4. SC-XRD molecular structures (50% ellipsoids) of **20P** (top) and **22D** (bottom): trisubstituted cyclohexene complexes derived from piperidine and imidazole.

When the diene ester complexes (**I** Scheme 7) are protonated and subsequently treated with a primary amine, what initially is a mixture of products resolves into one dominant compound in which the amine and ester form a bicyclic γ-lactam. This reaction appears to be general, occurring with a wide range of amine, ester, and arene precursors, and in all cases a cis-fused hexahydroindole core is formed. Four examples[15] are provided in Scheme 7 and two molecular structures derived from SC-XRD studies (**25**, **26**) are provided in the SI. As with the case of simple amine additions, the final stereochemistry of the CF_3 group is always trans to the tungsten, placing it in the concave side of the bicyclic lactam core.



Scheme 7. The stereoselective preparation of cis-fused bicyclic-γ-lactams.

Given the generality of the lactam formation and the ability to control the stereochemistry, the reaction sequence shown in Scheme 7 provided the opportunity to demonstrate the utility of the tungsten methodology in natural product synthesis. The lycorines are an abundant class of tetra- and pentacyclic molecules that are part of the Amaryllidaceae alkaloids family.[22] They are of interest for their diverse biological activity including inhibition of growth and cell division, treatment of Alzheimer's disease, and antitumor activity. They also are a popular target of synthetic chemists due to their complex structure and multiple stereocenters. Although γ-lycorane, (**27**) is not as pharmacologically active as some of its more oxidized cousins, it has been a popular target for demonstrating new synthetic methodologies. The first asymmetric synthesis of γ-lycorane was reported by Mori in 1995,[23] and its structure is considered prototypical for this important class of alkaloids. In just the past five years, well over a dozen new syntheses of the lycorine family have appeared.[24-37] Of these only one uses a benzene ring as the source of the C ring, which contains all of the stereocenters. Baudoin et al. reported a double C-H arylation of an acetanilide derivative followed by arene hydrogenation.[26] Given that all the

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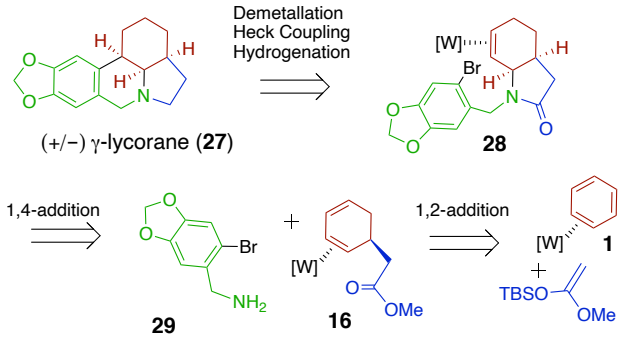
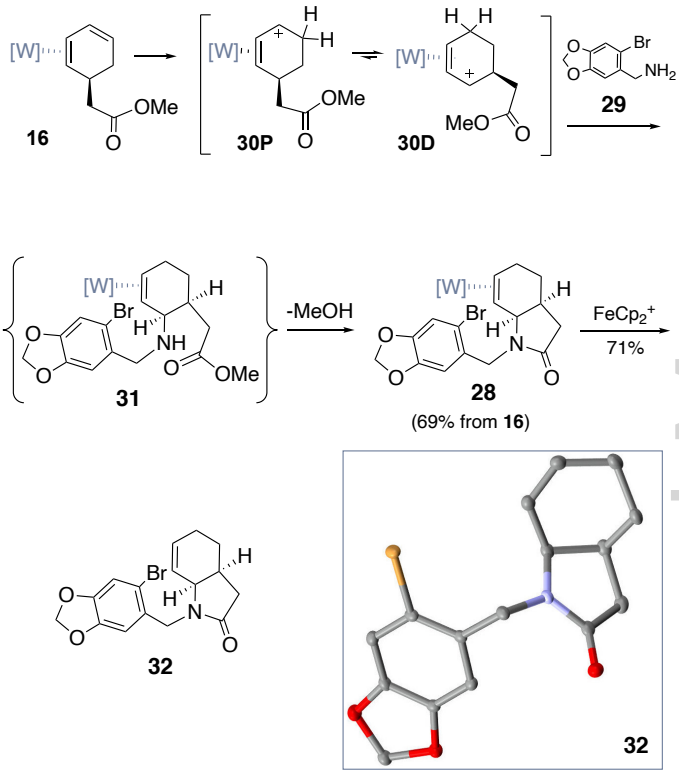
carbons in a benzene ring are unsaturated and that so many benzene derivatives are commercially available, approaches that utilize a benzene precursor as the C-ring could offer considerable diversity for medicinal chemists interested in exploring this scaffold. Our proposed route took advantage of the ability of benzene complex **1**, available on a 9 g scale,[38] and as either enantiomer,[39] to undergo an efficient sequence of reactions leading to the requisite cis-fused lactam (Scheme 8). Use of the appropriate benzylamine in the lactamization would set the stage for a Heck coupling and hydrogenation to form the desired product (**27**).



Scheme 8. Retrosynthetic analysis for the preparation of γ-lycorane.

Our synthesis (Scheme 9) commenced with the diene **16** prepared from benzene complex **1** and the TBS-protected enolate of methyl acetate. Treatment of the η^2-diene **16** with an acetonitrile solution of triflic acid results in conversion to the η^2-allyl complex **30P**, which as described above, exists in equilibrium with its thermodynamically favored conformational isomer **30D**.[20] In line with our earlier results, benzylamine **29** (prepared from piperonal)[40] purportedly reacts selectively with **30D** to form the 3-aminocyclohexene complex **31**. Addition of an excess of DBU ensures that the allyl amine will not eliminate in the presence of residual acid (via E1) nor isomerize to the potentially more stable 3,6-disubstituted cyclohexene complex (via **30P**). Continued stirring of the reaction mixture over several days promoted the desired lactamization and crystals of complex **28** precipitated out of solution (69% from **16**). A full 2D NMR analysis and SC-XRD analysis confirms that **28** was formed from the addition of the benzylamine anti to the metal with subsequent loss of the methoxy group. Key spectroscopic features include the loss of a methoxy group in the proton NMR and the shift of a C=O stretching frequency in the IR absorption spectrum to 1678 cm^{-1}, consistent with amide formation. At this stage, the mild one-electron oxidant $[FeCp_2]PF_6$ was added to a solution of **28**. Oxidation of the tungsten dramatically reduces backbonding to the cyclohexene ligand and induces the release of **32**. Crystals of **32** were grown from an ethyl acetate/CH_2Cl_2/ether (1:3:2) solution. A SC-XRD determination (see Scheme 9) confirms the molecular structure and stereochemistry of the lactam **32**, which was originally reported in Mori's landmark paper as an advanced intermediate in the synthesis of γ-lycorane.[23]



Scheme 9. Preparation of the lactam **32**, an advanced precursor to γ-lycorane (racemic).

To demonstrate the versatility of this method, we took advantage of the stereogenic tungsten center, which retains its configuration even through ligand exchange. Thus, in principle any of these compounds can be prepared enantioselectively, starting from the desired enantiomer of the benzene complex **1**. Given that the naturally occurring form of the alkaloid ((+)-γ-lycorane) has a *3aR, 3a'S, 12bR* configuration, the desired form of **1** was the *S* configuration. In a previous report,[39] we have

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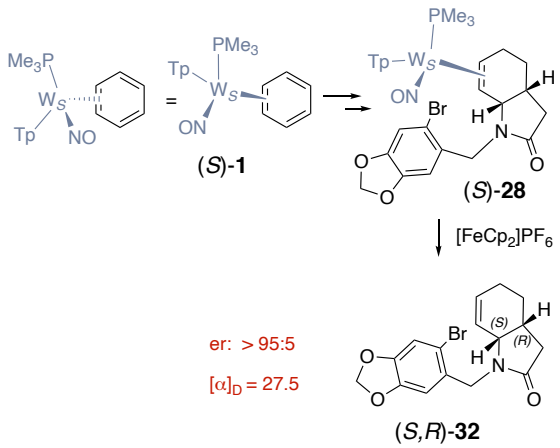
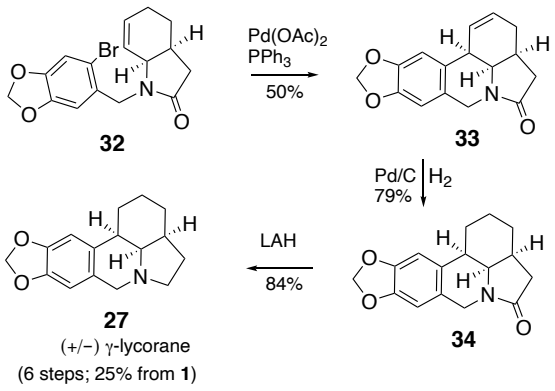
shown that either form of **1** is available starting from the appropriate dibenzoyltartaric acid salt of dimethoxybenzene (Scheme 10), which precipitates away from its diastereomeric salt in 2-butanone. In this case, D-dibenzoyl tartarate leads to *(S)*-**1** in ee from 90-99%, depending on processing time.[39] Using the procedures outlined above, *(S)*-**1** was converted into *(S,R)*-**32** in er = 95:5 thereby completing the formal synthesis of (+)-γ-lycorane (Scheme 10).



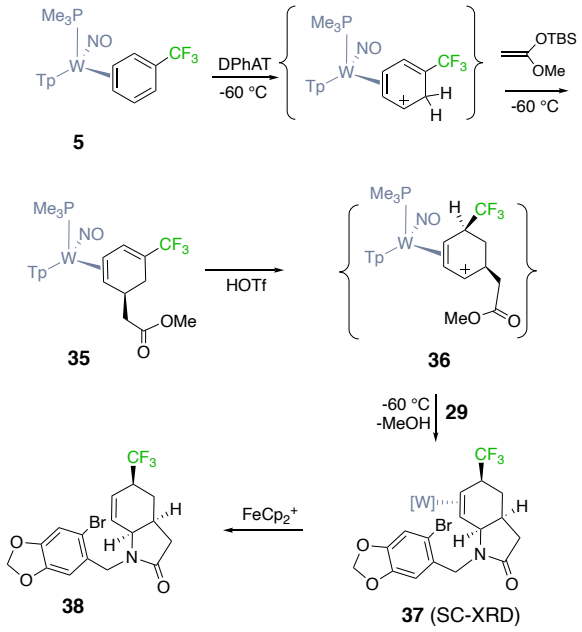
Scheme 10. The preparation of enantioenriched lactam **32**, a γ-lycorane precursor.

From this point, a sequence of Heck coupling, alkene hydrogenation, and reduction of the amide produced the target γ-lycorane. As a verification, we carried out the same sequence as reported in the literature to generate γ-lycorane. Under our unoptimized conditions, the yield of 33% fell short of expectations (cf. 86% over 3 steps), but spectral data matched that reported for **27**.



Scheme 11. The preparation of γ-lycorane (**27**) from lactam **32**.

The biggest potential advantage of the present approach to lycorane is the ability to readily exchange the benzene substrate with other arenes. To illustrate this, the sequence used to prepare the key lactam **37** (Scheme 12) was attempted, this time starting with trifluorotoluene complex **5**. Trifluoromethyl groups in agrochemicals and pharmaceuticals have been of continued interest because of their increased hydrolytic, oxidative, and metabolic stability, as well as their increased bioavailability.[41] While numerous methods are available for installing CF_3,[42-45] few approaches have been described that generate CF_3-substituted cyclohexenes from aromatic precursors.[46] As described earlier,[16] protonation of the trifluorotoluene complex (**5**) occurs selectively at the ortho carbon to generate the arenium complex (Scheme 12). When this species is treated with the silyl ketene acetal TBSME, addition occurs smoothly at C3 to generate the diene complex **35**. Thermodynamics favors protonation of the diene such that the CF_3 group is trans to the tungsten, and addition of the benzylamine ultimately leads to lactam **37**. A single crystal of **37** was grown from MeCN solution and the solid-state molecular structure confirms the assigned stereochemistry (Figure 5). Unfortunately, while the lactam **38** could be liberated from the metal, our attempts to close the final ring by Heck coupling proved unsuccessful.



Scheme 12. The preparation of **38**, the trifluoromethylated derivative of the γ-lycorane precursor lactam **32**.

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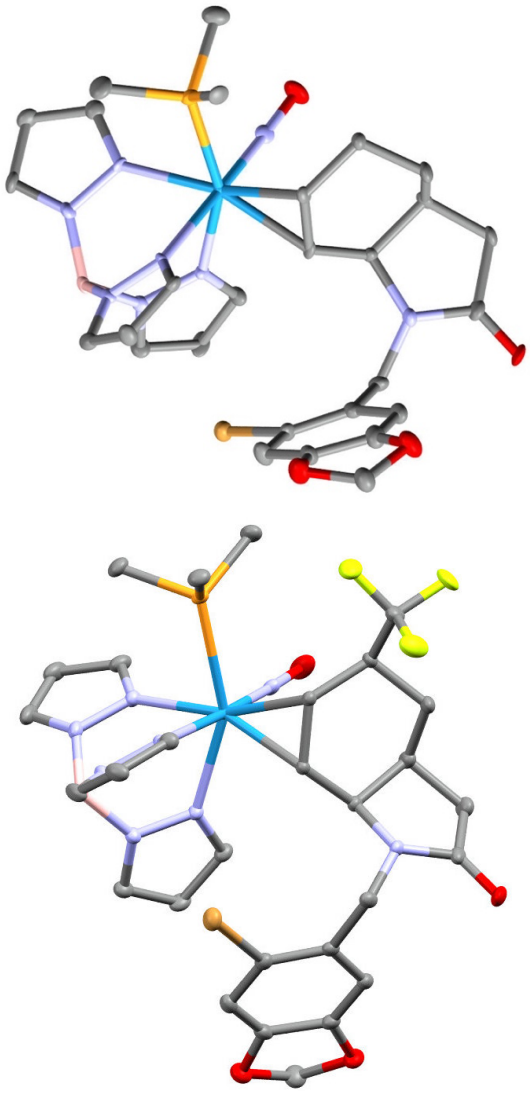

Figure 5. SC-XRD molecular structures (50% ellipsoids) of **28**, an advanced intermediate toward γ-lycorane (**27**), and the trifluoromethylated analog **37**.

Conclusions

The coordination of the tungsten complex WTp(NO)(PMe_3) to benzene or substituted benzenes activates the aromatic ligand toward protonation. Much like the venerable $[Fe(CO)_3(C_6H_7)]^+$ complex of Birch et al.,[10, 47] the addition of an amine nucleophile completes the hydroamination of the benzene ligand with good control of the regio- and stereochemistry. Carbon nucleophiles can also be added to the arenium intermediate to generate dihapto-coordinated diene complexes, and hydroamination of these diene ligands can also be accomplished in good yield. The hydroamination of the ester-diene complex **18** results in two different regioisomers, but when a primary amine is used, the addition at the adjacent ring carbon leads cleanly to bicyclic γ-lactams. In order to demonstrate the potential of this methodology in more complex synthetic targets, benzene was incorporated as the central ring of the pentacyclic molecule γ-lycorane.

Inspired by the chemistry pioneered by Kündig, Semmelhack, Pearson, Sweigart, Davies, and others who earlier demonstrated the synthetic power of transition metal arene complexes, this tungsten system offers complementary reaction patterns to the η^6 analogs. Here the metal acts as an electron donor, both for the arene ligand and diene species prepared from the arene complex. The ability to add amines, alkoxides, protected enolates, and cyanide under mild conditions allows the formation of up to three stereocenters to be prepared from carbons of the initial arene ring, with the product being potentially accessible in enantio-enriched form.[39]

Experimental Section

General Methods

NMR spectra were obtained on 500, 600 or 800 MHz spectrometers. Chemical shifts are referenced to tertramethylsilane (TMS) utilizing residual ^1H or ^{13}C signals of the deuterated solvents as internal standards. Phosphorus NMR signals are referenced to 85% H_3PO_4 (δ 0.00) using a triphenyl phosphate external standard (δ −16.58). Chemical shifts are reported in ppm and coupling constants (J) are reported in hertz (Hz). Infrared Spectra (IR) were recorded on a spectrometer as a glaze on a diamond anvil ATR assembly, with peaks reported in cm^{-1}. Electrochemical experiments were performed under a nitrogen atmosphere. Most cyclic voltammetric data were recorded at ambient temperature at 100 mV/s, unless otherwise noted, with a standard three electrode cell from +1.8 V to -1.8 V with a platinum working electrode, *N,N*-dimethylacetamide (DMA) or acetonitrile solvent, and tetrabutylammonium hexafluorophosphate (TBAH) electrolyte (~1.0 M). All potentials are reported versus the normal hydrogen electrode (NHE) using cobaltocenium hexafluorophosphate ($E_{1/2}$ = -0.78 V, -1.75 V) or ferrocene ($E_{1/2}$ = 0.55 V) as an internal standard. Peak separation of all reversible couples was less than 100 mV. All synthetic reactions were performed in a glovebox under a dry nitrogen atmosphere unless otherwise noted.

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All solvents were purged with nitrogen prior to use. Deuterated solvents were used as received from Cambridge Isotopes. NMR assignments of all compounds were determined using 2D NMR methods including NOESY, COESY, HMBC, and HSQC. When possible, pyrazole (Pz) protons of the (trispyrazolyl) borate (Tp) ligand were uniquely assigned (e.g., "PzB3") using two-dimensional NMR data (see Figure 1). If unambiguous assignments were not possible, Tp protons were labeled as "Pz3/5 or Pz4". All J values for Pz protons are 2 (±0.4) Hz. BH peaks (around 4-5 ppm) in the ^{1}H NMR spectra are not assigned due to their quadrupole broadening; however, confirmation of the BH group is provided by IR data (around 2500 cm^{-1}). High resolution electrospray ionization mass spectrometry (ESI-MS) analyses were taken on an Agilent 6545B Q-TOF LC/MS using purine and hexakis(1H, 1H, 3H-tetrafluoropropoxy)phosphazine as internal standards. Samples were dissolved in MeCN and eluted with a MeCN/H_2O solution containing 0.1% formic acid. The enantiomer ratios of *(R,S)*-**32** and *(S,R)*-**32** were determined using chiral HPLC with a Chiralpak IC-3 column. Compound **1**,[48] **2**,**3**,[14] **4**,[15] **5**,[16] **10**,[49] **17**,[15] **18**,**19**,[16] **23**, **24**,[15] and **29**[40] were reported previously.
Ground-state structures were optimized at the M06 level of theory using the 6-31G**[LANL2DZ for W] basis set in Gaussian 16. Previous literature demonstrates that this functional and basis set choice accurately corroborates experimental results. Vibrational frequency analysis verified that optimized structures were minima, and rigid-rotor-harmonic-oscillator thermochemical chemical corrections were applied at 298 K and 1 atm utilizing Gaussian's default implementation. When solvent corrections were applied to estimate ΔG_{solv}, optimization and frequency calculations were performed using the SMD continuum solvent model with the appropriate solvent's parameters from Gaussian.

Procedures

Compound 6. To a 4-dram vial charged with a stir pea were added **5** (500 mg, 0.770 mmol) followed by acetonitrile (2 mL, –30°C) and a 1M solution of HOTf in acetonitrile (1.54 mL, 1.54 mmol, –30°C), resulting in a homogeneous golden solution, which was allowed to sit for 15 min at –30°C. 2M H_2NMe/THF (3.85 mL, 7.70 mmol, –30°C) was then added to the reaction vial with stirring and allowed to sit at –30°C for 2.5 h. While the reaction was still cold, 1M tBuOK in *tert*-butanol (3.1 mL, 3.1 mmol) was added, and then the reaction solution was put back in the freezer at –30°C for 15 min. The reaction was then transferred to a filter flask and evaporated *in vacuo* to ~half volume. Precipitation was then induced by adding H_2O (20 mL), and the resulting pale yellow solid was collected on a 15 mL fine porosity fritted disc, washed with H_2O (1 mL), acetonitrile (1 mL), and pentane (2 x 5 mL) then desiccated overnight, yielding **6** (350 mg, 0.515 mmol, 67% yield). CV (DMAc) $E_{p,a}$ = +0.70 V (NHE). IR: ν(BH) = 2487 cm^{-1}, ν(NO) = 1565 cm^{-1}. Anal. Calc'd for $C_{20}H_{29}BF_3N_8OPW$: C, 35.32; H, 4.30; N, 16.48. Found: C, 35.59; H, 4.21; N, 16.20. ^{31}P NMR (d^6-DMSO, δ): -11.10 (J_{WP} = 279). ^{1}H NMR (CD_3CN, δ): 8.05 (d, 1H, PzB3), 7.98 (d, 1H, PzA3), 7.86 (t, 2H, PzB5 & PzC5), 7.77 (d, 1H, PzA5), 7.44 (d, 1H, PzC3), 7.16-7.20 (m, 1H, H2), 6.37 (t, 1H, PzB4), 6.29 (overlapping t, 2H, PzA4 & PzC4), 3.52 (dm, *J* = 5.3, 1H, H5), 2.75-2.83 (m, 1H, H3), 2.71 (dm, *J* = 16.5, 1H, H6x), 2.33 (buried, 1H, H6y), 2.32 (s, 3H, NMe), 1.36 (dm, *J* = 9.7, 1H, H4), 1.22 (d, *J* = 8.6, 9H, PMe_3). ^{13}C NMR (CD_3CN, δ): 144.5 (PzB3), 143.2 (PzA3), 141.9 (PzC3), 138.0 (PzC5), 137.4 (PzB5), 137.1 (PzA5), 136.8 (m, C2), 126.8 (q, *J* = 268.6, CF_3), 115.8 (q, *J* = 29.5, C1), 107.5 (Pz4), 107.2 (Pz4), 106.9 (Pz4), 60.2 (C4), 58.3 (C5), 47.6 (d, *J* = 9.6, C3), 34.7 (NMe), 26.1 (C6), 13.8 (d, *J* = 29.0, PMe_3).

Compound 7. To a 4-dram vial charged with a stir pea were added **5** (100 mg, 0.154 mmol) followed by acetonitrile (1 mL, -30°C) and a 1M solution of HOTf in acetonitrile (0.23 mL, 0.23 mmol, -30°C), resulting in a homogeneous golden solution, which was allowed to sit for 20 min at –30°C. 4-Chlorobenzylamine (370 mg, 2.61 mmol, –30°C) was added with stirring, and then the reaction solution was allowed to sit at –30°C for 19 h. While the reaction was still cold, 1M tBuOK in *tert*-butanol (0.62 mL, 0.62 mmol) was added, and then the reaction solution was put back in the freezer at -30°C for 10 min. The reaction was diluted with H_2O (10 mL), and extracted with Et_2O (10 mL). The organic layer was then evaporated *in vacuo*. The film was redissolved in minimal THF and added to stirring pentane (20 mL), which resulted in an oil. The liquid was decanted off, and the oil was redissolved in THF and added to pentane (20 mL). The resulting pale yellow solid was collected on a 15 mL fine porosity fritted disc, washed with pentane (2 x 5 mL) then desiccated overnight, yielding **7** (45 mg, 0.057 mmol, 37%

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yield). IR: *v*(BH)= 2487 cm^{-1}, *v*(NO) = 1561 cm^{-1}. Anal. Calc'd for $C_{26}H_{32}BClF_3N_8OPW$: C, 39.50; H, 4.08; N, 14.17. Found: C, 39.00; H, 3.89; N, 13.86. ^{1}H NMR (d^6-acetone, δ): 8.12 (d, 1H, Pz3/5), 7.97 (d, 1H, Pz3/5), 7.95 (d, 1H, Pz3/5), 7.89 (d, 1H, Pz3/5), 7.82 (d, 1H, Pz3/5), 7.61 (d, 1H, Pz3/5), 7.31 (d, *J* = 8.4, 2H, Ar-H), 7.25 (d, *J* = 8.4, 2H, Ar-H), 7.21-7.23 (m, 1H, H2), 6.40 (t, 1H, Pz4), 6.35 (t, 1H, Pz4), 6.25 (t, 1H, Pz4), 3.82 (d, *J* = 13.6, 1H, H7x), 3.78 (d, *J* = 13.6, 1H, H7x), 3.77 (buried, 1H, H5), 2.7-2.9 (m, 2H, H3 & H6x), 2.45 (d, *J* = 16.5, 1H, H6y), 1.55 (d, *J* = 9.6, 1H, H4), 1.30 (d, *J* = 8.5, 9H, PMe_3). ^{13}C NMR (d^6-acetone, δ): 144.4 (Pz3), 142.8 (Pz3), 142.0 (Pz3), 141.8 (Ar-C), 137.8 (Pz5), 137.2 (Pz5), 136.8 (m, C2), 136.7 (Pz5), 132.2 (Ar-C), 130.6 (2C, Ar-C), 128.8 (2C, Ar-C), 126.6 (q, *J* = 268.7, CF_3), 115.7 (q, *J* = 29.6, C1), 107.3 (Pz4), 107.1 (Pz4), 106.5 (Pz4), 60.5 (C4), 55.9 (C5/C5'), 51.4 (C5/C5'), 47.4 (d, *J* = 9.6, C3), 26.4 (C6), 13.8 (d, *J* = 28.6, PMe_3).

Compound 8. To a 4-dram vial charged with a stir pea were added **5** (200 mg, 0.308 mmol) followed by acetonitrile (2 mL, –30°C) and a 1M solution of HOTf in acetonitrile (0.46 mL, 0.46 mmol, –30°C), resulting in a homogeneous golden solution, which was allowed to sit for 20 min at –30°C. Morpholine (416 mg, 4.78 mmol) was added with stirring, and then the reaction solution was allowed to sit at –30°C for 17 h. While the reaction was still cold, 1M tBuOK in *tert*-butanol (1.23 mL, 1.23 mmol) was added. Precipitation was then induced by adding H_2O (6 mL) to the reaction solution with stirring, and the resulting pale yellow solid was collected on a 15 mL fine porosity fritted disc, washed with H_2O (2 x 3 mL), acetonitrile (0.5 mL), and pentane (3 x 5 mL) then desiccated overnight, yielding **8** (193 mg, 0.262 mmol, 85% yield). IR: *v*(BH) = 2487 cm^{-1}, *v*(NO) = 1559 cm^{-1}. Anal. Calc'd for $C_{23}H_{33}BF_3N_8O_2PW$: C, 37.52; H, 4.52; N, 15.22. Found: C, 37.48; H, 4.60; N, 15.17. ^{31}P NMR (d^6-acetone, δ): -11.74 (J_{WP} = 282). ^{1}H NMR (d^6-acetone, δ): 8.11 (d, 1H, PzB3), 8.06 (d, 1H, PzA3), 7.97 (d, 1H, PzC5), 7.95 (d, 1H, PzB5), 7.84 (d, 1H, PzA5), 7.71 (d, 1H, PzC3), 7.10-7.17 (m, 1H, H2), 6.40 (t, 1H, PzB4), 6.36 (t, 1H, PzC4), 6.30 (t, 1H, PzA4), 4.00 (d, *J* = 7.7, 1H, H5), 3.52 (t, *J* = 4.5, 4H, H2' & H6'), 3.00-3.10 (m, 1H, H3), 2.83 (buried, 1H, H6x), 2.75-2.85 (m, 2H, H3'/H5'), 2.51 (dt, *J* = 11.3, 4.5, 2H, H3'/H5'), 2.37 (d, *J* = 17.5, 1H, H6y), 1.32 (buried, 1H, H4), 1.30 (d, *J* = 8.5, 9H, PMe_3). ^{13}C NMR (d^6-acetone, δ): 144.5 (PzB3), 142.3 (PzA3), 142.0 (PzC3), 137.8 (PzC5), 137.2 (PzB5), 137.0 (PzA5), 136.6 (m, C2), 126.6 (q, *J* = 269.5, CF_3), 117.4 (q, *J* = 29.0, C1), 107.3 (PzB4), 107.1 (PzC4), 106.6 (PzA4), 68.2 (2C, C2' & C6'), 62.2 (C5), 52.6 (C4), 50.2 (2C, C3' & C5'), 49.6 (d, *J* = 9.5, C3), 22.5 (C6), 13.8 (d, *J* = 28.6, PMe_3). A SC-XRD study confirms the assigned structure.

Compound 9.

To a 4-dram vial charged with a stir pea were added **5** (200 mg, 0.31 mmol) followed by acetonitrile (2 mL, -30°C) and a 1M solution of HOTf in acetonitrile (0.46 mL, 0.46 mmol, -30°C), resulting in a homogeneous golden solution, which was allowed to sit for 15 min at -30°C. 2-Picolylamine (665 mg, 6.15 mmol, –30°C) was added with stirring, and then the reaction solution was allowed to sit at –30°C for 16 h. While the reaction was still cold, 1M tBuOK in *tert*-butanol (1.23 mL, 1.23 mmol) was added. Precipitation was then induced by adding H_2O (10 mL) to the reaction solution with stirring, and the resulting pale yellow solid was collected on a 15 mL fine porosity fritted disc, washed with H_2O (2 x 5 mL) and pentane (2 x 5 mL) then desiccated overnight, yielding **9** (198 mg, 0.26 mmol, 85% yield). ^{1}H NMR (CD_3CN, δ): 8.40 (d, *J* = 4.6, 1H, Ar-H), 8.04 (d, 1H, Pz3/5), 7.86 (bs, 3H, Pz3/5), 7.75 (d, 1H, Pz3/5), 7.6-7.7 (m, 1H, Ar-H), 7.43 (d, 1H, Pz3/5), 7.29 (d *J* = 7.9, 1H, Ar-H), 7.2-7.3 (m, 1H, Ar-H), 7.10-7.14 (m, 1H, Ar-H), 6.36 (t, 1H, Pz4), 6.29 (t, 1H, Pz4), 6.21 (t, 1H, Pz4), 3.83-3.87 (m, 2H, CH_2N), 3.74 (bs, 1H, H5), 2.81-2.85 (m, 1H, H3), 2.76 (d, *J* = 16.6, 1H, H6x), 2.37 (d, *J* = 16.6, 1H, H6y), 1.36 (d, *J* = 9.7, 1H, H4), 1.22 (d, *J* = 8.6, 9H, PMe_3). A SC-XRD study confirms the assigned structure.

Compound 11.

Compound **10** (0.100 g, 0.138 mmol) and MeCN were combined in a test tube to form an orange heterogeneous solution. Morpholine (0.18 mL, 0.18 g, 2.07 mmol) was added to a second test tube. Both solutions were cooled to 0 °C for 15 min. 1M HOTf/MeCN (0.21 mL, 0.210 mmol) was added to the reaction. Upon addition, the reaction became a dark red, homogeneous mixture. After 15 minutes, the reaction was added to the cooled morpholine test tube. The reaction was stirred overnight for 16 hrs. While the reaction was still in the cold probe, 1M tBuOK in tert-butanol (0.55 mL, 0.55 mmol) was added to the reaction and allowed to stir for an hour. The

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reaction was warmed to room temperature and removed from the glovebox. The reaction was diluted with 30 mL of H_2O and washed with 40 mL DCM. The aqueous layer was back extracted with DCM (25mL). The organic layers were combined and dried over $MgSO_4$ before being evaporated to dryness. The film was washed with hexanes and then ether. The remaining film was picked up in ethyl acetate and ran through a 30 mL basic alumina plug with 100 mL of ethyl acetate. The resulting filtrate was evaporated to dryness, pick up in minimal DCM, and crashed out into 50 mL of stirring pentane. The resulting brown precipitant was collected on a 15 mL fine porosity fritted disc, washed with ether (2 x 10 mL) and hexanes (3 x 10 mL), and desiccated to yield **11** (0.075 g, 0.093 mmol, 67%). CV (MeCN) $E_{p,a}$ = +0.77 V (NHE). IR: ν(BH) = 2484 cm^{-1}, ν(NO) = 1573 cm^{-1}, ν(SO) = 1407 cm^{-1}. Anal. Calc'd for $C_{28}H_{38}BN_8O_4PSW$: C, 41.60; H, 4.74; N, 13.86. Found: C, 41.54; H, 4.69; N, 13.66. ^{1}H NMR (CD_3CN, δ): 8.00 (1H, d, TpB3), 7.93 (1H, d, TpA3), 7.8-7.9 (2H, m, H16, H12), 7.86 (1H, d, TpC5), 7.85 (1H, d, TpB5), 7.84 (1H, dd J = 6.0, 2.6, H2), 7.76 (1H, d, TpA5), 7.55-7.59 (1H, m, H14), 7.53 (1H, d, TpC3), 7.5-7.6 (2H, m, H15, H13), 6.35 (1H, t, TpB4), 6.31 (1H, t, TpC4), 6.24 (1H, t, TpA4), 3.86 (1H, d J = 7.3, H5), 3.30-3.35 (4H, m, H10, H8), 3.03-3.07 (1H, m, H3), 2.69 (1H, dd J = 17.1, 7.7, H6a), 2.5-2.6 (2H, m, H9/H7), 2.43 (1H, d J = 17.1, H6b), 2.10-2.14 (2H, m, H9/H7), 1.25 (9H, d J = 8.5, PMe_3), 1.17 (1H, d J = 9.5, H4). ^{13}C NMR (CD_3CN, δ): 146.8 (1C, C2), 144.6 (1C, TpB3), 143.3 (1C, C11), 142.5 (1C, TpA3), 142.1 (1C, TpC3), 138.2 (1C, TpC5), 137.6 (1C, TpB5), 137.5 (1C, TpA5), 133.3 (1C, C14), 129.8 (2C, C15, C13), 138.7 (2C, C15, C12), 128.0 (1C, C1), 107.6 (1C, TpB4), 107.3 (1C, TpC4), 106.9 (1C, TpA4), 68.0 (2C, C10, C8), 62.5 (1C, C5), 53.2 (1C, C4), 51.2 (1C, C3), 50.0 (2C, C9, C7), 24.4 (1C, C6), 14.9 (3C, d J = 29.0, PMe_3).

Compound 12.

Compound **10** (0.100 g, 0.138 mmol) and MeCN were combined in a test tube to form an orange heterogeneous solution. Piperidine (0.18 mL, 0.18 g, 2.07 mmol) was added to a second test tube. Both solutions were cooled to 0 °C for 15 min. 1M HOTf/MeCN (0.21 mL, 0.210 mmol) was added to the reaction. Upon addition, the reaction became a dark red, homogeneous mixture. After 15 minutes, the reaction was added to the cooled piperidine test tube. The reaction was stirred overnight for 16 hrs. A white precipitant formed overnight. The test tube was removed from the glove box and the white solid was isolated on a 15 mL fine frit. The solid was washed with 5 mL H_2O followed by hexanes (2 x 15 mL) and desiccated overnight yielding **12** (0.063 g, 0.078 mmol, 57 %). CV (MeCN) $E_{p,a}$ = +0.71 V (NHE). IR: ν(BH) = 2488 cm^{-1}, ν(NO) = 1574 cm^{-1}, ν(SO) = 1406 cm^{-1}. Anal. Calc'd for $C_{29}H_{40}BN_8O_3PSW \cdot H_2O$: C, 42.25; H, 5.14; N, 13.59. Found: C, 42.22; H, 4.86; N, 13.53. ^{1}H NMR (CD_3CN, δ): 8.00 (1H, d, TpB3), 7.94 (1H, d, TpA3), 7.87-7.91 (2H, m, H17, H13), 7.86 (1H, d, TpC5), 7.84 (1H, d, TpB5), 7.82 (1H, dd J = 6.0, 2.7, H2), 7.76 (1H, d, TpA3), 7.55-7.59 (1H, m, H15), 7.51-7.53 (3H, m, TpC3, H16, H14), 6.35 (1H, t, TpB4), 6.31 (1H, t, TpC4), 6.24 (1H, t, TpA4), 3.90 (1H, d J = 8.0, H5), 3.02-3.06 (1H, m, H3), 2.65 (1H, dd J = 17.7, 8, H6a), 2.4-2.5 (4H, m, H11, H7), 2.38 (1H, d J = 17.7, H6b), 1.26 (9H, d J = 8.6, PMe_3), 1.2-1.3 (4H, m, H10, H8), 1.1-1.2 (3H, m, H9, H4). ^{13}C NMR (CD_3CN, δ): 146.7 (1C, C2), 144.6 (1C, TpB3), 143.3 (1C, C12), 142.4 (1C, TpA3), 142.1 (1C, TpC3), 138.1 (1C, TpC5), 137.5 (2C, TpA5, TpB5), 133.3 (1C, C15), 129.8 (2C, C16, C14), 138.7 (2C, C17, C13), 128.4 (1C, C1), 107.5 (1C, TpB4), 107.3 (1C, TpC4), 106.9 (1C, TpA4), 62.7 (1C, C5), 53.7 (1C, C4), 51.3 (1C, C3), 50.31 (2C, C11, C7), 27.43 (2C, C10, C8), 25.62 (1C, C9), 23.8 (1C, C6) 14.0 (3C, d J = 28.6, PMe_3).

Compound 13. To a 4-dram vial charged with a stir pea were added **6** (30 mg, 0.044 mmol), followed by acetonitrile (0.6 mL, –30°C), and a 1M solution of HOTf in acetonitrile (0.11 mL, 0.11 mmol, –30°C), resulting in a homogeneous golden solution, which was allowed to sit for 20 min at –30°C. 1M Bu_4NOH/MeOH (0.66 mL, 0.66 mmol, –30°C) was then added to the reaction vial with stirring, and the reaction was allowed to sit at –30°C for 19 h. The reaction was evaporated *in vacuo* to ~half volume then diluted with H_2O (10 mL) and extracted with Et_2O (10 mL). The organic layer was then dried over $MgSO_4$ and evaporated *in vacuo* to dryness. The film was redissolved in minimal THF and added to stirring pentane (15 mL, –30°C), which resulted in an oil. The solution was again evaporated *in vacuo* to dryness, redissolved in THF and added to pentane (15 mL, –30°C). The resulting pale yellow solid was filtered on a 15 mL fine porosity fritted disc and discarded. The filtrate was cooled to –30°C overnight, resulting in the precipitation of a crystalline solid. The solid was collected on a 15 mL fine porosity fritted disc, rinsed with pentane (2 mL, –30°C) then desiccated overnight, yielding **13** (10 mg, 0.014 mmol,

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32% yield). CV (DMAc) $E_{p,a}$ = +0.51 V (NHE). IR: *ν*(BH) = 2493 cm^{-1}, *ν*(NO) = 1549 cm^{-1}. ^{31}P NMR (CD_3CN, δ): -11.82 (J_{WP} = 283). ^{1}H NMR (CD_3CN, δ): 8.05 (d, 1H, PzB3), 7.87 (d, 1H, PzC5), 7.86 (d, 1H, PzB5), 7.77 (d, 1H, PzA5), 7.72 (d, 1H, PzA3), 7.33 (d, 1H, PzC3), 6.36 (t, 1H, PzB4), 6.30 (t, 1H, PzC4), 6.29 (t, 1H, PzA4), 4.00-4.02 (m, 1H, H4), 3.72-3.74 (m, 1H, H1), 3.11 (s, 3H, OMe), 3.09 (ddd, *J* = 12.3, 4.0, 2.6, 1H, H5), 2.73 (ddd, *J* = 13.6, 11.0, 2.3, 1H, H2), 2.45 (s, 3H, NMe), 1.67 (ddd, *J* = 11.8, 7.4, 4.0, 1H, H6x), 1.51 (q, *J* = 12.1, 1H, H6y), 1.30 (d, *J* = 11.0, 1H, H3), 1.13 (d, *J* = 8.5, 9H, PMe_3). ^{13}C NMR (CD_3CN, δ): 145.0 (PzB3), 144.7 (PzA3), 142.2 (PzC3), 138.0 (PzC5), 137.7 (2C, PzA5 & PzB5), 132.4 (q, *J* = 279.3, CF_3), 107.6 (PzB4), 107.3 (PzA4/PzC4), 107.0 (PzA4/PzC4), 81.6 (C4), 56.9 (OMe), 55.9 (C3) 55.3 (C5), 43.6 (q, *J* = 24.0, C1), 42.9 (d, *J* = 12.5, C2), 34.0 (NMe), 26.2 (m, C6), 13.6 (d, *J* = 28.8, PMe_3).

Compound 14. Compound **6** (11 mg, 0.016 mmol) was dissolved in d^6-acetone (0.7 mL) and monitored by ^{1}H NMR. Over time, the peaks for **6** decreased as a new product grew in. After 8 d, **6** had completely converted to **14**, and 2D NMR data was collected. ^{1}H NMR (d^6-acetone, δ): 8.11 (overlapping d, 2H, PzA3 & PzB3), 7.98 (d, 1H, Pz5), 7.97 (d, 1H, Pz5), 7.80 (d, 1H, Pz5), 7.70 (d, 1H, PzC3), 6.80-6.84 (m, 1H, H3), 6.41 (t, 1H, Pz4), 6.35 (t, 1H, Pz4), 6.28 (t, 1H, Pz4), 4.88 (dt, *J* = 9.6, 1.5, 1H, H2), 3.69 (bs, 1H, H6), 3.65-3.69 (m, 1H, H1), 2.96-3.00 (m, 1H, H5), 2.64 (s, 3H, NMe), 1.57-1.61 (m, 1H, H4), 1.33 (d, *J* = 8.4, 9H, PMe_3). A SC-XRD study of a recovered crystal from the NMR tube confirms the assigned structure.

Compound 15. To a 4-dram vial charged with a stir pea were added compound **6** (50 mg, 0.074 mmol), acetonitrile (1 mL, –30°C), and a 1M solution of HOTf in acetonitrile (0.18 mL, 0.18 mmol, –30°C) with stirring, resulting in a homogeneous golden/orange solution, which was allowed to sit for 15 min at –30°C. To this solution was added MMTP (107 mg, 0.614 mmol, -30°C). After 14 h at –30°C, Et_3N (72 mg, 0.71 mmol) was added to the reaction solution with stirring, then the reaction was left at –30°C for 6 h. The reaction was then warmed to room temperature and monitored by ^{31}P NMR. After 24 h at room temperature, the reaction solution was removed from the glove box, diluted with H_2O (20 mL) and extracted with DCM (2 x 20 mL). The combined organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to dryness. The film was re-dissolved in minimal DCM and added to stirring Et_2O (25 mL). The resulting pale solid was collected on a 15 mL fine porosity fritted disc, washed with pentane (2 x 3 mL) and desiccated overnight, yielding **15** (43 mg, 0.11 mmol, 66% yield). IR: *ν*(BH) = 2496 cm^{-1}, *ν*(NO) = 1548 cm^{-1}. ^{31}P NMR (d^6-acetone, δ): -11.39 (J_{WP} = 277). ^{1}H NMR (d^6-acetone, δ): 9.02 (bs, 1H, NH), 8.19 (d, 1H, PzB3), 8.08 (d, 1H, PzA3), 8.01 (d, 1H, PzC5), 7.99 (d, 1H, PzB5), 7.88 (d, 1H, PzA5), 7.65 (d, 1H, PzC3), 6.45 (t, 1H, PzB4), 6.39 (t, 1H, PzC4), 6.32 (t, 1H, PzA4), 5.62 (d, *J* = 12.5, 1H, H3a), 4.39 (dd, *J* = 12.5, 7.2, 1H, H7a), 3.47-3.53 (m, 1H, H6), 3.19 (s, 3H, NMe), 2.50-2.54 (m, 2H, H5 & H7x), 2.33 (s, 3H, C2-Me), 2.16 (d, *J* = 17.1, 1H, H7y), 1.24 (d, *J* = 8.5, 9H, PMe_3), 1.21 (buried, 1H, H4). ^{13}C NMR (d^6-acetone, δ): 165.6 (CN), 144.5 (PzB3), 143.2 (PzA3), 142.1 (PzC3), 138.4 (PzC5), 137.7 (PzA5), 137.6 (PzB5), 132.0 (q, *J* = 281.7, CF_3), 107.6 (PzB4), 107.4 (PzC4), 107.1 (PzA4), 58.3 (C7a), 57.7 (C3a), 48.2 (C4), 44.0 (d, *J* = 13.0, C5), 41.6 (q, *J* = 25.4, C6), 30.5 (NMe), 19.0 (C7), 12.8 (d, *J* = 28.6, PMe_3), 12.1 (C2-Me). A SC-XRD study confirms the assigned structure.

Compound 16D: Diphenylammonium triflate (DPhAT, 870 mg, 2.72 mmol) and propionitrile (13.5 mL, –30°C) were added to a screw top test tube and cooled to –60°C for 30 min. The DPhAT solution was then added to a screw top test tube containing **1** (1.50 g, 2.58 mmol) with stirring, and the resulting orange solution was stirred at –60°C for 20 min. 1-(tert-Butyldimethylsilyloxy)-1-methoxyethene (TBSME; 4.00 g, 21.7 mmol, –60°C) was then added to reaction solution with stirring. The dark golden reaction solution was stirring at -60°C for 17 h then stirred at –50°C for 7 h. The golden reaction solution was quenched with Et_3N (3 mL, 21.5 mmol). A 150 mL medium porosity fritted disc was filled ¾ full of silica gel and set in Et_2O. The reaction solution was loaded on the column and a pale yellow band was eluted with 300 mL of Et_2O. The filtrate was evaporated *in vacuo*, then re-dissolved in minimal THF and added to 40 mL stirring pentane (–30°C). The resulting pale yellow solid was collected on a 30 mL fine porosity fritted disc, washed with pentane (2 x 5 mL) and desiccated, yielding **16D** (1.02 g, 1.53 mmol, 59% yield. CV (DMAc) $E_{p,a}$ = +0.47 V (NHE). IR: *ν*(BH) = 2481 cm^{-1}, *ν*(CO) = 1725 cm^{-1}, *ν*(NO) = 1548 cm^{-1}. ^{31}P NMR (d_6-acetone, δ): -10.65 (J_{WP} = 287). ^{1}H NMR (d_6-acetone, δ): 8.11 (d, 1H, Pz3/5), 8.04 (d, 1H, Pz3/5), 7.90-7.93 (m, 2H, Pz3/5 & Pz3/5), 7.81 (d, 1H, Pz3/5), 7.52 (d, 1H, Pz3/5), 6.42-6.46

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(m, 1H, H2), 6.38 (t, 1H, Pz4), 6.32 (t, 1H, Pz4), 6.30 (t, 1H, Pz4), 4.84-4.88 (m, 1H, H1), 3.52 (s, 3H, OMe), 3.11-3.15 (m, 1H, H5), 2.86-3.00 (m, 1H, H3), 2.80 (dd, *J* = 16.5, 1H, H6x), 2.69 (dd, *J* = 14.5, 8.5, 1H, H7x), 2.37 (dd, *J* = 14.5, 5.7, 1H, H7y), 1.75 (dd, *J* = 16.5, 6.5, 1H, H6y), 1.29 (d, *J* = 8.4, 9H, PMe_3), 1.06 (bd, *J* = 10.1, 1H, H4). ^{13}C NMR (d_6-acetone, δ): 174.6, 144.2, 142.5, 141.7, 137.5, 136.9, 136.5, 132.1, 116.6, 107.0, 106.8, 106.5, 60.6, 51.1, 49.5 (d, *J* = 10.3), 45.0, 34.7, 28.5, 23.5, 13.8 (d, *J* = 28.1, PMe_3). A SC-XRD study confirms the assigned structure.

Compound 20P.

200 mg of compound **18** was dissolved in 2.0 mL of CH_3CN and the solution was brought to –30 °C. An excess of HOTf dissolved in CH_3CN was added (0.66 mL; 1M) followed after 15 minutes by 347 mg of piperidine. A light yellow ppt formed. The reaction mixture was quenched with the addition of 1.1 mL of ^{t}BuOK (1M in tBuOH) then treated with 4.5 mL of water. The resulting ppt was collected and washed with water and then with pentane. Yield: 173 mg, 78% as a mixture of two isomers. Crystals of compound **20P** were grown from the reaction mixture dissolved in CD_3CN and subjected to SC-XRD analysis.

^{1}H NMR (d^3-acetonitrile, δ): 8.00 (d, 1H, Pz), 7.85 (d, 1H, Pz), 7.83 (d, 1H, Pz), 7.82 (d, 1H, Pz), 7.76 (d, 1H, Pz), 7.31 (d, 1H, Pz3), 6.33 (t, 1H, Pz4), 6.29 (t, 1H, Pz4), 6.27 (t, 1H, Pz4), 3.65 (s, 3H, OMe), 3.6 - 3.7 (m, 2H, H4, H5), 2.85 (t, *J* = 12, 1H, H3), 2.2-2.1 (m, 3H, H1, pip), 1.96 (q, J = 13, 1H, H6a), 1.70-1.73 (m, 1H, H6b), 1.4-1.3 (m, 8H, pip), 1.32 (3H, Me), 1.30 (3H, Me), 1.13 (d, *J* = 8.5, 9H, PMe_3), 1.05 (d, *J* =12, 1H, H2).

Compound 20D. This isomer was prepared as part of a mixture with compound **20P**. See synthetic procedure above. ^{1}H NMR (d^3-acetonitrile, δ): 7.94 (d, 1H, Pz), 7.93 (d, 1H, Pz), 7.87 (d, 1H, Pz), 7.81 (d, 1H, Pz), 7.80 (d, 1H, Pz), 7.38 (d, 1H, Pz3), 6.31 (t, 1H, Pz4), 6.30 (t, 1H, Pz4), 6.26 (t, 1H, Pz4), 4.11 (d, *J* =4.6 1H, H5), 3.48 (s, 3H, OMe), 3.23-3.29 (m, 1H, H2), 2.90-2.94 (m, 1H, H1), 2.85 (t, *J* = 12, 1H, H4), 2.9 - 3.1 (4H, pip), 1.66 (q, J = 13, 1H, H6a), 1.45-1.55 (6H, pip), 1.38-1.42 (m, *J*= 13,7, 1H, $H6_b$), 1.21 (d, *J* = 8.5, 9H, PMe_3), 1.01 (d, *J* =12, 1H, H3), 0.77 (3H, Me), 0.68 (3H, Me).

Compound 20-O.

Outside of the glovebox, **20P** (100 mg, 0.120 mmol) was dissolved in MeCN (1.5 mL) in a 4-dram vial, then ferrocenium hexafluorophosphate (137 mg, 0.414 mmol) was added to the vial with stirring. The reaction solution was stirred for 5 h and then was evaporated *in vacuo* to a film. The resulting film was diluted with CH_2Cl_2 (30 mL) and washed with saturated aqueous sodium carbonate (20 mL). The aqueous layer was back extracted with CH_2Cl_2 (2 x 20 mL), then the combined organic layers were dried over $MgSO_4$ and evaporated to dryness. The resulting oil was loaded onto a 250 µm silica preparatory plate with MeCN (3 × 0.3 mL) and eluted with Et_3N/MeOH/CH_2Cl_2 (1%/5%/94%). A $KMnO_4$ active band at R_f = 0.1 was collected and sonicated in 6% MeOH in CH_2Cl_2(HPLC grade, 30 mL) for 15 min. The silica was filtered off on a 30 mL fine porosity fritted disc and washed with EtOAc (HPLC grade, 2 × 20 mL). The filtrate was evaporated *in vacuo*, yielding **39** (4 mg, 0.012 mmol, 10% yield). ^{1}H NMR (d_6-acetone, δ): 5.89 (ddd, *J* = 10.4, 4.5, 2.7, 1H, H3), 5.80 (bd, *J* = 10.4, 1H, H2), 3.65 (s, 3H, OMe), 3.30-3.34 (m, 1H, H4), 2.69-2.72 (m, 2H, pip), 2.50-2.53 (m, 3H, H1 and pip), 2.46-2.49 (m, 1H, H5), 1.76 (bd, *J* = 12.6, 1H, H6x), 1.63 (q, *J* = 12.6, 1H, H6y), 1.47-1.51 (m, 4H, pip), 1.33-1.37 (m, 2H, pip), 1.19 (s, 3H, Me), 1.17 (s, 3H, Me). ^{13}C NMR (d_6-acetone, δ): 177.5 (CO), 131.5 (C2) 128.7 (q, *J* = 278.8, CF_3), 126.4 (C3), 57.5 (C4), 53.9 (2C, pip), 52.1 (OMe), 45.6 (C7), 44.5 (q, *J* = 24.4, C5), 43.9 (C1), 27.7 (2C, pip), 25.3 (pip), 22.6 (Me), 22.2 (Me), 20.9 (C6).

Compound 21D. 102 mg of compound **18** was dissolved in 1.5 mL of CH_3CN and the solution was brought to –30 °C. An excess of HOTf dissolved in CH_3CN was added (0.3 mL; 1M) followed after 10 minutes by 174 mg of morpholine (~15 eq). A light yellow ppt formed. The reaction mixture was quenched with the addition of 0.53 mL of ^{t}BuOK (1M in tBuOH) and the ppt was collected and washed with water and then with pentane. Yield: 38 mg, 34%. ^{1}H NMR analysis found this to be roughly a 1:1 mixture of isomers. The filtrate was concentrated under vacuum, then treated with 4 mL water, upon which a second precipitate formed (37 mg; 33%). The recovered solid was found by proton NMR to be roughly a 4:1 mixture of isomers, favoring compound **21D**. A crystal was recovered from the first precipitate and subjected to SC-XRD analysis. In solution, both isomers are unstable with

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respect to isomerization and elimination, but partial characterization of **21D** follows:
^{1}H NMR (CD_2Cl_2, δ): 8.02 (d, 1H, Pz), 7.93 (d, 1H, Pz), 7.78 (d, 1H, Pz), 7.73 (d, 1H, Pz), 7.71 (d, 1H, Pz), 7.28 (d, 1H, Pz3), 6.28 (t, 2H, Pz4), 6.26 (t, 1H, Pz4), 4.07 (d, *J* =4.6 1H, H5), 3.67 (b,4H, morph), 3.49 (s, 3H, OMe), 3.33-3.39 (m, 1H, H2), 3.0-3.1 (4H, morph), 2.83-2.87 (m, 1H, H1), 2.81 (t, *J* = 12, 1H, H4), 1.65 (q, J = 13, 1H, H6a), 1.42-1.46 (m, *J*= 13,7, 1H, $H6_b$), 1.23 (d, *J* = 8, 9H, PMe_3), 1.02 (d, *J* =12, 1H, H3). 0.84 (3H, Me), 0.64 (3H, Me).

Compound 21P. Partial characterization. See above synthetic procedure. ^{1}H NMR (CD_2Cl_2, δ): 8.01 (d, 1H, Pz), 7.82 (d, 1H, Pz), 7.77 (d, 1H, Pz), 7.74 (d, 1H, Pz), 7.67 (d, 1H, Pz), 7.22 (d, 1H, Pz3), 6.29 (t, 1H, Pz4), 6.26 (t, 1H, Pz4), 6.21 (t, 1H, Pz4), ~3.7 (b,4H, morph), 3.68 (s, 3H, OMe), 3.65 (b, H4), 3.43 (m, 1H, H5), 3.10 (b, 2H, morph), 3.03 (b, 2H, morph) 2.81 (m, 1H, H3), 2.16 (dt, 1H, H1), 1.92 (q, J = 13, 1H, H6a), 1.76 (m, $H6_b$), 1.35 (6H, Me), 1.23 (d, *J* = 8, 9H, PMe_3), 1.03 (d, *J* =11, 1H, H2).

Compound 22D. WTp(NO)(PMe3)(L), where L = methyl 2-(2-(1*H*-imidazol-1-yl)-5-(trifluoromethyl)cyclohex-3-en-1-yl)-2-methylpropanoate. 100 mg of compound **18** was dissolved in 0.7 mL of CH_3CN and the solution was brought to –30 °C. An excess of HOTf dissolved in CH_3CN was added (0.2 mL; 1M) followed after 30 minutes by 136 mg of imidazole (15 eq). A yellow ppt formed. The reaction mixture was quenched with the addition of 0.5 mL of ^{t}BuOK (1M in tBuOH) and the ppt was collected and washed with water and finally with pentane. Yield: 86 mg, 79%. In solution, this compound is unstable with respect to formation of compound **22D**. A small crystal was recovered and subjected to SC-XRD in order to confirm the structure. Partial characterization follows:
^{1}H NMR (CD_2Cl_2, δ): 8.14 (d, 1H, Pz), 8.07 (d, 1H, Pz), 7.77 (d, 1H, Pz), 7.73 (d, 1H, Pz), 7.68 (d, 1H, Pz), 7.48 (b, 1H, Im), 7.23 (b, 1H, Im), 7.11 (d, 1H, Pz), 6.87 (b, 1H, Im), 6.34 (t, 1H, Pz4) 6.31 (t, 1H, Pz4) 6.20 (t, 1H, Pz4), 5.25(bs, 1H,H2), 3.90-3.94 (m, 1H, H5) 3.76 (s, 3H, OMe), 2.88 (ddd, *J* = 13,11,2.5, 1H, H4), 2.76 (dt, *J* = 14, 1H, H1) 1.82 (q, *J* = 13, 1H, $H6_a$), 1.74 (ddd, *J*= 13,7, 1H, H_b) 1.24 (3H, Me), 1.20 (d, *J* = 8, 9H, PMe_3), 0.96 (d, *J* =12.5, 1H, H3), 0.58 (3H, Me).

Compound 22P. The filtrate from the above procedure was treated with 2 mL water, upon which a second precipitate formed (12 mg; 11%). The recovered solid was found by proton NMR to be roughly 80% pure. Partial characterization follows: ^{1}H NMR (CD_3CN, δ): 7.99 (d, 1H, Pz), 7.98 (d, 1H, Pz), 7.86 (d, 1H, Pz), 7.85 (d, 1H, Pz), 7.85 (b, 1H, Im), 7.83 (d, 1H, Pz), , 7.44 (b, 1H, Im), 7.31 (d, 1H, Pz), 7.00 (b, 1H, Im), 6.34 (t, 1H, Pz4) 6.30 (t, 1H, Pz4) 6.27 (t, 1H, Pz4), 5.49 (b, 1H,H4), 3.51 (3H, OMe), 3.35 (ddd J = 2.5, 6.4, 13, H1) 3.29-3.33 (m, 1H, H5), 2.82 (dd, *J* = 13, 11 1H, H3), 1.71 (q, *J* = 13, 1H, $H6_a$), 1.64 (ddd, *J*= 13,7, 1H, $H6_b$), 1.10 (d, *J* = 8, 9H, PMe_3), 1.09 (d, *J* =12.5, 1H, H3), 0.85 (3H, Me), 0.78 (3H, Me). NOESY and COSY data confirm the regiochemical assignment above.

Compound 25.
To a 4-dram vial charged with a stir pea were added **18** (200 mg, 0.27 mmol) followed by MeCN (1.2 mL, –30°C) and a 1M solution of HOTf in acetonitrile (0.53 mL, 0.53 mmol, –30°C), resulting in a homogeneous golden solution, which was allowed to sit for 15 min at –30°C. 4-bromobenzylamine (690 mg, 3.71 mmol) was then added to reaction solution with stirring. The dark golden reaction solution was left at –30°C overnight then the reaction solution was warmed to room temperature and monitored by ^{1}H NMR and ^{1}H NMR until reaction was complete. The reaction was then removed from the glovebox, diluted with CH_2Cl_2 (40 mL), and washed with H_2O (2x 30 mL). The aqueous layer was back extracted with CH_2Cl_2 (2 x 20 mL), then the combined organic layers were dried over $MgSO_4$ and evaporated to dryness. The resulting film was redissolved in minimal CH_2Cl_2 and added to 15 mL stirring pentane. The resulting solid was collected on a 15 mL fine porosity fritted disc, washed with pentane (2 x 5 mL) and desiccated, yielding **25** (199 mg, 0.22 mmol, 81% yield. ^{1}H NMR (d_6-acetone, δ): 8.09 (d, 1H, Pz3/5), 8.03 (d, 1H, Pz3/5), 7.90 (d, 1H, Pz3/5), 7.75 (d, 1H, Pz3/5), 7.47 (d, 1H, Pz3/5), 7.36 (d, 1H, Pz3/5), 6.9-7.0 (m, 2H, Ar-H), 6.48 (t, 1H, Pz4), 6.41-6.45 (m, 2H, Ar-H), 6.34 (t, 1H, Pz4), 6.03 (t, 1H, Pz4), 4.72 (d, *J* = 14.6, 1H, CH_2N), 4.41 (bs, 1H, H7a), 3.77 (d, *J* = 14.6, 1H, CH_2N), 3.50-3.55 (m, 1H, H5), 2.83-2.87 (m, 1H, H6), 2.05-2.09 (m, 1H, H3a), 1.68 (dt, *J* = 12.6, 4.7, 1H, H4x), 1.23-1.27 (m, 1H, H4y), 1.22 (d, *J* = 8.5, 9H, PMe_3), 1.14 (s, 3H, Me), 1.10 (s, 3H, Me), 1.09 (buried, 1H, H7).

A SC-XRD study confirms the assigned structure.

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Compound 26.
To a 4-dram vial charged with a stir pea were added **18** (100 mg, 0.13 mmol) followed by CD_3CN (0.8 mL, –30°C) and a 1M solution of HOTf in acetonitrile (0.2 mL, 0.2 mmol, –30°C), resulting in a homogeneous golden solution, which was allowed to sit for 10 min at –30°C. 4-chlorobenzylamine (200 mg, 1.41 mmol, –30°C) was then added to reaction solution with stirring. The dark golden reaction solution was left at –30°C for 3.5 h then the reaction solution was warmed to room temperature and monitored by ^{1}H NMR. After stirring overnight, the reaction diluted with CH_2Cl_2 (20 mL) and washed with H_2O (20 mL). The aqueous layer was back extracted with CH_2Cl_2 (20 mL), then the combined organic layers were dried over $MgSO_4$ and evaporated to dryness. The resulting film was redissolved in minimal CH_2Cl_2 and added to 15 mL stirring pentane. The resulting solid was collected on a 15 mL fine porosity fritted disc, washed with pentane (2 x 5 mL) and desiccated, yielding **26** (88 mg, 0.102 mmol, 79% yield. IR: ν(BH) = 2486 cm^{-1}, ν(CO) = 1677 cm^{-1}, ν(NO) = 1558 cm^{-1}.^{1}H NMR (d_6-acetone, δ): 8.09 (d, 1H, Pz3/5), 8.03 (d, 1H, Pz3/5), 7.90 (d, 1H, Pz3/5), 7.73 (d, 1H, Pz3/5), 7.47 (d, 1H, Pz3/5), 7.36 (d, 1H, Pz3/5), 6.82-6.86 (m, 2H, Ar-H), 6.47-6.51 (m, 3H, Ar-H, and Pz4), 6.34 (t, 1H, Pz4), 6.02 (t, 1H, Pz4), 4.73 (d, *J* = 14.6, 1H, CH_2N), 4.40 (d, *J* = 4.2, 1H, H7a), 3.78 (d, *J* = 14.6, 1H, CH_2N), 3.54-3.58 (m, 1H, H5), 2.83-2.86 (m, 1H, H6), 2.07 (buried, 1H, H3a), 1.68 (dt, *J* = 12.5, 4.7, 1H, H4x), 1.23-1.26 (m, 1H, H4y), 1.22 (d, *J* = 8.5, 9H, PMe_3), 1.14 (s, 3H, Me), 1.10 (s, 4H, Me and H7).
A SC-XRD study confirms the assigned structure.

Compound 28. Compound **29** (281 mg, 1.22 mmol) and propionitrile (0.5 mL) were combined in a test tube and chilled to –60°C). To a screw-top test tube, charged with a stir pea were added **16** (300 mg, 0.458 mmol) followed by propionitrile (1.5 mL, –30°C) and a 1M solution of HOTf in acetonitrile (0.55 mL, 0.55 mmol, –30°C), resulting in a homogeneous golden solution, which was stirred at –60°C for 30 min. The solution of **29** was added to the reaction solution with stirring, then the reaction was stirred at -60°C for 5 h. DBU (124 mg, 0.815 mmol, –30°C) was added to the reaction solution while cold, and then the reaction was stirred at room temperature for 4 days. While stirring at room temperature, a solid precipitated from solution. The solid was collected on a 15 mL fine porosity fritted disc, washed with MeCN (2 x 0.5 mL, –30°C), H_2O (2 x 7 mL), and pentane (3 x 5 mL, –30°C) then desiccated, yielding **28** (270 mg, 0.316 mmol, 69% yield). CV (DMAc) $E_{p,a}$ = +0.52 V (NHE). IR: ν(BH) = 2481 cm^{-1}, ν(CO) = 1669 cm^{-1}, ν(NO) = 1538 cm^{-1}. ^{31}P NMR (CD_2Cl_2, δ): -10.06 (J_{WP} = 288). ^{1}H NMR (CD_2Cl_2, δ): 7.98 (d, 1H, Pz3/5), 7.77 (d, 1H, Pz3/5), 7.70-7.74 (m, 2H, Pz3/5), 7.56 (d, 1H, Pz3/5), 7.18 (d, 1H, Pz3/5), 6.66 (s, 1H, Ar-H), 6.61 (s, 1H, Ar-H), 6.30 (t, 1H, Pz4), 6.19 (t, 1H, Pz4), 5.95 (t, 1H, Pz4), 5.92-5.96 (m, 2H, OCH_2O), 4.78 (d, *J* = 4.9, 1H, H7a), 4.36 (d, *J* = 15.8, 1H, H9x), 4.11 (d, *J* = 15.8, 1H, H9y), 2.92-2.96 (m, 1H, H5x), 2.59-2.62 (m, 2H, H3x & H6), 2.49-2.52 (m, 2H, H3a & H5y), 2.24 (dd, *J* = 16.4, 2.4, 1H, H3y), 1.62-1.66 (m, 1H, H4x), 1.37-1.41 (m, 1H, H4y), 1.15 (d, *J* = 8.3, 9H, PMe_3), 1.14 (buried, 1H, H7). ^{13}C NMR (CD_2Cl_2, δ): 176.1 (C2), 148.1 (Ar-C), 147.5 (Ar-C), 143.7 (Pz3/5), 141.9 (Pz3/5), 140.8 (PzC3/5), 137.0 (PzC3/5), 136.5 (Pz3/5), 136.4 (Pz3/5), 131.3 (Ar-C), 113.1 (Ar-C), 112.9 (Ar-C), 109.1 (Ar-C), 106.8 (Pz4), 106.3 (Pz4), 106.1 (Pz4), 102.3 (OCH_2O), 62.3 (C7a), 51.0 (d, *J* = 11.9, C6), 49.3 (C7), 44.0 (C9), 38.8 (C3), 32.7 (C3a), 27.6 (2C, C4 & C5), 14.0 (d, *J* = 27.9, PMe_3). A SC-XRD study confirms the assigned structure.

Partial Characterization of intermediate **30P/30D.**
(d^3-acetonitrile, δ): 8.45 (d, 1H, Pz), 8.40 (d, 1H, Pz), 8.00 (d, 1H, Pz), 7.95 (d, 1H, Pz), 7.92 (d, 1H, Pz), 7.79 (d, 1H, Pz), 6.53 (t, 1H, Pz4), 6.51 (t, 1H, Pz4), 6.33 (t, 1H, Pz4) 6.27 (bd, *J* = 7, 1H, H1), 5.14 (bt, *J* = 7, 1H, H2), 4.38-4.42 (m, 1H, H3), 3.73 (s, 3H, OMe), 3.67-3.71 (m, 1H), 3.08-3.12 (m, 1H), 2.78 (dd, *J*= 17,5, 1H), 2.60 (dd, *J* = 17,10, 1H), 2.40-2.44 (m, 1H), 1.62-1.66 (m, 1H), 1.16 (d, *J* = 10, 9H, PMe_3).

Compound 32. Outside of the glovebox, **28** (250 mg, 0.293 mmol) was dissolved in CH_2Cl_2 (3.75 mL) in a 4-dram vial, then ferrocenium hexafluorophosphate (137 mg, 0.414 mmol) was added to the vial with stirring. The reaction solution was stirred for 2 h and then diluted with CH_2Cl_2 (60 mL) and washed with H_2O (50 mL). The aqueous layer was back extracted with CH_2Cl_2 (2 x 50 mL), then the combined organic layers were dried over Na_2SO_4 and evaporated to dryness. The film was redissolved in minimal CH_2Cl_2 and added to Et_2O (50 mL) with stirring. The resulting precipitate was collected on a 15 mL fine porosity fritted disc and washed with Et_2O (2 x 10 mL), and hexanes (10 mL). The precipitate was discarded, and the filtrate was evaporated *in vacuo* to a film. The film was dry loaded on silica then purified on the Combiflash® with a

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12 g silica column using a gradient solvent system starting at 100% hexanes and going to 100% EtOAc (Rf=0.59, 5:1 EtOAc/Hex). The combined fractions were evaporated *in vacuo*, yielding **32** (73 mg, 0.208 mmol, 71% yield). *Note: using CH_2Cl_2 as solvent results in minor side product that can be separated via chromatography- side product can be avoided if acetone is used as reaction solvent. IR: *ν*(CO) = 1680 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{16}BrNO_3Na$ 372.0211; Found 372.0209. ^1H NMR ($CDCl_3$, δ): 6.96 (s, 1H, Ar-H), 6.74 (s, 1H, Ar-H), 5.92-5.96 (m, 3H, H6 and OCH_2), 5.74 (bd, *J* = 10.2, 1H, H7), 4.75 (d, *J* = 15.6, 1H, H8x), 4.25 (d, *J* = 15.6, 1H, H8y), 3.83-3.87 (m, 1H, H7a), 2.52 (dd, *J* = 16.3, 8.3, 1H, H3x), 2.45-2.49 (m, 1H, H3a), 2.27 (dd, *J* = 16.3, 5.8, 1H, H3y), 2.07-2.10 (m, 1H, H5x), 1.97-2.01 (m, 1H, H5y), 1.68-1.72 (m, 1H, H4x), 1.55-1.59 (m, 1H, H4y). ^{13}C NMR ($CDCl_3$, δ): 174.8 (C2), 148.0 (2C, Ar-C), 132.1 (C6), 129.4 (Ar-C), 123.4 (C7), 113.7 (Ar-C), 112.8 (Ar-C), 109.5 (Ar-C), 102.0 (OCH_2O), 55.0 (C7a), 44.2 (C8), 35.9 (C3), 31.2 (C3a), 24.3 (C4), 22.4 (C5).

Crystals of racemic compound **32** were isolated from ethyl acetate:methylene chloride:ether mixture (1:3:2). The racemic mixture was resolved by analytical chiral HPLC (Agilent 1269 Infinity II system equipped with vial sampler, flexible pumps and DAD detector) as follows: Using isocratic elution of 1:1 hexanes ethyl acetate at flow rate of 1.0mL/min of sample (0.1mg/mL dissolved in ethyl acetate, 5.0μL per injection) with CHIRALPAK® IC-3 column (250mm L X 4.6 mm ID, particle size 3 μM, lot# IC30CE-WE008, Daicel Corporation, Japan), monitoring signal at 254nm, a good separation of two enantiomers (Rt = 11.77min; 50.03%, and 13.25min; 49.97%) was observed. The enantioenriched synthesis of compound **32** was realized following similar sequence of reactions derived from chiral complex (***S***)-**1**. The enantiomeric ratio was found to be >95:5 with major isomer (Rt=11.78min.), $[\alpha]_D$=27.5.[40, 50]

Compound 33. The following is a modification of previously published procedures.[23, 40] In a glove-box compound **32** (43 mg, 0.12 mmol) was dissolved in DMF (1.5 mL) in a 4-dram vial with a stir pea, then Hunig's base was added (0.05 mL). In a separate 4-dram vial $Pd(OAc)_2$ (1.5 mg, 0.0067 mmol) and $P(Ph)_3$ (6.7 mg, 0.026 mmol) were dissolved in DMF (0.5 mL). The catalyst solution was added to the solution of **32** with stirring, and then the reaction solution was slowly heated up to 100°C in an oil bath. After 7 h the reaction was removed from the heat, and the reaction was observed to be complete by ^1H NMR. Outside of the glove-box, H_2O (3 mL) was added to the reaction, and then the aqueous layer was extracted with EtOAc (5 x 5 mL). The combined organic layers were washed with brine, then dried over Na_2SO_4 and evaporated down. The resulting oil was loaded onto a 250 μm silica preparatory plate with DCM (3 × 0.3 mL) and eluted with 85% EtOAc/hexanes (HPLC grade, 200 mL). A $KMnO_4$ active band at R_f = 0.20−0.30 was collected and sonicated in 1% Et_3N in EtOAc (HPLC grade, 30 mL) for 20 min. The silica was filtered off on a 30 mL fine porosity fritted disc and washed with EtOAc (HPLC grade, 2 × 20 mL). The filtrate was evaporated *in vacuo*, yielding **33** (15 mg, 0.056 mmol, 50% yield).
HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{16}NO_3$ 270.1130; Found 270.1124. ^1H NMR ($CDCl_3$, δ): 6.66 (s, 1H), 6.57 (s, 1H), 5.91-5.95 (m, 2H), 5.86-5.90 (m, 1H), 5.64 (bd, *J* = 9.5, 1H), 4.78 (d, *J* = 17.0, 1H), 4.10 (d, *J* = 17.0, 1H), 4.04 (dd, *J* = 8.0, 5.1, 1H), 3.26-3.30 (m, 1H), 2.85-2.88 (m, 1H), 2.66 (ddd, *J* = 17.0, 9.6, 1.2, 1H), 2.17-2.21 (m, 1H), 2.08-2.12 (m, 2H). ^{13}C NMR ($CDCl_3$, δ): 174.5, 147.1, 147.0, 132.7, 129.9, 126.9, 124.4, 109.0, 106.3, 101.3, 56.7, 42.3, 39.0, 38.6, 29.3, 27.5.

Compound 34. The following closely follows the previously published procedures.[23, 40] **33** (14 mg. 0.052 mmol) was dissolved in MeOH (1.9 mL) in 2-neck round bottom flask with stir pea, then 5% Pd/C (14 mg) was added. The reaction mixture was stirred under H_2 (1 atm) for 2 h, and the reaction was checked for completion by TLC. The catalyst was filtered off on a celite pad in a 15 mL medium porosity fritted disc, and rinsed with MeOH. The filtrate was evaporated *in vacuo* to give the crude product as a film, which was dry loaded on silica then purified on the Combiflash® with a 4 g silica column using a gradient solvent system starting at 100% hexanes and going to 100% EtOAc (HPLC grade). The fractions containing **34** were combined and concentrated *in vacuo* to yield **34** as a white solid (11 mg, 0.041 mmol, 79% yield). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{18}NO_3$ 272.1287; Found 272.1280. ^1H NMR ($CDCl_3$, δ): 6.60 (s, 1H), 6.58 (s, 1H), 5.90-5.94 (m, 2H), 4.53 (d, *J* = 17.3, 1H), 4.32 (d, *J* = 17.3, 1H), 3.75 (t, *J* = 4.5, 1H), 2.74 (dt, *J* = 12.6, 4.5, 1H), 2.57 (dd, *J* = 16.1, 6.8, 1H), 2.39-2.42 (m, 1H), 2.08 (d, *J* = 16.1, 1H), 1.69-1.76 (m, 3H), 1.33-1.36 (m, 1H), 1.15-1.19 (m, 2H). ^{13}C NMR ($CDCl_3$, δ): 175.9, 146.9, 146.8, 131.8, 123.5,

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108.7, 106.9, 101.2, 55.9, 42.9, 40.5, 40.0, 33.2, 30.5, 28.1, 23.8. Proton NMR data match that of title compound **34**.

Compound 27. $LiAlH_4$ (20 mg, 0.53 mmol) and THF (0.7 mL) were added to a 2-neck round bottom flask with a stir pea, then cooled to 0°C under N_2. **34** (10 mg. 0.037 mmol) was dissolved in THF (1.9 mL, 0°C) then added to the reaction flask under N_2. The reaction was refluxed for 2 h, then checked for completion by TLC. After the reaction was complete, a saturated solution of Na_2SO_4 (2 mL) was added at 0°C, then stirred for 2 h. A 1 M NaOH solution (2 mL) was added, then we two layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, then dried over Na_2SO_4, filtered and evaporated *in vacuo* to give the crude product. The product was purified by flash chromatography on silica gel, eluting with EtOAc, then 1% Et_3N in EtOAc, yielding **27** (8 mg, 0.031, 84% yield) as an oil. Proton NMR data match that of title compound **27**. [24-37]

Compound 35.

To a 4-dram vial charged with a stir pea were added **5** (1.0 g, 1.54 mmol) followed by acetonitrile (7.5 mL, –30°C) and a 1M solution of HOTf in acetonitrile (2.3 mL, 2.3 mmol, -30°C), resulting in a homogeneous golden solution, which was allowed to sit for 15 min at –30°C. 1-(tert-Butyldimethylsilyloxy)-1-methoxyethene (TBSME; 1.43 g, 7.76 mmol, –30°C) was then added to reaction solution with stirring. The dark golden reaction solution was left at –30°C for 21 h then the reaction solution was quenched with Et_3N (2 mL, 14.34 mmol). A 150 mL medium porosity fritted disc was filled ¾ full of silica gel and set in Et_2O. The reaction solution was loaded on the column and a pale yellow band was eluted with Et_2O (~160 mL). The filtrate was removed from the glovebox and evaporated *in vacuo*, then redissolved in minimal CH_2Cl_2 and added to 40 mL stirring pentane. The resulting pale yellow solid was collected on a 30 mL fine porosity fritted disc, washed with pentane (2 x 7 mL) and desiccated, yielding **35** (927 mg, 1.28 mmol, 83% yield. ^{1}H NMR (d_6-acetone, δ): 8.12 (d, 1H, Pz3/5), 8.04 (d, 1H, Pz3/5), 7.94-7.98 (m, 2H, Pz3/5 & Pz3/5), 7.84 (d, 1H, Pz3/5), 7.59 (d, 1H, Pz3/5), 7.19 (bs, 1H, H2), 6.40 (t, 1H, Pz4), 6.35 (t, 1H, Pz4), 6.34 (t, 1H, Pz4), 3.53 (s, 3H, OMe), 3.27-3.31 (m, 1H, H5), 2.84-2.88 (m, 2H, H3 and H6x), 2.60 (dd, *J* = 14.9, 8.3, 1H, H7x), 2.37 (dd, *J* = 14.9, 5.9, 1H, H7y), 1.95 (d, *J* = 16.5, 1H, H6y), 1.31 (d, *J* = 8.5, 9H, PMe_3), 1.18-1.22 (m, 1H, H4). ^{13}C NMR (d_6-acetone, δ): 174.1, 144.3, 142.6, 141.8, 137.8, 137.2, 136.8, 136.6 (m), 126.5 (q, *J* = 268.9), 115.8 (m), 107.3, 107.1, 106.7, 61.2, 51.2, 46.6 (d, *J* = 9.6), 44.8, 34.1, 26.2, 13.8 (d, *J* = 28.6, PMe_3).

Compound 37.

Compound **29** (126 mg, 0.548 mmol) and MeCN (0.4 mL) were combined and chilled to –30°C). To a 4-dram vial charged with a stir pea were added **35** (99 mg, 0.137 mmol) followed by MeCN (0.6 mL, –30°C) and a 1M solution of HOTf in acetonitrile (0.55 mL, 0.55 mmol, -30°C), resulting in a homogeneous golden solution, which was stirred at room temperature for 10 min, then chilled at –30°C for 30 min. The chilled solution of **29** was added to the reaction solution with stirring, then the reaction was stirred at –30°C for 15 h. Precipitation occurs overnight. DBU (50 mg, 0.328 mmol, -30°C) was added to the reaction mixture while cold, and then the reaction mixture was stirred at room temperature for 10 days. The solid was collected on a 15 mL fine porosity fritted disc, washed with H_2O (2 x 7 mL), and pentane (2 x 5 mL) then desiccated, yielding **37** (102 mg, 0.111 mmol, 81% yield). ^{1}H NMR (CD_2Cl_2, δ): 7.97 (d, 1H, Pz3), 7.77 (d, 1H, Pz5) 7.72 (m, 1H, Pz5), 7.59 (d, 1H, Pz5), 7.55 (d, 1H, Pz3), 7.19 (d, 1H, Pz3), 6.52 (s, 1H, Ar-H), 6.51 (s, 1H, Ar-H), 6.29 (t, 1H, Pz4), 6.26 (t, 1H, Pz4), 5.99 (t, 1H, Pz4), 5.90-5.94 (m, 2H, OCH_2O), 4.56 (d, *J* = 5.7, 1H, H7a), 4.51 (d, *J* = 15.3, 1H, NCH_2), 4.14 (d, *J* = 15.3, 1H, NCH_2), 3.41-3.43 (m, 1H, H5), 2.73 (dd, *J* = 16.7, 8.2, 1H, H3x), 2.56-2.60 (m, 1H, H3a), 2.52-2.56 (m, 1H, H6), 2.14 (d, *J* = 16.7, 1H, H3y), 1.91-1.94 (m, 1H, H4x), 1.49 (m, 1H, H4y), 1.21 (d, *J* = 11.0, 1H, H7), 1.13 (d, *J* = 8.3, 9H, PMe_3). ^{13}C NMR (CD_2Cl_2, δ): 175.3 (C2), 147.7 (Ar-C), 147.4 (Ar-C), 144.0 (Pz3/5), 142.8 (Pz3/5), 141.0 (PzC3/5), 137.1 (PzC3/5), 136.7 (Pz3/5), 136.6 (Pz3/5), 131.2 (q, *J* = 280.2, CF_3), 130.2 (Ar-C), 113.1 (Ar-C), 112.6 (Ar-C), 109.6 (Ar-C), 106.7 (Pz4), 106.4 (Pz4), 106.0 (Pz4), 102.1 (OCH_2O), 59.9 (C7a), 48.8 (C7), 43.6 (CH_2N), 43.0 (d, *J* = 12.7, C6), 41.7 (q, *J* = 24.5, C5), 40.9 (C3), 27.6 (C3a), 26.2 (C4), 13.7 (d, *J* = 28.7, PMe_3). A SC-XRD study confirms the assigned structure.

Compound 38.

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Outside of the glovebox, **37** (98 mg, 0.106 mmol) was dissolved in acetone (0.5 mL) and MeCN (1.5 mL) in a 4-dram vial, then ferrocenium hexafluorophosphate (137 mg, 0.414 mmol) was added to the vial with stirring. The brown reaction solution was stirred for 1 h and then evaporated *in vacuo* to a film. The resulting film was dissolved in CH_2Cl_2 (40 mL) and washed with H_2O (30 mL). The aqueous layer was back extracted with CH_2Cl_2 (2 x 30 mL), then the combined organic layers were dried over Na_2SO_4 and evaporated to dryness. The film was redissolved in minimal CH_2Cl_2 and added to Et_2O (35 mL) with stirring. The resulting precipitate was collected on a 15 mL fine porosity fritted disc and washed with Et_2O (2 x 5 mL), and pentanes (5 mL). The precipitate was discarded, and the filtrate was evaporated *in vacuo* to a film. The film was dry loaded on silica then purified on the Combiflash® with a 4 g silica column using a gradient solvent system starting at 100% hexanes and going to 100% EtOAc. The combined fractions were evaporated *in vacuo*, yielding **38** (25 mg, 0.060 mmol, 57% yield). ^{1}H NMR ($CDCl_3$, δ): 6.97 (s, 1H, Ar-H), 6.69 (s, 1H, Ar-H), 6.01 (dt, *J* = 10.3, 2.7, 1H, H7), 5.96 (buried, 1H, H6), 5.93-5.97 (m, 2H, OCH_2), 4.73 (d, *J* = 15.7, 1H, H8x), 4.34 (d, *J* = 15.7, 1H, H8y), 3.89 (bs, 1H, H7a), 2.84-2.88 (m, 1H, H5), 2.81 (dd, *J* = 17.0, 8.1, 1H, H3x), 2.42-2.46 (m, 1H, H3a), 2.24 (d, *J* = 17.0, 1H, H3y), 1.93 (bd, *J* = 12.8, 1H, H4x), 1.50 (q, *J* = 12.8, 1H, H4y). ^{13}C NMR ($CDCl_3$, δ): 173.8 (C2), 148.0 (2C, Ar-C), 128.8 (Ar-C), 127.0 (2C, C6 and C7), 126.2 (q, *J* = 279.6, CF_3), 113.3 (Ar-C), 112.8 (Ar-C), 109.2 (Ar-C), 102.0 (OCH_2O), 54.0 (C7a), 44.1 (C8), 40.4 (q, *J* = 28.0, C5), 38.1 (C3), 29.6 (C3a), 24.9 (C4).

Supplementary Material

Supporting information for this article is available on the WWW under xxxxxx. CCDC 2082770-2082781 and CCDC 1970963-1970964 contain the supplementary crystallographic data for this work. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre through https://www.ccdc.cam.ac.uk/structures/.

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Author Contribution Statement

KBW, HSN, MDC, and SRS designed and performed the experiments, *KSW and MNE performed the calculations, DAD* carried out the crystallographic work, and *WDH* supervised the work and wrote this manuscript.

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