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[4 + 2] Cyclocondensation Reactions of Tungsten−Dihydropyridine Complexes and the Generation of Tri- and Tetrasubstituted Piperidines

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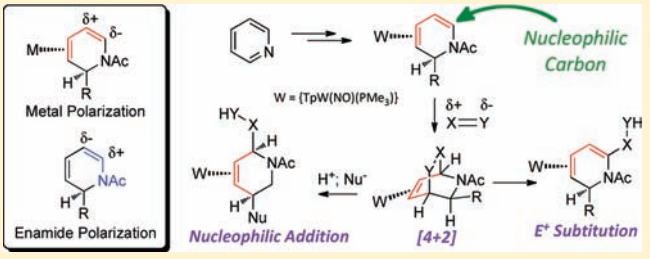
Supporting Information

ABSTRACT: A new method for the preparation of functionalized piperidines is described in which various dihydropyridine (DHP) complexes of {TpW(NO)(PMe$_3$)} that are derived from pyridine−borane undergo [4 + 2] cyclocondensation with enones, enals, nitrosobenzene, and several isocyanates to form [2.2.2] bicyclic species. In several cases the diazabicyclooctene products derived from DHP complexes and isocyanates can be further elaborated into novel *syn*-2,5-disubstituted and 2,3,6-trisubstituted piperidinamides.



1. INTRODUCTION

The recent emergence of several new synthetic strategies for the stereoselective formation of functionalized piperidines has led to heightened interest in indolizidine- and quinolizidine-based drug design.[1] Groups such as those of Comins,[1] Bosch,[2,3] Charette,[4] and Marazano[5] have developed methods that effect a broad range of regio- and stereoselective functional group attachments to the piperidine scaffold. Whereas most strategies to govern the stereochemistries of the piperidine ring carbons rely on the influence of a pre-existing sp^3 carbon stereocenter, the Liebeskind group has exploited the planar chirality found in heterocyclic π-complexes of molybdenum.[6] Our approach to preparing novel piperidine compounds lies in a similar vein.[7] Starting with pyridine−borane, a complex can be formed in which the π-base {TpW(NO)(PMe$_3$)} coordinates to C3 and C4 of the pyridine ring. Unmasking the pyridine nitrogen followed by its acetylation delivers the synthon [TpW(NO)(PMe$_3$)(*N*-acetylpyridinium)]OTf (**1**).[7] Compound **1**, isolated as the coordination diastereomer **1d** with a diastereomeric ratio (dr) of >10:1 (Scheme 1), has proven to be a versatile precursor to 3,4-η^2-coordinated 1,2-dihydropyridine (DHP) complexes (Scheme 1); it reacts with hydrides, cyanides, enolates, acetylides, and alkyl- or arylmetallics *exclusively at C2, anti to the tungsten*, and with complete retention of coordination stereochemistry.[8]

We recently used this array of DHP complexes (**2**−**8**) in the generation of 1,3-disubstituted and *syn*-1,2,5-trisubstituted tetrahydropyridines (THPs) (Scheme 2).[7] Following C6 protonation, the DHP ligand reacts with various nucleophilic reagents at C5, and as with the first addition, the second nucleophile adds exclusively *anti* to the tungsten, resulting in a *syn* relationship of the organic piperidine substituents. Of note, this transfomation represents a reversal (i.e., umpolung) of the natural tendency of enamides, 1,2-DHPs, and pyridines; thus, piperidines with novel substitution patterns are obtained by this method (Scheme 2). Considering the powerful π-donating properties of the tungsten group integral to complexes **2**−**8**, we queried whether DHP complexes of {TpW(NO)(PMe$_3$)} could also effect cyclocondensation reactions with reversed polarity, thereby generating azabicyclooctene cores with new substitution patterns. If realized, cycloadducts such as those depicted in Scheme 2 could be further elaborated, providing new piperidine structures. The following account details our findings.

2. RESULTS AND DISCUSSION

Monitoring reactions by ^{31}P NMR spectroscopy, we first explored the possibility of adding traditional dienophiles such as *N*-methylmaleimide, phenyl vinyl sulfone, methyl vinyl ketone (MVK), etc. to DHP complexes **2**−**8**. While metal coordination would be expected to preclude concerted cycloaddition reactions, an ionic (stepwise) mechanism seemed plausible. Exploring a wide range of solvents and concentrations, no reactivity was observed without the use of a Lewis acid, even with moderate heating (50−60 °C). However, when a methanol solution of MVK, Yb(OTf)$_3$, and **2** was monitored by ^{31}P NMR, two new species were observed to form as the signal for **2** diminished. The major species had a J_{WP} = 267 Hz (cf., for **2**, J_{WP} = 281 Hz),

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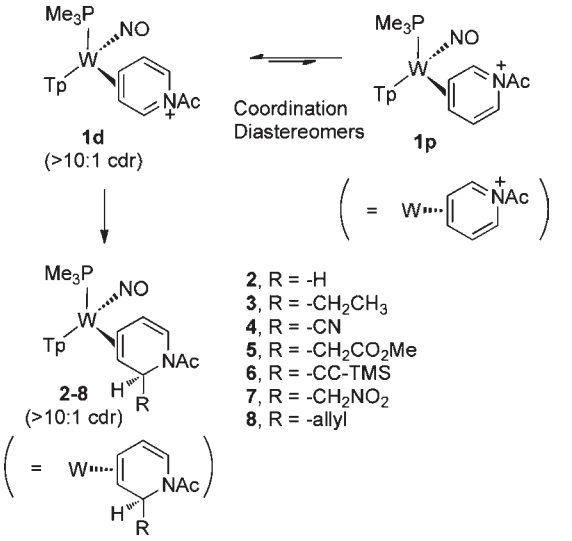
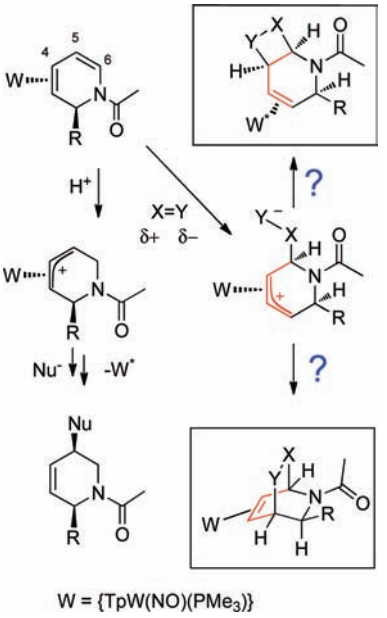
Scheme 1. Synthesis of Tungsten−DHP Complexes

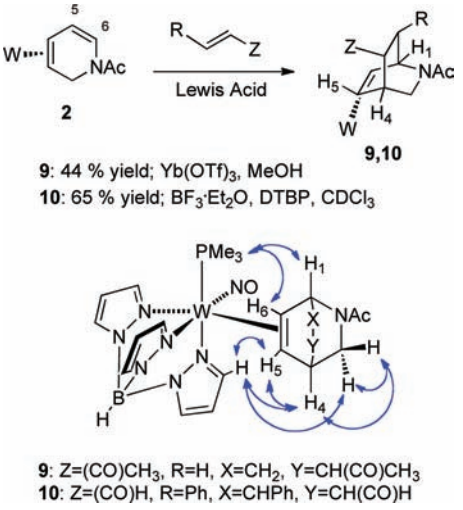


Scheme 2. Stereoselective Preparation of *syn*-2,5-Disubstituted Piperidines and Proposed Cyclocondensations with a DHP−Tungsten Complex



indicating the presence of a new TpW(NO)(PMe_3)(alkene) complex.[9] Product **9** was isolated as a 7:1 mixture of isomers (precipitated yield 40%). The lack of free alkene resonances and the appearance of five methine signals, two diastereotopic methylene group signals, and two methyl signals suggested that MVK had been incorporated into the pyridine ring. Correlation spectroscopy (COSY) data are consistent with **9** being the azabicyclooctene complex shown in Scheme 3, with nuclear Overhauser enhancement spectroscopy (NOESY) data supporting both the connectivity and stereochemical assignments. The key interactions include H1 with PMe_3 and H4 with a pyrazole proton *trans* to PMe_3. Additionally, a nuclear Overhauser effect (NOE) interaction between the ketone methyl (2.14 ppm) and a

Scheme 3. MVK Addition of 2 and Key NOE Interactions (in Blue) for the Major Species

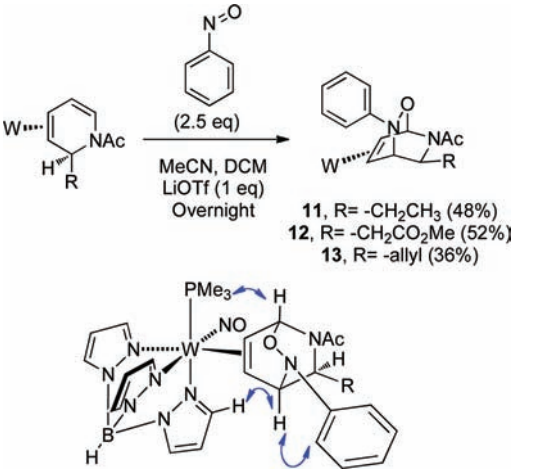


signal at 0.97 ppm indicates that the ketone group is in the vicinity of the bound alkene proton H5, qualifying **9** as an *endo* cycloadduct. Significantly, the enamide polarity has been reversed by the metal,[7] where the β carbon of MVK adds α to N (C6 of compound **2**). Characterization of the minor species was problematic due to overlapping resonances with the major one. However, we speculate that the minor species is likely to be an amide rotamer, given the similarity of the NMR signals to those of the major species, and that amide isomers have been confirmed for the organic ligand (vide infra). Repeating the synthesis of **9** in $CDCl_3$ with 2,6-di-*tert*-butylpyridine (DTBP) and $BF_3 \cdot Et_2O$ also gives satisfactory results.

Using either the Yb(OTf)$_3$ or BF_3 reaction conditions, which are effective for the reaction of MVK and **2**, cyclohex-2-enone, methyl acrylate, *N*-phenylmaleimide, phenyl vinyl sulfone, methyl propiolate, or dimethyl but-2-ynedioate, failed to deliver identifiable products. The reactions of **2** and β-nitrostyrene, acrolein, methacrolein, or crotonaldehyde in the presence of Yb(OTf)$_3$ were more promising. One major species ($J_{WP} \approx 260$ Hz) was observed in each case by ^{31}P NMR spectroscopy, but significant impurities (20−25%) were also present. However, when $BF_3 \cdot Et_2O$ was added to a $CDCl_3$ solution of **2**, *trans*-cinnamaldehyde, and DTBP, a precipitate formed (**10**), which after stirring for 18 h was isolated by filtration.[7,10] Compound **10** was fully characterized via 2D NMR techniques, which indicate the structure shown in Scheme 3. Of note, a signal at 1.34 ppm corresponding to the acetyl methyl (cf. ~2.1 ppm) indicates that the amide is in the shielding region of the phenyl group. Together with an NOE interaction of the aldehyde proton and H5, these data indicate the formation of an *endo* cycloadduct. In the presence of $BF_3 \cdot Et_2O$, other enones and enals also react with DHP complexes **3**−**8** to form new azabicyclooctene complexes, the details of which will be reported in due course.

Nitroso-Diels−Alder reactions with dienes are a valuable source of heteroatom incorporation into structural frameworks.[11−15] In one report, nitrosobenzene was found to undergo [4 + 2] hetero-Diels−Alder cycloaddition reactions with dihydropyridines similar to those bound to tungsten in **2**−**8** at room temperature and without the assistance of Lewis acids.[15] We queried whether DHPs complexed with {TpW(NO)(PMe_3)}

Scheme 4. Reaction of NOB with DHP Complexes 3, 5, and 8 and Selected NOESY Interactions of Cycloadducts (in Blue)



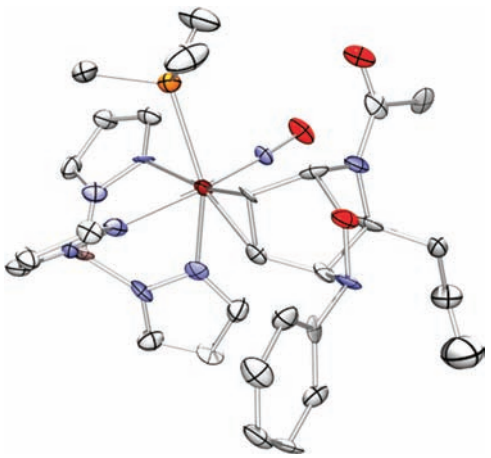
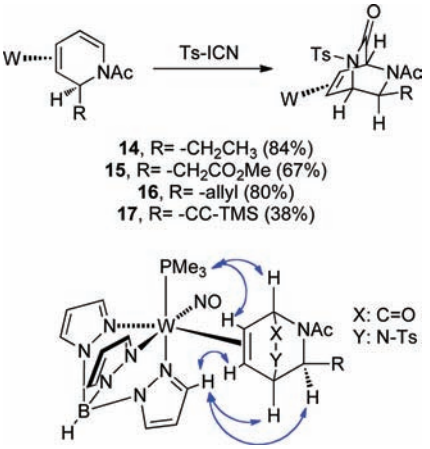


Figure 1. ORTEP diagram of cyclocondensation product **13**.

would produce bicyclic heterocycles with different regiochemistries than were observed for the organic reactions.

When commercially available nitrosobenzene (NOB) was combined with DHP complex **3**, **5**, or **8**, ^{1}H and ^{31}P NMR spectroscopic data indicated the gradual formation of new products, and the addition of LiOTf was found to modestly accelerate these reactions (see the Experimental Section). Complexes **11**−**13** could be isolated from hexanes as single diastereomers, but in reduced yields (Scheme 4; **3** → **11**, 48%; **5** → **12**, 52%; **8** → **13**, 36%). Each of these complexes gave a ^{1}H NMR spectrum with five methine signals, two of which were associated with bound carbons (^{31}P coupling). Analysis of NOESY data for **11**−**13** indicated an NOE interaction between the phenyl group and a methine resonance that also had an interaction with a pyrazole proton. This information, along with supporting heteronuclear single-quantum correlation (HSQC), heteronuclear multiple-bond correlation (HMBC), and COSY spectra, allows the assignment of **11**−**13** as the bicyclic structures shown in Scheme 4, in which the oxygen originating from the NOB is connected to C6 of the DHP ligand. A crystal of the R = allyl analogue **13** was grown (Scheme 4), and although internal

Scheme 5. Cyclocondensation of TsICN with 2-Substituted DHP Complexes



disorder prevented a high-resolution structural analysis, the X-ray diffraction data confirmed the proposed atom connectivity (Figure 1). In contrast to the results obtained for enones or enals, coordination of the metal was found to not alter the reactivity pattern of the DHPs with nitrosobenzene.

Earlier work from our laboratory found that ketenes combine with η^2 phenol complexes to give [2 + 2] cycloadducts in a reaction where the electrophilic carbon of the ketene adds to the *meta* phenol carbon.[16] Unfortunately, the reaction of the DHP complex **3** and those ketenes generated from chloroacetyl chloride or dichloroacetyl chloride and *N*,*N*-diisopropylethylamine (DIEA)[16] resulted in decomposition of the tungsten complex. However, isocyanates, the nitrogen congeners to ketenes, proved to be more amenable. When tosyl isocyanate (TsICN; 2 equiv) was added to a 0.14 M solution of **3** in $CDCl_3$, ^{31}P and ^{1}H NMR spectra recorded over 1 h marked the appearance of a single new compound as complex **3** was completely consumed. The new product, **14**, was isolated via precipitation in 84% yield. NMR data (COSY, NOESY, HSQC, and HMBC) are most consistent with a [4 + 2] cycloadduct, rather than the anticipated [2 + 2] isomer (vide supra). Supporting regio- and stereochemical assignments and NOE interactions are provided in Scheme 5.

To ensure that reaction with TsICN was not limited to just the ethyl derivative **3**, the analogous reaction was explored with other DHP complexes. Addition of TsICN to less sterically hindered **2** generated the desired species in <3 min, but several minor isomers were also observed by ^{31}P NMR. The reaction of TsICN and the cyano derivative **4** was much slower at similar concentrations, although some cycloadduct appeared to form (^{31}P NMR), but heating the reaction solution to 60 °C led to reformation of **4**. More promising were reactions with ester **5** or allyl **8**, which cleanly generated cycloadducts **15** and **16** with isolated yields of 67% and 80%, respectively (see Scheme 5). Furthermore, addition of TsICN to acetylene **6** induced a spontaneous precipitation of **17** from the reaction solution (38% isolated yield). The structures of **14**−**17** are supported by 2D NMR data (COSY, HSQC, HMBC, NOESY). A crystal of **16** was grown, and the X-ray data confirm its structural assignment (Figure 2). Additionally, this structure confirms the predicted regiochemistry and stereochemistry of the reaction, in which the electrophilic portion of the isocyanate (i.e., C═O)

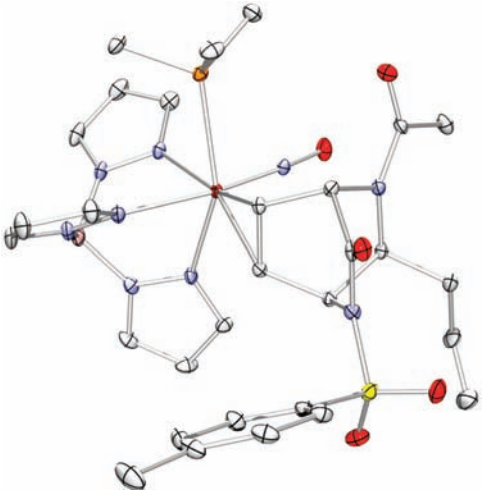
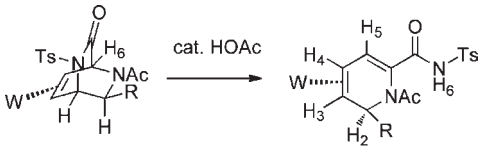


Figure 2. X-ray structure of **16**.

Scheme 6. Synthesis of Electrophilic Substitution Products of TsICN



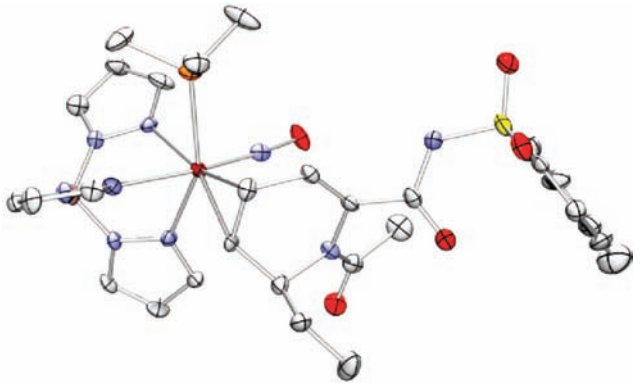
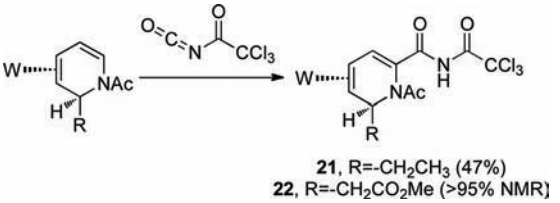


Figure 3. Crystal structure of complex **18** (hydrogen-bonded H_2O omitted).

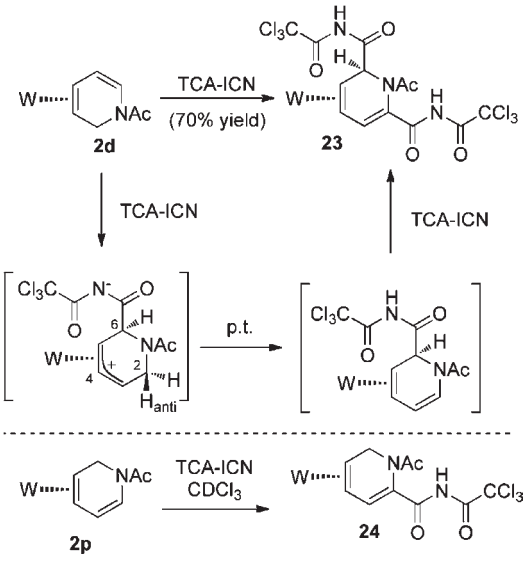
adds to C6 of the DHP ring *anti* to the metal. The umpolung nature of these isocyanate cyclization reactions is consistent with that observed for enones and enals (vide supra).

Upon standing in solution for several days, cycloadducts **14**−**16** each began to convert to a mixture comprised of a *new* DHP complex (**18**−**20**) and its forebearer (**3**, **5**, **8**). Acetic acid was an effective catalyst for the conversion of complexes **14**−**16** to their DHP analogues (**18**−**20**; Scheme 6). Isolations of complexes **18**−**20** were achieved after removal of acetic acid with a basic water workup ($NaHCO_3$, saturated, aqueous) followed by precipitation of the products from hexanes. NMR data (^1H, ^{13}C,

Scheme 7. Electrophilic Substitution with TCA-ICN



Scheme 8. Reaction of TCA-ICN with 2 and 2p



COSY, NOESY, HSQC, HMBC) were consistent with those of other DHP complexes,[8] indicating that the H6 proton had been transferred to the tosylated amide, thereby constituting a net electrophilic substitution at C6 of the DHP ligand. An X-ray structure of **18** was obtained that confirmed this notion (Figure 3).

In an effort to expand the scope of isocyanate addition to **2**−**8**, reaction with the phenyl derivative was explored (i.e., PhNCO). Unfortunately, even at elevated reaction temperatures, no reaction occurred other than decomposition. Addition of chlorosulfonyl isocyanate (CSI) led to intractable mixtures of products. However, addition of trichloroacetyl isocyanate (TCA-ICN) to **3** resulted in a mixture of [4 + 2] cycloadduct and electrophilic substitution isomers that eventually converted solely to the electrophilic substitution product **21**. Partial precipitation from hexanes delivered **21** in 47% isolated yield (Scheme 7). Repeating this experiment with DHP complex **5** and TCA-ICN also resulted in an initial mixture of isomers that eventually converted to a single product (**22**). All attempts to isolate the purported cycloadducts of TCA-ICN were unsuccessful.

Interestingly, addition of TCA-ICN to **2** produced a new complex that did not contain a diastereotopic geminal methylene group. The lack of this feature indicated that a simple electrophilic substitution analogous to those of other DHP complexes had not occurred. Two-dimensional NMR data and HRMS data are most consistent with the new product, **23**, being a double electrophilic substitution product (Scheme 8). Apparently, electrophilic addition at C6 is followed by proton transfer from C2

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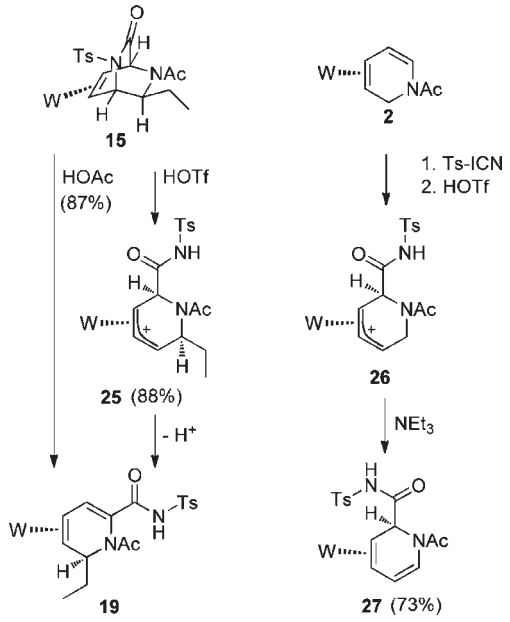
Scheme 9. Synthesis of 25 and Its Deprotonation To Form DHP 27



to generate a new DHP complex, which then rapidly undergoes a second electrophilic substitution to form **23**. Since no *anti* proton exists at C2 for **3** or **5**, the tautomerization is inhibited and the second electrophilic substitution does not occur. Of note, when **2p**, the coordination diastereomer of **2d**, is treated with TCA-ICN in $CDCl_3$, the electrophilic substitution product **24** is the dominant species formed (assignment based on COSY, NOESY, HSQC, and HMBC data; over several hours, the solution showed significant degradation, preventing isolation of the complex). The reactivity of **2d** and TCA-ICN is consistent with our earlier observations that π-allyl complexes of the THP fragment have significant η^2-character, with a strong preference to have the long W−C bond away from the phosphine.[17] Hence, deprotonation occurs at C2 rather than C6, setting the stage for further isocyanate addition. In contrast, the purported allyl derived from isocyanate addition to **2p** likely undergoes deprotonation at the carbonylated carbon to form **24**.

Organic *N*-carboalkoxy-1,2-dihydropyridines undergo cycloaddition reactions with MVK after mild heating (50 °C) for 6 days[18] and, in a separate report, with *N*-acryloyl-(1*S*)-2,10-camphorsultam in the presence of strong Lewis acids.[19,20] Enantioselective Diels−Alder reactions with α,β-unsaturated aldehydes have also been reported (0 °C, 1 day).[21] Other Michael acceptors undergo Diels−Alder reactions with DHPs as well.[22] *N*-Alkyl-1,2-dihydropyridines react with methyl acrylate to produce a [2 + 2] cycloadduct at low temperature (−10 °C) but a [4 + 2] cycloadduct at elevated temperature (80 °C).[23,24] In all of these cases, the regiochemical outcome is the same as that expected for dienamides or dienamines in general, where the more electrophilic carbon of the dienophile adds β to the dienamide or dienamine nitrogen, *in direct contrast* to what is observed for the tungsten−DHP complexes described above.[18−20,22−24] We are unaware of any reports in which organic DHPs react with isocyanates. However, when cyclohexadiene is subjected to CSI, a [2 + 2] cycloadduct is the kinetic product while a [4 + 2] cycloadduct and electrophilic substitution products are produced under thermodynamically controlled conditions.[25,26]

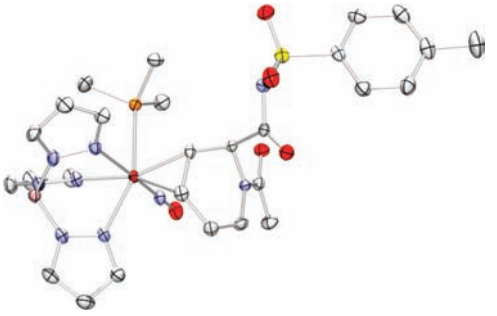
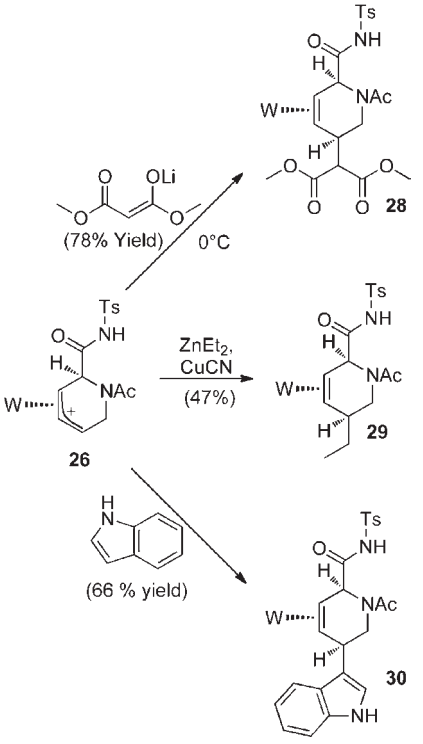


Figure 4. ORTEP diagram of complex **27**.

Scheme 10. Nucleophilic Addition Reactions with Allyl 26



Presumably, the DHP complexes **18**−**22** are formed via a π-allyl complex intermediate (see Scheme 8). We next attempted to isolate such complexes *directly* from the DHP compounds **2** and **3**. A solution of either **2** or **3** was treated with TsICN followed by triflic acid (HOTf). Addition of either reaction mixture to ether results in the isolation of allyl complexes **25** and **26** (Scheme 9).[17] Complex **25** can also be generated from cycloadduct **14** and triflic acid in 88% yield.

It was our hope that carbon nucleophiles could be added to these allyl systems, but when solutions of $Li[CH(CO_2Me)_2]$ (LiDMM) and **25** were combined, ^{31}P data indicated that the [4 + 2] cycloadduct **15** was initially re-formed and over time converted to the electrophilic substitution product **19**. In contrast, when the base triethylamine was added to the less substituted allyl **26**, deprotonation away from the amide group occurred to form **27**. Single crystals of **27** were grown, and the obtained structure confirms the regiochemistry of this deprotonation as well as the stereochemistry of C6 (Figure 4).

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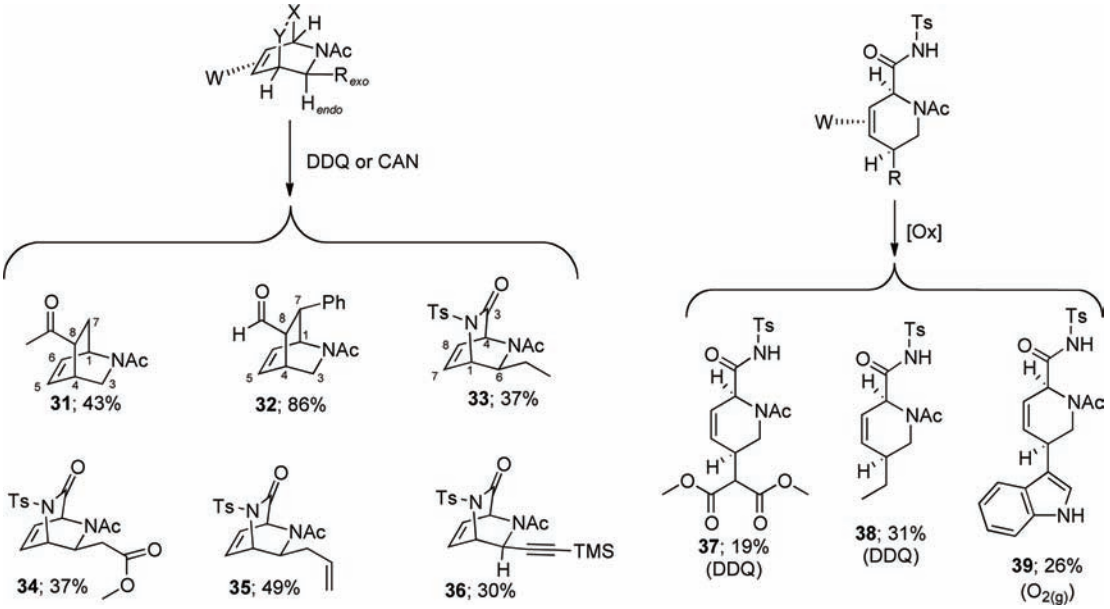
Scheme 11. Liberation of Azabicyclooctene, Diazabicyclooctene, and Carboxamoylpiperidinamides (Unoptimized Yields)



In contrast to what was observed for the ethyl derivative **25**, the reaction of LiDMM and **26** generates a THP complex (**28**) which when prepared at 0 °C can be recovered cleanly in 78% isolated yield (Scheme 10). Proton, carbon, COSY, and NOESY data indicate that **28** is a *syn*-2,5-substituted THP complex. Similarly, nucleophilic addition reactions were successful with $ZnEt_2$ and with indole, generating **29** and **30**, respectively, from allyl **26**. Of significance, complexes **28**−**30** represent piperidines prepared from a pyridine precursor with a *nucleophilic* α carbon and an *electrophilic* β carbon, the reverse of the natural polarization of pyridines.

Oxidative decomplexation of the pyridine-derived ligands of **9**, **10**, **14**−**17**, **28**, and **29** was achieved with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). Such action resulted in compounds **31**−**38** (Scheme 11) being isolated in 19−49% yield (unoptimized). The DDQ procedure failed in the case of **30**. Molecular oxygen was found to be effective in liberating **39** (Scheme 11) from the metal.[7] Compounds **33**−**36** possess a diazabicyclooctene core similar to those of the brevianamides and related compounds.[27−29] Brevianamides are toxic metabolites that were first isolated from penicillin.[30] In nature, these compounds are suspected to be produced through intramolecular Diels−Alder cycloadditions of pyrazinones,[31,32] and similar reactions have been performed on pyrazine systems.[33−36] The indole derivative **39** is structurally similar to several serotonin agonists and antagonists.[37] Some simple 3-substituted piperidines can be produced using radical cyclizations or ring-closing metathesis of open-chain enamides,[38−42] but in no other case are tri- or tetrasubstituted piperidines produced with substitution patterns similar to those of **37**−**39**.[7]

In general, dihydropyridines have not been observed to undergo nucleophilic addition β to N or electrophilic addition α to N. Palladium coupling, α-lithiation, or related techniques[43−46] can produce such regiochemistries, but only rearomatized products are isolated in these cases. Additionally, electrophilic substitution α to N is normally not observed for pyridines other than proton exchange,[47] although one report describes the nitration of 3,5-dimethoxypyridine 1-oxide.[48] We note that carbamoyl groups can be incorporated α to N in pyridine via hydration of 2-cyanopyridine[49] or Pd(0) catalysis with 2-halopyridines and formamide.[50]

3. CONCLUSIONS

Several different classes of X = Y electrophiles were explored to determine their ability to undergo cyclocondensation reactions with DHP complexes of {TpW(NO)(PMe_3)}. Michael acceptors, isocyanates, and nitrosobenzene successfully react to form the desired [4 + 2] cycloadducts. Significantly, for the alkenes and isocyanates examined, the electrophilic carbon adds regioselectively to the DHP ring α to N (C6), leading to organic DHP compounds with novel structural motifs.[18−20,22−24] These C6 electrophilic additions and subsequent reactions with nucleophiles at C3 are also stereoselective, with only the *syn* isomer being formed. The resulting mono- and bicyclic piperidines described in this paper are fundamentally different from those accessed by conventional organic methods, owing to the strong polarizing effect of the metal.[51−54]

4. EXPERIMENTAL SECTION

4.1. General Methods. NMR spectra were obtained on a 300, 500, or 600 MHz spectrometer (Varian INOVA or Bruker Avance). All chemical shifts are reported in parts per million, and proton and carbon shifts are referenced to tetramethylsilane (TMS) utilizing residual ^1H or ^{13}C signals of the deuterated solvents as an internal standard. Phosphorus NMR signals are referenced to 85% H_3PO_4 (δ = 0.00) using a triphenyl phosphate external standard (δ = −16.58). Coupling constants (J) are reported in hertz. Infrared (IR) spectra were recorded as a glaze on a MIDAC Prospect Series (model PRS) spectrometer fitted with a horizontal attenuated total reflectance (HATR) accessory (Pike Industries) or on a Nicolet Avatar 360 FT-IR spectrometer equipped with an ASI-DiComp diamond anvil attenuated total reflectance (ATR) assembly. Electrochemical experiments were performed under a dinitrogen atmosphere using a BAS Epsilon EC-2000 potentiostat. Cyclic voltammetry data were taken at ambient temperature at 100 mV/s (~25 °C) in a standard three-electrode cell with a glassy carbon working

electrode, *N*,*N*-dimethylacetamide (DMA) or acetonitrile (MeCN) solvent (unless otherwise specified), and tetrabutylammonium hexafluorophosphate (TBAH) electrolyte (approximately 0.5 M). All potentials are reported versus the NHE (normal hydrogen electrode) using cobaltocenium hexafluorophosphate ($E_{1/2}$ = −0.78 V), ferrocene ($E_{1/2}$ = +0.55 V), or decamethylferrocene ($E_{1/2}$ = +0.04 V) as an internal standard. The peak-to-peak separation was less than 100 mV for all reversible couples. Elemental analyses (EA) were obtained from Atlantic Microlabs and agree to within 0.4% for C, H, and N. High-resolution mass spectra were acquired on a Bruker BioTOF-Q running in electrospray ionization (ESI) mode from samples dissolved in an acetonitrile/water solution containing sodium trifluoroacetate (NaTFA), with some trifluoroacetic acid added. Mass spectra are reported for M^+ for monocationic complexes or for $(M + H)^+$ or $(M + Na)^+$ for neutral complexes using $[Na(NaTFA)_x]^+$ clusters as an internal standard. In all cases, observed isotopic envelopes were consistent with the molecular composition reported. For organic products, the monoisotopic ion is reported; for complexes, the major peaks in the isotopic envelope are reported. Unless otherwise noted, all synthetic reactions were performed in a glovebox under a dry nitrogen atmosphere. CH_2Cl_2 and benzene were purified by passage through a column packed with activated alumina. Other solvents and liquid reagents were thoroughly purged with dry nitrogen prior to use. Triflate salts were synthesized by addition of an Et_2O solution of triflic acid to the appropriate conjugate base dissolved in Et_2O. Deuterated solvents were used as received from Cambridge Isotopes. Pyrazole (Pz) protons of the trispyrazolyl borate (Tp) ligand were uniquely assigned using a combination of 2D NMR experiments and phosphorus−proton coupling (see Figure S1 in the Supporting Information). When unambiguous assignments were not possible, Pz protons were labeled as Tp protons. Coordination diastereomers are described by the defining feature's (i.e., carbocationic center) proximity to the PMe_3 ligand relative to the W−PMe_3 bond (e.g., the fewer number of bonds from the PMe_3 passing through the upper portion of the coordinated ring system to the defining feature dictates the proximal (P) ligand). Syntheses of compounds **2**−**8** have been previously reported.[8] TsICN, TCA-ICN, CSI, and NOB are commercially available and were used as received.

Note: Unless otherwise noted, ^{31}P data indicate that yields in a crude reaction mixture for these complexes are typically >90%. In most cases, tungsten complexes reported herein are isolated by their precipitation in hexanes. While this decreases the yield, it eliminates the need for chromatography.

4.2. Representative Syntheses and Characterizations. *4.2.1. TpW(NO)(PMe_3)(5,6-η^2-(1,1′-(2-azabicyclo[2.2.2]oct-5-ene-2,8-diyl)diethanone)) (**9**).* $Yb(OTf)_3$ (0.068 g, 0.11 mmol) was added to a homogeneous yellow solution of **2** (0.454 g, 0.725 mmol), MeOH (4.13 g), and MVK (0.132 g, 1.88 mmol). The solution was stirred for 17.5 h, then diluted with dichloromethane (DCM; 25 mL), and extracted with 3 × 15 mL portions of $NaHCO_3$ (aqueous, saturated) solution. The combined aqueous solution was back-extracted with 2 × 15 mL portions of DCM and combined with the original DCM extract. The resulting organic layer was dried with $MgSO_4$ and filtered through a medium-porosity fritted funnel. The filtrate solvent was evaporated, and the residue was dissolved in a premixed solution of DCM (6 mL) and EtOAc (6 mL). Et_2O (130 mL) was added to this yellow solution to make a precipitate form. The solution was filtered through a medium-porosity fritted funnel, and the filtrate solvent was evaporated. The residue was dissolved with a premixed solution of DCM (6 mL) and EtOAc (6 mL). Hexanes (130 mL) were added to this solution to make additional precipitate form. The flask was kept in an ice bath for 30 min with stirring. The yellow precipitate was collected on a medium-porosity fritted funnel and dried in vacuo to give **9** as a yellow powder (0.224 g, 0.322 mmol, 44% yield). ^1H NMR ($CDCl_3$, δ): 8.15 (d, J = 2.0, 1H, PzB3), 7.92 (d, J = 2.0, 1H, PzA3), 7.74 (d, J = 2.0, 1H, PzB5), 7.66 (d, J = 2.0, 1H, PzC5), 7.58 (d, J = 2.0, 1H, PzA5), 7.20 (d, J = 2.0, 1H, PzC3), 6.34 (t, J = 2.0, 1H, PzB4), 6.23 (t, J = 2.0, 1H, PzA4), 6.13 (t, J = 2.0, 1H, PzC4), 5.27 (dd, J = 6.8, 2.7, 1H, H1), 4.00 (dd, J = 10.1, 3.1, 1H, H3), 3.41 (dt, J = 10.1, 1.7, 1H, H3), 3.15 (ddd, J = 9.4, 4.3, 2.2, 1H, H8), 3.13 (s, 1H, H4), 2.58 (m, 1H, H7), 2.53 (m, 1H, H6), 2.18 (m, 1H, H7), 2.14 (s, 3H, acetyl Me), 2.02 (s, 3H, amide Me), 1.27 (d, J = 8.5, 9H, PMe_3), 0.97 (d, J = 11.6, m, 1H, H5). ^{13}C NMR ($CDCl_3$, δ): 209.0 (acetyl CO), 169.8 (amide CO), 144.2 (PzA3), 142.8 (PzB3), 140.3 (PzC3), 136.5 (PzC5), 135.7 (PzB5), 134.7 (PzA5), 106.4 (PzB4), 106.0 (PzA4), 105.8 (PzC4), 60.7 (C6), 54.0 (C8), 53.1 (C3), 51.0 (C5), 46.9 (C1), 37.7 (C4), 32.3 (C7), 28.5 (acetyl Me), 21.9 (amide Me), 13.5 (d, J = 28.8, PMe_3). ^{31}P NMR ($CDCl_3$, δ): −12.90 (J_{WP} = 267), −13.25 (J_{WP} = 266). CV (DMA): $E_{p,a}$ = +0.65 V. IR: ν_{BH} = 2448 cm^{-1}, ν_{CO} = 1701 cm^{-1}, ν_{amide} = 1624 cm^{-1}, ν_{NO} = 1554 cm^{-1}. ESI-MS (m/z, obsd (rel intens, %), calcd (rel intens, %), ppm, $(M + H)^+$): 695.2142 (84.2), 695.2149 (83.5), 1.0; 696.2157 (69.2), 696.2175 (80.4), 2.6; 697.2169 (100), 697.2174 (100), 0.6; 698.2197 (39.3), 698.2214 (44.2), 2.4; 699.2196 (77.0), 699.2206 (83.5), 1.5.

*4.2.2. TpW(NO)(PMe_3)(5,6-η^2-(2-acetyl-7-phenyl-2-azabicyclo[2.2.2]oct-5-ene-8-carbaldehyde)) (**10**).* Compound **2** (0.101 g, 0.161 mmol) was added to a vial, followed by DTBP (0.184 g, 0.962 mmol), then $CDCl_3$ (6.86 g), and then *trans*-cinnimaldehyde (0.178 g, 1.35 mmol), resulting in a homogeneous yellow solution. Addition of $BF_3 \cdot Et_2O$ (0.064 g, 0.45 mmol) to the vial containing the homogeneous solution induced the precipitation of a white solid. The heterogeneous solution was stirred rapidly overnight. After 21.5 h, the solution was removed from the glovebox and centrifuged for 10 min. The solvent was decanted and discarded. The solid was dissolved in 9 mL of DCM and diluted with 50 mL of Et_2O to precipitate some material in the separation funnel. The solution was extracted with 3 × 25 mL of $NaHCO_3$ (saturated, aqueous), back-extracted with 2 × 25 mL of Et_2O, dried with $MgSO_4$, filtered through a 30 mL coarse-porosity fritted funnel, and washed with 25 mL of DCM. The solvent was removed in vacuo and the residue dissolved in 1 mL of DCM and then 2 mL of EtOAc, followed by 10 mL of Et_2O. Hexanes (50 mL) were added to the resulting homogeneous solution to induce the precipitation of a white solid. The solution was cooled to 0 °C for 0.5 h, and then the precipitate was collected on a 15 mL medium-porosity fritted funnel, rinsed with 2 × 10 mL hexanes, and dried under static vacuum (0.086 g, 0.105 mmol, 65% yield). ^1H NMR ($CDCl_3$, δ): 9.69 (s, 1H, CHO), 8.12 (d, J = 2.0, 1H, PzB3), 7.93 (d, J = 2.0, 1H, PzA3), 7.74 (d, J = 2.0, 1H, PzB5), 7.68 (d, J = 2.0, 1H, PzC5), 7.58 (d, J = 2.0, 1H, PzA5), 7.35 (t, J = 7.8, 2H, H11), 7.24 (t, J = 7.8, 1H, H12), 7.21 (d, J = 7.8, 2H, H10), 7.19 (d, J = 2.0, 1H, PzC3), 6.32 (t, J = 3.0, 1H, PzB4), 6.23 (t, J = 3.0, 1H, PzA4), 6.17 (t, J = 3.0, 1H, PzC4), 4.15 (m, 1H, H1), 4.09 (dd, J = 5.0, 1.8, 1H, H7), 3.96 (dd, J = 12.2, 2.7, 1H, H3-syn), 3.77 (ddd, J = 12.2, 1.8, 1.8, 1H, H3-*anti*), 3.36 (s (br), 1H, H4), 3.30 (dd, J = 5.0, 1.8, 1H, H8), 2.78 (ddd, $^3J_{PH}$ = 14.3, J = 11.5, 2.9, 1H, H6), 1.35 (s, 3H, amide Me), 1.19 (d, $^2J_{PH}$ = 8.1, 9H, PMe_3), 1.06 (dddd, $^3J_{PH}$ = 1.7, J = 11.5, 3.9, 1.8, 1H, H5). ^{13}C NMR ($CDCl_3$, δ): 202.7 (aldehyde CO), 168.7 (amide CO), 144.8 (PzA3), 143 (C9), 142.9 (PzB3), 140.1 (PzC3), 136.7 (PzC5), 136.2 (PzB5), 135.1 (PzA5), 129.2 (C11), 128.4 (C10), 126.9 (C12), 106.9 (PzB4), 106.4/106.3 (PzA4/PzC4), 62.0 (C1), 61.5 (d, $^2J_{PC}$ = 14.5, C6), 60.0 (C8), 53.1 (C5), 51.9 (C3), 50.9 (C7), 34.8 (C4), 20.9 (amide Me), 13.6 (d, $^2J_{PC}$ = 27.8, PMe_3). ^{31}P NMR ($CDCl_3$, δ): −13.17 (J_{WP} = 266). IR: ν_{BH} = 2485 cm^{-1}, ν_{CHO} = 1718 cm^{-1}, ν_{amide} = 1633 cm^{-1}, ν_{NO} = 1564 cm^{-1}. CV (MeCN): $E_{p,a}$ = +0.67 V. ESI-MS (m/z, obsd (rel intens, %), calcd (rel intens, %), ppm, $(M + Na)^+$): 779.21301 (76), 779.21260 (81), 0.5; 780.21725 (62), 780.21512 (81), 2.7; 781.21419 (100), 781.21510 (100), 1.2; 782.21766 (43), 782.21896 (48), 1.7; 783.21758 (86), 783.21831 (82), 0.9.

*4.2.3. TpW(NO)(PMe_3)(7,8-η^2-(1-(6-ethyl-2-phenyl-3-oxa-2,5-diazabicyclo[2.2.2]oct-7-en-5-yl)ethanone)) (**11**).* DCM (4.20 g) and MeCN (6.50 g) were added to a vial containing **3** (0.655 g, 1.001 mmol), NOB (0.265 g, 2.474 mmol), and LiOTf (0.156 g, 1.000 mmol) to make a homogeneous dark yellow-brown solution. After 14.5 h, the reaction

solution was removed from the glovebox, diluted with 70 mL of DCM, extracted with 3 × 50 mL of $NaHCO_3$ (saturated, aqueous), back-extracted with 2 × 50 mL of DCM, dried with $MgSO_4$, and filtered through a 150 mL coarse-porosity fritted funnel, and the solvent was removed. The residue was dissolved in 10 mL of DCM and diluted with 175 mL of Et_2O to precipitate a tan solid that was collected on a 30 mL medium-porosity fritted funnel, washed with 2 × 15 mL of Et_2O, and discarded. The yellow filtrate solvent was removed. The residue was dissolved in 2 mL of EtOAc, a precipitate began to form, and 100 mL of hexanes was added to aid in precipitation. The solution was cooled to 0 °C for 2 h. A tan-peach solid was collected on a 30 mL medium-porosity fritted funnel, washed with 2 × 15 mL of hexanes, and placed under vacuum (0.368 g, 0.483 mmol, 48% yield). ^{1}H NMR ($CDCl_3$, δ): 8.21 (d, J = 2.0, 1H, PzB3), 7.82 (d, J = 2.0, 1H, PzA3), 7.75 (d, J = 2.0, 1H, PzB5), 7.62 (d, J = 2.0, 1H, PzC5), 7.56 (d, J = 2.0, 1H, PzA5), 7.18 (m, 2H, H13), 7.14 (m, 2H, H12), 7.09 (d, J = 2.0, 1H, PzC3), 6.84 (d, J = 3.8, 1H, H4), 6.79 (m, 1H, H14), 6.36 (t, J = 2.0, 1H, PzB4), 6.26 (t, J = 2.0, 1H, PzA4), 6.08 (t, J = 2.0, 1H, PzC4), 4.65 (dd, J = 4.9, 2.7, 1H, H1), 4.15 (m, 1H, H6), 2.80 (ddd, J = 11.6, 3.8, $^3J_{PH}$ = 11.6, 1H, H8), 2.41 (m, 1H, H9), 2.16 (s, 3H, amide Me), 2.03 (m, 1H, H9′), 1.50 (ddd, J = 11.6, 4.9, $^3J_{PH}$ = 2.5, 1H, H7), 1.27 (d, $^2J_{PH}$ = 8.6, 9H, PMe_3), 1.20 (t, J = 7.5, 3H, H10). ^{13}C NMR ($CDCl_3$, δ): 169.4 (amide CO), 152.1 (C11), 144.8 (PzA3), 142.5 (PzB3), 140.1 (PzC3), 136.7 (PzC5), 136.0 (PzB5), 135.0 (PzA5), 128.5/116.4 (C12/C13), 120.5 (C14), 106.8 (PzB4), 106.5 (PzA4), 106.2 (PzC4), 83.7 (C4), 63.8 (C10), 51.3 (C6), 56.6 (d, J = 14.3, C8), 50.0 (C7), 25.2 (C9), 23.7 (amide Me), 13.7 (d, J = 28.8, PMe_3), 11.1 (C10). ^{31}P ($CDCl_3$, δ): ∼−14 (J_{WP} = 263). IR: ν_{BH} = 2486 cm^{-1}, ν_{amide} = 1624 cm^{-1}, ν_{NO} = 1563 cm^{-1}. CV (MeCN): $E_{p,a}$ = +0.53 V. ESI-MS (m/z, obsd (rel intens, %), calcd (rel intens, %), ppm, $(M + H)^+$): 760.2391 (110.5), 760.2415 (81.2), 3.2; 761.2438 (89.4), 761.2441 (81.2), 0.4; 762.2438 (100), 762.244 (100), 0.3; 763.2459 (60.3), 763.2479 (47.2), 2.6; 764.2467 (95.6), 764.2472 (82.5), 0.7.

*4.2.4. TpW(NO)(PMe_3)(7,8-η^2-(methyl 2-(5-acetyl-2-phenyl-3-oxa-2,5-diazabicyclo[2.2.2]oct-7-en-6-yl)acetate)) (**12**).* DCM (4.12 g) was added to a heterogeneous solution of **5** (0.698 g, 1.006 mmol), NOB (0.273 g, 0.273 mmol), LiOTf (0.157 g, 1.006 mmol), and MeCN (6.44 g) to make a dark brown homogeneous solution. After 21 h, the reaction solution was removed from the glovebox, diluted with 70 mL of DCM, extracted with 3 × 50 mL of $NaHCO_3$ (saturated, aqueous), back-extracted with 2 × 50 mL of DCM, dried with $MgSO_4$, and filtered through a 150 mL coarse-porosity fritted funnel, and the solvent was removed. The residue was dissolved in 10 mL of DCM and diluted with 175 mL of Et_2O to precipitate a tan solid that was collected on a 30 mL medium-porosity fritted funnel, washed with 2 × 15 mL of Et_2O, and discarded. The yellow filtrate solvent was removed. The residue was dissolved in 2 mL of EtOAc, a precipitate began to form, and 100 mL of hexanes was added to aid in precipitation. The solution was cooled to 0 °C for 2 h. A tan-peach solid was collected on a 30 mL medium-porosity fritted funnel, washed with 2 × 15 mL of hexanes, and placed under vacuum (0.422 g, 0.524 mmol, 52% yield). ^{1}H NMR ($CDCl_3$, δ): 8.19 (d, J = 2.0, 1H, PzB3), 8.09 (d, J = 2.0, 1H, PzA3), 7.75 (d, J = 2.0, 1H, PzB5), 7.62 (d, J = 2.0, 1H, PzA5), 7.55 (d, J = 2.0, 1H, PzC5), 7.15 (dd, J = 8.4, 7.4, 2H, H12), 7.08 (d, J = 8.4, 2H, H11), 7.07 (d, J = 2.0, 1H, PzC3), 6.80 (m, 2H, H4 + H13), 6.36 (t, J = 2.0, 1H, PzB4), 6.3 (t, J = 2.0, 1H, PzA4), 6.08 (t, J = 2.0, 1H, PzC4), 4.89 (dd, J = 5.1, 2.5, 1H, H1), 4.74 (dt, J = 10.4, 2.5, 1H, H6), 3.8 (s, 3H, ester Me), 3.71 (dd, J = 17.2, 10.4, 1H, H9), 2.95 (dd, J = 17.2, 2.5, 1H, H9′), 2.81 (ddd, J = 11.4, 4.0, $^3J_{PH}$ = 11.9, 1H, H8), 2.16 (s, 3H, amide Me), 1.44 (ddd, J = 11.4, 5.1, $^3J_{PH}$ = 2.7, 1H, H7), 1.28 (d, $^2J_{PH}$ = 8.5, 9H, PMe_3). ^{13}C NMR ($CDCl_3$, δ): 172.9 (ester CO), 169.3 (amide CO), 151.7 (C10), 145.4 (PzA3), 142.5 (PzB3), 140.0 (PzC3), 136.7 (PzA5), 136 (PzB5), 134.9 (PzC5), 128.5 (C12), 120.8 (C13), 116.7 (C11), 106.8 (PzA4/PzB4), 106.1 (PzC4), 83.6 (C4), 65.5 (C1), 56.3 (C6), 56.2 (d, $^2J_{PC}$ = 14.3, C8), 51.8 (ester Me), 49.4 (C7), 36.6 (C9), 23.4 (amide Me), 13.9 (d, $^1J_{PC}$ = 28.8, PMe_3). ^{31}P ($CDCl_3$, δ): −14.21 (J_{WP} = 262). IR: ν_{BH} = 2488 cm^{-1}, ν_{ester} = 1729 cm^{-1}, ν_{amide} = 1632 cm^{-1}, ν_{NO} = 1564 cm^{-1}. CV (MeCN): $E_{p,a}$ = +0.65 V. ESI-MS (m/z, obsd (rel intens, %), calcd (rel intens, %), ppm, $(M + H)^+$): 804.2314 (91.9), 804.2314 (80.4), 0.0; 805.2336 (89.7), 805.2339 (81.2), 0.4; 806.2329 (100), 806.2339 (100), 1.2; 807.2375 (52.8), 807.2377 (48.1), 0.3; 808.2371 (91.3), 808.2371 (82.4), 0.0.

*4.2.5. 1,1′-(2-Azabicyclo[2.2.2]oct-5-ene-2,8-diyl)diethanone (**31**).* A solution of ceric ammonium nitrate (CAN; 0.106 g, 0.193 mmol) in MeCN (7.17 g) was added to a vial containing **9** (0.102 g, 0.147 mmol). The resulting heterogeneous solution was transferred to an NMR tube, and the reaction was monitored by ^{31}P NMR spectroscopy. After 1 h, the reaction solution was diluted with DCM (15 mL) and extracted with 3 × 25 mL portions of $NaHCO_3$ (aqueous, saturated) solution. The combined aqueous solution was back-extracted with 2 × 10 mL portions of DCM and combined with the original DCM extract. The resulting DCM solution was dried with $MgSO_4$ and filtered through a medium-porosity fritted funnel. The filtrate was evaporated, and the residue was dissolved with DCM. The residue was loaded onto a 500 μm × 20 cm × 20 cm silica preparatory TLC plate and eluted with 1:6 MeOH/EtOAc. The band between R_f = 0.37 and R_f = 0.47 was removed from the plate, sonicated in a test tube containing 20 mL of EtOAc for 30 min, filtered through a 30 mL medium-porosity fritted funnel, and washed with 200 mL of EtOAc, and the solvent was removed to yield a tan solid (0.012 g, 0.063 mmol, 43% yield). ESI-MS (m/z, obsd (rel intens, %), calcd (rel intens, %), ppm, $(M + Na)^+$): 216.10037 (100), 216.09950 (100), 4.0.

4.2.5.1. Data for Major Diastereomer. ^{1}H NMR ($CDCl_3$, δ): 6.40 (m, 1H, H6), 6.30 (m, 1H, H5), 5.27 (m, 1H, H1), 3.39 (m, 1H, H3-*exo*), 3.17 (m, 1H, H4), 3.08 (m, 1H, H3-*endo*), 2.79 (m, 1H, H8), 2.19 (m, 1H, H7-*trans*), 2.11 (s, 3H, acetyl Me), 1.95 (s, 3H, amide Me), 1.66 (ddd, J = 12.96, 5.36, 2.11, 1H, H7-cis). ^{13}C NMR ($CDCl_3$, δ): 207.6 (acetyl CO), 169.1 (amide CO), 133.6 (C6), 131.8 (C5), 49.1 (C3), 48.5 (C8), 43.3 (C1), 33.2 (C4), 29.9 (C7), 28.1 (acetyl Me), 22.2 (amide Me).

4.2.5.2. Data for Minor Diastereomer. ^{1}H NMR ($CDCl_3$, δ): 6.40 (m, 1H, H6), 6.30 (m, 1H, H5), 4.40 (m, 1H, H1), 3.40 (m, 1H, H3-*exo*), 3.17 (m, 1H, H4), 3.08 (m, 1H, H3-*endo*), 2.79 (m, 1H, H8), 2.15 (s, 3H, acetyl Me), 2.09 (s, 3H, amide Me), 2.08 (m, 1H, H7), 1.86 (ddd, J = 12.90, 5.14, 2.20, 1H, H7). ^{13}C NMR ($CDCl_3$, δ): 207.4 (acetyl CO), 168.7 (amide CO), 132.4 (C5), 132.2 (C6), 48.8 (C1), 48.1 (C8), 47.3 (C3), 33.17 (C4), 30.2 (C7), 28.3 (acetyl Me), 21.9 (amide Me).

*4.2.6. 2-Acetyl-7-phenyl-2-azabicyclo[2.2.2]oct-5-ene-8-carbaldehyde (**32**).* A solution of CAN (0.052 g, 0.095 mmol) in MeCN (2.05 g) was added to a vial containing **10** (0.044 g, 0.058 mmol). The resulting heterogeneous solution was transferred to an NMR tube, and the reaction was monitored by ^{31}P NMR spectroscopy. After 40 min, the reaction solution was diluted with DCM (20 mL) and extracted with 4 × 25 mL portions of $NaHCO_3$ (aqueous, saturated) solution. The combined aqueous solution was back-extracted with 2 × 10 mL portions of DCM and combined with the original DCM extract. The resulting DCM solution was dried with $MgSO_4$ and filtered through a medium-porosity fritted funnel. The filtrate solvent was evaporated, and the residue was dissolved with DCM. The residue was loaded onto a 500 μm × 20 cm × 20 cm silica preparatory TLC plate and eluted with EtOAc. The band between R_f = 0.20 and R_f = 0.31 was removed from the plate, sonicated in a test tube containing 25 mL of EtOAc for 30 min, filtered through a 30 mL medium-porosity fritted funnel, and washed with 100 mL of EtOAc, and the solvent was removed to yield a white solid (0.013 g, 0.050 mmol, 85% yield). ESI-MS (m/z, obsd (rel intens, %), calcd (rel intens, %), ppm, $(M + Na)^+$): 278.11537 (100), 278.11515 (100), 0.8. ESI-MS (m/z, obsd (rel intens, %), calcd (rel intens, %), ppm, $(M + H)^+$): 256.1335 (100), 256.13321 (100), 1.1. ESI-MS for carboxylic acid ($C_{16}H_{17}NO_3$) via air oxidation (m/z,

obsd (rel intens, %), calcd (rel intens, %), ppm, $(M + H)^+$): 272.128 (100), 272.12812 (100), 0.4. ^{1}H NMR ($CDCl_3$, δ): 9.56 (s, 1H, aldehyde H), 7.3 (m, 5H, phenyl), 6.60 (ddd, J = 7.9, 6.2, 1.55, 1H, H6), 6.40 (ddd, J = 7.9, 6.3, 1.3, 1H, H5), 4.20 (ddd, J = 6.2, 1.5, 1.3, 1H, H1), 3.68 (dd, J = 11.9, 2.1, 1H, H3-*exo*), 3.38 (ddddd, J = 6.3, 2.3, 2.1, 2.1, 1.55, 1H, H4), 3.33 (dd, J = 5.6, 1.5, 1H, H7), 3.26 (dd, J = 11.9, 2.3, 1H, H3-*endo*), 2.87 (dd, J = 5.6, 2.1, 1H, H8), 1.42 (s, 3H, amide Me). ^{13}C NMR ($CDCl_3$, δ): 199.9 (aldehyde CO), 170.2 (amide CO), 133.6 (C6), 133.0 (C5), 129.3 to 127.3 (phenyl), 56.6 (C1), 53.5 (C8), 47.7 (C3), 46.3 (C7), 31.6 (C4), 20.8 (amide Me).

■ ASSOCIATED CONTENT

Supporting Information. Full experimental procedures for all previously unpublished compounds and descriptions of their spectroscopic analysis, ^{1}H and ^{13}C NMR spectra of selected compounds, and CIF files for the structures of compounds **13**, **16**, **18**, and **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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