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A Highly Divergent Synthesis of 3-Aminotetrahydropyridines

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Abstract

Dihapto-coordinate 1,2-dihydropyridine complexes of the metal fragment $\{WTP(NO)(PMe_3)\}$ (Tp = tris(pyrazolyl)borate), derived from pyridine, are demonstrated to undergo protonation at C6 followed by regioselective amination at C5 with a variety of primary and secondary amines. The addition takes place stereoselectively *anti* to the metal center, producing exclusively *cis*-disubstituted products. The resulting 1,2,5,6-tetrahydropyridines can be successfully liberated by oxidation, providing a route to novel molecules of potential medicinal interest.

Graphical Abstract

Piperidines are abundant in natural products and FDA-approved small-molecule drugs.^{1,2} Many of these molecules also feature exocyclic nitrogen functional groups, such as the 3-aminopiperidine structural motif found in drugs including troxipide, alogliptin, relebactam,³ the JAK3 inhibitors tasocitinib, and PF-06651600.^{4–6} The amine functionality can be difficult to incorporate into the piperidine core, especially stereoselectively. For example, while the parent 3-piperidin-amine is commercially available, approaches to the

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Supporting Information

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Crystallographic data for compound **2** (CIF)

¹H and ¹³C{¹H} NMR spectra of selected compounds and crystallographic information for compound **2** (PDF)

The authors declare no competing financial interest.

CCDC 1994298 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

stereoselective synthesis of its derivatives have taken many different forms, ranging from cyclizations,⁷ ring expansion of pyrrolidines,^{8,9} Curtius¹⁰ and Hofmann rearrangements,¹¹ reductive amination of piperidin-3-ones,¹² and hydrogenation of hydroxy- or aminopyridines (Figure 1),¹³ often via Buchwald-Hartwig amination of a 3-halopyridine.^{14,15} The latter approach would seem to be the most general, allowing for the greatest diversity, but two challenges emerge: the lack in availability of the corresponding substituted aminopyridine, and the ability to control the stereochemistry of the hydrogenation.^{4,13}

Our longstanding interest in the activation of aromatic molecules through their dihapto-coordination to a transition metal¹⁶ prompted us to consider whether a general route to functionalized 3-aminopiperidines could be developed using pyridines as the foundation. Previously, we investigated nucleophilic additions of the complex [Wtp(NO)(PMe₃)(*N*-acetylpyridinium)]⁺.^{17–19} This complex, derived from commercially available pyridine-borane (overall 75% in 3 steps), readily undergoes selective addition of a wide range of nucleophiles including hydrides, enolates, organometallics, and electron-rich aromatics to yield the 1,2-dihydropyridine (DHP) products shown in Scheme 1.^{18,19}

In all cases, the 1,2-dihydropyridine complex is prepared stereoselectively and is altogether free of any 1,4-dihydropyridine impurities. Our hope was that these DHP complexes would be valuable synthetic precursors to aminotetrahydropyridines (ATHPs). 3-ATHPs are readily hydrogenated to make the corresponding aminopiperidines (Figure 1).^{20–22} Alternatively, they can be dihydroxylated using the Upjohn process,^{23,24} as has been done to make acetamido-1,2-dideoxyiminosugars,²⁴ which are known glycosidase inhibitors.

In previous work,¹⁹ DHP complexes such as those shown in Scheme 1 were shown to undergo chemoselective protonation at C6, where tungsten, rather than the nitrogen, was the primary π -donor to the C5–C6 double bond. The resulting “ η^2 -allyl” complex²⁵ was then combined with carbon nucleophiles such as dimethyl malonate and diethylzinc to produce various 2,3- or 2,5-disubstituted 1,2,5,6-tetrahydro-pyridine (THP) complexes. Noting that these C3 or C5 addition reactions represent a reverse in the natural polarization of pyridine, our hope was that amines could be added in a similar manner to provide the desired aminopiperidine core. For demonstration purposes, we chose DHP complexes with ethyl (**1**), allyl (**3**), and carboethoxymethyl (**2**) substituents, as well as the parent (**4**). Compounds **1–4** all undergo facile protonation to yield η^2 -allyl complexes **5–8** (Scheme 2).¹⁹ These triflate salts are readily isolated and stored under ambient conditions, and their full synthesis and characterization have been described elsewhere.¹⁹

The allyl complexes **5–8** exist in solution as two rapidly equilibrating conformational isomers (Scheme 2), which are best described as η^2 -alkene complexes with a loosely associated allylic carbocation (denoted herein with a positive charge).²⁵ While they can be generated with acids as weak as diphenylammonium triflate, we found it most convenient to use an acetonitrile solution of triflic acid, followed by precipitation with ether.

Of the two allylic conformations shown in Scheme 2, the dominant form is one in which the carbocation is oriented distal to the PMe₃.²⁵ Hence, our initial expectation was that amine nucleophiles would add to C3, provided that there was not a significant steric interaction

with the C2 substituent of the DHP complex (Scheme 3).¹⁹ However, treating **5** with methylamine in THF at 0 °C resulted only in the reformation of the precursor DHP complex (**2**). Repeating this experiment at –30 °C likewise yielded only the DHP complex. Only when the reaction of **5** and methylamine was conducted at –40 °C, and the reaction mixture was analyzed by ¹H NMR at low temperature, was spectroscopic evidence for an amine addition observed (Scheme 3). NMR data (*vide infra*) indicated that the reaction with methylamine resulted exclusively in a 2,5-disubstituted THP complex (**9**). We speculate that since a purported amine addition at C3 would be highly reversible, the ultimate regioselectivity of the amine addition at C5 is likely the result of thermodynamic factors alone (Scheme 3).¹⁹

Unfortunately, warming the sample of **9** to ambient temperature caused the immediate reversion of **9** to the DHP precursor **2**. Similar behavior was also seen with other amines (*vide infra*). It thus became evident that the desired allylamine complexes (**iv**; e.g., **9**) were highly vulnerable to a proton-initiated E1-type elimination mechanism. Apparently, the ammonium salt generated in the course of the reaction can reprotonate the amine (**iii**), triggering its departure, with the π -basic tungsten stabilizing the developing carbocation (**ii**) (Scheme 3). Deprotonation of the resulting allyl complex (**ii**, e.g., **5**) by the excess of free amine present in the reaction then returns the DHP complex (e.g., **2**). With the strong π -donor tungsten coordinated, the η^2 -dihydropyridine elimination product (Scheme 3, **i**) is thermodynamically favored over the ATHP complex (Scheme 3, **iv**). It is therefore only by the *kinetic* preference at –40 °C for addition at C5 over deprotonation at C6 that tetrahydropyridine addition products of type **iv** can be formed.

Hence, our strategy shifted to employing a base that would inhibit E1 elimination once the allylamine was formed. At the same time, too strong of a base could enable an E2 elimination mechanism across C5 and C6. Fortunately, we found that quenching the reaction mixture with potassium *tert*-butoxide before returning the reaction mixture to ambient temperature largely prevented elimination. A small amount of DHP product (**i**; ~10%) was still observed in the quenched crude reaction mixtures, which is presumed to be the result of direct deprotonation of the allyl complex (**ii**) by the free amine.

Attempts to precipitate the ATHP complexes in water failed due to the E1 elimination described above, but they were fairly stable to extraction with basic aqueous solution. Hence, basified ATHP reaction mixtures were diluted with CH₂Cl₂, extracted with saturated aqueous Na₂CO₃, and then treated with Et₂O or hexanes to induce precipitation of the tungsten complex.²⁶

As an example, the tungsten ATHP complex **9** was characterized by ¹H, ¹³C{¹H}, NOESY, COSY, HMBC, and HSQC NMR experiments (SI). It was determined that addition had occurred exclusively at C5. As mentioned earlier, this selectivity is in contrast to that sometimes observed for additions to carbocyclic allyl complexes of tungsten.^{19,27}

Consistent with precedent, however, was that the nucleophilic addition occurs exclusively *anti* to the face of metal coordination; an NOE interaction was observed between H5 and

PMe₃. Chemical exchange peaks in the NOESY spectrum also revealed the presence of an amide rotamer (4:1 rotamer ratio in CD₃CN).¹⁹

Given that the ATHP complex (**9**) slowly eliminates in solution, we attempted to oxidatively decomplex the ATHP without further purification. A variety of oxidants were screened, including NOPF₆, FeCp₂PF₆, DDQ, CAN, and O₂/silica. CAN oxidation resulted in complete destruction of the desired organic product, while FeCp₂PF₆ and O₂/silica gave incomplete oxidation. Both NOPF₆ and DDQ provided satisfactory recovery of the desired free amine (**10**; Figure 2) in similar yields. It was found that higher recovery of the free amine could be achieved by conducting the oxidation under acidic conditions, by premixing the oxidant solution with HOTf. Presumably, protonation of the amine prevents oxidation of the amino group by the oxidant or oxidized metal byproducts, and once the metal is no longer coordinated, the allyl amine resists elimination. However, in order to prevent elimination preempting oxidation of the tungsten, the complex was first dissolved in MeCN and the solution was cooled to -40 °C before a cold solution of oxidant/HOTf in MeCN was added. It is imperative that the complex be completely dissolved, as the oxidant appears to oxidize the free amine if the metal complex is not immediately available for oxidation. Proper stoichiometry is also crucial, with the best results being obtained with 1 mol equiv of oxidant. Under these optimized conditions, the ATHP **10** was oxidatively decomplexed with about 50% efficiency, as determined by ¹H NMR spectra using a durene internal standard.²⁸

Following decomplexation and purification, the ATHP **10** (Scheme 4) was characterized by ¹H, ¹³C{¹H}, NOESY, COSY, HMBC, and HSQC NMR, as well as HRMS. **10** was found to exist as a 5:2 mixture of rotamers in CD₃CN at 25 °C, with chemical exchange evident by NOESY. Unlike complex **9**, the free allylamine **10** was found to be stable to elimination, even under acidic aqueous conditions. The relative stability of the decomplexed product supports the notion that the tungsten facilitates E1 elimination of the protonated amine in the complex (**9**), via stabilization of the resulting allyl cation.

With the reaction and workup conditions optimized for the addition of methylamine to yield **10**, the reaction was repeated under identical conditions with the allyl derivative **6** in place of **5**, in order to determine if variation of the C2 substituent would affect the outcome of the reaction. An analogous addition complex (**11**) was isolated, which was also successfully oxidized with DDQ to yield compound **12** with no noticeable loss in yield (cf. **10**). Next, we expanded the range of primary and secondary amines to include various functional groups that could serve as further points of diversity in medchem studies such as alkenes, alkynes, benzyl halides, esters, strained amines, and nitrogen heterocycles. Complexes resulting from amine addition to allyl complexes **5–8** were successfully formed from morpholine (**13** and **14**), propargyl-amine (**15**), benzylamines (**16** and **17**), an azetidine (**17**), and the nitrogen heterocycle imidazole (**18**). Spectra (¹H NMR) of the intermediate ATHP complexes all indicated between 10% and 20% impurity from elimination (i.e., **1–4**). The complexes were oxidized by DDQ without further purification, yielding organic compounds **19–25**, as shown in Figure 2 in yields ranging from 17% to 48%, which represents an *overall yield* of 14–42% from a single common pyridinium complex (see Scheme 1).

To our knowledge, none of the 3-ATHPs in Figure 2 have been previously prepared. The closest examples are 2-hydroxymethyl 5-amino- derivatives prepared from cyclizations of dienes.^{24,29} To further explore the range of organic products accessible by this methodology, we included an example in which the DHP complex **4** is combined with the carbon electrophile tosyl isocyanate, rather than H⁺. Their reaction provides the allyl complex **26** (Scheme 5) after treatment with triflic acid.³⁰ Unlike in previous examples, the substituent on the piperidine ring in **26** acts as an electron-withdrawing group and directs the carbocation to C3 in order to separate positive charge (Scheme 5). Despite the acidic nature of the acylsulfonamide moiety,³⁰ the reaction of **26** with piperidine at -40 °C in MeCN yielded the ATHP complex **27**. As expected, this species was substantially more prone to elimination than the other ATHP complexes, and could not be purified. Instead, the reaction mixture was quenched with NaO^tBu/THF, evaporated to near-dryness *in vacuo*, dissolved in minimal DCM, and precipitated into Et₂O. The isolated solid **27** was oxidized with DDQ and HOTf in MeCN to yield the free organic **28** (16% from **4**; 3 steps), which was now stable to purification conditions. We note that while **28** is a new compound, acyl sulfonamides such as this are of considerable interest in medicinal chemistry and are considered valuable bioisosteres of carboxylic acids.³¹

CONCLUSIONS

This tungsten-mediated approach to access cis-2-substituted 5-amino-1,2,5,6-tetrahydropyridines (i.e., 3-aminotetrahydropyridines) enables the rapid generation of a diverse range of new compounds with a biologically privileged scaffold. The C2 nucleophile, C6 electrophile, and amine may all be varied, presenting the opportunity for a convenient, divergent synthetic protocol. Given the demonstrated diversity, this methodology has potential advantages in the realm of discovery chemistry: The universal acetylpyridinium tungsten precursor can be economically prepared on large scale (10 g)^{17,32} and is air and water tolerant; the range of nucleophiles that can be selectively added to C2 include Grignards, organozincs, enolates, indoles, and pyrroles; and the amine addition can be carried out without the need of precious metals or advanced aryl halides, with complete control of the ring stereocenters. From pyridine borane, these compounds are available with *overall yields* ranging from 9% to 16% over 7 steps (71–77% per step). All additions are regio- and stereoselective (dr of isolated products >15:1), and single enantiomers of the ATHPs should be accessible based on the previously demonstrated enantioenrichment and stereochemical retention of {Wtp(NO)(PMe₃)},^{27,33} and its application toward pyridine-derived bicyclic amines.³⁴ Efforts to explore the full scope of this methodology, adjusting pyridine nitrogen, C2, C5, C6, and amine substituents, are currently underway.

EXPERIMENTAL SECTION

General Methods.

NMR spectra were obtained on a 600 or 800 MHz spectrometer. All chemical shifts are reported in ppm, and proton and carbon shifts are referenced to tetramethylsilane (TMS) utilizing residual ¹H or ¹³C signals of the deuterated solvents as an internal standard. Coupling constants (*J*) are reported in hertz (Hz). Infrared spectra (IR) were recorded as a

glaze on a spectrometer fitted with a horizontal attenuated total reflectance (HATR) accessory or on a diamond anvil ATR assembly. Unless otherwise noted, all synthetic reactions were performed in a glovebox under a dry nitrogen atmosphere. Deuterated solvents were used as received. BH ^1H NMR peaks (around 4–5 ppm) are not identified due to their quadrupole broadening; IR data are used to confirm the presence of a BH group (around 2500 cm^{-1}). Compounds **1–8** were previously reported.^{17–19}

All organic compounds were synthesized according to the general method presented for compound **25** unless otherwise specified. Compound **24** presents a method for the amine addition using an ammonium salt as opposed to a free amine.

Large-Scale Synthesis of WTP(NO)(PMe₃)(3,4- η^2 -*N*-acetylpyridinium)(OTf).

WTP(NO)(PMe₃)(3,4- η^2 -pyridinium)(OTf). (10.75 g, 14.68 mmol) and acetic anhydride (22.68 g, 0.2222 mol) were combined in a 100 mL flame-dried round-bottom flask containing a stir pea. MeCN (28 mL) and 2,6-di-*tert*-butylpyridine (3.52 g, 18.4 mmol) were added to the reaction mixture. The reaction was stirred for 90 min at room temperature and then placed in an oil bath heated at +55 °C for 5.5 h. After heating, the round-bottom flask containing the reaction mixture was removed from the oil bath and allowed to cool for 15 min. The reaction mixture was filtered through 1 cm Celite in a 15 mL medium porosity fritted funnel into stirring Et₂O (3.75 L) in a 4 L filter flask. The resulting suspension was stirred for several minutes and then stirring was discontinued. After allowing the precipitate to settle, the supernatant was decanted. The solid material was isolated on a 150 mL medium porosity fritted funnel, washed with Et₂O (3 × 100 mL), and desiccated under vacuum to yield a vivid orange solid (10.57 g, 93%). Characterization of this compound has been previously reported.¹⁷

Synthesis of WTP(NO)(PMe₃)(3,4- η^2 -ethyl 2-(1-acetyl-5-(methylamino)-1,2,5,6-tetrahydropyridin-2-yl)acetate) (**9**).

Compound **5** (360 mg, 0.418 mmol) and MeCN (4.0 mL) were combined in a test tube containing a stir pea. The solution was cooled in a cold bath at –40 °C for 15 min, and then a –30 °C solution of 2 M methylamine in THF (2.2 mL, 4.4 mmol) was added. The reaction mixture was stirred at –40 °C for 16 h, and then 1 M potassium *tert*-butoxide solution in *tert*-butanol was added (1.8 mL, 1.8 mmol). The reaction mixture was diluted with DCM (75 mL) and extracted with saturated aqueous sodium carbonate (100 mL). The organic layer was dried with sodium sulfate, filtered, and evaporated to dryness under vacuum. The residue was redissolved in DCM (4 mL) and added to stirring hexanes (100 mL). The precipitate was isolated on a 15 mL fine porosity fritted funnel, washed with hexanes (3 × 10 mL), and desiccated under vacuum to yield a tan solid (174 mg, 56% by mass). Two rotamers **A**:**B** = 4:1. Only **A** designated due to extensive overlap. ^1H NMR (CD₃CN, 600 MHz): δ_{H} 8.30 (d, 1H, $J = 2.0\text{ Hz}$), 8.00 (d, 1H, $J = 2.0\text{ Hz}$), 7.84 (d, 1H, $J = 2.0\text{ Hz}$), 7.83 (d, 1H, $J = 2.0\text{ Hz}$), 7.75 (d, 1H, $J = 2.0\text{ Hz}$), 7.36 (d, 1H, $J = 2.0\text{ Hz}$), 6.35 (t, 1H, $J = 2.0\text{ Hz}$), 6.29 (t, 1H, $J = 2.0\text{ Hz}$), 6.26 (t, 1H, $J = 2.0\text{ Hz}$), 5.72 (dd, 1H, $J = 7.5\text{ Hz}$, 6.8 Hz), 3.86 (m, 1H), 3.78 (m, 1H), 3.74 (dd, 1H, $J = 12.9\text{ Hz}$, 5.8 Hz), 3.64 (dd, 1H, $J = 6.1\text{ Hz}$, 5.8 Hz), 3.15 (dd, 1H, $J = 12.9\text{ Hz}$, 6.1 Hz), 3.04 (dd, 1H, $J = 13.8\text{ Hz}$, 6.8 Hz), 2.89 (dd, 1H, $J = 13.8\text{ Hz}$, 7.5 Hz), 2.54 (s, 3H), 2.49 (ddd, 1H, $J = 11.5\text{ Hz}$, 11.2 Hz, 2.2 Hz), 1.96 (s, 3H), 1.20 (d,

9H, $J = 8.4$ Hz), 0.91 (d, 1H, $J = 11.2$ Hz), 0.87 (t, 3H, $J = 7.1$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (CD_3CN , 200 MHz): δ_{C} 172.2, 170.3, 143.8, 142.9, 139.9, 136.4, 136.0, 135.8, 106.2, 106.0, 105.8, 59.8, 58.1, 54.6, 51.6, 47.3, 46.3, 44.6, 34.3, 22.8, 13.6, 13.3 (d, $J_{\text{PC}} = 27.6$ Hz). $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_3CN , 243 MHz): $\delta_{\text{P}} -11.83$ (d, $J_{\text{WP}} = 274$ Hz). Compound is too sensitive to elimination for EA/HRMS.

Synthesis of Ethyl 2-(1-Acetyl-5-(methylamino)-1,2,5,6-tetrahydropyridin-2-yl)acetate (**10**).

Step 1.—Compound **5** (180 mg, 0.209 mmol) and MeCN (2.0 mL) were combined in a test tube containing a stir pea. The solution was cooled in a cold bath at -40 °C for 15 min, and then a -30 °C solution of 2 M methylamine in THF (1.1 mL, 2.2 mmol) was added. The reaction mixture was stirred at -40 °C for 16 h, and then 1 M potassium *tert*-butoxide solution in *tert*-butanol was added (0.9 mL, 0.9 mmol). The reaction mixture was diluted with DCM (40 mL) and extracted with saturated aqueous sodium carbonate (100 mL). The organic layer was dried with sodium sulfate, filtered, and evaporated to dryness under vacuum. The residue was redissolved in DCM (2 mL) and added to stirring hexanes (50 mL). The precipitate was isolated on a 15 mL fine porosity fritted funnel, washed with hexanes (3×10 mL), and desiccated under vacuum to yield a tan solid, **9** (96 mg).

Step 2.—This solid (**9**) was dissolved in MeCN (2 mL) in a small test tube and cooled at -40 °C in a cold bath for 15 min. Separately, NOPF₆ (42 mg, 0.242 mmol) was dissolved in MeCN (2.0 mL). The NOPF₆ solution was added to the solution of the metal complex, and the reaction mixture was allowed to stir for 5 min. The reaction mixture was then removed from the glovebox, diluted with DCM (40 mL), and extracted with saturated sodium carbonate (15 mL). The aqueous layer was back extracted with DCM (20 mL). The combined organic layers were dried with sodium sulfate, filtered, and evaporated to dryness onto basic alumina. The product was purified by Combiflash flash chromatography on an 8 g of basic alumina column using a gradient elution of 0–100% EtOAc in hexanes. The fractions containing the product (~100% EtOAc) were evaporated to yield **10** as a colorless oil (10.0 mg, 20% over two steps). Two rotamers **A**:**B** = 5:2. ^1H NMR (CD_3CN , 800 MHz): δ_{H} **A** 5.81 (dd, 1H, $J = 10.3$ Hz, 1.5 Hz), 5.74 (ddd, 1H, $J = 10.3$ Hz, 3.8 Hz, 2.3 Hz), 5.02 (m, 1H), 4.07 (m, 2H), 3.89 (dd, 1H, $J = 13.3$ Hz, 5.4 Hz), 3.13 (m, 1H), 2.75 (dd, 1H, $J = 13.3$ Hz, 10.4 Hz), 2.49 (dd, 1H, $J = 14.2$ Hz, 6.4 Hz), 2.43 (dd, 1H, $J = 14.2$ Hz, 8.1 Hz), 2.39 (s, 3H), 2.04 (s, 3H), 1.21 (t, 3H, $J = 6.7$ Hz). **B** 5.81 (dd, 1H, $J = 10.3$ Hz, 1.5 Hz), 5.74 (m, 1H), 4.64 (dd, 1H, $J = 12.6$ Hz, 5.6 Hz), 4.59 (m, 1H), 4.10 (m, 2H), 2.99 (m, 1H), 2.62 (m, 2H), 2.38 (s, 3H), 2.29 (dd, 1H, $J = 12.6$ Hz, 10.2 Hz), 2.05 (s, 3H), 1.21 (t, 3H, $J = 6.2$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (CD_3CN , 200 MHz): δ_{C} **A** 171.7, 169.7, 131.5, 128.4, 61.3, 54.9, 48.2, 46.3, 38.5, 33.6, 22.0, 14.5. **B** 171.6, 169.7, 132.2, 128.2, 61.5, 54.1, 52.4, 40.6, 39.5, 33.7, 21.6, 14.5. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{12}\text{H}_{21}\text{N}_2\text{O}_3$ 241.1547; Found 241.1548.

Synthesis of 1-(6-Allyl-3-(methylamino)-3,6-dihydropyridin-1(2H)-yl)ethan-1-one (**12**).

Step 1.—Compound **6** (413 mg, 0.506 mmol) and MeCN (4.0 mL) were combined in a test tube containing a stir pea. The solution was cooled in a cold bath at -40 °C for 15 min, and then a -30 °C solution of 2 M methylamine in THF (2.5 mL, 5.0 mmol) was added. The reaction mixture was stirred at -40 °C for 16 h, and then 2 M sodium *tert*-butoxide solution

in THF was added (0.7 mL, 1.4 mmol). The reaction mixture was diluted with DCM (75 mL) and extracted with saturated aqueous sodium carbonate (50 mL). The organic layer was dried with sodium sulfate, filtered, and evaporated to dryness under vacuum. The residue was redissolved in 50:50 DCM/EtOAc (6 mL) and added to stirring hexanes (100 mL). The precipitate was isolated on a 15 mL fine porosity fritted funnel, washed with hexanes (3 × 10 mL), and desiccated under vacuum to yield a tan solid, **11** (283 mg, 80%).

Step 2.—The solid **11** (283 mg, 0.406 mmol) was dissolved in MeCN (2 mL) in a small test tube and cooled at −40 °C in a cold bath for 15 min. Separately, DDQ (89.5 mg, 0.394 mmol) was dissolved in MeCN (2.0 mL). HOTf (177.5 mg, 1.18 mmol) was added to the DDQ solution. The DDQ/HOTf solution was cooled at −40 °C in a cold bath for 10 min, and then this solution was added to the solution of **11**. The reaction mixture was allowed to stir for 5 min. The reaction mixture was then removed from the glovebox, diluted with DCM (50 mL), and extracted with saturated sodium carbonate (25 mL). The aqueous layer was back extracted with DCM (2 × 15 mL). The combined organic layers were dried with sodium sulfate, filtered, and evaporated to dryness onto basic alumina. The product was purified by Combiflash flash chromatography on an 8 g basic alumina column using a gradient elution of 0–100% EtOAc in hexanes. The fractions containing the product (~100% EtOAc) were evaporated to yield **25** as a colorless oil (21.6 mg, 22% over two steps). Two rotamers **A**:**B** = 3:2. ¹H NMR (CD₃CN, 800 MHz): δ_H **A** 5.82 (m, 1H), 5.79 (m, 1H), 5.74 (ddd, 1H, *J* = 10.3 Hz, 4.5 Hz, 2.0 Hz), 5.04 (m, 2H), 4.90 (m, 1H), 3.88 (dd, 1H, *J* = 13.2 Hz, 5.5 Hz), 3.16 (m, 1H), 2.85 (dd, 1H, *J* = 13.2 Hz, 10.5 Hz), 2.51 (s, 3H), 2.33 (m, 2H), 2.12 (s, 3H). **B** 5.82 (m, 1H), 5.79 (m, 1H), 5.73 (ddd, 1H, *J* = 10.3 Hz, 4.0 Hz, 2.5 Hz), 5.12 (m, 2H), 4.88 (dd, 1H, *J* = 13.2 Hz, 5.8 Hz), 4.14 (m, 1H), 3.16 (m, 1H), 2.51 (s, 3H), 2.38 (buried, 1H), 2.33 (m, 2H), 2.10 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 200 MHz): δ_C **A** 169.0, 134.6, 129.6, 128.6, 117.6, 54.1, 50.1, 46.0, 37.8, 33.5, 22.1. **B** 169.3, 133.6, 130.5, 128.1, 118.8, 54.8, 53.3, 40.1, 38.8, 33.6, 21.8. HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₁₁H₁₉N₂O 195.1492; Found 195.1491.

Synthesis of WTP(NO)(PMe)(3,4- η^2 3-ethyl 2-(1-acetyl-5-(1*H*-imidazol-1-yl)-1,2,5,6-tetrahydropyridin-2-yl)acetate (18**).**

Compound **5** (365 mg, 0.423 mmol) and MeCN (7.0 g) were combined in a test tube containing a stir pea. The solution was cooled in a cold bath at −40 °C for 15 min, and then imidazole (400 mg, 5.88 mmol) was added. The reaction mixture was stirred at −40 °C for 16 h, and then 2 M sodium *tert*-butoxide solution in THF was added (0.9 mL, 1.8 mmol). The reaction mixture was diluted with DCM (60 mL) and extracted with saturated aqueous sodium carbonate (3 × 75 mL). The aqueous layer was back-extracted with DCM (15 mL). The combined organic layers were dried with sodium sulfate, filtered, and evaporated to ~1 mL volume under vacuum. The concentrate was diluted with EtOAc (4 mL) and added to stirring hexanes (125 mL). The precipitate was isolated on a 15 mL fine porosity fritted funnel, washed with hexanes (3 × 10 mL), and desiccated under vacuum to yield a pale tan solid, **18** (250 mg, 73% by mass). Two rotamers **A**:**B** = 6:1. Only **A** assigned due to extensive overlap. ¹H NMR (CD₃CN): δ_H 8.60 (d, 1H, *J* = 2.0 Hz), 7.99 (d, 1H, *J* = 2.0 Hz), 7.96 (t, 1H, *J* = 1.5 Hz), 7.85 (d, 1H, *J* = 2.0 Hz), 7.83 (d, 1H, *J* = 2.0 Hz), 7.79 (d, 1H, *J* = 2.0 Hz), 7.55 (t, 1H, *J* = 1.5 Hz), 7.31 (d, 1H, *J* = 2.0 Hz), 7.08 (t, 1H, *J* = 1.5 Hz), 6.35 (t,

1H, $J = 2.0$ Hz), 6.32 (t, 1H, $J = 2.0$ Hz), 6.26 (t, 1H, $J = 2.0$ Hz), 6.04 (dd, 1H, $J = 7.8$ Hz, 6.8 Hz), 5.53 (dd, 1H, $J = 9.9$ Hz, 6.4 Hz), 3.83–3.79 (m, 2H), 3.83 (buried, 1H), 3.25 (dd, 1H, $J = 13.7$ Hz, 9.9 Hz), 2.89 (ddd, 1H, $J = 13.7$ Hz, 11.2 Hz, 2.7 Hz), 2.81 (dd, 1H, $J = 13.6$ Hz, 6.8 Hz), 2.59 (dd, 1H, $J = 13.8$ Hz, 7.8 Hz), 2.02 (s, 3H), 0.91 (buried, 1H), 0.90 (d, 9H, $J = 8.4$ Hz), 0.86 (t, 3H, $J = 7.1$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (CD_3CN , 200 MHz): δ_{C} 172.2, 170.3, 144.8, 144.0, 141.4, 137.8, 137.7, 137.6, 137.6, 130.1, 119.2, 107.6, 107.3, 107.0, 60.7, 55.8, 55.6, 48.3, 48.1, 47.6, 44.8, 23.4, 14.2, 13.5 (d, $J_{\text{W,P}} = 28.5$ Hz). $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_3CN , 243 MHz): $\delta_{\text{P}} -11.35$ (d, $J_{\text{W,P}} = 275$ Hz). Compound is too sensitive to elimination for EA/HRMS.

Synthesis of 1-(6-Allyl-3-morpholino-3,6-dihydropyridin-1(2H)-yl)ethan-1-one (19).

Yield: 17 mg (23% over two steps), as a colorless oil. Two rotamers **A**:**B** = 5:4. ^1H NMR (CDCl_3 , 800 MHz): δ_{H} **A** 5.86 (m, 2H), 5.81 (m, 1H), 5.05 (m, 2H), 4.91 (m, 1H), 3.73 (dd, 1H, $J = 12.8$ Hz, 5.0 Hz), 3.71 (m, 4H), 3.20 (m, 1H), 3.16 (m, 1H), 2.65 (m, 4H), 2.35–2.32 (m, 2H), 2.11 (s, 3H). **B** 5.86 (m, 2H), 5.81 (m, 1H), 5.13–5.11 (m, 2H), 4.75 (dd, 1H, $J = 12.5$ Hz, 5.5 Hz), 4.12 (m, 1H), 3.71 (m, 4H), 3.20 (m, 1H), 2.65 (m, 4H), 2.64 (buried, 1H), 2.35–2.32 (m, 2H), 2.10 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 200 MHz): δ_{C} **A** 169.2, 134.5, 130.9, 126.9, 117.6, 67.5, 59.0, 49.9, 49.3, 41.1, 37.9, 22.1. **B** 169.5, 133.6, 129.7, 129.4, 118.9, 67.5, 58.0, 54.7, 49.3, 38.8, 34.8, 21.8. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{14}\text{H}_{23}\text{N}_2\text{O}_2$ 251.1754; Found 251.1755.

Synthesis of Ethyl 2-(1-Acetyl-5-morpholino-1,2,5,6-tetrahydropyridin-2-yl)acetate (20).

Yield: 13.1 mg (20% over two steps), as a colorless oil. Two rotamers **A**:**B** = 2:1. ^1H NMR (CD_3CN , 800 MHz): δ_{H} **A** 5.88 (m, 1H), 5.84 (m, 1H), 5.03 (m, 1H), 4.09–4.05 (m, 2H), 3.76 (dd, 1H, $J = 13.6$ Hz, 5.6 Hz), 3.62–3.58 (m, 4H), 3.27 (m, 1H), 3.10 (dd, 1H, $J = 13.6$ Hz, 10.8 Hz), 2.61 (m, 4H), 2.47 (m, 2H), 2.04 (s, 3H), 1.21 (t, 3H, $J = 6.7$ Hz). **B** 5.88 (m, 1H), 5.84 (m, 1H), 4.60 (m, 1H), 4.52 (dd, 1H, $J = 12.5$ Hz, 5.6 Hz), 4.13–4.08 (m, 2H), 3.62–3.58 (m, 4H), 3.11 (m, 1H), 2.64–2.58 (m, 4H), 2.61 (buried, 1H), 2.60 (buried, 2H), 2.06 (s, 3H), 1.21 (t, 3H, $J = 6.7$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (CD_3CN , 200 MHz): δ_{C} **A** 171.6, 170.0, 130.2, 129.7, 68.0, 61.3, 59.4, 49.9, 48.1, 41.3, 38.4, 22.0, 14.5. **B** 171.6, 169.9, 130.6, 130.1, 68.0, 61.6, 58.7, 52.4, 49.9, 39.4, 35.6, 21.6, 14.5. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{15}\text{H}_{25}\text{N}_2\text{O}_4$ 297.1809; Found 297.1808.

Synthesis of Ethyl 2-(1-Acetyl-5-(prop-2-yn-1-ylamino)-1,2,5,6-tetrahydropyridin-2-yl)acetate (21).

Yield: 15 mg (26% over two steps), as a colorless oil. Two rotamers **A**:**B** = 7:3. ^1H NMR (CD_3CN , 800 MHz): δ_{H} **A** 5.80 (m, 1H), 5.76 (m, 1H), 5.01 (m, 1H), 4.10–4.05 (m, 2H), 3.95 (dd, 1H, $J = 13.6$ Hz, 5.5 Hz), 3.47 (s, 2H), 3.40 (m, 1H), 2.77 (dd, 1H, $J = 13.6$ Hz, 10.4 Hz), 2.49 (dd, 1H, $J = 14.2$ Hz, 6.1 Hz), 2.46 (t, 1H, $J = 2.4$ Hz), 2.44 (dd, 1H, $J = 14.2$ Hz, 8.1 Hz), 2.04 (s, 3H), 1.21 (t, 3H, $J = 7.2$ Hz). **B** 5.80 (m, 1H), 5.76 (m, 1H, H3), 4.67 (dd, 1H, $J = 12.7$ Hz, 5.6 Hz), 4.60 (m, 1H), 4.15–4.10 (m, 2H), 3.45 (m, 2H), 3.27 (m, 1H), 2.62 (m, 2H), 2.43 (t, 1H, $J = 2.6$ Hz), 2.32 (dd, 1H, $J = 12.7$ Hz, 10.4 Hz), 2.06 (s, 3H), 1.22 (t, 3H, $J = 7.1$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (CD_3CN , 200 MHz): δ_{C} **A** 171.6, 169.7, 131.3, 128.7, 83.4, 72.6, 61.3, 52.5, 48.1, 46.4, 38.4, 22.0, 14.5. **B** 171.6, 169.8, 131.7, 128.6, 83.4, 72.4,

61.6, 52.3, 51.5, 40.7, 39.4, 21.6, 14.5. HRMS (ESI-TOF) m/z : $[M + H]^+$ Calcd for $C_{14}H_{21}N_2O_3$ 265.1547; Found 265.1548.

Synthesis of Ethyl 2-(1-Acetyl-5-((4-bromobenzyl)amino)-1,2,5,6-tetrahydropyridin-2-yl)acetate (22).

Yield: 14 mg (17% over two steps), as a near-colorless oil. Two rotamers **A**:**B** = 7:3. 1H NMR (CD_3CN , 800 MHz): δ_H **A** 7.48 (m, 2H), 7.29 (m, 2H), 5.83 (m, 1H), 5.75 (m, 1H), 5.00 (m, 1H), 4.07 (m, 2H), 3.86 (dd, 1H, J = 13.5 Hz, 5.5 Hz), 3.84 (d, 1H, J = 13.7 Hz), 3.80 (d, 1H, J = 13.7 Hz), 3.25 (m, 1H), 2.79 (dd, 1H, J = 13.5 Hz, 10.4 Hz), 2.49 (dd, 1H, J = 14.3 Hz, 6.4 Hz), 2.43 (dd, 1H, J = 14.3 Hz, 8.1 Hz), 1.99 (s, 3H), 1.20 (t, 3H, J = 7.2 Hz). **B** 7.48 (m, 2H), 7.29 (m, 2H), 5.85 (m, 1H), 5.76 (m, 1H), 4.65 (dd, 1H, J = 12.5 Hz, 5.7 Hz), 4.59 (m, 1H), 4.11 (m, 2H), 3.80 (s, 2H), 3.11 (m, 1H), 2.62 (m, 2H), 2.35 (dd, 1H, J = 12.5 Hz, 10.4 Hz), 2.04 (s, 3H), 1.21 (t, 3H, J = 7.3 Hz). $^{13}C\{^1H\}$ NMR (CD_3CN , 200 MHz): δ_C **A** 171.6, 169.8, 141.6, 132.2, 131.7, 131.1, 128.6, 120.9, 61.3, 53.0, 50.6, 48.2, 46.6, 38.4, 22.0, 14.5. **B** 171.6, 169.7, 141.5, 132.2, 132.1, 131.1, 128.5, 120.9, 61.6, 52.3, 52.0, 50.4, 40.9, 39.4, 21.5, 14.5. HRMS (ESI-TOF) m/z : $[M + H]^+$ Calcd for $C_{18}H_{24}BrN_2O_3$ 395.0965; Found 395.0967.

Synthesis of 1-(3-((4-Chlorobenzyl)amino)-6-ethyl-3,6-dihydropyridin-1(2H)-yl)ethan-1-one (23).

Yield: 32 mg (22% over two steps), as a colorless oil. Two rotamers **A**:**B** = 5:4. 1H NMR ($CDCl_3$, 800 MHz): δ_H **A** 7.48 (m, 4H), 5.79 (m, 1H), 5.76 (m, 1H), 4.75 (m, 1H), 3.84 (m, 2H), 3.80 (dd, 1H, J = 13.3 Hz, 5.4 Hz), 3.27 (m, 1H), 2.83 (dd, 1H, J = 13.3 Hz, 10.5 Hz), 2.06 (s, 3H), 1.56 (m, 2H), 0.92 (t, 3H, J = 7.5 Hz). **B** 7.48 (m, 4H), 5.79 (m, 1H), 5.76 (m, 1H), 4.89 (dd, 1H, J = 12.4 Hz, 5.5 Hz), 3.98 (m, 1H), 3.85 (m, 2H), 3.27 (m, 1H), 2.37 (dd, 1H, J = 12.4 Hz, 10.5 Hz), 2.08 (s, 3H), 1.66 (m, 2H), 0.98 (t, 3H, J = 7.5 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 200 MHz): δ_C **A** 170.0, 138.6, 133.2, 130.3, 129.6, 128.9, 128.6, 52.4, 51.6, 50.5, 46.4, 27.4, 22.0, 10.8. **B** 169.3, 138.6, 133.0, 130.5, 129.7, 128.8, 128.6, 56.1, 51.5, 50.4, 40.6, 26.3, 21.6, 11.0. HRMS (ESI-TOF) m/z : $[M + H]^+$ Calcd for $C_{16}H_{22}ClN_2O$ 293.1415; Found 293.1415.

Synthesis of Methyl 1-(1-Acetyl-6-(2-ethoxy-2-oxoethyl)-1,2,3,6-tetrahydropyridin-3-yl)azetidine-3-carboxylate (24).

Step 1.—Compound **5** (370 mg, 0.429 mmol) and MeCN (4.0 mL) were combined in a test tube containing a stir pea. In a separate test tube, 3-(methoxycarbonyl)azetidin-1-ium chloride (325 mg, 2.15 mmol) was dissolved in MeCN (2.0 mL). Both solutions were cooled in a cold bath at $-40^\circ C$ for 10 min, and then a 2 M solution of LDA in THF (1.0 mL, 2.0 mmol) was added dropwise to the 3-(methoxycarbonyl)azetidin-1-ium chloride solution. After a few seconds, a white solid (LiCl) precipitated. After 5 min of stirring at $-40^\circ C$, the basified amine solution was added to the solution of compound **5**. The reaction mixture was stirred at $-40^\circ C$ for 12 h, and then 2 M sodium *tert*-butoxide THF solution was added (0.9 mL, 1.8 mmol). The reaction mixture was diluted with DCM (50 mL) and extracted with saturated aqueous sodium carbonate (2×100 mL). The aqueous layer was back-extracted with DCM (15 mL). The combined organic layers were dried with sodium sulfate, filtered,

and evaporated to dryness under vacuum. The residue was redissolved in EtOAc (4 mL) and added to stirring hexanes (150 mL). The precipitate was isolated on a 15 mL fine porosity fritted funnel, washed with hexanes (3 × 10 mL), and desiccated under vacuum to yield a tan solid, **17** (274 mg, 77% by mass with 5% elimination product).

Step 2.—The solid **17** from step 1 (265 mg, 0.320 mmol) was dissolved in a mixture of MeCN (6.0 mL) and DCM (4.0 mL) in a small test tube and cooled at –40 °C in a cold bath for 15 min. Separately, DDQ (72 mg, 0.317 mmol) was dissolved in MeCN (2.0 mL). HOTf (161 mg, 1.07 mmol) was added to the DDQ solution, and the resulting mixture was cooled to –40 °C for 10 min. The DDQ solution was then added to the solution of the metal complex, and the reaction mixture was allowed to stir for 1 min. The reaction mixture was then removed from the glovebox, diluted with DCM (50 mL), and extracted with saturated sodium carbonate (60 mL). The aqueous layer was back extracted with DCM (20 mL). The combined organic layers were dried with sodium sulfate, filtered, and evaporated to dryness onto basic alumina. The product was purified by Combiflash flash chromatography on an 8 g basic alumina column using a gradient elution of 0–100% EtOAc in hexanes. The fractions containing the product (~80% EtOAc) were evaporated to yield **24**. Yield: 49 mg (36% over two steps), as a near colorless oil. Two rotamers **A**:**B** = 5:3. ¹H NMR (CD₂Cl₂, 800 MHz): δ_H **A** 5.84 (ddd, 1H, *J* = 10.3 Hz, 3.8 Hz, 2.1 Hz), 5.72 (m, 1H), 5.07 (m, 1H), 4.09 (m, 2H), 3.69 (s, 3H), 3.66 (dd, 1H, *J* = 13.3 Hz, 5.5 Hz), 3.56 (m, 2H), 3.42 (m, 2H), 3.31 (m, 1H), 2.93 (m, 1H), 2.76 (dd, 1H, *J* = 13.3 Hz, 10.4 Hz), 2.52 (dd, 1H, *J* = 14.6 Hz, 6.2 Hz), 2.43 (dd, 1H, *J* = 14.2 Hz, 8.2 Hz), 2.06 (s, 3H), 1.23 (t, 3H, *J* = 7.2 Hz). **B** 5.79 (ddd, 1H, *J* = 10.3 Hz, 3.9 Hz, 2.0 Hz), 5.72 (m, 1H), 4.58 (m, 1H), 4.57 (dd, 1H, *J* = 12.7 Hz, 5.5 Hz), 4.13 (m, 2H), 3.69 (s, 3H), 3.56 (m, 1H), 3.50 (m, 1H), 3.44 (m, 1H), 3.40 (m, 1H), 3.29 (m, 1H), 2.87 (m, 1H), 2.60 (m, 2H), 2.28 (dd, 1H, *J* = 12.7 Hz, 10.3 Hz), 2.09 (s, 3H), 1.24 (t, 3H, *J* = 7.2 Hz). ¹³C{¹H} NMR (CD₂Cl₂, 200 MHz): δ_C **A** 173.7, 171.1, 169.2, 129.4, 125.8, 61.4, 60.9, 55.1, 54.9, 52.4, 47.8, 43.9, 39.3, 34.6, 21.7, 14.5. **B** 173.8, 171.0, 169.5, 128.4, 127.3, 61.4, 60.3, 55.4, 55.0, 52.4, 51.8, 39.3, 38.1, 34.6, 21.7, 14.5. HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₁₆H₂₅N₂O₅ 325.1758; Found 325.1758.

Synthesis of Ethyl 2-(1-Acetyl-5-(1*H*-imidazol-1-yl)-1,2,5,6-tetrahydropyridin-2-yl)acetate (**25**).

Step 1.—Compound **5** (365 mg, 0.423 mmol) and MeCN (7.00 g) were combined in a test tube containing a stir pea. The solution was cooled in a cold bath at –40 °C for 10 min, and then imidazole (400 mg, 5.88 mmol) was added. The reaction mixture was stirred at –40 °C for 16 h, and then 2 M sodium *tert*-butoxide THF solution was added (0.9 mL, 1.8 mmol). The reaction mixture was diluted with DCM (50 mL) and extracted with saturated aqueous sodium carbonate (3 × 75 mL). The aqueous layer was back-extracted with DCM (15 mL). The combined organic layers were dried with sodium sulfate, filtered, and evaporated to dryness under vacuum. The residue was redissolved in EtOAc (3 mL) and added to stirring hexanes (125 mL). The precipitate was isolated on a 15 mL fine porosity fritted funnel, washed with hexanes (3 × 10 mL), and desiccated under vacuum to yield a tan solid, **18** (250 mg, 73%).

Step 2.—The solid **18** from step 1 (240 mg, 0.308 mmol) was dissolved in MeCN (4.0 mL) in a small test tube and cooled at -40°C in a cold bath for 15 min. Separately, DDQ (71 mg, 0.313 mmol) was dissolved in MeCN (1.0 mL). HOTf (141 mg, 0.940 mmol) was added to the DDQ solution, and the resulting mixture was cooled to -40°C for 10 min. The DDQ solution was then added to the solution of **18**, and the reaction mixture was allowed to stir for 1 min. The reaction mixture was then removed from the glovebox, diluted with DCM (50 mL), and extracted with saturated sodium carbonate (60 mL). The aqueous layer was back extracted with DCM (20 mL). The combined organic layers were dried with sodium sulfate, filtered, and evaporated to dryness onto basic alumina. The product was purified by Combiflash flash chromatography on an 8 g basic alumina column using a gradient elution of 0–100% EtOAc in hexanes followed by a gradient of 0–15% MeOH in DCM. The fractions containing the product (~15% MeOH in DCM) were evaporated to yield **25**. Yield: 57 mg (48% over two steps), as a near colorless oil. Two rotamers **A**:**B** = 1:1. ^1H NMR (CDCl_3 , 800 MHz): δ_{H} **A** 7.76 (s, 1H, H13), 7.01 (s, 1H, H11), 6.96 (s, 1H, H12), 6.11 (ddd, 1H, $J = 10.2$ Hz, 4.0 Hz, 2.6 Hz, H3), 5.86 (d, 1H, $J = 10.2$ Hz, H3), 5.21 (m, 1H, H2), 4.86 (m, 1H, H5), 4.13 (m, 2H, H9), 4.04 (dd, 1H, $J = 13.2$ Hz, 5.7 Hz, H6), 3.31 (dd, 1H, $J = 13.2$ Hz, 10.7 Hz, H6'), 2.62 (m, 2H, H8), 2.14 (s, 3H, H7), 1.22 (t, 3H, $J = 7.2$ Hz, H10). **B** 7.61 (s, 1H, H13), 7.01 (s, 1H, H11), 6.93 (s, 1H, H12), 6.06 (ddd, 1H, $J = 10.2$ Hz, 4.0 Hz, 2.6 Hz, H3), 5.93 (d, 1H, $J = 10.2$ Hz, H3), 4.91 (dd, 1H, $J = 12.9$ Hz, 5.8 Hz, H6), 4.77 (m, 1H, H5), 4.72 (m, 1H, H2), 4.13 (m, 2H, H9), 2.69 (buried, 1H, H6'), 2.69 (m, 2H, H8), 2.18 (s, 3H, H7), 1.24 (t, 3H, $J = 7.2$ Hz, H10). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 200 MHz): δ_{C} **A** 170.4 (Ester CO), 169.0 (Amide CO), 136.1 (C13), 131.8 (C3), 129.2 (C11), 125.8 (C4), 117.2 (C12), 60.9 (C9), 51.8 (C5), 46.9 (C2), 46.9 (C6), 37.1 (C8), 21.8 (C7), 14.2 (C10). **B** 170.0 (Ester CO), 169.7 (Amide CO), 135.9 (C13), 131.1 (C3), 129.3 (C11), 127.6 (C4), 117.4 (C12), 61.3 (C9), 51.0 (C2), 50.8 (C5), 41.2 (C6), 38.4 (C8), 21.2 (C7), 14.1 (C10). HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{14}\text{H}_{20}\text{N}_3\text{O}_3$ 278.1499; Found 278.1500.

Synthesis of 1-Acetyl-5-(piperidin-1-yl)-*N*-tosyl-1,2,5,6-tetrahydropyridine-2-carboxamide (28).

Yield: 8 mg (16% over two steps), as a near colorless solid. Two rotamers **A**:**B** = 7:1. ^1H NMR (CD_3CN containing 10 wt % TFA, 800 MHz): δ_{H} **A** 7.84 (m, 2H, H8), 7.40 (m, 2H, H9), 6.24 (dd, 1H, $J = 10.1$ Hz, 4.6 Hz, H3), 6.16 (ddd, 1H, $J = 10.1$ Hz, 4.5 Hz, 1.6 Hz, H4), 4.88 (dt, 1H, $J = 4.6$ Hz, 1.6 Hz, H2), 3.94 (m, 1H, H5), 3.82 (dd, 1H, $J = 14.0$ Hz, 6.0 Hz, H6), 3.72 (dd, 1H, $J = 14.0$ Hz, 3.7 Hz, H6'), 3.46 (d, 1H, $J = 12.1$ Hz, H11), 3.09 (d, 1H, $J = 12.1$ Hz, H11), 2.95 (m, 1H, H11), 2.86 (m, 1H, H11), 2.42 (s, 3H, H10), 2.10 (s, 3H, H7), 1.92 (d, 1H, $J = 14.9$ Hz, H12), 1.82 (d, 1H, $J = 14.9$ Hz, H12), 1.75–1.72 (m, 2H, H12), 1.54 (m, 1H, H13), 1.41 (m, 1H, H13). **B** extensively buried; not characterized. $^{13}\text{C}\{^1\text{H}\}$ NMR (CD_3CN containing 10 wt % TFA, 200 MHz): δ_{C} **A** 172.5 (Acetyl CO), 169.8 (Amide CO), 146.6 (C9a), 136.1 (C8a), 130.5 (C9), 129.6 (C3), 128.9 (C8), 125.2 (C4), 59.0 (C5), 57.0 (C2), 52.0 (C11), 52.0 (C11'), 42.2 (C6), 24.2 (C12), 24.1 (C12'), 21.9 (C10), 21.9 (C13), 21.6 (C7). HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{20}\text{H}_{28}\text{N}_3\text{O}_4\text{S}$ 406.1795; Found 406.1790.

Supplementary Material

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Routes to 3-aminopiperidines *From hydroxy- or aminopyridine* *Proposed general route*

Figure 1.
Approaches to the synthesis of 3-piperidinamines.

Figure 2.
Range of amine organics produced by tungsten-mediated amination of pyridine (yield over 2 steps).

Scheme 1. Synthesis of Dihydropyridine Complexes $[W] = \text{WTp}(\text{NO})(\text{PMe}_3)$

Scheme 2.

Synthesis of Allyl Complexes 5–8 via Protonation with Triflic Acid; [W] = WTp(NO) (PMe₃); SC-XRD-Derived Molecular Structures of 2 and η^2 -Allyl Complex 7 (7·1/2 HOTf·1/2CH₃CN)^{19a}

^aTriflate anions and some hydrogens removed for clarity.

Scheme 3.

Reversible Addition of an Amine to a Tungsten Allyl Complex and Irreversible Elimination upon Warming

Scheme 4.

Synthesis of 3-Amino-1,2,3,6-tetrahydropyridine (3-ATHP) 10 from Methylamine and 5
Followed by Oxidative Decomplexation with DDQ

Scheme 5.

An Aminotetrahydropyridine Prepared as an Acylsulfonamide Derivative