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Route to Highly Substituted Pyridines

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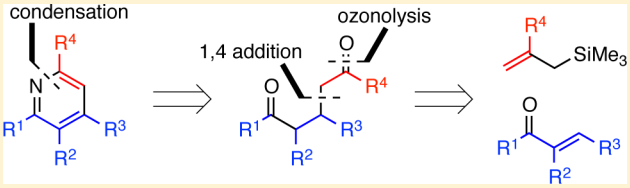
Supporting Information

ABSTRACT: Pyridine rings are common structural motifs found in a number of biologically active compounds, including some top-selling pharmaceuticals. We have developed a new approach to access substituted pyridines. The method aims to provide a reliable synthesis of a diverse range of substituted pyridines through a three-step procedure. Readily available enones are first converted into 1,5-dicarbonyls through a two-step Hosomi–Sakurai allylation/oxidative cleavage sequence, which is followed by subsequent cyclization to the corresponding pyridine using hydroxylamine hydrochloride. A variety of substituted pyridines have been synthesized using this method.



INTRODUCTION

Pyridines and pyridine rings fused to other heterocycles are very commonly found in pharmaceutical lead compounds and are well represented in clinically approved pharmaceuticals.[1] These compounds have drawn inspiration from naturally occurring pyridine-containing molecules, including vitamins B_3 and B_6, as well as NADP and nicotine.[2] Pyridine rings are also excellent ligands for first-row transition metals,[3] forming reactive complexes capable of unique transformations.[4] For many applications in this area, multiple pyridine rings are preferred because they act as polydentate ligands.[5] The synthesis of substituted pyridines is usually approached in one of two ways: (1) site-specific functionalization of an existing pyridine[6] or (2) construction of the pyridine ring from functionalized precursors. The latter strategy has been an area of study for over a century,[7] exemplified by a few classic named reactions.[8] Several examples are illustrated in Figure 1. In an approach related to Kröhnke's method, researchers have utilized a Michael addition of a ketone equivalent to an enone to generate 1,5-diketones, which are subsequently cyclized to pyridines with substitution at both the 2- and 6-positions.[9] Accessing pyridines without 6-substitution can be difficult using these methods. More recently, routes based on modern transition-metal catalysis have gained popularity, utilizing a variety of transition metals including Ti,[10] Mn,[11] Ni,[12] Cu,[13] Zr,[14] Ru,[15] Rh,[16] and Pd.[17] Although many of the recently published methods for synthesizing pyridines are high yielding, most require the use of expensive reagents and catalysts. In addition, the synthesis of starting materials required for some of these transformations are often lower yielding than the methods themselves. With many options to choose from, the availability and cost of starting materials and reagents needed for a method are often taken into consideration. When faced with an apparent simple problem in pyridine ring construction from readily available starting materials, we were dismayed to find that neither the classic condensation routes,[8a,b] a more modern hetero Diels–Alder approach,[18] nor the recent organometallic methods were effective or applicable.[10−17] We developed an alternative route from several stalwart reactions that allowed us to construct the requisite pyridine target and report a brief exploration of the scope of the method herein.

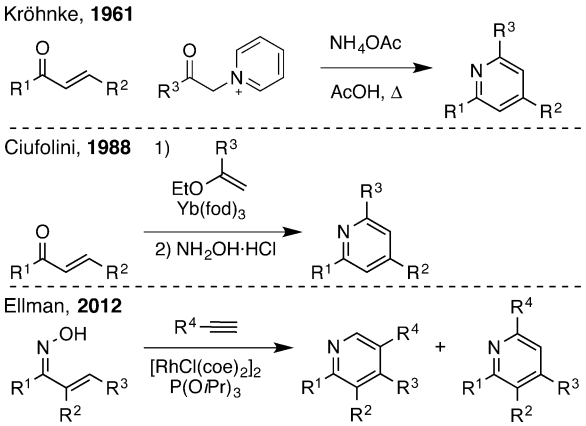


Figure 1. Common approaches to pyridine ring construction.

The method utilizes robust chemistry to provide a simple, yet reliable way of accessing substituted pyridines from starting materials that are easily synthesized or are commercially available. The general approach is outlined in Figure 2. Condensation of a functionalized 1,5-dicarbonyl would provide pyridines using well-established cyclization chemistry.[19] The dicarbonyl intermediate could be accessed from enones, an easily accessible motif commonly synthesized in high yield through a variety of methods including aldol condensations and HWE olefinations.[20] In order to introduce the two-carbon unit needed, we envisioned a two-step procedure, by first

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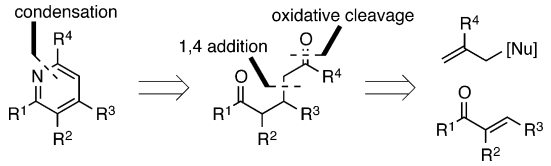


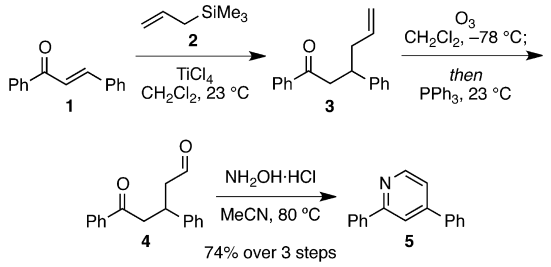
Figure 2. Retrosynthesis approach to pyridines with enone and allyl nucleophile components.

introducing an allylic nucleophile to the Michael acceptor, followed by oxidative cleavage of the resulting olefin.

RESULTS AND DISCUSSION

Initial studies focused on a general procedure for converting enones (chalcone derivatives) to the desired pyridines, Scheme 1. Optimization of the sequence was accomplished using

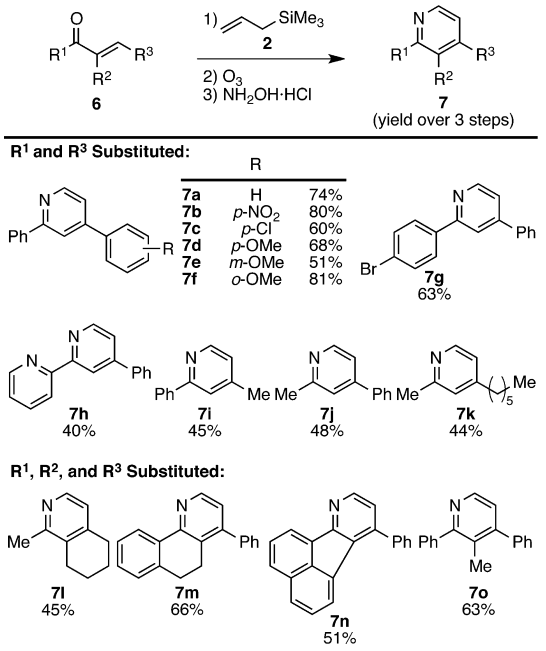
Scheme 1. Optimized Synthetic Route to a Pyridine Ring Using Chalcone and Allyltrimethylsilane



chalcone (**1**) as the enone precursor. The conjugate addition was achieved by reacting enone **1** with commercially available allyltrimethylsilane (**2**) under Hosomi–Sakurai reaction conditions.[21] A variety of Lewis acids and additives can be used to effect this transformation,[22] but $TiCl_4$ was found to work best for most of the substrates tested in the course of our investigation. Oxidation of olefin **3** was carried out using ozonolysis.[23] Other oxidations were also competent in this sequence, including Johnson–Lemieux conditions,[24] but the ozonolysis procedure provided the desired crude aldehyde **4** with good purity and minimal side products. Finally, the cyclization of aldehyde **4** was carried out using hydroxylamine hydrochloride at elevated temperatures to provide pyridine **5** in modest to high yields. Several solvents were investigated for the cyclization, and acetonitrile was found to be superior to alcohol solvents with respect to scope and yield. The synthesis uses two purifications by column chromatography, one after oxidation of the olefin and another following the cyclization. In many cases, the first purification can be omitted.

With an optimized procedure in hand, the substrate scope was explored. Sakurai reactions using allyltrimethylsilane (**2**) were the primary focus, yielding pyridines without substitution at the 5 and 6 positions (Table 1). Reactions using aryl–aryl-disubstituted enones provided 2,4-substituted pyridines (**7a–g**) in 60–80% yield. The three-step sequence was tolerant of a variety of substitution patterns and substituents, including electron-donating and -withdrawing groups. More notably, halogenated aromatic systems could be used (**7c,g**) without concern of loss of the halogen, since no oxidative addition steps with transition metals are used in the sequence. These substrates also provide a handle for further functionalization using traditional cross-coupling reactions. The 2,2′-bipyridines (**7h**), as well as alkyl-substituted pyridines (**7i–k**), can also be

Table 1. Scope of 2,4- and 2,3,4-Substituted Pyridines

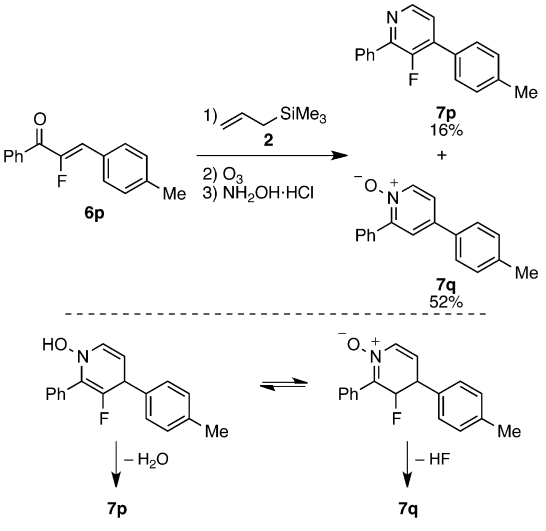


synthesized using the same three-step procedure, albeit in slightly diminished yields.

Substitution at the 3-position of the pyridine can be introduced with the use of α-substituted enones. This modification allows for the synthesis of polycyclic pyridines, as demonstrated by **7l–n**, as well as 2,3,4-trisubstituted pyridines **7o**. The method can be used with a variety of simple substituents to produce disubstituted and trisubstituted pyridine rings.

Using the method to introduce a fluorine atom on the pyridine ring[25] led to an unexpected result, Scheme 2. Fluoroenone **6p** reacted with allylsilane as expected to give the alkene. Ozonolysis produced the aldehyde in good yield, but treatment with hydroxylamine hydrochloride went astray. The expected 3-fluoropyridine **7p** was produced, but as the minor component of the product mixture. The major product

Scheme 2. Competitive Elimination for Fluorine in the Aromatization Step



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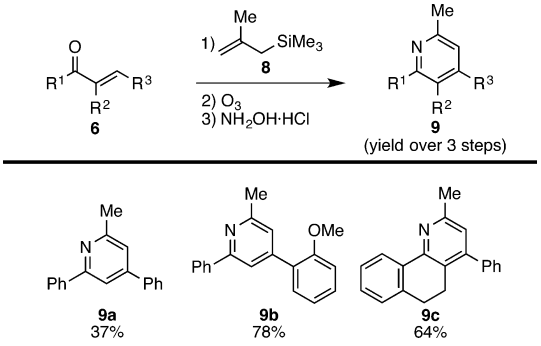
was identified as the pyridine *N*-oxide **7q**, which was isolated in 52% yield. One can envision intermediates that would either eliminate water to give **7p**, the normal course of the reaction, or eliminate HF to give the *N*-oxide **7q**. Both pathways are competitive with fluorine; presumably, better leaving groups would lead entirely to the *N*-oxide structure.

Further investigation of the scope of the method is presented in Table 2. The allylsilane component can carry additional

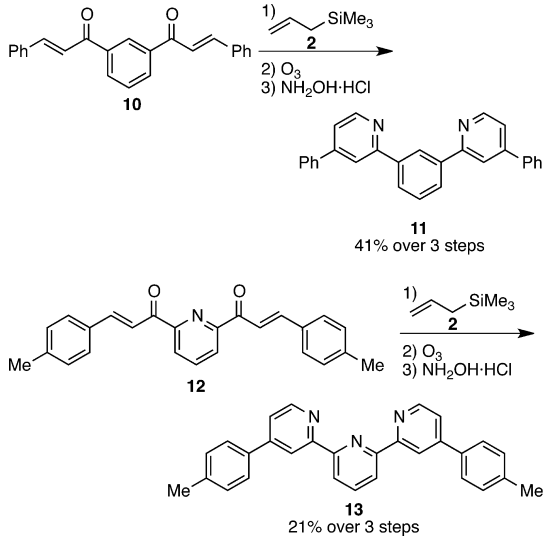
Table 2. Scope of 6-Substituted Pyridines



substituents. Commercially available methallyltrimethylsilane (**8**) was evaluated in order to introduce a methyl group at the 6-position of the constructed pyridine ring. The Hosomi–Sakurai reactions using methallyltrimethylsilane were not as widely effective as those using allyltrimethylsilane.[26] At this time, it is unclear why these reactions were difficult to carry out on some substrates, while others worked without issue.[27] In cases where the Sakurai addition worked well, the oxidation and cyclization reactions proceeded uneventfully to provide the desired pyridines, Table 2. Pyridine **9c** offers an example of a tetrasubstituted pyridine prepared by this strategy.

The construction of bis- and tris-pyridines was also explored using symmetric enones, Scheme 3. Bis-enone **10** underwent Sakurai addition successfully. Oxidation gave the bis-aldehyde, which was treated with hydroxylamine hydrochloride under standard conditions to deliver bis-pyridine **11** in 41% yield. In this case, the yield is slightly lower than one might predict from

Scheme 3. Synthesis of Bis-pyridines by Simultaneous Construction of Pyridine Rings from Bis-enones



squaring the yield of the single ring formation of **7a**. Using bis-enone **12** with an existing pyridine ring, a tris-pyridine ligand **13** was assembled in 21% yield using this method. This approach may provide a useful entry into new polydentate pyridine ligands.[28]

A simple method for constructing highly substituted pyridine rings was developed. It begins with an enone structure, itself available with many substitution patterns. Hosomi–Sakurai addition with allylsilanes provided a robust method to add the remaining carbon atoms for the ring. Oxidation and cyclization with hydroxylamine completes the synthesis. The method has a reasonable scope, uses simple and reliable steps, and should be useful for the preparation of new bioactive materials or metal ligands.

EXPERIMENTAL SECTION

General Information. ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature. The data are reported as follows: chemical shift in ppm on a δ scale and referenced to internal tetramethylsilane or residual solvent (^{1}H NMR = TMS: δ 0.00 or $CHCl_3$: δ 7.26; ^{13}C NMR = $CHCl_3$: δ 77.16), multiplicity (appar = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, m = multiplet), coupling constants (Hz), and integration. Infrared (IR) spectra were obtained. Accurate mass spectra were acquired on a quadrupole time-of-flight spectrometer and were obtained by peak matching. Analytical thin layer chromatography was performed on glass-backed silica gel 60 Å F_{254} plates and visualized by UV light, *p*-anisaldehyde, potassium permanganate, or vanillin. Liquid chromatography was performed using forced flow (flash chromatography) with an automated purification system on prepacked silica gel (SiO_2) columns. CH_2Cl_2 was dried by filtration through alumina according to the method of Grubbs.[29] All reactions using CH_2Cl_2 as solvents were run under an atmosphere of argon in glassware that was flame- or oven-dried, unless otherwise stated. All commercially available reagents were used as received unless stated otherwise. Enone starting materials were either commercially available or were synthesized using aldol condensation conditions. Spectral data of all synthesized enones matched previously reported literature data.

General Procedure Using Allyltrimethylsilane (2). *Hosomi–Sakurai Addition.* To a stirred solution of enone (1.0 mmol) in CH_2Cl_2 (1.5 mL) was added titanium tetrachloride (1.2 mmol) as a single portion, and the solution turned dark red. A separate solution of allyltrimethylsilane (**2**) (1.3 mmol) in CH_2Cl_2 (1.5 mL) was prepared and then added as a single portion to the stirring enone solution. The reaction mixture was allowed to stir at room temperature for 2 h. Once the reaction was complete, the reagents were quenched with the slow addition of H_2O (3 mL), resulting in a cloudy biphasic solution. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were dried over Na_2SO_4, run through a plug of silica gel, and concentrated in vacuo. The resulting crude oil was taken on to the next step without further purification.

General Procedure. *Ozonolysis.* A stirred solution of olefin (1.0 mmol) in CH_2Cl_2 (7 mL) was cooled to −78 °C. Ozone was then bubbled through the solution until a blue color persisted for 1 min. Oxygen was then bubbled through the solution for 5 min to displace any remaining ozone in solution. Triphenylphosphine (1.5 mmol) was then added, and the mixture was capped and stirred overnight at room temperature. Once the reaction was complete, the solvent was evaporated and PPh_3 and $OPPh_3$ were removed using ISCO flash chromatography on SiO_2 (elution gradient of hexanes with EtOAc = 0–100%). All fractions not containing PPh_3 and $OPPh_3$ were combined, concentrated, and carried on to the next step.

General Procedure. *Cyclization of the Pyridine Ring.* To a scintillation vial containing a solution of aldehyde (1.0 mmol) in acetonitrile (12 mL) was added hydroxylamine hydrochloride (3.0 mmol). (Larger scale reactions were run in a round-bottom flask equipped with a stir bar and a reflux condenser.) After capping the vial,

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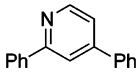
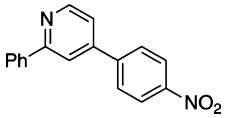
the mixture was heated to 80 °C, where it was left to stir overnight. The next day, the reaction was cooled to room temperature, and the MeCN was removed under reduced pressure. The dark-colored solid was then dissolved in 10 mL of saturated aqueous K_2CO_3/H_2O (1:1) and was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified using ISCO flash chromatography on SiO_2 (elution gradient of hexanes with EtOAc = 0−100%) to afford the desired pyridine. All yields presented are over the three steps of the procedure.



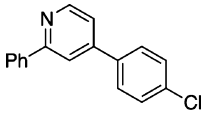
7a

*2,4-Diphenylpyridine (**7a**).* Colorless oil (171 mg, 74%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (d, J = 5.0 Hz, 1H), 8.04 (d, J = 7.3 Hz, 2H), 7.91 (s, 1H), 7.67 (d, J = 6.8 Hz, 2H), 7.50−7.41 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 150.1, 149.3, 139.5, 138.6, 129.16, 129.07, 128.8, 127.12, 127.07, 120.3, 118.8; ^{1}H and ^{13}C NMR spectral data are in agreement with previously reported literature data.[30]



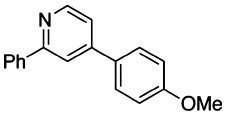
7b

*4-(4-Nitrophenyl)-2-phenylpyridine (**7b**).* White solid (221 mg, 80%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (d, J = 4.5 Hz, 1H), 8.38 (d, J = 8.8 Hz, 2H), 8.06 (d, J = 7.1 Hz, 2H), 7.94 (s, 1H), 7.85 (d, J = 8.8 Hz, 2H), 7.52 (t, J = 7.1 Hz, 2H), 7.47 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 150.7, 148.4, 147.1, 145.1, 139.1, 129.6, 129.1, 128.3, 127.2, 124.5, 120.4, 118.9; ^{1}H and ^{13}C NMR spectral data are in agreement with previously reported literature data.[31]



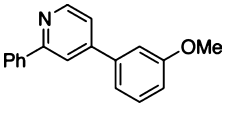
7c

*4-(4-Chlorophenyl)-2-phenylpyridine (**7c**).* Brown oil (160 mg, 60%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (d, J = 5.2 Hz, 1H), 8.06−7.97 (m, 2H), 7.83 (d, J = 0.8 Hz, 1H), 7.58−7.54 (m, 2H), 7.51−7.39 (m, 5H), 7.36−7.32 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 150.3, 148.0, 139.3, 136.9, 135.3, 129.4, 129.2, 128.9, 128.4, 127.1, 120.0, 118.5; ^{1}H and ^{13}C NMR spectral data are in agreement with previously reported literature data.[32]



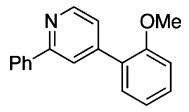
7d

*4-(4-Methoxyphenyl)-2-phenylpyridine (**7d**).* White solid (178 mg, 68%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (d, J = 5.1 Hz, 1H), 8.04−8.03 (m, 2H), 7.89 (s, 1H), 7.65 (d, J = 8.8 Hz, 2H), 7.51−7.41 (m, 4H), 7.03 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7, 158.2, 150.2, 148.9, 139.8, 130.9, 129.1, 128.9, 128.4, 127.2, 119.9, 118.4, 114.7, 55.6; ^{1}H and ^{13}C NMR spectral data are in agreement with previously reported literature data.[30]



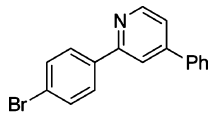
7e

*4-(3-Methoxyphenyl)-2-phenylpyridine (**7e**).* Brown oil (133 mg, 51%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (d, J = 5.1 Hz, 1H), 8.07 (d, J = 7.1 Hz, 2H), 7.93 (s, 1H), 7.51 (t, J = 7.1 Hz, 2H), 7.47−7.39 (m, 3H), 7.28 (d, J = 8.3 Hz, 1H), 7.23−7.21 (m, 1H), 7.00 (dd, J = 8.3, 2.5 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2, 158.1, 150.1, 149.2, 140.1, 139.5, 130.2, 129.1, 128.8, 127.1, 120.4, 119.6, 118.9, 114.3, 113.0, 55.4; IR (thin film) 1593, 1543, 1210, 772, 691 cm^{-1}; accurate mass (ES/MeOH) m/z calcd for $C_{18}H_{15}NONa$ (M + Na)$^+$ 284.1051, found 284.1049.



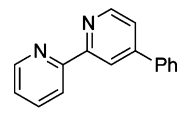
7f

*4-(2-Methoxyphenyl)-2-phenylpyridine (**7f**).* Light pink oil (212 mg, 81%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (d, J = 5.1 Hz, 1H), 8.06−8.00 (m, 2H), 7.90 (s, 1H), 7.49 (t, J = 7.5 Hz, 2H), 7.45−7.38 (m, 4H), 7.09 (t, J = 7.5 Hz, 1H), 7.04 (d, J = 8.1 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5, 156.7, 149.5, 147.3, 139.9, 130.6, 130.3, 128.9, 128.8, 128.2, 127.2, 123.0, 121.6, 121.2, 111.6, 55.8; ^{1}H and ^{13}C NMR spectral data are in agreement with previously reported literature data.[30]



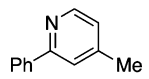
7g

*2-(4-Bromophenyl)-4-phenylpyridine (**7g**).* White solid (248 mg, 80%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (d, J = 5.1 Hz, 1H), 7.93 (d, J = 8.7 Hz, 2H), 7.88 (s, 1H), 7.67 (dd, J = 7.2, 1.1 Hz, 2H), 7.61 (d, J = 8.7 Hz, 2H), 7.54−7.42 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 150.3, 149.6, 138.5, 132.0, 129.3, 128.7, 127.2, 123.7, 120.7, 118.6; ^{1}H and ^{13}C NMR spectral data are in agreement with previously reported literature data.[30]



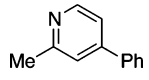
7h

*4-Phenyl-2,2′-bipyridine (**7h**).* Light yellow oil (93 mg, 40%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75−8.64 (m, 3H), 8.45 (d, J = 8.0 Hz, 1H), 7.81 (td, J = 7.5, 1.8 Hz, 1H), 7.75 (m, 2H), 7.52 (dd, J = 5.1, 1.9 Hz, 1H), 7.50−7.45 (m, 2H), 7.45−7.39 (m, 1H), 7.30 (ddd, J = 7.5, 4.8, 1.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 156.2, 149.7, 149.4, 149.3, 138.3, 137.0, 129.1, 129.1, 127.2, 123.9, 121.7, 121.3, 119.1; IR (thin film) 3055, 1582, 1456, 1389, 759, 694 cm^{-1}; accurate mass (ES/MeOH) m/z calcd for $C_{16}H_{12}N_2H$ (M + H)$^+$ 233.1079, found 233.1069.



7i

*4-Methyl-2-phenylpyridine (**7i**).* Colorless oil (76 mg, 45%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (d, J = 4.8 Hz, 1H), 7.97 (d, J = 8.2 Hz, 2H), 7.55 (s, 1H), 7.47 (t, J = 7.4 Hz, 2H), 7.45−7.37 (m, 1H), 7.06 (d, J = 4.4 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5, 149.6, 147.9, 139.7, 129.0, 128.8, 127.1, 123.3, 121.7, 21.4; ^{1}H and ^{13}C NMR spectral data are in agreement with previously reported literature data.[32]



7j

*2-Methyl-4-phenylpyridine (**7j**).* Orange oil (81 mg, 48%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, J = 5.3 Hz, 1H), 7.61 (d, J = 8.5 Hz, 2H), 7.50−7.44 (m, 2H), 7.41 (m, 1H), 7.36 (s, 1H), 7.30 (d, J = 5.3 Hz, 1H), 2.62 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 149.7, 148.8, 138.5, 129.1, 129.0, 127.1, 121.3, 119.0, 24.7; ^{1}H and ^{13}C NMR spectral data are in agreement with previously reported literature data.[30]

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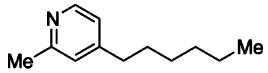
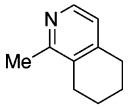


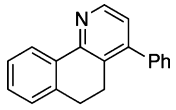
7k

*4-Hexyl-2-methylpyridine (**7k**).* Brown oil (78 mg, 44%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, J = 5.1 Hz, 1H), 6.97 (s, 1H), 6.91 (d, J = 5.1 Hz, 1H), 2.57−2.53 (t, J = 7.5 Hz, 2H), 2.52 (s, 3H), 1.60 (dt, J = 15.2, 7.5 Hz, 2H), 1.37−1.21 (m, 6H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 152.3, 149.0, 123.6, 121.2, 35.4, 31.8, 30.5, 29.0, 24.4, 22.7, 14.2; IR (thin film) 2926, 2856, 1604, 1456 cm^{-1}; accurate mass (ES/MeOH) m/z calcd for $C_{12}H_{19}NH$ $(M + H)^+$ 178.1596, found 178.1604.



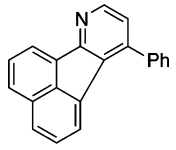
7l

*1-Methyl-5,6,7,8-tetrahydroisoquinoline (**7l**).* Light orange oil (66 mg, 45%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, J = 5.1 Hz, 1H), 6.83 (d, J = 5.1 Hz, 1H), 2.72 (t, J = 6.3 Hz, 2H), 2.62 (t, J = 6.4 Hz, 2H), 2.43 (s, 3H), 1.89−1.82 (m, 2H), 1.81−1.72 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 146.0, 145.3, 131.0, 122.2, 29.5, 26.1, 23.1, 22.3, 22.2; IR (thin film) 2928, 1587, 1428, 1411, 834, 807 cm^{-1}; accurate mass (ES/MeOH) m/z calcd for $C_{10}H_{13}NH$ $(M + H)^+$ 148.1126, found 148.1123.



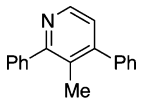
7m

*4-Phenyl-5,6-dihydrobenzo[h]quinoline (**7m**).* Tan solid (176 mg, 66%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (d, J = 4.9 Hz, 1H), 8.36 (dd, J = 7.7, 1.0 Hz, 1H), 7.46−7.28 (m, 7H), 7.19 (d, J = 7.4 Hz, 1H), 7.09 (d, J = 4.9 Hz, 1H), 2.90−2.87 (m, 2H), 2.80−2.78 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1, 148.7, 147.3, 139.0, 138.2, 135.0, 129.6, 129.2, 128.9, 128.6, 128.2, 127.6, 127.3, 125.6, 123.4, 28.2, 25.6; ^{1}H and ^{13}C NMR spectral data are in agreement with previously reported literature data.[30]



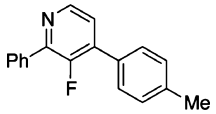
7n

*10-Phenylacenaphtho[1,2-b]pyridine (**7n**).* Orange oil (143 mg, 51%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (d, J = 5.1 Hz, 1H), 8.35 (d, J = 6.9 Hz, 1H), 7.98 (d, J = 8.1 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.76 (t, J = 7.5 Hz, 1H), 7.67 (dd, J = 8.0, 1.7 Hz, 2H), 7.61−7.53 (m, 3H), 7.52−7.42 (m, 2H), 7.18 (d, J = 5.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7, 147.8, 145.7, 138.7, 135.3, 133.5, 132.3, 131.0, 129.8, 129.0, 128.9, 128.6, 128.4, 128.0, 127.8, 123.9, 123.0, 121.9; IR (thin film) 3053, 1428, 825, 776, 763, 701 cm^{-1}; accurate mass (ES/MeOH) m/z calcd for $C_{21}H_{13}NH$ $(M + H)^+$ 280.1126, found 280.1123.



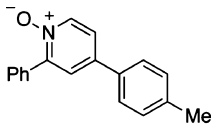
7o

*3-Methyl-2,4-diphenylpyridine (**7o**).* Brown oil (155 mg, 63%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, J = 5.0 Hz, 1H), 7.57 (d, J = 8.2 Hz, 2H), 7.51−7.44 (m, 4H), 7.44−7.35 (m, 4H), 7.16 (d, J = 5.0 Hz, 1H), 2.23 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 151.0, 146.5, 141.1, 139.9, 129.2, 128.8, 128.6, 128.5, 128.2, 128.0, 123.3, 18.1; ^{1}H and ^{13}C NMR spectral data are in agreement with previously reported literature data.[30]



7p

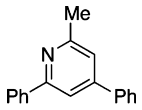
*3-Fluoro-2-phenyl-4-(p-tolyl)pyridine (**7p**).* Tan solid (42 mg, 16%): mp 76−77 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, J = 4.8 Hz, 1H), 7.98 (d, J = 7.3 Hz, 2H), 7.55 (dd, J = 7.9, 1.2 Hz, 2H), 7.51 (t, J = 7.3 Hz, 2H), 7.48−7.43 (m, 1H), 7.37−7.28 (m, 3H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7 (d, J = 260.8 Hz), 147.2 (d, J = 13.0 Hz), 145.4 (d, J = 6.7 Hz), 139.4, 137.4 (d, J = 13.0 Hz), 135.8 (d, J = 4.9 Hz), 130.6, 130.0, 129.6, 129.2, 129.15 (d, J = 5.5 Hz), 129.0 (d, J = 3.2 Hz), 128.9, 128.5, 127.1 (d, J = 18.4 Hz), 123.7, 21.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ − 130.65; IR (thin film) 2915, 1597, 1396, 1204, 815, 750, 695, 497 cm^{-1}; accurate mass (ES/MeOH) m/z calcd for $C_{18}H_{14}FNNa$ $(M + Na)^+$ 286.1008, found 286.1019.



7q

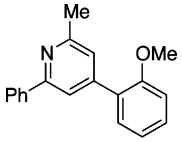
*2-Phenyl-4-(p-tolyl)pyridine N-Oxide (**7q**).* Yellow oil (136 mg, 52%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, J = 7.0 Hz, 1H), 7.82 (d, J = 7.0 Hz, 2H), 7.58 (dd, J = 2.5 Hz, 1H), 7.47−7.37 (m, 6H), 7.23 (d, J = 8.0 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.1, 140.4, 139.3, 138.8, 133.4, 132.8, 130.1, 129.7, 129.4, 128.4, 126.3, 124.7, 122.0, 21.3; IR (thin film) 3395, 2919, 1468, 1420, 1249, 812 cm^{-1}; accurate mass (ES/MeOH) m/z calcd for $C_{18}H_{15}ONNa$ $(M + Na)^+$ 284.1051, found 284.1041.

General Procedure Using Methallyltrimethylsilane (8). *Hosomi−Sakurai Addition.* To a cooled (−78 °C) solution of enone (1.0 mmol) in CH_2Cl_2 (4 mL) was added titanium tetrachloride (1.2 mmol) dropwise, and the solution turned red. A separate solution of methallyltrimethylsilane (**8**) (1.4 mmol) in CH_2Cl_2 (1.5 mL) was prepared and then added dropwise to the stirring enone solution after it had stirred for 10 min. The reaction mixture was allowed to stir at −78 °C for 2 h. Once the reaction was complete, the reagents were quenched by the slow addition of H_2O (3 mL), and the mixture was warmed to room temperature, resulting in a cloudy biphasic solution. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were dried over Na_2SO_4, run through a plug of silica gel, and concentrated in vacuo. The resulting crude oil was taken on to the next step without further purification.



9a

*2-Methyl-4,6-diphenylpyridine (**9a**).* Brown oil (91 mg, 37%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, J = 7.1 Hz, 2H), 7.73 (s, 1H), 7.69 (d, J = 7.1 Hz, 2H), 7.52−7.41 (m, 6H), 7.34 (s, 1H), 2.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 157.6, 150.0, 138.8, 129.1, 129.01, 128.96, 128.8, 127.3, 127.2, 120.0, 116.4, 24.8; ^{1}H and ^{13}C NMR spectral data are in agreement with previously reported literature data.[33]



9b

*4-(2-Methoxyphenyl)-2-methyl-6-phenylpyridine (**9b**).* Colorless oil (215 mg, 78%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 8.2 Hz, 2H), 7.68 (s, 1H), 7.46 (t, J = 7.5 Hz, 2H), 7.42−7.34 (m, 3H), 7.26 (s, 1H), 7.06 (t, J = 7.5 Hz, 1H), 7.01 (d, J = 8.2 Hz, 1H), 3.84 (s,

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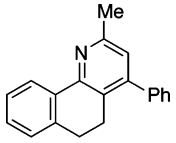
3H), 2.67 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 157.0, 156.7, 147.4, 140.3, 130.6, 130.0, 128.8, 128.7, 128.5, 127.3, 122.4, 121.1, 118.9, 111.5, 55.7, 25.0; IR (thin film) 1604, 1399, 1246, 1024, 751, 693 cm^{-1}; accurate mass (ES/MeOH) m/z calcd for $C_{19}H_{17}NONa$ $(M + Na)^+$ 298.1208, found 298.1204.



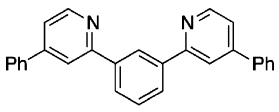
9c

*2-Methyl-4-phenyl-5,6-dihydrobenzo[h]quinoline (**9c**).* Orange oil (174 mg, 64%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, J = 7.6 Hz, 1H), 7.46 (m, 2H), 7.43−7.38 (m, 1H), 7.35 (m, 3H), 7.30 (td, J = 7.4, 1.3 Hz, 1H), 7.20 (d, J = 7.4 Hz, 1H), 7.00 (s, 1H), 2.88−2.83 (m, 2H), 2.83−2.77 (m, 2H), 2.63 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 152.4, 148.8, 139.4, 138.3, 135.3, 128.94, 128.90, 128.5, 128.0, 127.5, 127.2, 126.4, 125.5, 122.9, 28.4, 25.3, 24.6; IR (thin film) 2927, 1590, 1547, 1497, 750, 701 cm^{-1}; accurate mass (ES/MeOH) m/z calcd for $C_{20}H_{17}NH$ $(M + H)^+$ 272.1439, found 272.1426.

General Procedure Using Bis-enones. *Hosomi−Sakurai Addition.* To a stirring solution of bis-enone (0.50 mmol) in CH_2Cl_2 (1.5 mL) was added titanium tetrachloride (1.2 mmol) as a single portion, and the solution turned dark red. A separate solution of allyltrimethylsilane (**2**) (1.3 mmol) in CH_2Cl_2 (1.5 mL) was prepared and then added as a single portion to the stirring enone solution. The reaction mixture was allowed to stir at room temperature for 2 h. Once the reaction was complete, the reagents were quenched with the slow addition of H_2O (3 mL), resulting in a cloudy biphasic solution. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were dried over Na_2SO_4, run through a plug of silica gel, and concentrated in vacuo. The resulting crude oil was taken on to the next step without further purification.

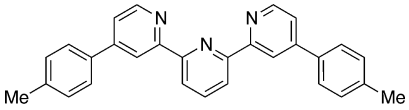
General Procedure Using Bis-enones. *Ozonolysis.* A stirring solution of bis-olefin (0.50 mmol) in CH_2Cl_2 (7 mL) was cooled to −78 °C. Ozone was then bubbled through the solution until a blue color persisted for 1 min. Oxygen was then bubbled through the solution for 5 min to displace any remaining ozone in solution. Triphenylphosphine (1.5 mmol) was then added, and the reaction was capped and stirred overnight at room temperature. Once the reaction was complete, the solvent was evaporated and PPh_3 and $OPPh_3$ were removed using flash chromatography on SiO_2 (hexanes/EtOAc = 75:25). All fractions not containing PPh_3 and $OPPh_3$ were combined, concentrated, and carried on to the next step.

General Procedure Using Bis-enones. *Cyclization of the Pyridine Rings.* To a scintillation vial containing a solution of bis-aldehyde (0.50 mmol) in acetonitrile (12 mL) was added hydroxylamine hydrochloride (3 mmol). After the vial was capped, the solution was heated to 80 °C, where it was left to stir overnight. The next day, the reaction mixture was cooled to room temperature, and the MeCN was removed under reduced pressure. The dark-colored solid was then dissolved in 10 mL of saturated aqueous K_2CO_3/H_2O (1:1) and was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified using flash chromatography on SiO_2 (hexanes/EtOAc = 70:30) to afford the desired bis-pyridine. All yields presented are over the three steps.



11

*1,3-Bis(4-phenylpyridin-2-yl)benzene (**11**).* Light red oil (79 mg, 41%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (d, J = 5.1 Hz, 2H), 8.71 (s, 1H), 8.14 (dd, J = 7.8, 1.8 Hz, 2H), 8.05 (s, 2H), 7.72 (m, 4H), 7.64 (t, J = 7.8 Hz, 1H), 7.58−7.41 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 150.3, 149.6, 140.3, 138.7, 129.4, 129.3, 129.2, 127.9, 127.3, 125.9, 120.6, 119.1; IR (thin film) 1592, 1542, 758, 728, 692, 613 cm^{-1}; accurate mass (ES/MeOH) m/z calcd for $C_{28}H_{20}N_2H$ $(M + H)^+$ 385.1705, found 385.1694.



13

*4,4″-Di-p-tolyl-2,2′:6′,2″-terpyridine (**13**).* Tan solid (43 mg, 21%): mp 210−211 °C (decomposition); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.86 (d, J = 1.1 Hz, 2H), 8.73 (d, J = 5.1 Hz, 2H), 8.49 (d, J = 7.8 Hz, 2H), 7.99 (t, J = 7.8 Hz, 1H), 7.70 (d, J = 8.0 Hz, 4H), 7.55 (dd, J = 5.1, 1.8 Hz, 2H), 7.33 (d, J = 8.0 Hz, 4H), 2.45 (s, J = 10.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9, 155.6, 149.7, 149.2, 139.3, 138.1, 135.7, 130.0, 127.1, 121.6, 121.4, 119.1, 21.4; IR (thin film) 2920, 1572, 1383, 802, 453 cm^{-1}; accurate mass (ES/MeOH) m/z calcd for $C_{29}H_{23}N_3Na$ $(M + Na)^+$ 436.1790, found 436.1782.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01370.

Spectroscopic characterization for all products (PDF)

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Notes

The authors declare no competing financial interest.

†ISHC member.

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