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# Synthesis of Pyridines from Ketoximes and Terminal Alkynes via C–H Bond Functionalization

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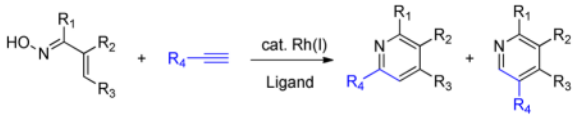
## Abstract




An expedient one-pot rhodium catalyzed C–H bond functionalization/electrocyclization/dehydration procedure has been developed for the synthesis of highly substituted pyridine derivatives from terminal alkynes and *α*,*β*-unsaturated ketoximes. The use of electron deficient phosphite ligands is important to suppress dimerization of the terminal alkynes to enynes.

The modular synthesis of highly substituted nitrogen heterocycles is an important area of research due to their prevalence in natural products and drugs. In particular, pyridines are the most extensively used nitrogen heterocycles in pharmaceutical research.[1–3] We have previously reported an efficient synthesis of highly substituted pyridines from *α*,*β*-unsaturated imines and alkynes.[4] In this sequence, rhodium-catalyzed C-H alkenylation of the imine is followed by in situ electrocylization to afford a dihydropyridine, which can be aromatized to the corresponding pyridine in one pot (Scheme 1). Additionally, the Cheng group reported an analogous synthesis from *α*,*β*-unsaturated ketoximes and alkynes where dehydration occurs in situ after electrocyclization to provide the corresponding pyridine directly (Scheme 1).[5] However, for neither method, with the exception of phenyl acetylene, were terminal alkynes competent substrates.

Numerous transition metal-mediated head-to-head dimerizations of alkynes have been developed as an atom economical and expedient route to enynes, which are present in natural products and serve as handles for further synthetic elaboration.[6–12] Unfortunately, the very facility with which terminal alkynes dimerize has rendered their application as coupling partners problematic for a variety of transition-metal mediated functionalizations.[13–16] In our previous attempts to employ terminal alkynes as coupling partners for pyridine synthesis alkyne dimerization proved competitive with the desired functionalization for both α,β-unsaturated *N*-benzyl imines and oximes.[2] Herein, we report an effective method for the synthesis of highly substituted pyridines via the C–H bond functionalization of *α*,*β*-unsaturated ketoximes with terminal alkynes through the use of

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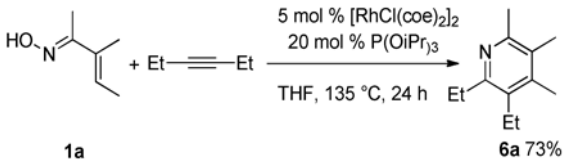
Supporting information. Reaction optimization table. Copies of $^{1}$H NMR and $^{13}$C NMR sprectroscopic data for compounds. This material is available free of charge via the internet at http://pubs.acs.org.

inexpensive trisopropyl phosphite as a key ligand for minimizing alkyne homocoupling side reactions.

In performing a ligand screen we serendipitously discovered that phosphites and phosphoramidites provided an active Rh-catalyst system for the desired C–H alkenylation, while suppressing the undesired competing terminal alkyne dimerization. For example, ketoxime **1a** and 1-hexyne provided pyridine products in high yield as a 3 to 1 mixture of regioisomers **2a** and **3a** when $P(OiPr)_3$ was used as the ligand (entry 1, Table 1). Different Rh-ligand stoichiometries were evaluated with 2 equivalents of the phosphite providing optimal results (entry 1–2).[17] At 105 °C comparable yields and regioselectivities were observed for THF, toluene, and cyclopentyl methyl ether (CPME) as solvents (entries 1, 3 and 4). Because we anticipated that higher temperatures might be required for the electrocyclization and dehydration steps for more hindered coupling partners, the reaction was also performed at 135 °C and resulted in nearly identical yields and regioselectivity (entry 5). Moreover, lower catalyst loading (1 mol % of the Rh-precatalyst), and fewer equivalents of alkyne (1.5 equiv) gave similar yields and regioselectivity at this higher temperature (entries 6 and 7). A ligand screen comprised of other phosphites and phosphoramidites such as $P(OPh)_3$, $P(OtBu)_3$, $P(OiPr)_2NEt_2$ and $P(OiPr)_2NiPr_2$ with varying steric and electronic properties was undertaken; however, none proved to be superior to the simple and inexpensive $P(OiPr)_3$ in terms of yield or regioselectivity (see Supporting Information).

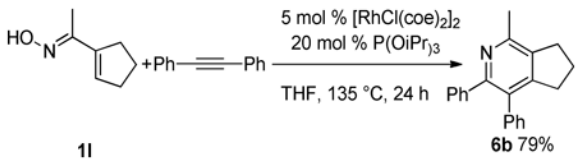
We next sought to evaluate the substrate scope for the preparation of differentially substituted pyridine products using a variety of α,β-unsaturated oximes. The ketoxime starting material lacking either α- or β-substitution provided the disubstituted pyridine product **2b–2c** in moderate yield as a single regioisomer.[18] Ketoximes with only α-substitution gave pyridines in good yields and with good to high regioselectivities that ranged from 2.3:1 to a single regioisomer depending on the structure of the α-substituent (**2c–2f** and **3d–3f**). Ketoximes with only β-substitution resulted in pyridine products with generally lower regioselectivities (**2g–2j** and **3g–3j**). It is noteworthy that cyclic ketoximes (**2k–2l** and **3k–3l**) and ketoximes substituted with both aromatic and branched and unbranched alkyl groups were all well tolerated. Under our standard conditions, aldoximes proved to be challenging substrates, consistent with Cheng's report on coupling internal alkynes,[5] necessitating higher reaction temperatures and resulting in diminished yield (2m and 3m).

Terminal alkyne scope was also quite reasonable. Both phenylacetylene and benzylacetylene reacted to give a single pyridine regioisomer in good yield (**4a, 4b**). In addition, α- and β-branched terminal alkynes coupled in high yields and with reasonable regioselectivities (**4c–4d** and **5c–5d**, respectively). Additionally, the use of internal alkynes afforded pyridines **6a** and **6b** in high yield (eq 1 and 2)




**1a** **6a** 73%

(1)




(2)

In summary, we have developed a one step synthesis of pyridines by rhodium-catalyzed C–H bond functionalization of *α,β*-unsaturated ketoximes with terminal alkynes to afford substituted pyridines in moderate to excellent regioselectivities through the use of triisopropyl phosphite as a simple and inexpensive ligand that suppresses the undesired competitive dimerization of terminal alkynes. The use of phosphate ligands may also prove useful for suppressing competitive terminal alkyne dimerization for other Rh(I)-catalyzed transformations of alkynes.

## EXPERIMENTAL SECTION

### General Procedure for Pyridine Synthesis

The desired alkyne (2.5 mmol) was placed in a sealable glass vessel in an inert atmosphere box. To the reaction vessel was added $[RhCl(coe)_2]_2$[19] (21.8 mg, 0.025 mmol, 5 mol %) dissolved in 1 mL of THF, triisopropyl phosphite (25.2 mg, 0.050 mmol, 20 mol %) dissolved in 1 mL of THF, the desired oxime (0.500 mmol) dissolved in 1 mL of THF, and finally 2 mL of THF. The reaction vessel was then sealed, removed from the inert atmosphere box, and heated in a 135 °C oil bath for 24 h. The reaction vessel was then allowed to cool to ambient temperature, opened, and the solvent removed in vacuo. The resulting oil was dissolved in 10 mL of $CH_2Cl_2$ and washed with 10 mL of 0.1 M NaOH. The resulting aqueous layer was extracted with $CH_2Cl_2$ (2 × 10 mL). The combined organic layers were dried over $Na_2SO_4$, and the solvents were removed in vacuo. The resulting residue was purified by column chromatography on silica gel.

### 5-Butyl-2,3,4-trimethylpyridine (2a) and 6-butyl-2,3,4-trimethylpyridine (3a)

3-Methyl-3-pentene-2-one oxime (68.0 mg) and 1-hexyne (0.29 mL) were subjected to the standard procedure with purification by chromatography (10:1:0.01 hexanes:*tert*-butyl methyl ether:triethylamine). 5-Butyl-2,3,4-trimethylpyridine was obtained in 56% yield (49 mg, 0.27 mmol) as a brown oil. $^1$H NMR ($CDCl_3$) δ 8.02 (s, 1H), 2.57 – 2.48 (m, 2H), 2.44 (s, 3H), 2.16 (s, 3H), 2.15 (s, 3H), 1.51 – 1.40 (m, 2H), 1.34 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H). $^{13}$C NMR ($CDCl_3$) δ 154.1, 146.6, 143.5, 134.0, 130.0, 33.0, 31.1, 23.4, 22.8, 15.4, 15.3, 14.1. HRMS (ES+) calcd for $C_{12}H_{19}N$ $(M + H)^+$: 178.1590. Found: 178.1589. 6-Butyl-2,3,4-trimethylpyridine was obtained in 17% yield (15 mg, 0.09 mmol) as a brown oil. $^1$H NMR ($CDCl_3$) δ 6.77 (s, 1H), 2.69 – 2.62 (m, 2H), 2.48 (s, 3H), 2.22 (s, 3H), 2.14 (s, 3H), 1.64 (m, 2H), 1.37 (m, 2H), 0.92 (m, 3H). $^{13}$C NMR ($CDCl_3$) δ 158.6, 155.9, 145.9, 127.4, 122.1, 38.0, 32.8, 23.3, 23.0, 20.3, 14.7, 14.3. HRMS (ES+) calcd for $C_{12}H_{19}N$ $(M + H)^+$: 178.1590. Found: 178.1589.

### 5-Butyl-2,3-dimethylpyridine (2b)

3-Methyl-3-butene-2-one oxime (60.0 mg) and 1-hexyne (0.29 mL) were subjected to the standard procedure. 5-Butyl-2,3-dimethylpyridine was purified by chromatography (20:1:0.01 hexanes:ethyl acetate:triethylamine) in 39% yield (29 mg, 0.20 mmol) as a brown oil. $^1$H NMR ($CDCl_3$) δ 8.14 (s, 1H), 7.21 (s, 1H), 2.56 – 2.50 (m, 2H), 2.45 (s, 3H), 2.25 (s, 3H), 1.60 – 1.52 (m, 2H), 1.34 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). $^{13}$C NMR ($CDCl_3$) δ 154.5,

146.6, 137.5, 135.6, 131.0, 33.7, 32.4, 22.5, 22.3, 19.4, 14.1. HRMS (ES+) calcd for $C_{10}H_{15}N$ $(M + H)^+$: 150.1277. Found: 150.1274.

### 5-Butyl-2,3-dimethylpyridine (2c)

3-Butene-2-one oxime (51.4 mg) and 1-hexyne (0.29 mL) were subjected to the standard procedure. 5-Butyl-2,3-dimethylpyridine was purified by chromatography (20:1:0.01 hexanes:ethyl acetate:triethylamine) in 54% yield (45 mg, 0.27 mmol) as a brown oil. $^1$H NMR ($CDCl_3$) δ 8.30 (d, J = 2.0 Hz, 1H), 7.37 (dd, J = 7.9, 2.0 Hz, 1H), 7.05 (d, J = 7.9 Hz, 1H), 2.58 – 2.53 (m, 2H), 2.50 (s, 3H), 1.57 (m, 2H), 1.34 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H). $^{13}$C NMR ($CDCl_3$) δ 155.8, 149.4, 136.6, 135.1, 123.1, 33.7, 32.6, 24.2, 22.5, 14.2. HRMS (ES+) calcd for $C_{11}H_{17}N$ $(M + H)^+$: 164.1434. Found: 164.1430.

### 5-Butyl-3-ethyl-2-methylpyridine (2d)

3-Ethyl-3-pentene-2-one oxime (68.0 mg) and 1-hexyne (0.29 mL) were subjected to the standard procedure. 5-Butyl-3-ethyl-2-methylpyridine was purified by column chromatography (10:1:0.01 hexanes:*tert*-butyl methyl ether:triethylamine) in 50% yield (44 mg, 0.25 mmol) as a brown oil. $^1$H NMR ($CDCl_3$) δ 8.18 (s, 1H), 6.90 (s, 1H), 2.58 – 2.51 (m, 2H), 2.45 (s, 3H), 2.24 (s, 2H), 1.55 – 1.47 (m, 2H), 1.37 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H). $^{13}$C NMR ($CDCl_3$) δ 155.8, 149.5, 145.5, 133.8, 124.9, 32.7, 30.1, 24.1, 22.9, 18.9, 14.2. HRMS (ES+) calcd for $C_{12}H_{19}N$ $(M + H)^+$: 178.1590. Found: 178.1588.

### 5-Butyl-3-isopropyl-2-methylpyridine (2e) and 6-butyl-3-isopropyl-2-methylpyridine (3e)

3-isopropyl-3-pentene-2-one oxime (77.0 mg) and 1-hexyne (0.29 mL) were subjected to the standard procedure with purification by chromatography (10:1:0.01 hexanes:*tert*-butyl methyl ether:triethylamine). 5-Butyl-3-isopropyl-2-methylpyridine was obtained in 62% yield (60 mg, 0.31 mmol) as a brown oil. $^1$H NMR ($CDCl_3$) δ 8.13 (s, 1H), 7.30 (s, 1H), 3.11 – 3.01 (m, 1H), 2.58 – 2.47 (m, 5H), 1.59 – 1.50 (m, 2H), 1.38 – 1.15 (m, 8H), 0.90 (t, *J* = 7.3 Hz, 3H). $^{13}$C NMR ($CDCl_3$) δ 152.9, 146.0, 141.5, 136.0, 133.2, 33.7, 32.8, 29.3, 23.1, 22.6, 21.6, 14.1. HRMS (ES+) calcd for $C_{13}H_{21}N$ $(M + H)^+$: 192.1747. Found: 192.1750. 6-Butyl-3-isopropyl-2-methylpyridine was obtained in 10% yield (10 mg, 0.05 mmol) as a brown oil. $^1$H NMR ( $CDCl_3$) δ 7.41 (d, *J* = 7.9 Hz, 1H), 6.94 (d, *J* = 7.9 Hz, 1H), 3.09 (m, 1H), 2.75 – 2.68 (m, 2H), 2.54 (s, 3H), 1.71 – 1.61 (m, 2H), 1.44 – 1.35 (m, 2H), 1.21 (d, *J* = 6.9 Hz, 6H), 0.93 (t, *J* = 7.4 Hz, 3H). $^{13}$C NMR ($CDCl_3$) δ 159.0, 155.2, 138.8, 133.2, 120.5, 38.2, 32.7, 29.2, 23.3, 23.0, 22.4, 14.3. HRMS (ES+) calcd for $C_{13}H_{21}N$ $(M + H)^+$: 192.1747. Found: 192.1746.

### 5-Butyl-3-ethyl-2-methylpyridine (2f) and 6-butyl-3-ethyl-2-methylpyridine (3f)

3-Phenyl-3-pentene-2-one oxime (97.6 mg) and 1-hexyne (0.29 mL) were subjected to the standard procedure with purification by chromatography (10:1:0.01 hexanes:*tert*-butyl methyl ether:triethylamine). 5-Butyl-3-phenyl-2-methylpyridine was obtained in 36% yield (41 mg, 0.18 mmol) as a brown oil. $^1$H NMR ($CDCl_3$) δ 8.35 (s, 1H), 7.44 (m, 2H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.36 – 7.30 (m, 3H), 2.62 (t, *J* = 7.7 Hz, 2H), 2.49 (s, 3H), 1.67 – 1.57 (m, 2H), 1.39 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H). $^{13}$ C NMR ($CDCl_3$) δ 153.3, 148.4, 140.6, 137.6, 136.9, 135.6, 129.4, 128.7, 127.7, 33.8, 32.6, 23.3, 22.7, 14.3. HRMS (ES+) calcd for $C_{16}H_{19}N$ $(M + H)^+$: 226.1590. Found: 226.1588. 6-Butyl-3-phenyl-2-methylpyridine was obtained in 16% yield (18 mg, 0.08 mmol) as a brown oil. $^1$H NMR ($CDCl_3$) δ 7.42 (m, 3H), 7.36 (m, 1H), 7.33 – 7.29 (m, 2H), 7.04 (d, *J* = 7.7 Hz, 1H), 2.83 – 2.78 (m, 2H), 2.49 (s, 3H), 1.78 – 1.69 (m, 2H), 1.43 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). $^{13}$C NMR ($CDCl_3$) δ 161.1, 155.3, 140.6, 137.9, 134.4, 129.5, 128.7, 127.5, 120.1, 38.4, 32.7, 23.7, 23.0, 14.3. HRMS (ES+) calcd for $C_{16}H_{19}N$ $(M + H)^+$: 226.1590. Found: 226.1588.

### 5-Butyl-2,4-dimethylpyridine (2g) and 6-butyl-2,4-dimethylpyridine (3g)

3-Pentene-2-one oxime (60.0 mg) and 1-hexyne (0.29 mL) were subjected to the standard procedure with purification by chromatography (10:1:0.01 hexanes:*tert*-butyl methyl ether:triethylamine). 5-Butyl-2,4-dimethylpyridine was obtained in 43% yield (35 mg, 0.22 mmol) as a brown oil. $^{1}$H NMR ($CDCl_3$) δ 8.16 (s, 1H), 6.88 (s, 1H), 2.58 – 2.47 (m, 2H), 2.43 (s, 3H), 2.22 (s, 3H), 1.49 (m, 2H), 1.35 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H). $^{13}$C NMR ($CDCl_3$) δ 155.6, 149.3, 145.4, 133.6, 124.7, 32.5, 30.0, 23.9, 22.7, 18.8, 14.1. HRMS (ES+) calcd for $C_{11}H_{17}N$ $(M + H)^+$: 164.1434. Found: 164.1429. 6-Butyl-2,4-dimethylpyridine was obtained in 9% yield (7 mg, 0.05 mmol) as a brown oil. $^{1}$H NMR ($CDCl_3$) δ 6.77 (d, J = 6.3 Hz, 2H), 2.73 – 2.66 (m, 2H), 2.48 (s, 3H), 2.26 (s, 3H), 1.66 (m, 2H), 1.38 (m, 3H), 0.93 (t, J = 7.4 Hz, 4H). $^{13}$C NMR ($CDCl_3$) δ 162.0, 157.7, 147.7, 121.7, 120.8, 38.5, 32.7, 24.6, 23.0, 21.2, 14.3. HRMS (ES+) calcd for $C_{11}H_{17}N$ $(M + H)^+$: 164.1434. Found: 164.1431.

### 5-Butyl-2-methyl-4-isopropylpyridine (2h)

5-Methyl-3-hexene-2-one oxime (77.0 mg) and 1-hexyne (0.29 mL) were subjected to the standard procedure. 5-Butyl-2-methyl-4-*iso*-propylpyridine was purified by chromatography (20:1:0.01 hexanes:*tert*-butyl methyl ether:triethylamine) in 46% yield (45 mg, 0.23 mmol) as a brown oil. $^{1}$H NMR ($CDCl_3$) δ 8.20 (s, 1H), 6.98 (s, 1H), 3.09 (m, 1H), 2.65 – 2.53 (m, 2H), 2.49 (s, 3H), 1.57 – 1.46 (m, 3H), 1.39 (m, 3H), 1.21 (d, *J* = 6.8 Hz, 7H), 0.94 (t, *J* = 7.2 Hz, 4H). $^{13}$C NMR ($CDCl_3$) δ 156.1, 155.9, 150.1, 132.2, 119.9, 34.1, 29.8, 28.6, 24.4, 23.6, 22.9, 14.2. HRMS (ES+) calcd for $C_{13}H_{21}N$ $(M + H)^+$: 192.1747. Found: 192.1744.

### 5-Butyl-2-methyl-4-phenylpyridine (2i) and 6-butyl-2-methyl-4-phenylpyridine (3i)

4-Phenyl-3-butene-2-one oxime (97.6 mg) and 1-hexyne (0.29 mL) were subjected to the standard procedure with purification by chromatography (10:1:0.01 hexanes:*tert*-butyl methyl ether:triethylamine). 5-Butyl-2-methyl-4-phenylpyridine and 6-butyl-2-methyl-4-phenylpyridine were obtained as a 1.6:1 mixture in 53% yield (60 mg, 0.27 mmol) as a brown oil. $^{1}$H NMR (MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.62 – 7.58 (m, 1.25H), 7.47 – 7.34 (m, 4.25H), 7.29 – 7.25 (m, 2.63H), 7.16 (d, *J* = 4.2 Hz, 1.25H), 6.97 (s, 1H), 2.86 – 2.78 (m, 2H), 2.61 – 2.52 (m, 6H), 1.73 (m, 2H), 1.47 – 1.34 (m, 4H), 1.19 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 2H), 0.77 (t, *J* = 7.3 Hz, 3H). $^{13}$C NMR ($CDCl_3$) δ 162.8, 158.4, 155.7, 150.4, 149.8, 149.2, 139.8, 139.2, 132.6, 129.2, 129.0, 128.7, 128.6, 128.0, 127.3, 124.1, 118.8, 118.0, 38.7, 33.5, 32.7, 29.8, 24.9, 24.1, 22.9, 22.6, 14.3, 14.0. HRMS (ES+) calcd for $C_{16}H_{19}N$ $(M + H)^+$: 226.1590. Found: 226.1587.

### 5-Butyl-2-ethyl-4-methylpyridine (2j) and 6-butyl-2-ethyl-4-methylpyridine (3j)

4-Pentene-3-one oxime (68.0 mg) and 1-hexyne (0.29 mL) were subjected to the standard procedure with purification by chromatography (20:1:0.01 hexanes:ethyl acetate:triethylamine). 5-Butyl-2-ethyl-4-methylpyridine was obtained in 49% yield (44 mg, 0.25 mmol) as a brown oil. $^{1}$H NMR ($CDCl_3$) δ 8.17 (s, 1H), 6.86 (s, 1H), 2.69 (m, 2H), 2.55 – 2.47 (m, 2H), 2.22 (s, 3H), 1.53 – 1.42 (m, 2H), 1.38 – 1.29 (m, 2H), 1.23 (t, *J* = 7.6 Hz, 3H), 0.89 (t, *J* = 7.3 Hz, 3H). $^{13}$C NMR ($CDCl_3$) δ 161.0, 149.5, 145.6, 133.9, 123.6, 32.6, 31.0, 30.1, 22.9, 19.0, 14.3, 14.2. HRMS (ES+) calcd for $C_{12}H_{19}N$ $(M + H)^+$: 178.1590. Found: 178.1587. 6-Butyl-2-ethyl-4-methylpyridine was obtained in 20% yield (18 mg, 0.10 mmol) as a brown oil. $^{1}$H NMR ($CDCl_3$) δ 6.78 (d, *J* = 4.7 Hz, 2H), 2.73 (m, 4H), 2.28 (s, 3H), 1.72 – 1.62 (m, 2H), 1.38 (m, 2H), 1.27 (t, *J* = 8.5 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H). $^{13}$C NMR ($CDCl_3$) δ 163.1, 162.0, 147.7, 121.0, 120.2, 38.5, 32.7, 31.7, 23.0, 21.3, 14.6, 14.3. HRMS (ES+) calcd for $C_{12}H_{19}N$ $(M + H)^+$: 178.1590. Found: 178.1588.

### 3-Butyl-2-methyl-5,6,7,8-tetrahydroisoquinoline (2k) and 2-butyl-2-methyl-5,6,7,8-tetrahydroisoquinoline (3k)

1-Acetyl-1-cylohexene oxime (84.2 mg) and 1-hexyne (0.29 mL) were subjected to the standard procedure with purification by chromatography (10:1:0.01 hexanes:*tert*-butyl methyl ether:triethylamine). 3-Butyl-2-methyl-5,6,7,8-tetrahydroisoquinoline was obtained in 54% yield (55 mg, 0.27 mmol) as a brown oil. $^{1}$H NMR ($CDCl_3$) δ 8.01 (s, 1H), 2.63 (t, *J* = 6.0 Hz, 2H), 2.58 (t, *J* = 6.0 Hz, 2H), 2.50 – 2.45 (m, 2H), 2.37 (s, 3H), 1.76 (m, 4H), 1.49 (m, 2H), 1.35 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H). $^{13}$C NMR ($CDCl_3$) δ 154.5, 145.9, 144.0, 133.7, 130.5, 32.5, 29.8, 26.7, 26.3, 23.0, 22.8, 22.5, 22.3, 14.2. HRMS (ES+) calcd for $C_{14}H_{21}N$ $(M + H)^+$: 204.1747. Found: 204.1744. 2-Butyl-2-methyl-5,6,7,8-tetrahydroisoquinoline was obtained in 15% yield (15 mg, 0.08 mmol) as a brown oil. HRMS (ES+) calcd for $^{1}$H NMR ($CDCl_3$) δ 6.68 (s, 1H), 2.70 – 2.63 (m, 4H), 2.57 (t, J = 6.4 Hz, 2H), 2.40 (s, 3H), 1.86 – 1.79 (m, 2H), 1.77 – 1.70 (m, 2H), 1.64 (m, 2H), 1.42 – 1.33 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H). $^{13}$C NMR ($CDCl_3$) δ 158.0, 156.5, 146.3, 128.1, 120.9, 38.0, 32.8, 29.8, 26.1, 23.5, 23.0, 22.6, 22.40 14.3. HRMS (ES+) calcd for $C_{14}H_{21}N$ $(M + H)^+$: 204.1747. Found: 204.1744.

### 3-Butyl-1-methyl-6,7-dihydro-5H-cyclopenta[c]pyridine (2l) and 2-butyl-1-methyl-6,7-dihydro-5H-cyclopenta[c]pyridine (3l)

1-Acetyl-1-cylopentene oxime (75.8 mg) and 1-hexyne (0.29 mL) were subjected to the standard procedure with purification by chromatography (10:1:0.01 hexanes:*tert*-butyl methyl ether:triethylamine). 3-Butyl-1-methyl-6,7-dihydro-5H-cyclopenta[c]pyridine and 2-butyl-1-methyl-6,7-dihydro-5H-cyclopenta[c]pyridine were obtained as a 2.1:1 mixture of isomers in 89% yield (84 mg, 0.45 mmol) as a brown oil. $^{1}$H NMR ($CDCl_3$) δ 8.04 (s, 1H), 6.83 (s, 0.47H), 2.88 – 2.75 (m, 5.88H), 2.71 – 2.65 (m, 1H), 2.54 – 2.47 (m, 2H), 2.40 (m, 4.41H), 2.04 (m, 3H), 1.63 (m, 1H), 1.55 – 1.46 (m, 2H), 1.41 – 1.27 (m, 3H), 0.89 (m, 4.41H). $^{13}$C NMR ($CDCl_3$) δ 159.9, 154.0, 153.1, 152.0, 151.4, 147.0, 137.7, 135.3, 131.7, 116.6, 38.4, 33.1, 33.0, 32.5, 31.5, 31.1, 30.7, 30.5, 24.6, 24.3, 22.9, 22.7, 22.3, 22.0, 14.3, 14.1. HRMS (ES+) calcd for $C_{13}H_{19}N$ $(M + H)^+$: 190.1590. Found: 190.1585.

### 3- Butyl-5-methylpyridine (2m) and 2-*N*-butyl-5-methylpyridine (3m)

4-Phenyl-3-butene-2-one oxime (51.0 mg) and 1-hexyne (0.29 mL) were subjected to the standard procedure with purification by chromatography (10:1:0.01 hexanes:*tert*-butyl methyl ether:triethylamine). 3-Butyl-5-methylpyridine and 2-butyl-5-methylpyridine were obtained as a 2.4:1 mixture in 20% yield (15.4 mg, 0.10 mmol) as a brown oil. $^{1}$H NMR ($CDCl_3$) δ 8.32 (s, 1H), 8.23 (s, 2.4H), 8.22 (s, 2.4H), 7.35 (d, J = 7.9 Hz, 1H), 7.27 (s, 2.4H), 7.00 (d, J = 7.9 Hz, 1H), 2.75 – 2.68 (m, 2H), 2.57 – 2.51 (m, 4.8H), 2.28 (s, 7.2H), 2.26 (s, 3H), 1.70 – 1.61 (m, 2H), 1.56 (m, 4.8H), 1.40 – 1.28 (m, 6.8H), 0.94 – 0.82 (m, 10.2H). $^{13}$C NMR ($CDCl_3$) δ 159.8, 149.8, 147.9, 147.4, 137.6, 137.1, 136.7, 132.8, 130.2, 122.4, 37.9, 33.6, 32.8, 32.5, 22.8, 22.5, 18.6, 18.3, 14.2, 14.1.

### 5-Phenyl-2,3-dimethylpyridine (4a)

3-Methyl-3-butene-2-one oxime (60.0 mg) and ethynylbenzene (0.26 mL) were subjected to the standard procedure. 5-Phenyl-2,3-dimethylpyridine was purified by chromatography (20:1:0.01 hexanes:ethyl acetate:triethylamine) in 63% yield (58 mg, 0.32 mmol) as a brown oil. $^{1}$ H NMR ($CDCl_3$) δ 8.55 (s, 1H), 7.60 (s, 1H), 7.55 (d, *J* = 7.7 Hz, 2H), 7.45 (m, 2H), 7.36 (m, 1H), 2.54 (s, 3H), 2.34 (s, 3H). $^{13}$C NMR ($CDCl_3$) δ 156.2, 145.0, 138.2, 135.9, 134.5, 131.6, 129.3, 128.0, 127.3, 22.5, 19.5. HRMS (ES+) calcd for $C_{13}H_{13}N$ $(M + H)^+$: 184.1121. Found: 184.1119.

### 5-Benzyl-2,3-dimethylpyridine (4b)

3-Methyl-3-butene-2-one oxime (60.0 mg) and 2-propynylbenzene (0.29 mL) were subjected to the standard procedure. 5-Benzyl-2,3-dimethylpyridine was purified by column chromatography (20:1:0.01 hexanes:ethyl acetate:triethylamine) in 61% yield (61 mg, 0.31 mmol) as a brown oil. $^{1}$H NMR ($CDCl_3$) δ 8.13 (s, 1H), 7.19 (m, 2H), 7.09 (m, 4H), 3.80 (s, 2H), 2.37 (s, 3H), 2.11 (s, 3H). $^{13}$ C NMR ($CDCl_3$) δ 155.2, 146.8, 140.7, 137.9, 134.1, 131.4, 129.0, 128.9, 126.6, 38.8, 22.4, 19.4. HRMS (ES+) calcd for $C_{14}H_{15}N$ $(M + H)^+$: 198.1277. Found: 198.1274.

### 5-Cyclohexyl-2,3-dimethylpyridine (4c) and 6-cyclohexyl-2,3-dimethylpyridine (5c)

3-Methyl-3-butene-2-one oxime (60.0 mg) and ethynylcyclohexane (0.32 mL) were subjected to the standard procedure with purification by chromatography (10:1:0.01 hexanes:*tert*-butyl methyl ether:triethylamine). 5-Cyclohexyl-2,3-dimethylpyridine was obtained in 53% yield (50 mg, 0.26 mmol) as a brown oil. $^{1}$ H NMR ($CDCl_3$) δ 8.16 (s, 1H), 7.21 (s, 1H), 2.44 (s, 3H), 2.24 (s, 3H), 1.87 – 1.70 (m, 7H), 1.43 – 1.33 (m, 4H). $^{13}$C NMR ($CDCl_3$) δ 154.7, 145.6, 140.7, 135.9, 131.1, 41.9, 34.6, 27.1, 26.3, 22.4, 19.5. HRMS (ES+) calcd for $C_{13}H_{19}N$ $(M + H)^+$: 190.1590. Found: 190.1588. 6-Cyclohexyl-2,3-dimethylpyridine was obtained in 18% yield (17 mg, 0.09 mmol) as a brown oil. $^{1}$H NMR ($CDCl_3$) δ 7.31 (d, *J* = 7.8 Hz, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 2.64 (m, 1H), 2.47 (s, 3H), 2.22 (s, 3H), 1.94 (m, 2H), 1.85 – 1.70 (m, 4H), 1.49 – 1.35 (m, 4H). $^{13}$C NMR ($CDCl_3$) 163.8, 156.3, 137.9, 128.6, 118.0, 46.6, 33.6, 27.0, 26.5, 23.0, 19.1. HRMS (ES+) calcd for $C_{13}H_{19}N$ $(M + H)^+$: 190.1590. Found: 190.1588.

### 5-(Cyclohexylmethyl)-2,3-dimethylpyridine (4d)

3-Methyl-3-butene-2-one oxime (60.0 mg) and 2-propynylcyclohexane (0.36 mL) were subjected to the standard procedure with purification by chromatography (10:1:0.01 hexanes:*tert*-butyl methyl ether:triethylamine) in 64% yield (66 mg, 0.32 mmol) as a brown oil. $^{1}$H NMR ($CDCl_3$) δ 8.08 (s, 1H), 7.15 (s, 1H), 2.45 (d, *J* = 10.0 Hz, 3H), 2.37 (t, *J* = 11.4 Hz, 2H), 2.21 (d, *J* = 15.8 Hz, 3H), 1.65 (t, *J* = 11.2 Hz, 6H), 1.51 – 1.39 (m, 1H), 1.27 – 1.06 (m, 4H), 0.97 – 0.84 (m, 2H). $^{13}$C NMR ($CDCl_3$) δ 154.3, 146.9, 138.3, 134.1, 131.0, 40.7, 39.8, 33.2, 26.7, 26.4, 22.1, 19.3. HRMS (ES+) calcd for $C_{14}H_{21}N$ $(M + H)^+$: 204.1747. Found: 204.1744.

### 2,3-Diethyl-4,5,6-trimethylpyridine (6a)

Pentene-3-one oxime (68.0 mg) and 3-hexyne (0.29 mL) were subjected to the standard procedure. Purification by chromatography (10:1:0.01 hexanes:*tert*-butyl methyl ether:triethylamine) provide **6a** in 73% yield (66.1 mg, 0.37 mmol). The analytical data for this compound are consistent with previously reported data.[4]

### 1-Methyl-3,4-diphenyl-6,7-dihydro-5*H*-cyclopenta[*C*]pyridine (6b)

1-Acetyl-1-cylohexene oxime (84.2 mg) and diphenylacetylene (445 mg) were subjected to the standard procedure. Purification by chromatography on silica gel (10:1:0.01 hexanes:*tert*-butyl methyl ether:triethylamine) provided 6b in 79% yield (112 mg, 0.40 mmol). The analytical data for this compound are consistent with previously reported data.[5]

### Oxime Substrate Preparation

The syntheses of oximes **1a**,[5] **1b**,[5] **1c**,[20] **1f**,[21] **1g**,[5] **1i**,[5] **1k**,[22] **1l**[5] and **1m**[23] from commercially available ketones have been previously reported. Oxime **1h** was prepared from the corresponding ketone prepared according to literature methods.[24] The remaining oximes, **1d** and **1e** were prepared from the common Weinreb amide intermediate 2,2-

diethoxy-*N*-methoxy-*N*-methylpropanamide prepared from 2,2-diethoxypropionic acid ethyl ester.[25]

### 3-Methylenepentan-2-one oxime (1d)

In a 100 mL round bottom flask equipped with a stir bar, were added 4.0 g of Weinreb amide (19.5 mmol, 1.0 equiv) and 24 mL of THF. The flask was cooled to −20 °C, and 29.2 mL of ethylmagnesium chloride (58.5 mmol, 3.0 M., 3.0 equiv) was added slowly and allowed to warm to room temperature with stirring. After 14 h, the reaction mixture was cooled to 0 °C, and the reaction was quenched by slow addition of 1 N HCl (40 mL). The mixture was diluted with water (120 mL) and extracted with diethyl ether (3 × 120 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. The resulting oil was purified by chromatography (5:1 hexanes:ethyl acetate) to yield diethoxypentan-3-one as a colorless oil (1.8 g, 40%). $^{1}$H NMR ($CDCl_3$) δ 3.58 – 3.34 (m, 4H), 2.63 (q, *J* = 7.3 Hz, 2H), 1.37 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 6H), 1.04 (t, *J* = 7.3 Hz, 3H). $^{13}$C NMR ($CDCl_3$) δ 210.7, 102.5, 57.9, 31.5, 21.3, 15.7, 7.8. HRMS (ES+) calcd for $C_9H_{18}O_3$ $(M + Na)^+$: 197.1148. Found: 197.1179.

In a 100 mL round bottom flask equipped with a stir bar was combined 3.4 g of 2,2-diethoxypentan-3-one (19.5 mmol, 1.0 equiv), 10.5 g of methyltriphenylphosphonium bromide (30.0 mmol, 1.5 equiv), 3.3 g of potassium *t*-butoxide (30.0 mmol, 1.5 equiv), and 110 mL of toluene. The slurry was then heated to 110 °C with stirring for 14 h. The reaction mixture was cooled and solvents removed in vacuo. The resulting residue was filtered over basic alumina (hexanes) to yield a colorless oil (2.2 g, 65%) used without further purification. $^{1}$H NMR ($CDCl_3$) δ 5.36 (s, 1H), 4.97 (s, 1H), 3.47 – 3.29 (m, 4H), 2.09 – 2.00 (m, 2H), 1.36 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 6H), 1.07 (t, *J* = 7.4 Hz, 3H). $^{13}$C NMR ($CDCl_3$) δ 151.4, 110.6, 101.4, 56.3, 23.5, 23.37, 15.4, 12.4.

In a 4 dram vial, equipped with a stir bar, was combined 1.0 g of 2,2-diethoxy-3-methylenepentane (5.8 mmol, 1.0 equiv), 605 mg of hydroxylamine hydrochloride (8.7 mmol, 1.5 equiv), 667 mg of sodium acetate (8.1 mmol, 1.4 equiv) and 15 mL of methanol. The resulting slurry was stirred for 14 h at ambient temperature. The solvents were removed in vacuo. The white residue was dissolved in DCM (15 mL), filtered over Celite and the filtrate was concentrated in vacuo. The resulting oil was purified by chromatography (5:1 hexanes:ethyl acetate) to yield a colorless oil (230 mg, 35%).$^{1}$H NMR ($CDCl_3$) δ 9.63 (s, 1H), 5.40 (s, 1H), 5.26 (s, 1H), 2.36 (q, *J* = 7.1 Hz, 2H), 2.06 (s, 3H), 1.10 (t, *J* = 7.4 Hz, 3H). $^{13}$C NMR ($CDCl_3$) δ 156.5, 147.0, 115.7, 25.3, 13.2, 10.8. HRMS (ES+) calcd for $C_6H_{11}NO$ $(M + H)^+$: 114.0913. Found: 114.0911.

### 4-Methyl-3-methylenepentan-2-one oxime (1e)

In a 100 mL round bottom flask equipped with a stir bar, were added 5.0 g of Weinreb amide (24.3 mmol, 1.0 equiv) and 30 mL of THF. The round bottom flask was cooled to −20 °C, and 36.5 mL of isopropylmagnesium chloride (73.1 mmol, 2.0 M., 3.0 equiv) was added slowly and allowed to warm to room temperature with stirring. After 14 h, the reaction mixture was cooled to 0 °C, and the reaction was quenched by slow addition of 1 N HCl (40 mL). The mixture was diluted with water (120 mL) and extracted with diethyl ether (3 x 120 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. The resulting oil was purified by chromatography (5:1 hexanes:ethyl acetate) to yield a colorless oil (1.8 g, 54%).$^{1}$H NMR ($CDCl_3$) δ 3.50 (m, 2H), 3.39 (m, 2H), 3.23 (m, 1H), 1.37 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 6H), 1.07 (d, *J* = 6.8 Hz, 6H). $^{13}$C NMR ($CDCl_3$) δ214.7, 103.1, 57.9, 35.7, 21.5, 19.2, 15.7. HRMS (ES+) calcd for $C_{10}H_{20}O_3$ $(M + Na)^+$: 211.1305. Found: 211.1306.

In a 100 mL round bottom flask equipped with a stir bar was combined 1.5 g of 2,2-diethoxy-4-methylpentan-3-one (8.0 mmol, 1.0 equiv), 4.3 g of methyltriphenylphosphonium bromide (12.0 mmol, 1.5 equiv) and 1.3 g of potassium *t*-butoxide (12.0 mmol, 1.5 equiv), and 45 mL of toluene. The slurry was then heated to 110 °C with stirring for 14 h. The reaction mixture was cooled and solvents removed in vacuo. The resulting residue was filtered over basic alumina (hexanes) to yield a colorless oil (840 mg, 57%) used without further purification. $^{1}$H NMR ($CDCl_3$) δ 5.37 (d, *J* = 1.3 Hz, 1H), 5.07 (d, *J* = 1.2 Hz, 1H), 3.49 – 3.36 (m, 4H), 2.47 (sept, *J* = 6.8 Hz, 1H), 1.41 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 6H), 1.09 (d, *J* = 6.9 Hz, 6H). $^{13}$C NMR ($CDCl_3$) δ 110.9, 101.8, 56.6, 23.8, 23.7, 15.6, 12.7.

In a 4 dram vial, equipped with a stir bar, was combined 500 mg of 2,2-diethoxy-4-methyl-3-methylenepentane (2.7 mmol, 1.0 equiv), 280 mg of hydroxylamine hydrochloride (4.0 mmol, 1.5 equiv), 308 mg of sodium acetate (3.8 mmol, 1.4 equiv) and 13 mL of methanol. The slurry was stirred for 14 h at ambient temperature. The solvents were removed in vacuo. The white residue was dissolved in DCM (7 mL), filtered over Celite and the filtrate was concentrated in vacuo. The resulting oil was purified by chromatography (5:1 hexanes:ethyl acetate) to yield a colorless oil (160 mg, 47%).$^{1}$H NMR ($CDCl_3$) δ 8.79 (s, 1H), 5.36 (s, 1H), 5.24 (s, 1H), 2.94 – 2.83 (m, 1H), 2.05 (s, 3H), 1.09 (d, *J* = 6.8 Hz, 6H). $^{13}$C NMR ($CDCl_3$) δ 156.8, 152.4, 113.7, 29.0, 22.7, 11.4. HRMS (ES+) calcd for $C_7H_{13}NO$ $(M + H)^+$: 128.1069. Found: 128.1057.

### 5-Methylhex-3-en-2-one oxime (1h)

In a 100 mL round bottom flask equipped with a stir bar was combined 1.20 g (10.7 mmol) of 5-methylhex-3-en-2-one, 1.10 g of hydroxylamine hydrochloride (16.0 mmol), 1.30 g of sodium acetate (16.0 mmol) and 25 mL of methanol. The resulting slurry was stirred for 14 h at ambient temperature. The solvents were removed in vacuo. The resulting white residue was dissolved in DCM (25 mL). The resulting mixture was filtered over Celite, and the filtrate was concentrated in vacuo. The oxime was isolated by column chromatography (5:1 hexanes:ethyl acetate) in a 3.7:1 ratio of isomers as a colorless oil (550 mg, 40%). $^{1}$H NMR ($CDCl_3$) δ 9.13 (s, 1H), 6.83 (dd, *J* = 16.2, 1.4 Hz, 0.27H), 6.14 (dd, *J* = 16.2, 6.9 Hz, 1H), 6.11 – 5.99 (m, 2H), 2.41 (m, 1.27H), 1.99 (s, 3H), 1.98 (s, 0.81H), 1.07 (d, *J* = 6.8 Hz, 1.62H), 1.04 (d, *J* = 6.8 Hz, 6H). $^{13}$C NMR ($CDCl_3$) δ 156.8, 153.7, 147.4, 143.4, 124.9, 117.1, 32.1, 31.7, 22.4, 22.2, 17.2, 10.0. HRMS (ES+) calcd for for $C_7H_{13}NO$ $(M + H)^+$: 128.1070. Found: 128.1068.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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17. When 1-hexyne was heated in the presence of $[RhCl(coe)_2]_2$ and $P(OiPr)_3$, in THF for 24 h at 135 °C, no new alkene peaks, e.g. from alkyne dimerization, were observed by $^1H$ NMR analysis.
18. In all cases where a single regioisomer resulted, no other isomers were observed by $^1H$ NMR or GC/MS analysis of the crude material.
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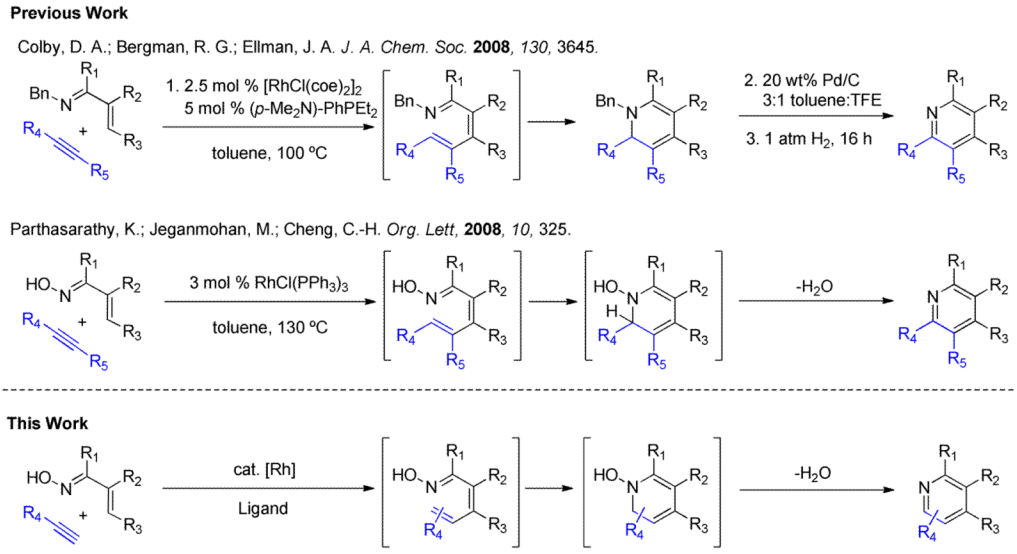
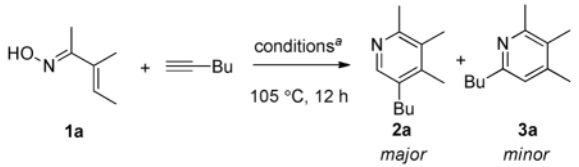



**Scheme 1.**
Synthesis of Pyridines via Rhodium-Catalyzed C–H Bond Functionalization

**Table 1**

Reaction Optimization[a]




**1a** **2a** *major* **3a** *minor*

| entry | $[RhCl(coe)_2]_2$ (mol %) | $P(OiPr)_3$ (mol %) | solvent | yield[b] (%) | ratio 2a:3a |
|---|---|---|---|---|---|
| 1 | 5 | 10 | THF | 81 | 2.9:1 |
| 2 | 5 | 20 | THF | 92 | 3.2:1 |
| 3 | 5 | 10 | toluene | 75 | 2.6:1 |
| 4 | 5 | 10 | CPME | 83 | 3.1:1 |
| 5[c] | 5 | 20 | THF | 92 | 2.9:1 |
| 6[c] | 1 | 4 | THF | 84 | 2.4:1 |
| 7[c,d] | 5 | 20 | THF | 92 | 2.3:1 |

[a] All reactions were performed by employing 0.05 mmol of ketoxime 1a and 0.25 mmol of 1-hexyne.

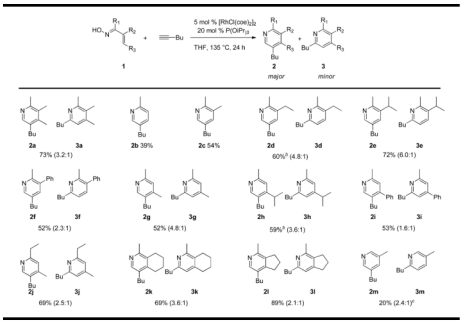
[b] Yields determined by $^1H$ NMR relative to 2,6-dimethoxytoluene as an internal standard.

[c] 135 °C.

[d] 1.5 equiv of 1-hexyne.

## Table 2

Substrate Scope of Oxime[a]



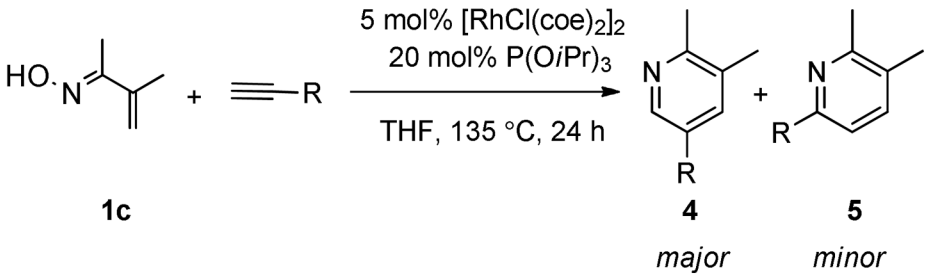

[a] All reactions were performed by heating ketoxime **1** (1 equiv), alkyne (5 equiv), $[RhCl(coe)_2]_2$ (5 mol %), $P(OiPr)_3$ (20 mol %), in THF (0.1 M) in a sealed tube for 24 h at 135 °C. Yields represent isolated material. When a mixture of isomers is indicated, yields correspond to the combined yield of both isomers.

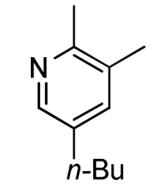
[b] Major isomer isolated; ratio determined by NMR analysis of the crude material.

[c] 48 h at 175 °C

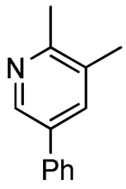
**Table 3**

Substrate Scope of Terminal Alkynes[a]

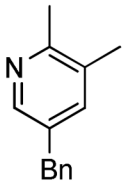


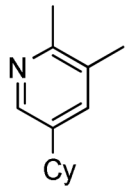

**2c** 54%



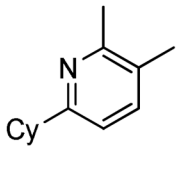

**4a** 63%




**4b** 61%

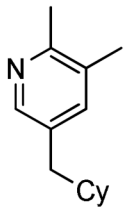



**4c**[b]

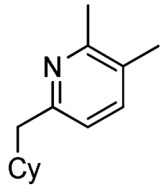



**5c**[b]

70% (3.0:1)




**4d**




**5d**

84%[c] (3.2:1)

[a] See footnote a in Table 1.

[b] 48 h.

[c] Ratio determined by NMR analysis of the crude material.