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

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Supporting Information

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 phenylacetylene, 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*-benzylimines 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 inexpensive triisopropyl 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 3:1 mixture of regioisomers **2a** and **3a** when P(O-*i*-Pr)$_3$ was used as the ligand (entry 1, Table 1). Different Rh−ligand stoichiometries were evaluated with 2 equiv of the phosphite providing optimal results (entries 1 and 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 composed of other phosphites and phosphoramidites such as P(OPh)$_3$, P(O-*t*-Bu)$_3$, P(O-*i*-Pr)$_2$NEt$_2$, and P(O-*i*-Pr)$_2$N-*i*-Pr$_2$ with varying steric and electronic properties was undertaken; however, none proved to be superior to the simple and inexpensive P(O-*i*-Pr)$_3$ 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 (Table 2). The ketoxime starting material lacking either α- or β-substitution provided the disubstituted pyridine product **2b**,**c** 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**−**f** and **3d**−**f**). Ketoximes with only β-substitution resulted in pyridine products with generally lower regioselectivities (**2g**−**j** and **3g**−**j**). It is noteworthy that cyclic ketoximes (**2k**,**l** and **3k**,**l**) and ketoximes substituted with

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

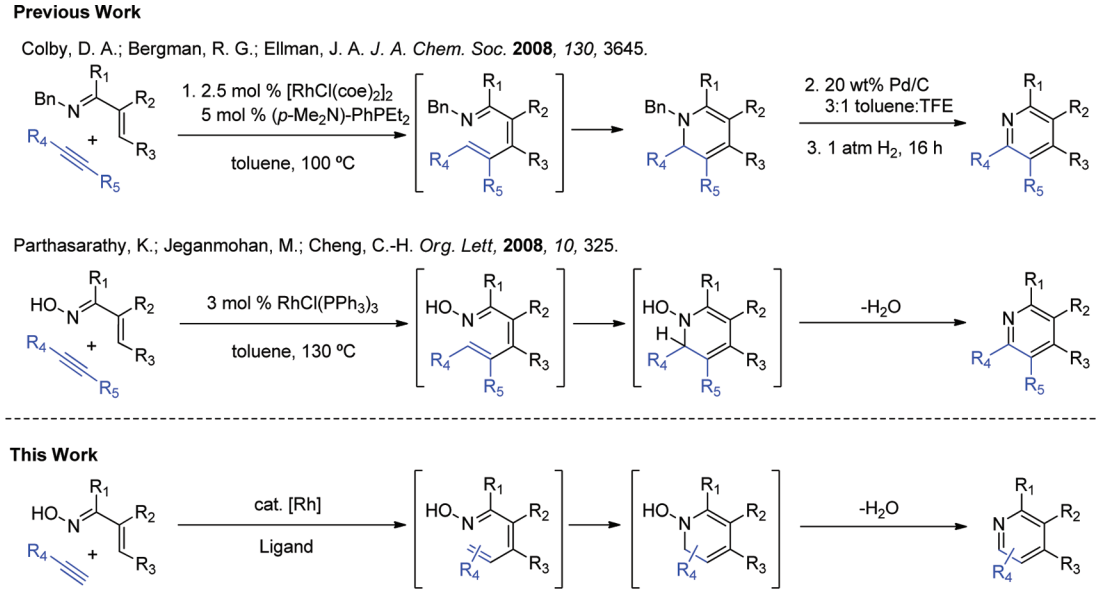
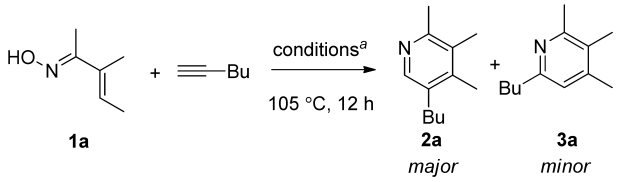


Table 1. Reaction Optimization[a]



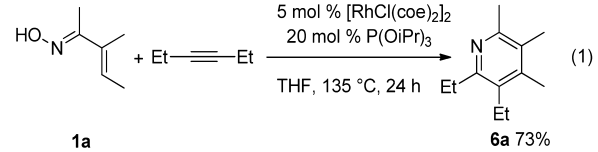
entry	$[RhCl(coe)_2]_2$ (mol %)	$P(OiPr)_3$ (mol %)	solvent	yield[b] (%)	ratio **2a**:**3a**
1	5	10	THF	81	2.9:1
2	5	20	THF	92	3.2:1
3	5	10	toluene	75	2.6:1
4	5	10	CPME	83	3.1:1
5[c]	5	20	THF	92	2.9:1
6[c]	1	4	THF	84	2.4:1
7[c,d]	5	20	THF	92	2.3:1

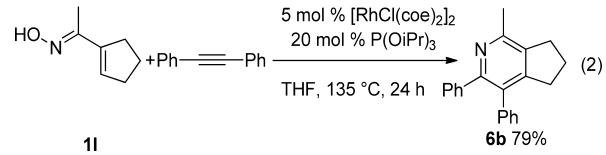
[a]All reactions were performed by employing 0.05 mmol of ketoxime **1a** and 0.25 mmol of 1-hexyne. [b]Yields determined by ^1H NMR relative to 2,6-dimethoxytoluene as an internal standard. [c]135 °C. [d]1.5 equiv of 1-hexyne.

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 (Table 3). 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,d** and **5c,d**, respectively). Additionally, the use of internal alkynes afforded pyridines **6a** and **6b** in high yield (eq 1 and 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. This affords 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 phosphite 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

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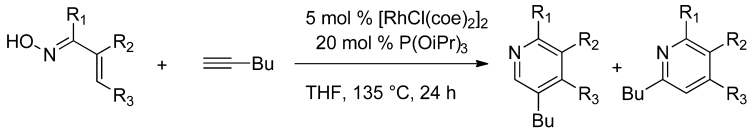
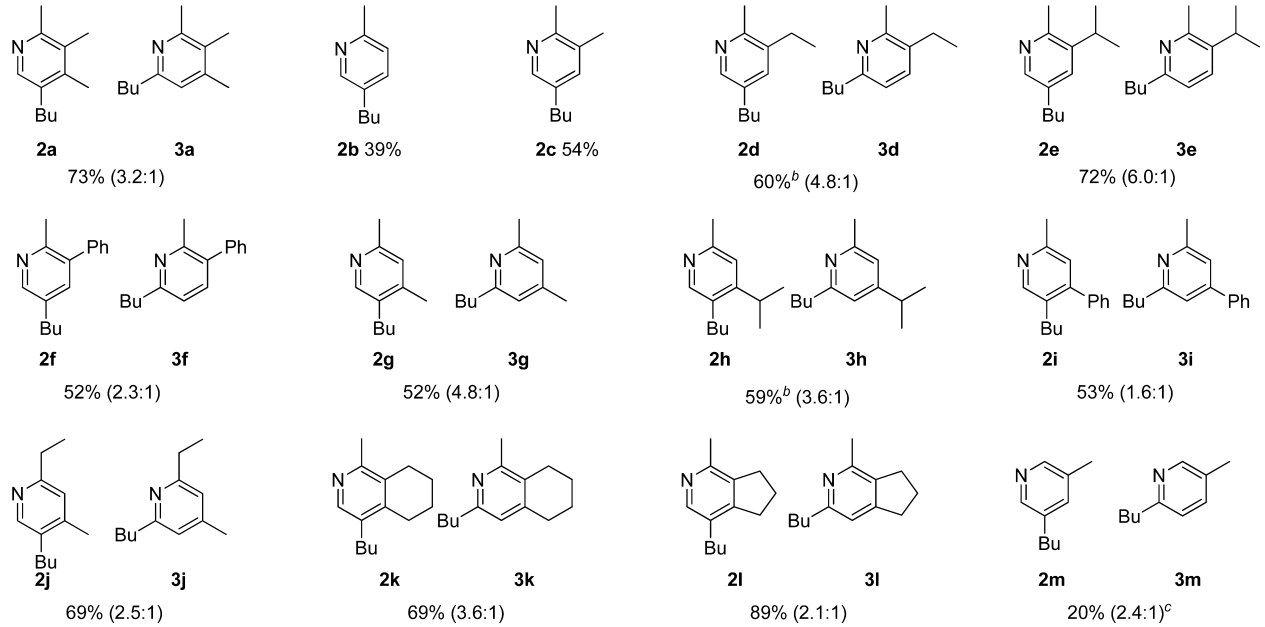
Table 2. Substrate Scope of Oxime[a]

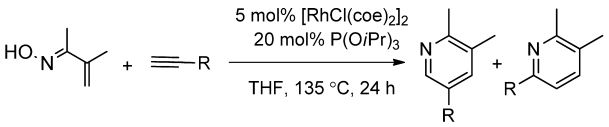


1 → 2 (major) + 3 (minor)

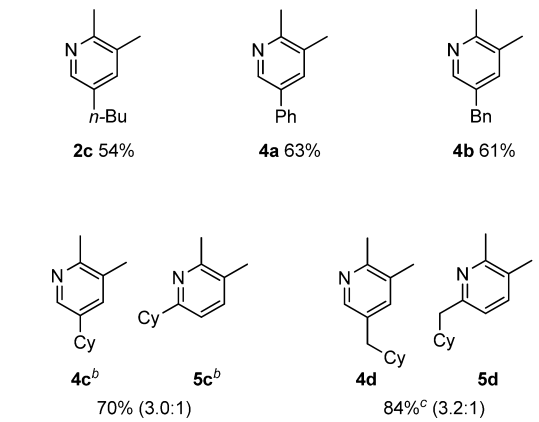


[a]All reactions were performed by heating ketoxime **1** (1 equiv), alkyne (5 equiv), $[RhCl(coe)_2]_2$ (5 mol %), and $P(O\text{-}i\text{-}Pr)_3$ (20 mol %) in THF (0.1 M) in a sealed tube for 24 h at 135 °C. Yields represent isolated material. When a mixture of isomers is indicated, yields correspond 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]



1c → 4 (major) + 5 (minor)



[a]See footnote a in Table 2. [b]48 h. [c]Ratio determined by NMR analysis of the crude material.

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 and 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 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 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-buten-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,

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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-Buten-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-Penten-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-hexen-2-one oxime (77.0 mg) and 1-hexyne (0.29 mL) were subjected to the standard procedure. 5-Butyl-2-methyl-4-isopropylpyridine 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-buten-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-Penten-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.

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3-Butyl-1-methyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine (2l) and 2-Butyl-1-methyl-6,7-dihydro-5*H*-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-5*H*-cyclopenta[*c*]pyridine and 2-butyl-1-methyl-6,7-dihydro-5*H*-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-buten-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-buten-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-buten-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-buten-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-buten-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). Penten-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) provides **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, which was synthesized 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, 29.2 mL of ethylmagnesium chloride (58.5 mmol, 3.0 M., 3.0 equiv) was added slowly, and the mixture was 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 *tert*-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 were 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) and 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

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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 × 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 ($CDCl_3$) δ 214.7, 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), 1.3 g of potassium *tert*-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 were 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) and 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 were 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.

■ ASSOCIATED CONTENT

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.

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Notes

The authors declare no competing financial interest.

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