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Synthesis of Pharmaceutically Relevant Nitrogen Heterocycles via Rhodium Catalyzed C–H Bond Functionalization

by

Rhia Marissa Martin

A dissertation submitted in partial satisfaction of the
requirements for the degree of
Doctor of Philosophy
in Chemistry
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of the
University of California, Berkeley

Committee in Charge:

Professor Robert G. Bergman, Chair
Professor F. Dean Toste
Professor Leonard F. Bjeldanes

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Abstract

Synthesis of Pharmaceutically Relevant Nitrogen Heterocycles viaRhodium Catalyzed C–H Bond Functionalization

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Doctor of Philosophy in Chemistry

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Professor Robert G. Bergman, Chair

Chapter 1. An introduction to my work on the development of new methodologies based upon the rhodium catalyzed C–H bond functionalization is presented. The intermediacy of 1,2-dihydropyridines towards the preparation of several important classes of nitrogen heterocycles is discussed.

Chapter 2. A method for the preparation of pyridines from α,β-unsaturated ketoximes and terminal alkynes is developed. Elements of regioselectivity in the C–H bond alkenylation step are explored.

Chapter 3. The synthesis of highly substituted isoquinuclidines is described. The 1,2-dihropyridines that result from C–H bond functionalization of α,β-unsaturated imines serve as diene components in the Diels-Alder cycloaddition with a variety of dienophiles.

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Acknowledgements

In my formative years, it seemed that the adults were infinitely wise. I knew several children in secondary school, and they were not wise; they were yet children. But, somehow the adults had it; so clearly then, wisdom was something conferred in university. At seventeen, I remember preparing to begin Georgetown University, eagerly awaiting the keys to the "wisdom safe" that must be distributed at convocation. However, four years later as a senior, while appreciative of the many glorious things I did find at that fine institution, I was dismayed that I still had much ground to cover before anyone would think to call me wise. But, I was about to begin graduate school. Surely, Wisdom 101 would be a mandatory part of the curriculum there?

I have since given up on garnering "wisdom" from institutes of higher learning. But, I realize now that while searching for that nebulous wisdom, I have retained quite a bit of knowledge along the way. So regardless of what I *have* retained, first I must thank my advisors: Jon and Bob, for trying to impart so much more. I have been privileged to work for advisors who were also excellent teachers. Inside the classroom and without, it appeared as if they felt it their duty to nurture my mind, to mold me into an organic chemist, of whom someday I hope they will be proud.

And, while I am still a little unsure about economics, it seems to me, at least, knowledge does trickle down. Much of what I've learned in graduate school has come from other graduate students, most notably, the ones I found when I arrived. Among the most senior of which was Denise Colby; she was an excellent mentor when I joined the Ellman and Bergman groups. With her seeming boundless knowledge of physical organic chemistry and practical laboratory skills, she was the graduate scientist to whom I aspired. She was helpful and patient, and in many ways, when I grow up I still want to be like her.

Not only did MaryAnn Robak welcome me to the Ellman laboratory, but on most weekends, she also welcomed me into her home. All of the members of Chez Robak have earned a special place in my heart. And I know you will be the kind of friends on whom I can always rely.

Directly senior to me were Sirilata (Van) Yotphan, Andy "Double A" Tsai and Peter Marsden. Pete and Van were a helpful and entertaining duo. I'm sure it's the many coffee breaks with Pete, leading up to my qualifying exam, which kept me as sane as could be expected. Double A always had the most creative solutions to common laboratory problems. I will always be thankful that he taught me the proper use for a popsicle stick.

Kyle Kimmel was my first friend at Berkeley. We met on the first day of graduate school. We looked for groups and ultimately joined the Ellman group at the same time. Together with our friend Jane Wang, Kyle got me through hours of preparation for our qualifying examinations. And to keep me company, he took his exam within a week of me. Kyle, we may yet end up working side by side, exclusively on chemistry that is autocatalytic and has a pleasant odor.

Tyler "T-bags" Baguley joined the group after us. While he may be known for his fluorescent colored clothing and his unyielding wit, I can also attest that he is a wonderful friend and

officemate. If he should ever offer to move out someone else's equipment and move yours into his workspace, I highly recommend that you let him.

The following year, the lab took on Andrew Buesking. Without a doubt Andrew is the most mild-mannered and polite person I have ever met. I have greatly enjoyed being a corrupting influence. To the group members who entered with Andrew (Jason and Vivian): I wish you could have spent more time with us.

In addition to the graduate students, the postdocs (Jason, Eric, Yajing, Simon, and the Michael's) played a vital part in the group. They contributed techniques from other research groups around the world.

To Sodom and Gomorrah: I will miss you. To the Bergman group members who gave me a second home at Berkeley. To my roommates (Alex and Emily), who gave me a home apart from the lab. To the members of my incoming graduate class in other groups who helped me through (Jane, Rachel and Steve). To everyone I'm leaving behind (Tyler, Andrew, James, Shuming and Apiwat): I know the lab will be in excellent hands, but only a trained expert should feed the lion.

To the village that it took to raise me. To my grandmother, aunts, uncle, cousins, and most importantly, my parents. They took a basically apathetic child and pushed her to excel. I never would have spent the last five, long, years in graduate school without you. So, umm… thanks. To my sister, Rhandi, who has been my closest confidant and primary emotional support.

To everyone I have been remiss in not mentioning.

To you all.

Thank you.

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Chapter 1. Introduction

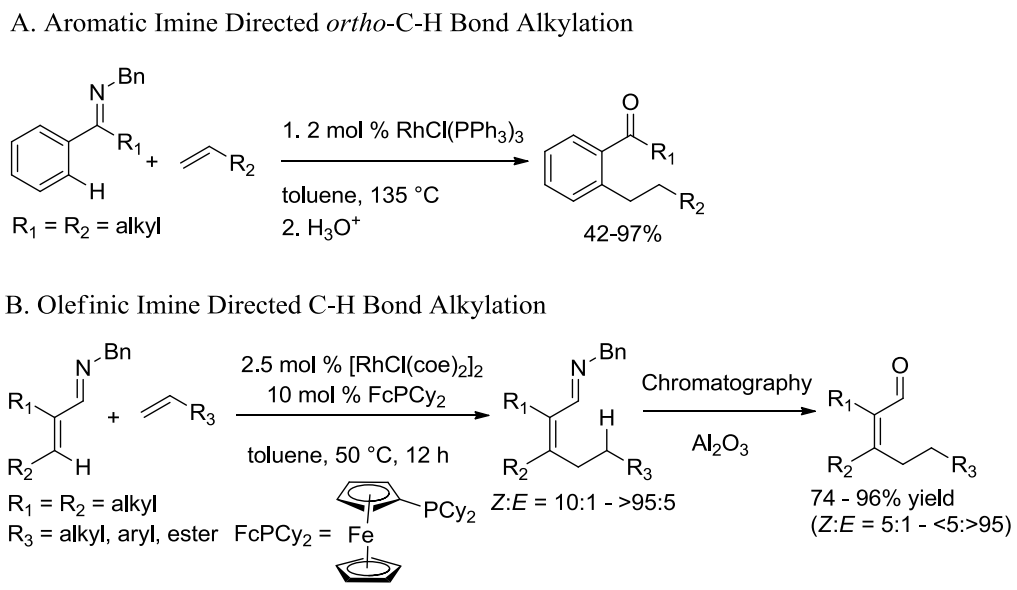
Recently in the Ellman and Bergman groups a method was discovered for preparing 1,2-dihydropyridines via rhodium-catalyzed coupling of α,β-unsaturated imines and alkynes. Subsequent in situ oxidation provides access to the corresponding pyridines. This method was expanded to include terminal alkynes, challenging substrates for transition-metal mediated transformations. In contrast formal reduction of the dihydropyridine intermediates through Diels-Alder reaction with alkenes provides access to isoquinuclidines, an important class of piperidines, in excellent diastereoselectivities.

Introduction

Some of the most important recent advances in synthetic organic chemistry have been in the development of methods for the formation of C–C bonds. Many coupling methods have been developed to affect this transformation that tolerate a wide variety of functional groups. While these methods provide access to many products with different substitution patterns, their substrate scope is limited by the need for prefunctionalization. An alternative approach that has received significant attention is the activation and functionalization of otherwise chemically inert C–H bonds as a means to C–C bond formation. C–H bond functionalization is a more efficient route to a diverse collection of targets due to the abundance of C–H bonds in organic compounds. Furthermore, it proves to be a more economical approach with reduced production of metallated and halogenated byproducts. However, the same ubiquity of C–H bonds that makes this chemistry robust creates the challenge of controlling the selectivity of the transformation.

To address this issue of chemoselectivity, several approaches have been established for guiding the reaction selectivity, such as utilizing the inherent stereoelectronic reactivity of a molecule or relying on the chelation assistance afforded by pendant heteroatoms. One of the first synthetically useful C–H bond functionalization methodologies was reported by Jun and coworkers.[1] They established that imines could be utilized to direct the *ortho*-functionalization of aromatic C–H bonds (Scheme 1.1A). In this strategy, using Wilkinson's catalyst, coordination of metal affords selective activation of *ortho*-C–H bonds and subsequent addition across unactivated terminal alkenes.

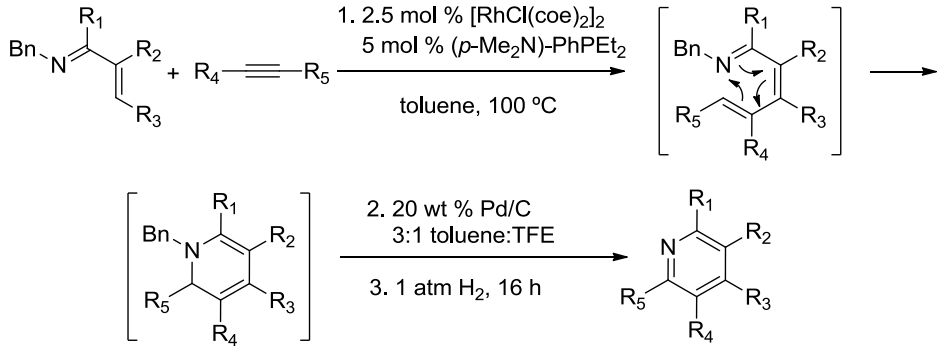
Scheme 1.1. Imine Directed C–H Bond Alkylation



While *aromatic* C–Hfunctionalization has been well established, the analogous functionalization of *olefinic* C–H bonds has been less explored. Recent work in the Ellman and Bergman groups established that imines were also competent directing groups for the C–H activation of α,β-unsaturated imines.[2-4] This method afforded the *Z* isomer of corresponding alkylated product exclusively and, following hydrolysis, provided access to functionalized tri- and tetrasubstitutedα,β-unsaturated aldehydes and ketones (Scheme 1.1B).[2]

Furthermore, use of an alkyne successfully resulted in an alkenylated product. However, it was discovered that the coupling of internal alkynes did not lead to the expected conjugated products, but rather, *in situ* intramolecular electrocyclization yielded 1,2-dihydropyridines, which have been demonstrated to be versatile intermediates (Scheme 1.2).Subsequent oxidation and removal of the benzyl protecting group yielded highly substituted pyridines in an overall one-pot procedure (Scheme 1.2).[3] C–H bond functionalization is a powerful strategy for the preparation of nitrogen heterocycles which are prevalent structural motifs in natural products and drug candidates.[5] In particular, pyridines are the most used nitrogen heterocycle in pharmaceutical research.[6]

Scheme 1.2. One-Pot Synthesis of Functionalized Pyridines from α,β-unsaturated Imines



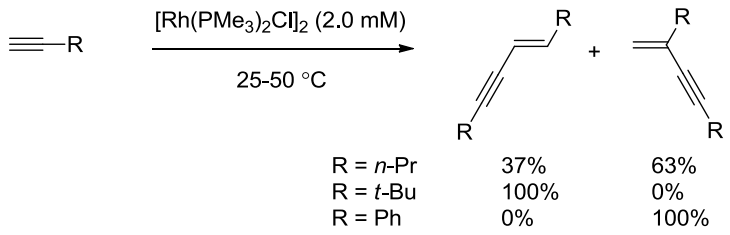
Synthesis of Pyridines using Terminal Alkynes

While we had developed a stereoselective C–H bond functionalization methodology for the synthesis of highly substituted pyridines from α,β-unsaturated imines and internal alkynes, terminal alkynes remained challenging coupling partners. With the exception of the electronically deactivated phenylacetylene, efforts to employ terminal alkynes in this transformation led to intractable mixtures.[3,7] In efforts to expand the substrate scope of our pyridine synthesis, my first project was therefore to develop conditions for the coupling of terminal alkynes.

Late transition metals, such as palladium[8], ruthenium[9], iridium[10] and rhodium[11-12], are known to mediate the dimerization of terminal alkynes.In particular, a survey of the literature revealed that electron rich ligands provided efficient catalyst systems for the rhodium-catalyzed

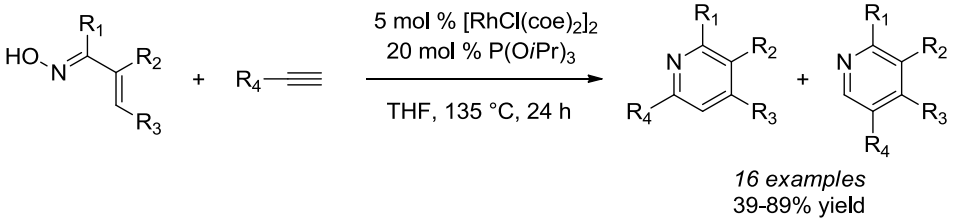
dimerization (Scheme 1.3). Therefore, the aniline based phosphine ligands that we had developed for olefinic alkenylation were competitively producing the dimer side products.

Scheme 1.3. Rhodium Mediated Enyne Dimerization[11]



In contrast, as discussed in Chapter 2, we discovered that electron deficient phosphites and phosporamidites suppress the deleterious enyne dimerization while performing the desired C–H bond alkenylation. Triisopropylphosphite was demonstrated to afford the desired pyridine products, in moderate to excellent regioselectivities (Scheme 1.4).[13]

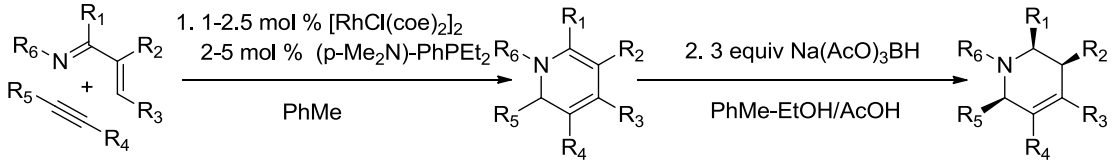
Scheme 1.4. Synthesis of Pyridines from Ketoximes and Terminal Alkynes



Synthesis of Isoquinuclidines

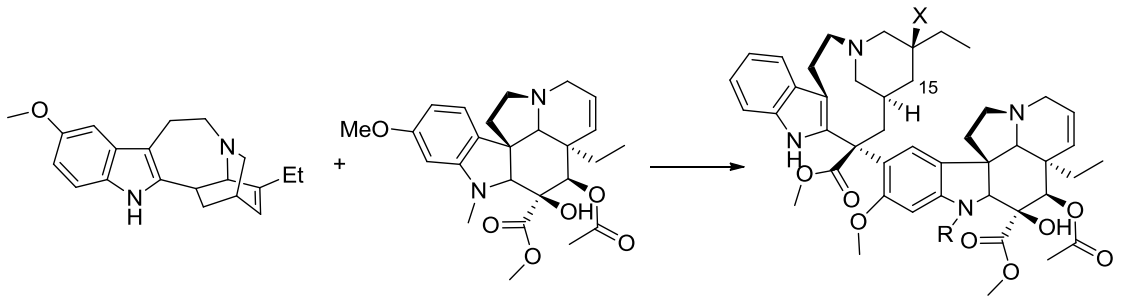
After showing that the 1,2-dihydropyridines that result from rhodium-catalyzed alkenylation of α,β-unsaturated imines can be efficiently oxidized to the corresponding pyridines, we next investigated the opposite mode of reactivity through their reduction to piperidine derivatives. Recently, the Ellman and Bergman groups demonstrated a one-pot procedure for the highly diastereoselective synthesis of 1,2,3,6-tetrahydropyridines via a C–H activation-cyclization-reduction cascade (Scheme 1.5).[14] In this strategy, stereoselective protonation of the dihydropyridine intermediate is followed by *in situ* reduction of the resulting iminium ion. As described in Chapter 3, we were interested in further using 1,2-dihydropyridines as intermediates for the synthesis of isoquinuclidines, which are even more complex bridged bicyclic piperidines with interesting biological activities.

Scheme 1.5. Highly Diastereoselective Synthesis of Tetrahydropyridines



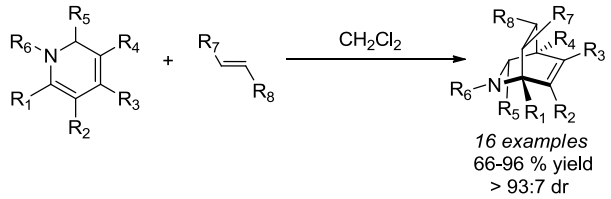
Isoquinuclidines constitute an important class of piperidines that form the core of several classes of natural products. In particular, Iboga alkaloids have been used to treat human addiction to multiple drugs of abuse.[15] They are characterized by an indole-[2,3] fusion of an isoquinuclidine and a seven-membered indolazepine ring. Analog synthesis has primarily focused on modifications to the indolazepine ring.[16,17] Furthermore, vinca alkaloids, which are derived from the dimerization of the Iboga alkaloid, catharanthine, and vindoline (Figure 1.1), have engendered much attention due to their use as cancer therapeutics.[18] The preparation of analogs for pharmacological studies has involved modification of the naturally occurring dimer[19] as well as the synthesis and coupling of modified versions of the monomers.[20] As such, a method for preparing differentially substituted isoquinuclidines would provide access to a variety of pharmaceutically relevant targets.

Figure 1.1. Synthesis of Vinca Alkaloids



We found that the thermal Diels-Alder reaction of *N*-alkyl and -aryl 1,2-dihydropyridines with a variety of dienophiles resulted in isoquinuclidines with high and differential substitution (Chapter 3). Furthermore, this reaction proceeded with outstanding diastereoselectivities (Scheme 1.6). The Lewis acid additive, zinc chloride, was identified to promote Diels-Alder reaction with the electronically deactivated crotonaldehyde.

Scheme 1.6. Synthesis of Isoquinuclidines from 1,2-Dihydropyridines via Diels-Alder Reaction



Conclusion

We demonstrated that 1,2-dihydropyridines are versatile intermediates for the preparation of several classes of pharmaceutically relevant nitrogen heterocycles. Our method for their preparation proceeds through rhodium-catalyzed alkenylation of α,β-unsaturated imines with alkynes and subsequent electrocyclization. This convergent synthesis allows for the introduction of a high degree of differential substitution to the resulting dihydropyridines. After oxidation, this substitution is translated to the corresponding pyridines. We expanded the substrate scope of this process to include terminal alkynes, while suppressing deleterious enyne dimerization side reactions. Finally, we describe in chapter 3 that through Diels-Alder reaction between these dihydropyridines and a variety of dienophiles, substituted isoquinuclidines could be accessed with high diastereoselectivities.

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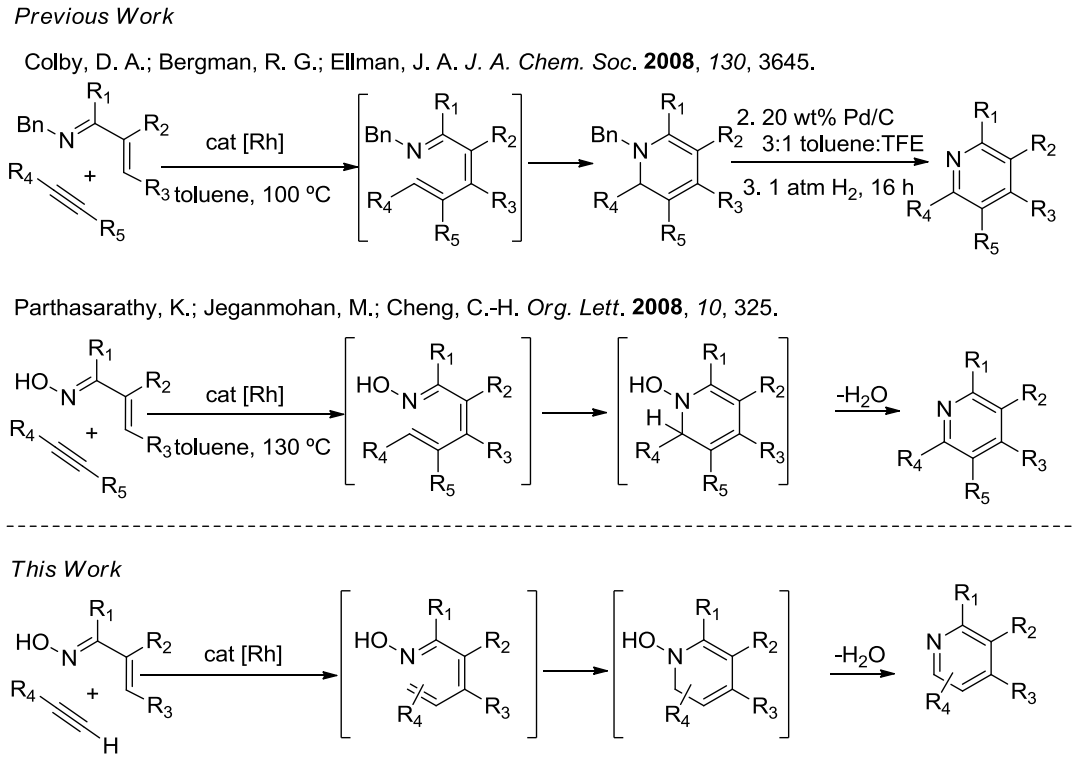
Chapter 2. Synthesis of Pyridines from Ketoximes and Terminal Alkynes via C–H Bond Functionalization

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 or phosphoramidite ligands is important to suppress dimerization of the terminal alkynes to enynes. This work has been published (Martin, R. M.; Bergman, R. G.; Ellman, J. A. J. Org. Chem. ***2012****, 77, 2501).*

Introduction

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] We have previously reported an efficient synthesis of highly substituted pyridines from *α,β*-unsaturated imines and alkynes.[2-4] 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 2.1). 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 2.1).[5] However, for neither method, with the exception of the electronically deactivated phenylacetylene, were terminal alkynes competent substrates.

Scheme 2.1. Synthesis of Pyridines via Rhodium-Catalyzed C-H Bond Functionalization



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 made their application to a variety of transition-metal mediated C≡C functionalizations that employ alkynes as coupling partners a challenging problem.[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]

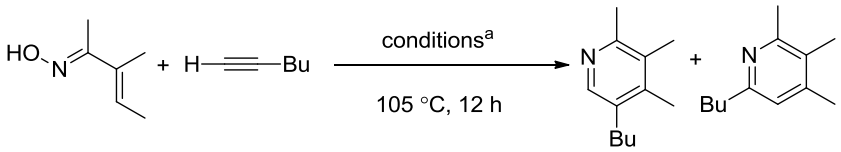
Herein, we report an effective method for the synthesis of highly substituted pyridines via the C–H bond functionalization of *α,β*-unsaturated ketoximes with terminal alkynes through the use of inexpensive trisopropyl phosphite as a key ligand for minimizing alkyne homocoupling side reactions.

Results and Discussion

I. Reaction Development

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 **2.1a** and 1-hexyne provided pyridine products in high yield as a mixture of regioisomers **2.2a** and **2.3a,** in good ratio when P(O*i*Pr)$_3$ was used as the ligand (Table 2.1, entry 1). Different Rh-ligand stoichiometries were evaluated with 2 equiv of the phosphite providing optimal results (entry 1-2). 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 6). Moreover, lower catalyst loading (1 mol % of the Rh-precatalyst) at this higher temperature gave similar yields and regioselectivity (entry 5).

Table 2.1. Reaction Optimization[a]



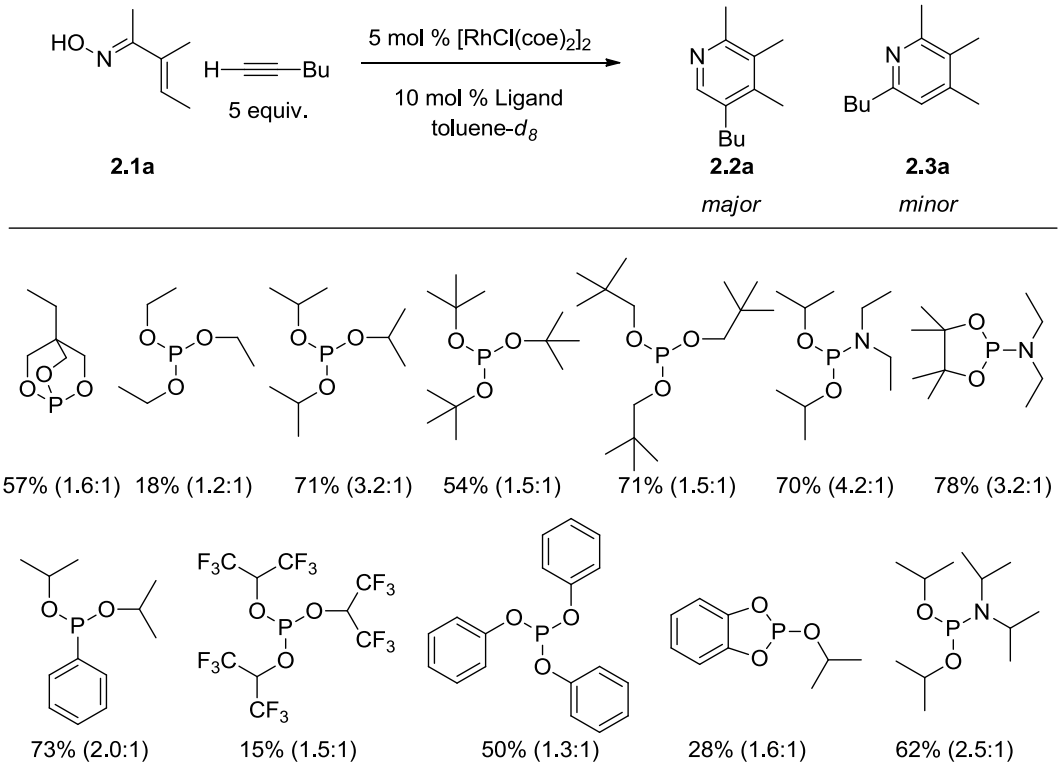
2.1a **2.2a** *major* **2.3a** *minor*

entry	[RhCl(coe)$_2$]$_2$ (mol %)	P(O*i*Pr)$_3$ (mol %)	solvent	yield[b] (%)	ratio **2.2a**:**2.3a**
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

[a]All reactions were performed by employing 0.05 mmol of ketoxime **2.1a** and 0.25 mmol of 1-hexyne.[b]Yields determined by ^{1}H NMR relative to 2,6-dimethoxytoluene as an internal standard. [c] 135 °C.

A ligand screen comprised of other phosphites and phosphoramidites with varying steric and electronic properties was undertaken (Table 2.2). Despite the large number of ligands evaluated, trends based upon parameters such as ligand sterics or donor properties were not apparent. Moreover, none of the ligands proved to be superior to the simple and inexpensive P(O*i*Pr)$_3$, in terms of yield or regioselectivity.

Table 2.2. Ligands Screened for C-H Bond Alkenylation[a]



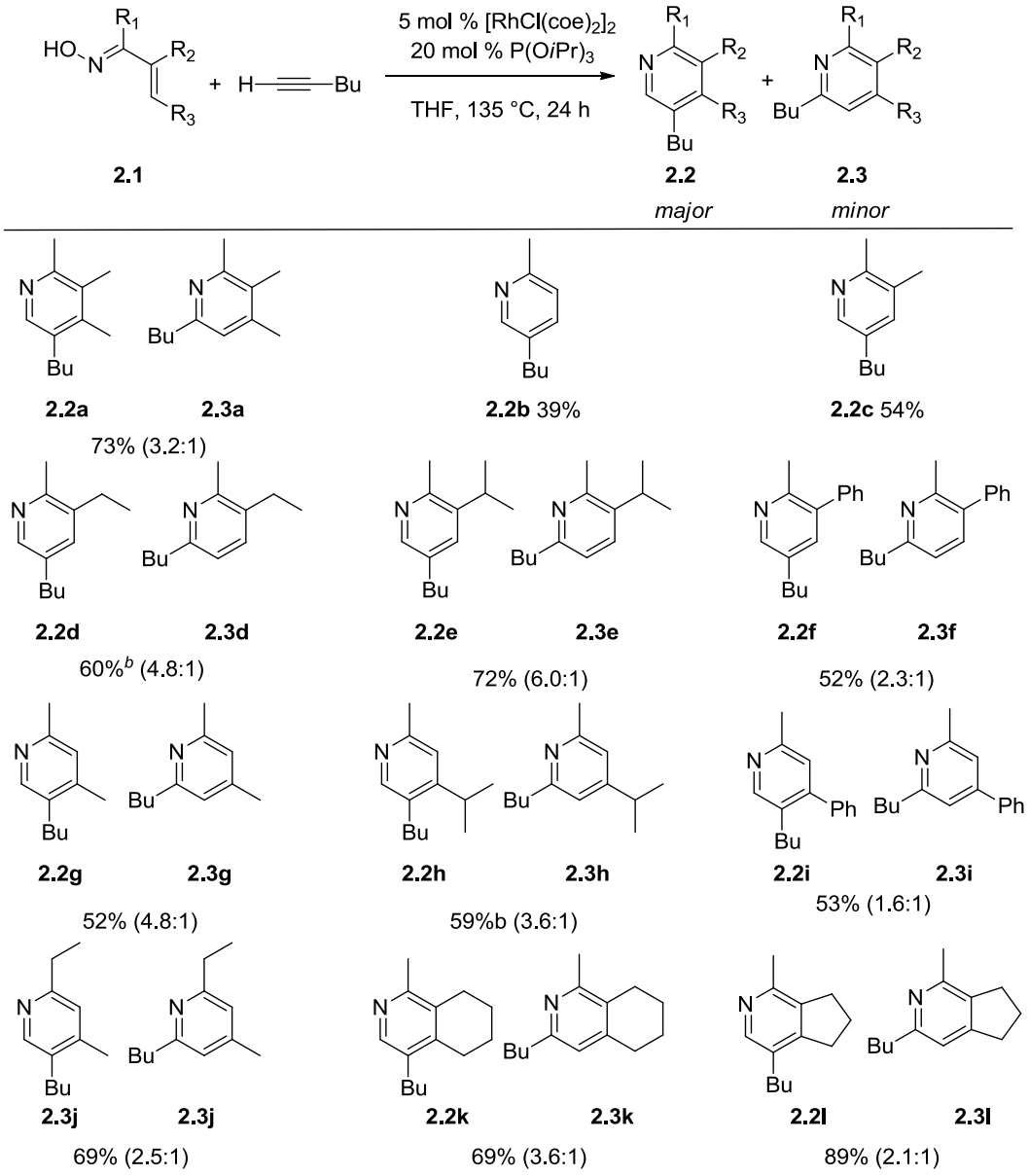
[a] All reactions were performed by employing 0.05 mmol of ketoxime **2.1a** and 0.25 mmol of 1-hexyne. Yields and ratios were determined by ^{1}H NMR relative to 2,6-dimethoxytoluene as an internal standard.

II. Synthetic Scope

We next sought to evaluate the substrate scope for the preparation of differentially substituted pyridine products using a variety of α,β-unsaturated ketoximes. The ketoxime starting material lacking either α- or β-substitution provided the disubstituted pyridine product **2.2b**-**2.2c** in moderate yield as a single regioisomer (Table 2.3).[17] 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 (**2.2c**-**2.2f** and **2.3d**-**2.3f**). Ketoximes with only β-substitution resulted in pyridine products with generally lower regioselectivities (**2.2g**-**2.2j** and **2.3g**-**2.3j**). It is noteworthy that cyclic ketoximes (**2.2k**-**2.2l** and

2.3k-**2.3l**) and ketoximes substituted with both aromatic and branched and unbranched alkyl groups were all well tolerated.

Table 2.3. Substrate Scope of Ketoxime[a]

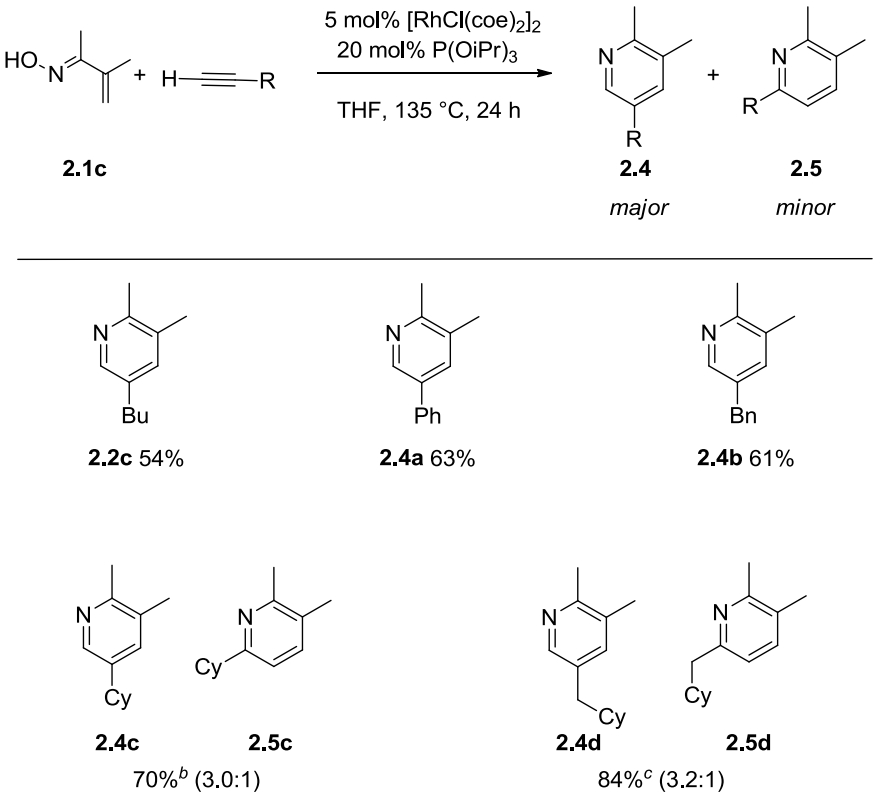


[a]All reactions were performed by heating ketoxime **2.1** (1 equiv), alkyne (5 equiv), $[RhCl(coe)_2]_2$ (5 mol %), $P(OiPr)_3$ (20 mol %), in THF (0.1 M) in a sealed tube for 24 h at 135ºC; yields represent isolated material. [b] Ratio determined by NMR analysis of the crude material.

Terminal alkyne scope was also quite reasonable (Table 2.4). Both phenylacetylene and phenylmethylacetylene reacted to give a single pyridine regioisomer in good yield (**2.4a, 2.4b**).

In addition,α- and β-branched terminal alkynes coupled in high yields and with reasonable reioselectivities (**2.4c**-**2.4d** and **2.5c**-**2.5d**, respectively).

Table 2.4. Substrate Scope of Terminal Alkynes[a]

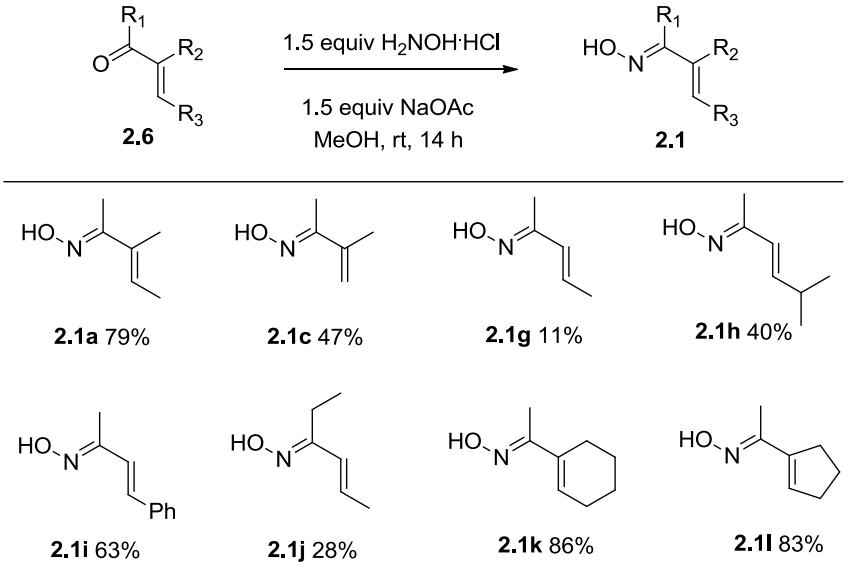


[a]All reactions were performed by heating ketoxime **2.1c** (1 equiv), alkyne (5 equiv), $[RhCl(coe)_2]_2$ (5 mol %), $P(OiPr)_3$ (20 mol %), and THF (0.1 M) in a sealed tube for 24 h at 135ºC; yields represent isolated material. [b] 48 h. [c] Ratio determined by NMR analysis of the crude material.

III. Substrate Preparation

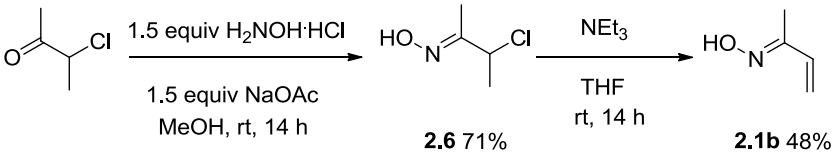
Generally, α,β-unsaturated oximes were synthesized through condensation of the corresponding α,β-unsaturated enones with hydroxylamine (Table 2.5). As preparation of α,β-unsaturated oximes was not the focus of our investigation, isolation of pure material was our primary goal and yields were not optimized. α,β-dialkyl oximes (**2.1a**, **2.1k**, and **2.1l**) as well as oxime **2.1i**, bearing an aromatic β-substituent, were obtained in high yield. β-Alkyl oximes (**2.1g**, **2.1h** and **2.1j**), which are more susceptible to Michael additions, were also obtained in pure form albeit in lower yields.

Table 2.5. General Synthesis of α,β-Unsaturated Enones



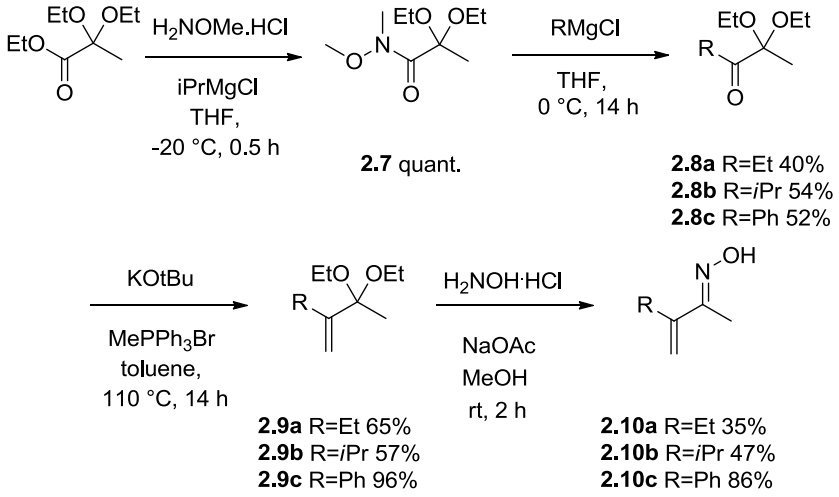
Due to the enhanced reactivity of methyl vinyl ketone, an alternate route to **2.1b** was developed (Scheme 2.1). First, condensation of hydroxylamine with 3-chloro-2-butanone, provided oxime **2.6** in good yield. Subsequent chloride elimination from **2.6** provided access to oxime **2.1b**.

Scheme 2.1. Preparation of But-3-en-2-one Oxime (**2.1b**)



Additionally, a route to α-alkyl α,β-unsaturated oximes was developed (Scheme 2.2). Conversion of 2,2-diethoxypropionic acid ethyl ester to the corresponding acetal protected Weinreb amide **2.7** afforded a common intermediate for introduction of the α-alkyl group. Next, Grignard addition to **2.7** and subsequent Wittig homologation provided access to α,β-unsaturated acetals **2.8a-c**. Finally, acid catalyzed acetal deprotection wasfollowed by *in situ* conversion of the corresponding ketones to the desired α-alkyl α,β-unsaturated oximes **2.10a-c**.

Scheme 2.2. Preparation of α-Alkyl α,β-Unsaturated Oximes



Conclusion

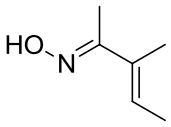
In summary, we have developed a high yielding rhodium-catalyzed C–H bond functionalization of *α,β*-unsaturated ketoximes with terminal alkynes to afford substitutedpyridines in moderate to excellent regioselectivities through the use of triisopropyl phosphite as a simple and inexpensive ligand that suppresses the undesired competitive dimerization of terminal alkynes.

Experimental Section

I. General Experimental Methods. All catalytic reactions were set up inside an inert atmosphere (N_2) glovebox utilizing glassware that was oven-dried (150 ºC) and evacuated while hot prior to use, whereas the work-up and isolation of the products from the catalytic reactions were conducted on the bench-top using standard techniques. Tetrahydrofuran was passed through a column of activated alumina under nitrogen and stored in a glovebox over activated 4 Å molecular sieves prior to use. Toluene-d_8 was deoxygenated by sparging with nitrogen gas followed by storage over activated 4 Å molecular sieves for 24 h prior to use. Chloroform-d_1 was used as received. Unless otherwise noted, all reagents and materials were obtained from commercial suppliers and used without further purification. Chromatography was performed on 230-240 mesh silica gel. ^{1}H and ^{13}C{^{1}H} NMR characterization data were collected at 300 K on a spectrometer operating at 500.1 and 125.8 MHz (respectively) with chemical shifts reported in parts per million relative to $CHCl_3$ (^{1}H NMR; 7.26 ppm, ^{13}C{^{1}H} NMR; 77.23 ppm). Mass spectra were obtained using a Q-TOF mass spectrometer. High resolution mass spectra (HRMS) were obtained using a Bruker 9.4 TAPEXQeFT-ICR mass spectrometer. Low resolution mass

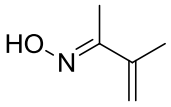
spectra were obtained using anAgilent 6890 gas chromatograph mass spectrometer, equipped with an EI detector (LRMS).Melting points were determined on an Electrothermal melting point apparatus and are reported uncorrected.

III. General Procedure for the Synthesis of α,β-unsaturated Oximes. In a 100 mL round bottom flask equipped with a stir bar was combined ketone (1.0 equiv), hydroxylamine hydrochloride (1.5 equiv), sodium acetate (1.5 equiv), and methanol (0.44 M). 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 (0.44 M). The resulting mixture was filtered over Celite, and the filtrate was concentrated in vacuo. The pure oxime product was then obtained either by column chromatography or recrystallization.



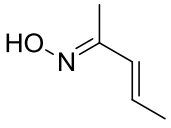
2.1a

3-Methyl-3-penten-2-one (2.1a). The general procedure was employed using 1.2 mL (10.7 mmol) of 3-methyl-3-penten-2-one, 1.1 g of hydroxylamine hydrochloride (16.0 mmol), 1.3 g of sodium acetate (16.0 mmol) and 25 mL of methanol. Following work-up, the oxime was purified by recrystallization from hexanes to yield a white crystalline solid (1.0 g, 79%). mp 67.5–69.0 ºC.δ 8.26 (s, 1H), 6.04 (q, *J* = 6.9 Hz, 1H), 2.06 (s, 3H), 1.88 (s, 3H), 1.83 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 158.01, 133.62, 127.47, 14.39, 12.65, 10.32. HRMS (ES+) calcd for $C_6H_{11}NO$ $(M + H)^+$: 114.0913. Found: 114.0975.



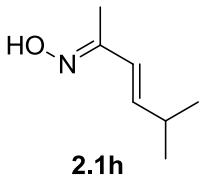
2.1c

3-Methyl-3-buten-2-one oxime (2.1c). The general procedure was employed using 3.00 mL (31.4 mmol) of 3-methyl-3-buten-2-one, 3.4 g of hydroxylamine hydrochloride (48.1 mmol), 4.00 g of sodium acetate (48.1 mmol) and 75 mL of methanol. Following work-up, the oxime was purified by recrystallization from hexanes to yield a white crystalline solid (1.5 g, 47%). mp 36.5-37.5 ºC. ^{1}H NMR ($CDCl_3$) δ 8.25 (s, 1H), 5.38 (s, 1H), 5.28 (s, 1H), 2.05 (s, 3H), 1.95 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 156.51, 140.68, 117.38, 19.08, 9.87. LRMS (EI+) Calcd for C_5H_9NO $(M)^+$: 99. Found 99.



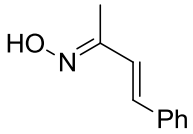
2.1g

Pent-3-en-2-one oxime (2.1g). The general procedure was employed using 1.00 mL (10.7 mmol) of pent-3-ene-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. Following work-up, the oxime was purified by column chromatography (5:1 hexanes:ethyl acetate) to yield a colorless oil (200 mg, 11%). HRMS (ES+): ^{1}H NMR ($CDCl_3$) δ 6.17 – 6.01 (m, 2H), 1.97 (s, 3H), 1.83 (d, *J* = 5.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 156.75, 131.53, 128.92, 18.76, 9.96. (EI+) Calcd for C_5H_9NO $(M)^+$: 99. Found 99.



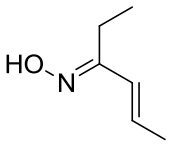
2.1h

5-Methylhex-3-en-2-one oxime (2.1h). The general procedure was employed using 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. Following work-up, the oxime was isolated by column chromatography (5:1 hexanes:ethyl acetate) in a 3.7:1 ratio of isomers to yield 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 $C_7H_{13}NO$ $(M + H)^+$: 128.1070. Found: 128.1068.



2.1i

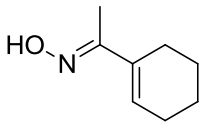
4-Phenylbut-3-en-2-one oxime (2.1i). The general procedure was employed using 1.60 mL (10.7 mmol) of benzylideneactone, 1.10 g of hydroxylamine hydrochloride (16.0 mmol), 1.30 g of sodium acetate (16.0 mmol) and 25 mL of methanol. Following work-up, the oxime was purified by column chromatography (5:1 hexanes:ethyl acetate) to yield a white, crystalline solid (1.1 g, 63%). mp 97.0–99.5 ºC. ^{1}H NMR ($CDCl_3$) δ 7.49 – 7.44 (m, 2H), 7.38 – 7.31 (m, 2H), 7.29 (m, 1H), 6.88 (m, 2H), 2.15 (s, 3H).^{13}C NMR ($CDCl_3$) δ 157.13, 136.66, 133.76, 129.09, 128.78, 127.22, 126.09, 10.06. HRMS (ES+) calcd for $C_{10}H_{11}NO$ $(M + H)^+$: 162.0913. Found: 162.0910.



2.1j

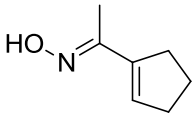
Hex-4-en-3-one (2.1j). The general procedure was employed using 3.0 mL (31.4 mmol) of hex-4-en-3-one, 3.4 g of hydroxylamine hydrochloride (48.1 mmol), 4.0 g of sodium acetate (48.1 mmol) and 75 mL of methanol. Following work-up, the oxime was purified by column chromatography (5:1 hexanes:ethyl acetate) to yield a 2.3:1 mixture of isomers as a colorless oil (1.1 g, 28%). ^{1}H NMR ($CDCl_3$) δ 8.19 (s, 1.23H), 6.78 (m, 0.30H), 6.22 (m, 0.30H), 6.07 (m,

2H), 2.51 (q, *J* = 7.6 Hz, 2H), 2.39 (q, *J* = 7.5 Hz, 0.30H), 1.89 (dd, *J* = 6.7, 1.7 Hz, 0.91H), 1.85 (dd, *J* = 6.2, 1.1 Hz, 3H), 1.11 (m, 3.91H). ^{13}C NMR ($CDCl_3$) δ 160.76, 156.79, 134.45, 130.49, 127.36, 120.04, 24.07, 18.79, 18.34, 17.44, 11.89, 10.88. HRMS (ES+) calcd for $C_6H_{11}NO$ $(M + H)^+$: 114.0913. Found: 114.0938.



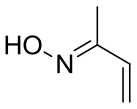
2.1k

1-Acetyl-1-cyclohexene oxime (2.1k). The general procedure was employed using 1.4 mL (10.7 mmol) of 1-acetyl-1-cyclohexene, 1.1 g of hydroxylamine hydrochloride (16.0 mmol), 1.3 g of sodium acetate (16.0 mmol) and 25 mL of methanol. Following work-up, the oxime was purified by column chromatography (5:1 hexanes:ethyl acetate) to a yield a white, crystalline solid (1.3 g, 86%). The analytical data for this compound are consistent with previously reported data.[4]



2.1l

1-Acetyl-1-cyclopentene oxime (2.1l). The general procedure was employed using 0.6 mL (5.2 mmol) of 1-acetyl-1-cyclopentene, 0.6 g of hydroxylamine hydrochloride (7.8 mmol), 0.54 g of sodium acetate (7.8 mmol) and 15 mL of methanol. Following work-up, the oxime was purified by column chromatography (5:1 hexanes:ethyl acetate) to yield a white, crystalline solid (540 mg, 83%). mp 88.0–89.0 ºC. ^{1}H NMR ($CDCl_3$) δ 9.72 (s, 1H), 6.14 (s, 1H), 2.56 (m, 2H), 2.46 (m, 2H), 2.08 (s, 3H), 1.93 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 154.23, 141.34, 133.67, 33.41, 31.61, 23.43, 11.53. HRMS (ES+) calcd for $C_7H_{11}NO$ $(M + H)^+$: 126.0913. Found: 126.0919.

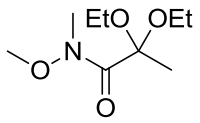


2.1b

But-3-en-2-one oxime (2.1b). 3-Chlorobutan-2-one oxime was prepared by the general procedure using 2.2 mL (21.8 mmol) of 3-chloro-2-butanone, 2.3 g of hydroxylamine hydrochloride (32.7 mmol), 2.7 g of sodium acetate (32.7 mmol) and 50 mL of methanol. Following work-up, the oxime was purified by column chromatography (5:1 hexanes:Ethyl acetate) to yield a colorless oil (1.5 g, 71%). The analytical data for this compound are consistent with previously reported data.[18]

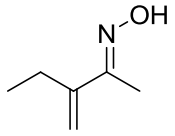
In a 4 dram vial, equipped with a stir bar, was combined 3-chlorobutan-2-one oxime (1.5 g, 13.1 mmol), triethyl amine (5.1 mL, 36.9 mmol) and Et_2O (5 mL). The resulting slurry was stirred for 14 h at ambient temperature. The solvents were removed in vacuo. The resulting white residue was dissolved in DCM (10 mL), filtered and the filtrate concentrated in vacuo. The resulting white residue was purified by column chromatography (5:1 hexanes:ethyl acetate) to yield a

colorless oil (670 mg, 48%). ^{1}H NMR ($CDCl_3$) δ 9.06 (br s, 1H), 6.42 (m, 1H), 5.58 (m, 1H), 5.43 (m, 1H), 2.00 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 156.81, 134.40, 118.92, 9.25. LRMS (EI+) Calcd for C_4H_7NO $(M)^+$: 86. Found 86.



2.7

2,2-Diethoxy-*N*-methoxy-*N*-methylpropanamide. To a solution of 2,2-diethoxypropionic acid ethyl ester[25](17.6 g, 92.5 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (13.5 g, 138 mmol) in THF (175 mL) was added *iso*-propylmagnesium chloride (139 mL of 2.0 M in THF, 278 mmol) at –20 °C dropwise. After the mixture was stirred at –20 °C for 30 min, aqueous ammonium chloride (350 mL) was slowly added with stirring. The mixture was warmed to ambient temperature and the resulting layers were separated. The aqueous phase was extracted with ethyl acetate (3 x 30 mL). The combined organic phases were dried over sodium sulfate and concentrated in vacuo to yield the desired Weinreb amide analytically pure and in quantitative yield (19.0 g). ^{1}H NMR ($CDCl_3$) δ 3.67 (s, 3H), 3.60 – 3.47 (m, 4H), 3.23 (s, 3H), 1.49 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 170.0, 101.3, 61.0, 58.0, 35.2, 20.8, 15.5. HRMS (ES+) calcd for $C_9H_{19}NO_4$ $(M + Na)^+$: 228.1213. Found: 228.1202.



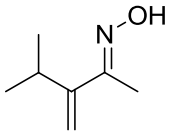
2.1d

3-Methylenepentan-2-one oxime (2.1d). To 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 round bottom flask was cooled to -20 ºC, 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 ºC, 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 column 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 resulting slurry was then heated to 110 ºC and stirred for 14 hrs. 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%), and 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 resulting white residue was dissolved in DCM (15 mL), filtered over Celite and the filtrate was concentrated in vacuo. The resulting oil was purified by column 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.



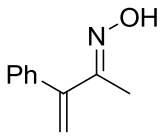
2.1e

4-Methyl-3-methylenepentan-2-one oxime (2.1e). To 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 ºC, 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 ºC, 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 column 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) and 1.3 g of potassium *t*-butoxide (12.0 mmol, 1.5 equiv), and 45 mL of toluene. The resulting slurry was then heated to 110 ºC and stirred for 14 hrs. 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%), and 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 resulting slurry was stirred for 14 h at ambient temperature. The solvents were removed in vacuo. The resulting white residue was dissolved in DCM (7 mL), filtered over Celite and the filtrate was concentrated in vacuo. The resulting oil was purified by column 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.



2.1f

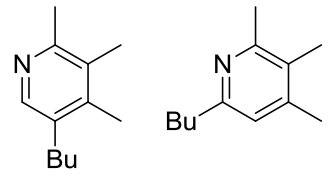
3-Phenylbut-3-en-2-one oxime (2.1f). To a 100 mL round bottom flask equipped with a stir bar, were added 0.5 g of Weinreb amide (2.4 mmol, 1.0 equiv) and 8 mL of THF. The round bottom flask was cooled to -20 ºC, and 2.6 mL of phenylmagnesium chloride (7.3 mmol, 2.8 M, 3.0 equiv) was added slowly and allowed to warm to room temperature with stirring. After 14 h, the reaction mixture was cooled to 0 ºC, and the reaction was quenched by slow addition of 1 N HCl (2 mL). The mixture was diluted with water (15 mL) and extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. The resulting oil was purified by column chromatography (5:1 hexanes:ethyl acetate) to yield a colorless oil (281 g, 52%). ^{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 214.73, 103.11, 57.93, 35.69, 21.52, 19.22, 15.71. HRMS (ES+) calcd for $C_{13}H_{18}O_3$ $(M + Na)^+$: 245.1148. Found: 245.1142.

In a 4 dram vial, equipped with a stir bar, was combined 900.0 mg of 2,2-diethoxy-1-phenylpropan-1-one (8.0 mmol, 1.0 equiv), 2.2 g of methyltriphenylphosphonium bromide (6.1 mmol, 1.5 equiv) and 637 mg of potassium *t*-butoxide (5.7 mmol, 1.5 equiv)), and 20 mL of toluene. The resulting slurry was then heated to 110 ºC and stirred for 14 h. The reaction mixture was cooled and solvents removed in vacuo. The resulting residue was filtered over basic alumina (hexanes) to yield to yield a colorless oil (867 mg, 96%) that used without further purification. ^{1}H NMR ($CDCl_3$) δ 7.45 (dd, J = 8.1, 1.6 Hz, 2H), 7.32 – 7.23 (m, 3H), 5.71 (s, 1H), 5.39 (s, 1H), 3.58 – 3.43 (m, 4H), 1.37 (s, 3H), 1.21 (t, J = 7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 149.10, 140.60 , 128.29, 128.18, 127.53, 117.48, 100.73, 56.71, 24.21, 15.55.

In a 4 dram vial, equipped with a stir bar, was combined 423 mg (1.9 mmol) of (3,3-diethoxybut-1-en-2-yl)benzene, 200 mg of hydroxylamine hydrochloride (2.8 mmol, 1.5 equiv), 234 mg of

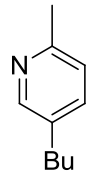
sodium acetate (2.8 mmol, 1.5 equiv) and 6 mL of methanol. The resulting slurry was stirred for 14 h at ambient temperature. The solvents were removed in vacuo. The resulting white residue was dissolved in DCM (5 mL) and filtered over Celite. The filtrate was then concentrated in vacuo. The resulting residue was purified by column chromatography to yield a white, crystalline solid (266 mg, 86%). ^{1}H NMR ($CDCl_3$) δ 8.61 (s, 1H), 7.55 – 7.24 (m, 5H), 5.57 (d, *J* = 0.9 Hz, 1H), 5.43 (d, *J* = 0.9 Hz, 1H), 2.06 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 157.47, 147.10, 139.48, 128.66, 128.48, 128.09, 118.15, 12.22. (ES+) calcd for $C_{10}H_{11}O_3$ $(M + Na)^+$: 184.0733. Found: 184.0732.

III. General Procedure for Pyridine Synthesis. The desired alkyne (2.5 mmol) was placed in a sealable glass vessel in a inert atmosphere box. To the reaction vessel was added $[RhCl(coe)_2]_2$ (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 x 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.



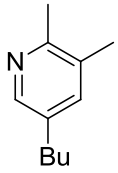
2.2a **2.3a**

5-*n*-Butyl-2,3,4-trimethylpyridine (2.2a) and 6-*n*-butyl-2,3,4-trimethylpyridine (2.3a). 3-Methyl-3-pentene-2-one oxime (68.0 mg) and 1-hexyne (0.29 mL) were subjected to the standard procedure. 5-*n*-Butyl-2,3,4-trimethylpyridine and 6-*n*-butyl-2,3,4-trimethylpyridine were purified by column chromatography on silica gel (10:1:0.01 hexanes:*tert*-butylmethyl ether:triethylamine). 5-*n*-Butyl-2,3,4-trimethylpyridine was obtained in a 56% isolated 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 154.06, 146.60, 143.54, 134.01, 130.03, 32.96, 31.08, 23.40, 22.80, 15.38, 15.28, 14.14. HRMS (ES+) calcd for $C_{12}H_{19}N$ $(M + H)^+$: 178.1590. Found: 178.1589. 6-*n*-Butyl-2,3,4-trimethylpyridine was obtained in a17% isolated 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 158.61, 155.91, 145.85, 127.44, 122.07, 38.00 , 32.79, 23.31, 22.95, 20.25, 14.68, 14.31. HRMS (ES+) calcd for $C_{12}H_{19}N$ $(M + H)^+$: 178.1590. Found: 178.1589.



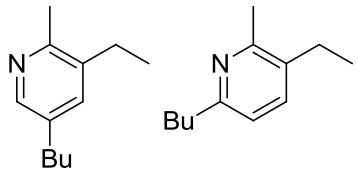
2.2b

5-*n*-Butyl-2,3-dimethylpyridine (2.2b). 3-Methyl-3-butene-2-one oxime (60.0 mg) and 1-hexyne (0.29 mL) were subjected to the standard procedure. 5-*n*-butyl-2,3-dimethylpyridine was purified by column chromatography on silica gel (20:1:0.01 hexanes:ethyl acetate:triethylamine) in a 39% isolated 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 154.47, 146.61, 137.45, 135.55, 131.03, 33.69, 32.43, 22.49, 22.31, 19.35, 14.12. HRMS (ES+) calcd for $C_{10}H_{15}N$ $(M + H)^+$: 150.1277. Found: 150.1274.



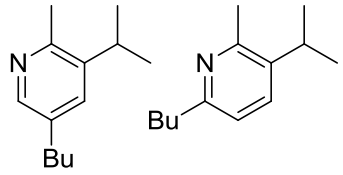
2.2c

5-*n*-Butyl-2,3-dimethylpyridine (2.2c). 3-Butene-2-one oxime (51.4 mg) and 1-hexyne (0.29 mL) were subjected to the standard procedure. 5-*n*-Butyl-2,3-dimethylpyridine was purified by column chromatography on silica gel (20:1:0.01 hexanes:ethyl acetate:triethylamine) in a 54% isolated 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 155.83, 149.42, 136.58, 135.09, 123.12, 33.70, 32.61, 24.23, 22.52, 14.18. HRMS (ES+) calcd for$C_{11}H_{17}N$ $(M + H)^+$: 164.1434. Found: 164.1430.



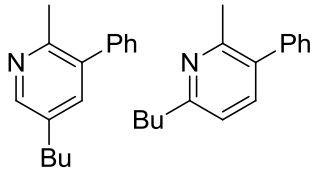
2.2d **2.3d**

5-*n*-Butyl-3-ethyl-2-methylpyridine (2.2d). 3-Ethyl-3-pentene-2-one oxime (68.0 mg) and 1-hexyne (0.29 mL) were subjected to the standard procedure. 5-*n*-Butyl-3-ethyl-2-methylpyridine was purified by column chromatography on silica gel (10:1:0.01 hexanes:*tert*-butylmethyl ether:triethylamine) in a 50% isolated 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 155.77, 149.51, 145.50, 133.76, 124.87, 32.68, 30.13, 24.07, 22.88, 18.94, 14.22. HRMS (ES+) calcd for$C_{12}H_{19}N$ $(M + H)^+$: 178.1590. Found: 178.1588.



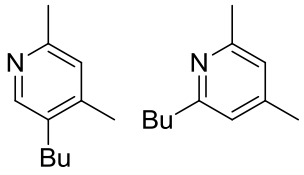
2.2e **2.3e**

***n*-Butyl-3-isopropyl-2-methylpyridine (2.2e) and 6-*n*-butyl-3-isopropyl-2-methylpyridine (2.3e)**. 3-isopropyl-3-pentene-2-one oxime (77.0 mg) and 1-hexyne (0.29 mL) were subjected to the standard procedure. 5-*n*-butyl-3-isopropyl-2-methylpyridine and 6-*n*-butyl-3-isopropyl-2-methylpyridine were purified by column chromatography on silica gel (10:1:0.01 hexanes:*tert*-butylmethyl ether:triethylamine).5-*n*-Butyl-3-isopropyl-2-methylpyridine was obtained in a62% isolated 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 152.93, 146.01, 141.50, 136.00, 133.16, 33.72, 32.76, 29.26, 23.12, 22.56, 21.60, 14.13. HRMS (ES+) calcd for$C_{13}H_{21}N$ $(M + H)^+$: 192.1747. Found: 192.1750. 6-*n*-Butyl-3-isopropyl-2-methylpyridine was obtained in a10% isolated 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 159.04, 155.15, 138.83, 133.17, 120.50, 38.17, 32.71, 29.18, 23.28, 22.97, 22.36, 14.33. HRMS (ES+) calcd for$C_{13}H_{21}N$ $(M + H)^+$: 192.1747. Found: 192.1746.



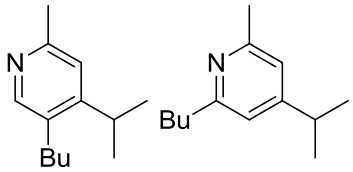
2.2f **2.3f**

5-*n*-Butyl-3-ethyl-2-methylpyridine (2.2f) and 6-*n*-butyl-3-ethyl-2-methylpyridine (2.3f). 3-Phenyl-3-pentene-2-one oxime (97.6 mg) and 1-hexyne (0.29 mL) were subjected to the standard procedure. 5-*n*-butyl-3-ethyl-2-methylpyridine and 6-*n*-butyl-3-ethyl-2-methylpyridine were purified by column chromatography on silica gel (10:1:0.01 hexanes:*tert*-butylmethyl ether:triethylamine). 5-*n*-Butyl-3-phenyl-2-methylpyridine was obtained in a36% isolated 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 153.34, 148.35, 140.60, 137.60, 136.85, 135.57, 129.43, 128.73, 127.73, 33.75, 32.60, 23.28, 22.67, 14.28. HRMS (ES+) calcd for$C_{16}H_{19}N$ $(M + H)^+$: 226.1590. Found: 226.1588. 6-*n*-Butyl-3-phenyl-2-methylpyridine was obtained in a16% isolated 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 161.11, 155.26, 140.59, 137.87, 134.43, 129.47, 128.65, 127.52, 120.11, 38.36, 32.68, 23.69, 22.98, 14.34. HRMS (ES+) calcd for$C_{16}H_{19}N$ $(M + H)^+$: 226.1590. Found: 226.1588.



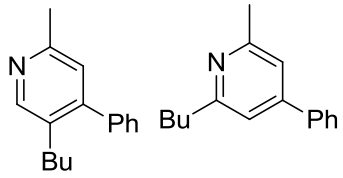
2.2g **2.3g**

5-*n*-Butyl-2,4-dimethylpyridine (2.2g) and 6-*n*-butyl-2,4-dimethylpyridine (2.3g). 3-Pentene-2-one oxime (60.0 mg) and 1-hexyne (0.29 mL) were subjected to the standard procedure. 5-*n*-butyl-2,4-dimethylpyridine and 6-*n*-butyl-2,4-dimethylpyridine were purified by column chromatography on silica gel (10:1:0.01 hexanes:*tert*-butylmethyl ether:triethylamine). 5-*n*-Butyl-2,4-dimethylpyridine (mg, mmol) was obtained in a43% isolated 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 155.61, 149.34, 145.36, 133.62, 124.73, 32.54, 29.98, 23.91, 22.73, 18.78, 14.07. HRMS (ES+) calcd for$C_{11}H_{17}N$ $(M + H)^+$: 164.1434. Found: 164.1429. 6-*n*-Butyl-2,4-dimethylpyridine was obtained in a9% isolated 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 162.03, 157.68, 147.70, 121.72, 120.79, 38.48, 32.76, 24.64, 22.97, 21.19, 14.33. HRMS (ES+) calcd for$C_{11}H_{17}N$ $(M + H)^+$: 164.1434. Found: 164.1431.



2.2h **2.3h**

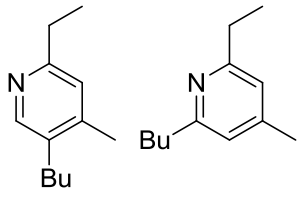
5-*n*-Butyl-2-methyl-4-isopropylpyridine (2.2h). 5-Methyl-3-hexene-2-one oxime (77.0 mg) and 1-hexyne (0.29 mL) were subjected to the standard procedure. 5-*n*-Butyl-2-methyl-4-*iso*-propylpyridine was purified by column chromatography on silica gel (20:1:0.01hexanes:*tert*-butylmethyl ether:triethylamine) in a 46% isolated 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 156.11, 155.85, 150.12, 132.22, 119.91, 34.12, 29.75, 28.63, 24.37, 23.61, 22.94, 14.23. HRMS (ES+) calcd for$C_{13}H_{21}N$ $(M + H)^+$: 192.1747. Found: 192.1744.



2.2i **2.3i**

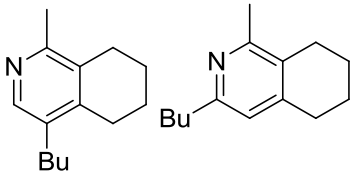
5-*n*-Butyl-2-methyl-4-phenylpyridine (2.2i) and 6-*n*-butyl-2-methyl-4-phenylpyridine (2.3i). 4-Phenyl-3-butene-2-one oxime (97.6 mg) and 1-hexyne (0.29 mL) were subjected to the standard procedure. 5-*n*-butyl-2-methyl-4-phenylpyridine and 6-*n*-butyl-2-methyl-4-phenylpyridine were purified by column chromatography on silica gel (10:1:0.01 hexanes:*tert*-butylmethyl ether:triethylamine). 5-*n*-Butyl-2-methyl-4-phenylpyridine and 6-*n*-butyl-2-methyl-

4-phenylpyridine were obtained as a 1.6:1 mixture in a53% isolated 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 162.75, 158.42, 155.67, 150.41, 149.79, 149.24, 139.79, 139.18, 132.61, 129.20, 128.95, 128.74, 128.56, 127.95, 127.31, 124.13, 118.83, 117.97, 38.71, 33.53, 32.73, 29.81, 24.91, 24.13, 22.92, 22.60, 14.28, 13.97. HRMS (ES+) calcd for$C_{16}H_{19}N$ $(M + H)^+$: 226.1590. Found: 226.1587.



2.3j **2.3j**

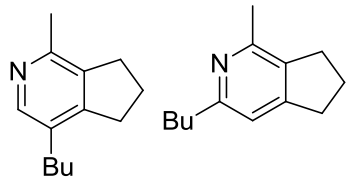
5-*n*-Butyl-2-ethyl-4-methylpyridine (2.2j) and 6-*n*-butyl-2-ethyl-4-methylpyridine (2.3j). 4-Pentene-3-one oxime (68.0 mg) and 1-hexyne (0.29 mL) were subjected to the standard procedure. 5-*n*-butyl-2-ethyl-4-methylpyridine and 6-*n*-butyl-2-ethyl-4-methylpyridine were purified by column chromatography on silica gel (20:1:0.01 hexanes:ethyl acetate:triethylamine). 5-*n*-Butyl-2-ethyl-4-methylpyridine was obtained in a49% isolated 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 160.96, 149.47, 145.58, 133.93, 123.60, 32.63, 31.03, 30.14, 22.88, 19.00, 14.29, 14.19. HRMS (ES+) calcd for$C_{12}H_{19}N$ $(M + H)^+$: 178.1590. Found: 178.1587. 6-*n*-Butyl-2-ethyl-4-methylpyridine was obtained in a20% isolated 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 163.09, 162.04, 147.73, 120.98, 120.22, 38.52, 32.74, 31.69, 22.97, 21.29, 14.63, 14.34. HRMS (ES+) calcd for$C_{12}H_{19}N$ $(M + H)^+$: 178.1590. Found: 178.1588.



2.2k **2.3k**

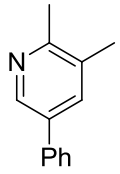
3-*n*-Butyl-2-methyl-5,6,7,8-tetrahydroisoquinoline (2.2k) and 2-*n*-butyl-2-methyl-5,6,7,8-tetrahydroisoquinoline (2.3k). 1-Acetyl-1-cylohexene oxime (84.2 mg) and 1-hexyne (0.29 mL) were subjected to the standard procedure. 3-*n*-butyl-2-methyl-5,6,7,8-tetrahydroisoquinoline and 2-*n*-butyl-2-methyl-5,6,7,8-tetrahydroisoquinoline were purified by column chromatography on silica gel (10:1:0.01 hexanes:*tert*-butylmethyl ether:triethylamine). 3-*n*-Butyl-2-methyl-5,6,7,8-tetrahydroisoquinoline was obtained in a54% isolated 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 154.53, 145.91, 143.95, 133.67, 130.48, 32.45, 29.84, 26.73, 26.25, 22.97, 22.82, 22.49, 22.34, 14.17. HRMS (ES+) calcd for$C_{14}H_{21}N$ $(M + H)^+$: 204.1747. Found:

204.1744. 2-*n*-Butyl-2-methyl-5,6,7,8-tetrahydroisoquinoline was obtained in a15% isolated 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 158.03, 156.46, 146.34, 128.13, 120.87, 38.03, 32.81, 29.75, 26.05, 23.50, 22.96, 22.55, 22.40, 14.32. HRMS (ES+) calcd for$C_{14}H_{21}N$ $(M + H)^+$: 204.1747. Found: 204.1744.



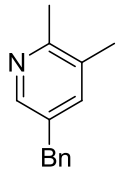
2.2l **2.3l**

3-*n*-Butyl-1-methyl-6,7-dihydro-5H-cyclopenta[c]pyridine (2.2l) and 2-*n*-butyl-1-methyl-6,7-dihydro-5H-cyclopenta[c]pyridine (2.3l). 1-Acetyl-1-cylopentene oxime (75.8 mg) and 1-hexyne (0.29 mL) were subjected to the standard procedure. 3-*n*-butyl-1-methyl-6,7-dihydro-5H-cyclopenta[c]pyridine and 2-*n*-butyl-1-methyl-6,7-dihydro-5H-cyclopenta[c]pyridine were purified by column chromatography on silica gel (10:1:0.01 hexanes:*tert*-butylmethyl ether:triethylamine). 3-*n*-Butyl-1-methyl-6,7-dihydro-5H-cyclopenta[c]pyridine and 2-*n*-butyl-1-methyl-6,7-dihydro-5H-cyclopenta[c]pyridine were obtained and a 2.1:1 mixture of isomers in a89% isolated 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 159.88, 153.98, 153.10, 151.85, 151.38, 146.94, 137.68, 135.34, 131.74, 116.56, 38.38, 33.06, 32.94, 32.50, 31.49, 31.14, 30.71, 30.54, 24.58, 24.28, 22.88, 22.71, 22.33, 22.04, 14.25, 14.14. HRMS (ES+) calcd for$C_{13}H_{19}N$ $(M + H)^+$: 190.1590. Found: 190.1585.



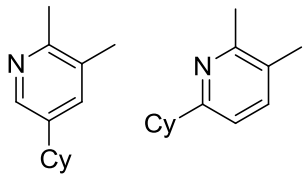
2.4a

5-Phenyl-2,3-dimethylpyridine (2.4a). 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 column chromatography on silica gel (20:1:0.01hexanes:ethyl acetate:triethylamine) in a 63 % isolated 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 156.23, 145.01, 138.24, 135.94, 134.54, 131.56, 129.25, 127.97, 127.25, 22.53, 19.51. HRMS (ES+) calcd for$C_{13}H_{13}N$ $(M + H)^+$: 184.1121. Found: 184.1119.



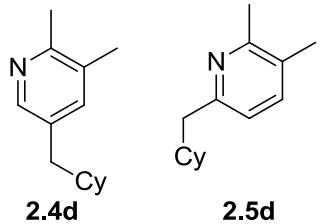
2.4b

5-Benzyl-2,3-dimethylpyridine (2.4b). 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 on silica gel (20:1:0.01hexanes:ethyl acetate:triethylamine) in a 61% isolated 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 155.18, 146.83, 140.65, 137.90, 134.09, 131.44, 129.03, 128.85, 126.57, 38.83, 22.36, 19.37. HRMS (ES+) calcd for $C_{14}H_{15}N$ $(M + H)^+$: 198.1277. Found: 198.1274.



2.4c **2.5c**

5-Cyclohexyl-2,3-dimethylpyridine (2.4c) and 6-cyclohexyl-2,3-dimethylpyridine (2.5c). 3-Methyl-3-butene-2-one oxime (60.0 mg) and ethynylcyclohexane (0.32 mL) were subjected to the standard procedure. 5-cyclohexyl-2,3-dimethylpyridine and 6-cyclohexyl-2,3-dimethylpyridine were purified by column chromatography on silica gel (10:1:0.01 hexanes:*tert*-butylmethyl ether:triethylamine). 5-Cyclohexyl-2,3-dimethylpyridine was obtained in a 53% isolated 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 154.67, 145.56, 140.74, 135.85, 131.14, 41.85, 34.55, 27.07, 26.32, 22.35, 19.50. HRMS (ES+) calcd for $C_{13}H_{19}N$ $(M + H)^+$: 190.1590. Found: 190.1588. 6-Cyclohexyl-2,3-dimethylpyridine was obtained in a 18% isolated 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 ($CDCl_3$) 163.76, 156.27, 137.85, 128.64, 117.97, 46.64, 33.60, 26.99, 26.50, 22.94, 19.11. HRMS (ES+) calcd for $C_{13}H_{19}N$ $(M + H)^+$: 190.1590. Found: 190.1588.



2.4d **2.5d**

5-(Cyclohexylmethyl)-2,3-dimethylpyridine (2.4d). 3-Methyl-3-butene-2-one oxime (60.0 mg) and 2-propynylcyclohexane (0.36 mL) were subjected to the standard procedure. 5-(cyclohexylmethyl)-2,3-dimethylpyridine was purified by column chromatography on silica gel (10:1:0.01 hexanes:*tert*-butylmethyl ether:triethylamine). 5-(Cyclohexylmethyl)-2,3-

dimethylpyridine (66 mg, 0.32 mmol) was obtained in a64% isolated yield 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 154.28, 146.91, 138.31, 134.11, 131.00, 40.71, 39.75, 33.20, 26.67, 26.42, 22.06, 19.30. HRMS (ES+) calcd for $C_{14}H_{21}N$ $(M + H)^+$: 204.1747. Found: 204.1744.

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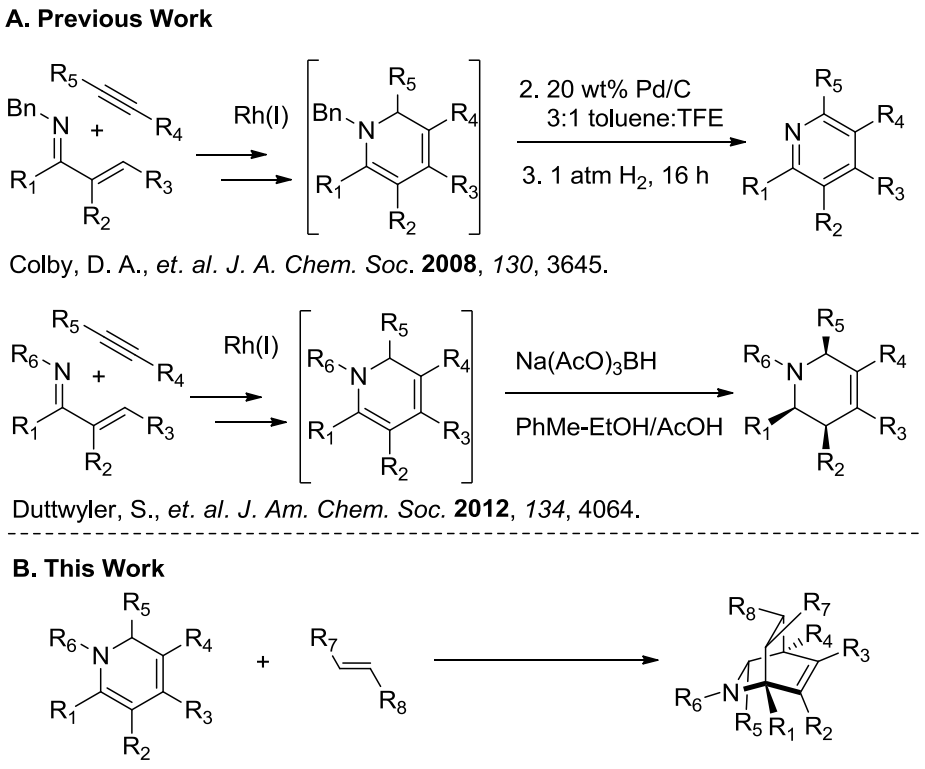
Chapter 3. Synthesis of Isoquinuclidines from Dihydropyridines and Alkenes via Diels-Alder Reaction.

A highly stereoselective Diels-Alder reaction for the synthesis of highly substituted isoquinuclidines from dihydropyridines and alkenes has been developed. While reactions with activated dienophiles proceed readily under thermal conditions, the use of Lewis acid additives is necessary to facilitate cycloadditions with challenging dienophiles. This procedure affords the target compounds in high yields and diastereoselectivities. This work has been published in a communication (Martin, R. M.; Bergman, R. G.; Ellman, J. A. Org. Lett. ***2012****, submitted*).

Introduction

The synthesis of nitrogen heterocycles is an important area of research due their prevalence in natural products and drugs.[1,2] Recently, we reported Rh (I)-catalyzed *β*-C–H bond alkenylation of *α,β*-unsaturated imines followed by *in situ* electrocylization to give *N*-alkyl and aryl 1,2-dihydropyridines (Scheme 3.1A).[3] The highly substituted dihydropyridines accessible by this approach would be difficult to prepare by alternative methods.[4] In this convergent method, they can be prepared from readily available alkynes, and imines that are in turn derived from diverse primary amines and *α,β*-unsaturated carbonyl compounds. Moreover, these 1,2-dihydropyridine products have proven to be versatile intermediates in routes to other classes of heterocycles. For example, aromatization to the corresponding pyridines can be accomplished in an overall one pot procedure (Scheme 3.1A).[3a,5] Alternatively, 1,2,3,6-tetrahydropyridines can be obtained with high diastereoselectivities via protonation of the enamine followed by *in situ* reduction of the resulting iminium.[3b]

Scheme 3.1. Rh-Catalyzed C–H Functionalization Provides Versatile 1,2-Dihydropyridine Intermediates



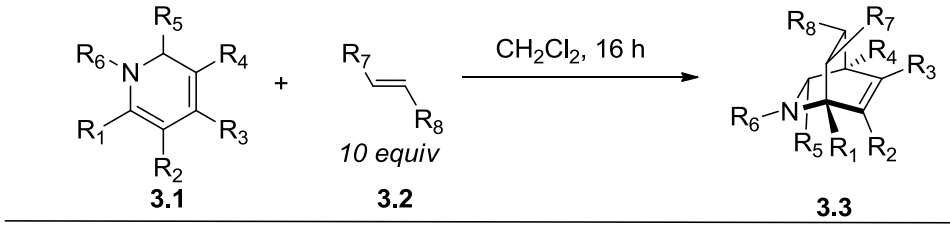
In our efforts to further harness the 1,2-dihydropyridine intermediates generated through Rh-catalyzed C-H activation, we became interested in the potential of generating isoquinuclidines utilizing a Diels-Alder reaction (Scheme 3.1B). Isoquinuclidines have been utilized as intermediates in the preparation of tetrahydroisoquinoline alkaloids,[6] piperidines,[7] Iboga

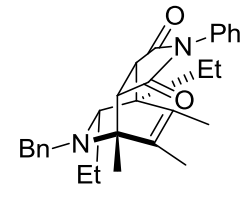
alkaloids[8] and the related Cantharanthus alkaloids,[9] which have been utilized as cancer therapeutics. Isoquinuclidines are most often prepared by Diels-Alder reaction of 1,2-dihydropyridines generated by acylation followed by nucleophilic addition to pyridines.[10,13] However, the incorporation of an acyl protecting group attenuates the nucleophilicity of the dihydropyridine substrates.[11] Moreover, reliance on pyridine inputs generally results in dihydropyridine products lacking a high degree of substitution.[4] Herein, we report that isoquinuclidines with unprecedented substitution levels are obtained in good yield and with high regio- and stereoselectivities by Diels-Alder reaction between highly substituted *N*-alkyl and aryl-1,2-dihydropyridines and electron deficient alkenes.

Results and Discussion

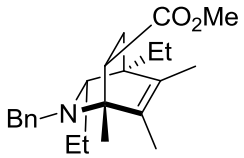
Diels-Alder reactions for a range of dienophiles with differential relative reactivity were first investigated (products **3.3a-d**, Table 1). The most reactive dienophile, *N*-phenyl maleimide, underwent efficient cycloaddition to give quinuclidine **3.3a** at 0 °C within 6 h with only the endo isomer detected by ^{1}H and ^{13}C NMR analysis of the unpurified reation mixture. Methyl acrylate and acrylonitrile required more forcing conditions, but provided the desired products **3.3b** and **3.3c**, respectively, in high yield when run neat with heating to 105 °C. Isoquinuclidines **3.3b** and **3.3c** were each produced as a single regioisomer, and for **3.3b** only the endo product was observed while for **3.3c** a 93:7 endo/exo ratio was obtained.

Table 3.1. Substrate Scope of Diels-Alder Reactions.[a]

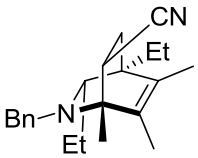




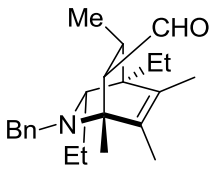
3.3a 84%[c]
>95:5



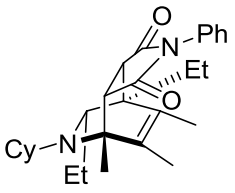
3.3b 89%[d]
>95:5



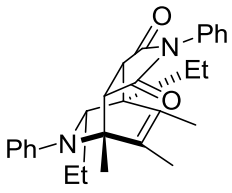
3.3c 90%[d]
93:7



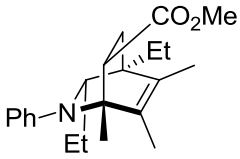
3.3d 65%[b]
>95:5



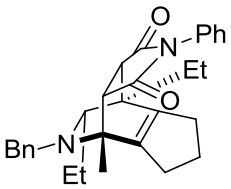
3.3e 79%[c]
>95:5



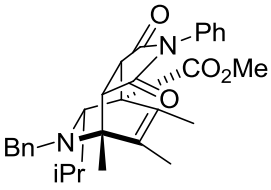
3.3f 70%[c]
>95:5



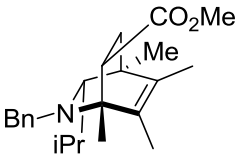
3.3g 84%[d,f]
>95:5



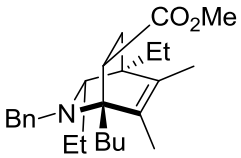
3.3h 73%[c,e]
>95:5



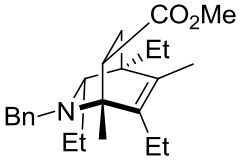
3.3i 73%[g]
>95:5



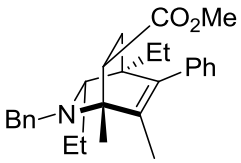
3.3j 96%[d]
>95:5



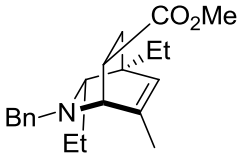
3.3k 66%[d,h]
>95:5



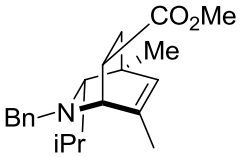
3.3l 90%[d]
>95:5



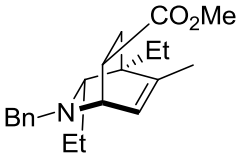
3.3m 73%[d]
>95:5



3.3n 79%[d]
>95:5



3.3o 89%[d]
>95:5



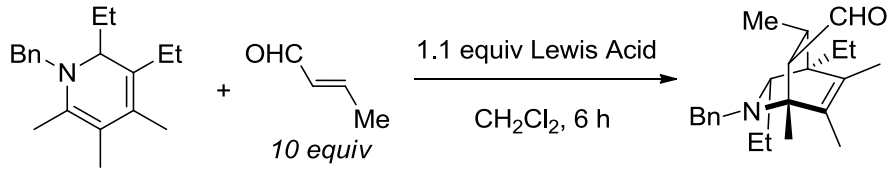
3.3p 81%[d]
94:6

[a] Yields correspond to the overall yields of isolated products. The diastereoselectivities were determined by ^{1}H NMR analysis of unpurified material. [b] $ZnCl_2$ (1.1 equiv), 0.5 M CH_2Cl_2, 0 °C, 6 h. [c] 0.1 M CH_2Cl_2, rt. [d] Neat, 105 °C. [e] 24 h. [f] 72 h. [g] 0.5 M CH_2Cl_2, 50 °C. [h] 48 h.

Identifying effective conditions for coupling the less reactive crotonaldehyde required significant optimization (Table 3.2). Performing the reaction at 0.1 or 0.5 M in CH_2Cl_2 with heating to 50 °C provided little if any conversion (entries 1 and 2). Even when performing the

reaction neat with excess crotonaldehyde at 105 °C gave only trace amounts of product (entry 3). Lewis acid additives have proven to be effective for increasing the rate of Diels-Alder reactions for dienes incorporated within nitrogen heterocycles.[6a,e,12] We therefore examined their effect upon our substrate combination (entries 4-6). The aluminium-based Lewis acids $AlEtCl_2$ and $AlCl_3$ led to modest yields of the isoquinuclidine **3.3d** (entries 4 and 5). Employing $ZnCl_2$ as a Lewis acid additive at 0 °C provided even better results, with **3.3d** obtained as a single diastereomer in 59% yield (entry 6).

Table 3.2. Optimization of Diels-Alder Reaction with Crotonaldehyde.[a]



3.1a **3.2d** **3.3d**

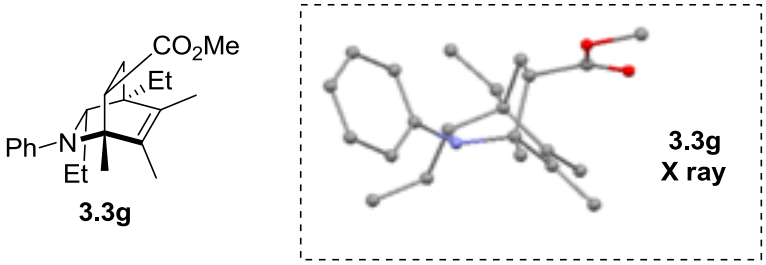
Entry	Lewis Acid	Concentration (M)	Temperature (°C)	Yield[b] (%)
1	-	0.1	50	trace
2	-	0.5	50	trace
3	-	-	105	trace
4	$AlEtCl_2$	0.5	0	10[c]
5	$AlCl_3$	0.5	0	43
6	$ZnCl_2$	0.5	0	59

[a] All reactions were performed using 0.05 mmol of dihydropyridine **3.1a** and 0.5 mmol of crotonaldehyde. [b] Yields were determined by NMR relative to 1,3,5-trimethoxybenzene. [c] Reaction was performed in 1:1 CH_2Cl_2:hexanes.

As illustrated in Table 3.1, a range of differently substituted 1,2-dihydropyridines underwent Diels-Alder reactions in high yields. A variety of nitrogen substituents were well-tolerated, including *N*-benzyl (**3.3a-d**, **h-p**), branched *N*-alkyl (**3.3e**) and *N*-phenyl (**3.3f-g**) groups. Different substitution patterns at other sites within the dihydropyridine ring were also acceptable. The tetracyclic isoquinuclidine **3.3h** was prepared as a single diastereomer in high yield. Dihydropyridines substituted with the branched isopropyl group were also effective coupling partners (**3.3i, j** and **o**). Even a dihydropyridine bearing an electronically deactivating methyl ester group reacted with *N*-phenyl maleimide to provide **3.3i** in good yield and as a single isomer. A 4-phenyl substituted dihydropyridine also underwent Diels Alder reaction to provide isoquinuclidine **3.3m** as a single isomer. Additionally, as should be expected, isoquinuclidines can be prepared in high yields and excellent selectivities from 1,2-dihydropyridines with modestly lower substitution levels (**3.3n-p**).

The relative configuration of isoquinuclidine **3.3g** was established by X-ray crystallography (Figure 3.1). By analogy, we assigned the endo configuration to the other dihydropyridine products.

Figure 3.1. Absolute Configuration and Ball-and-Stick Representation of **3.3g**.



Conclusion

The 1,2-dihydropyridines that result from the rhodium-catalyzed C-H alkenylation of *α,β*-unsaturated imines and subsequent electrocyclization are versatile intermediates for the preparation of highly functionalized nitrogen heterocycles. Diels-Alder reaction with a variety of dienophiles provides access to isoquinuclidines with unprecedented substitution levels in high yields and with excellent regio- and stereoselectivities.

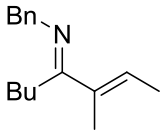
Experimental Section

I. General Experimental Methods. All catalytic reactions were set up inside an inert atmosphere (N_2) glovebox utilizing glassware that was oven-dried (150 ºC) and evacuated while hot prior to use, whereas the work-up and isolation of the products from the catalytic reactions were conducted on the bench-top using standard techniques. Dichloromethane and tetrahydrofuran were passed through a column of activated alumina under nitrogen and stored in a glovebox over activated 4 Å molecular sieves prior to use. Chloroform-d_1 and benzene-d_6 were used as received. Unless otherwise noted, all reagents and materials were obtained from commercial suppliers and were repurified by distillation. *N*-methylmaleimide was used without further purification. Chromatography was performed on 230-240 mesh silica gel. Molecular sieves were activated by heating them to 280 °C in a vacuum (*ca.* 0.1 Torr) for 6–12 h. ^{1}H and ^{13}C{^{1}H} NMR characterization data were collected at 300 K on a spectrometer operating at 500.1 and 125.8 MHz, respectively, with chemical shifts reported in parts per million relative to $CHCl_3$ (^{1}H NMR; 7.26 ppm, ^{13}C{^{1}H} NMR; 77.36 ppm) or C_6D_6 (^{1}H NMR; 7.16 ppm, ^{13}C{^{1}H} NMR; 128.06 ppm). IR spectra were recorded on a Nicolet 6700 FT-IR instrument. High resolution mass spectra (HRMS) were obtained using using a Bruker 9.4 TAPEXQe FT-ICR mass spectrometer. Melting points were determined on an Electrothermal melting point apparatus and are reported uncorrected.

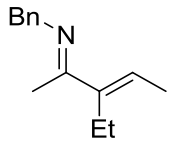
II. Substrate Preparation. Rhodium Catalyst. $[RhCl(coe)_2]_2$[15] and [4-(dimethylamino)phenyl]diethylphosphine[16] were synthesized according to published procedures.

Enones. 3-Ethylpent-3-en-2-one[17] and 3-methyloct-2-en-4-one[18] were prepared according to literature procedures.

Imines.



***N*-Benzyl-3-methyloct-2-en-4-imine**. In a 4 dram vial, equipped with a stir bar, were combined 0.77 g of 3-methyloct-2-en-4-one (5.5 mmol, 1.0 equiv), 0.62 mL of benzylamine (5.8 mmol, 1.05 equiv), 5.0 g of titanium(IV) ethoxide (22 mmol, 4 equiv) and 6.0 mL of tetrahydrofuran. The resulting mixture was heated to 50 °C for 2 h. The reaction mixture was cooled to ambient temperature, and 6.0 mL of *N*,*N*,*N'*,*N'*-tetrakis(2-hydroxyethyl)ethylenediamine was added, and the resulting mixture heated to 50 °C for 20 min. The mixture was then cooled to ambient temperature, diluted with 45 mL of ethyl acetate and washed with a mixture of 30 mL of ammonium hydroxide and 15 mL of saturated sodium chloride solution. The resulting organic layer was washed with 45 mL of saturated sodium chloride solution, dried over Na_2SO_4, and the solvents were then removed in vacuo. The resulting residue was filtered over neutral activity I alumina, eluting with hexanes. The solvents were removed in vacuo to yield a yellow oil (700 mg, 56%), which was used without further purification. ^{1}H NMR (C_6D_6) δ 7.53 – 7.48 (m, 2H), 7.27 (m, 2H), 7.18 – 7.12 (m, 1H), 6.03 (q, *J* = 6.6 Hz, 1H), 4.62 (s, 2H), 2.36 – 2.29 (m, 2H), 2.10 (s, 3H), 1.65 (d, *J* = 6.6 Hz, 3H), 1.35 – 1.25 (m, 2H), 1.19 (m, 2H), 0.79 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (C_6D_6) δ 170.2, 142.1, 139.0, 128.6, 128.0, 127.0, 126.6, 54.9, 30.2, 27.2, 23.4, 14.6, 14.1, 13.3.

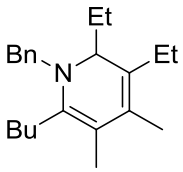


***N*-Benzyl-3-ethylpent-3-en-2-imine**. In a 4 dram vial, equipped with a stir bar, were combined 0.75 g of 3-ethylpent-3-en-2-one (6.7 mmol, 1.0 equiv), 0.70 mL of benzylamine (6.7 mmol, 1.0 equiv), 6.1 g of titanium(IV) ethoxide (26.7 mmol, 4 equiv) and 6.0 mL of tetrahydrofuran. The resulting mixture was heated to 50 °C for 2 h. The reaction mixture was cooled to ambient temperature, and 6.0 mL of *N*,*N*,*N'*,*N'*-tetrakis(2-hydroxyethyl)ethylenediamine was added, and the resulting mixture heated to 50 °C for 20 min. The mixture was then cooled to ambient temperature, diluted with 45 mL of ethyl acetate and washed with a mixture of 30 mL of ammonium hydroxide and 15 mL of saturated sodium chloride solution. The resulting organic layer was washed with 45 mL of saturated sodium chloride solution, dried over Na_2SO_4, and the solvents were then removed in vacuo. The resulting residue was filtered over neutral activity I alumina, eluting with hexanes. The solvents were removed in vacuo to yield a brown oil (917 mg, 65%), which was used without further purification. ^{1}H NMR (C_6D_6) δ 7.47 (d, *J* = 7.4 Hz, 2H), 7.26 (m, 2H), 7.13 (t, *J* = 7.4 Hz, 1H), 5.87 (q, *J* = 6.9 Hz, 1H), 4.46 (s, 2H), 2.71 (q, *J* = 7.4

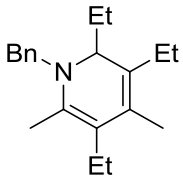
Hz, 2H), 1.63 (m, 6H), 1.15 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (C_6D_6) δ 165.5, 146.2, 142.0, 128.6, 127.9, 126.9, 126.6, 55.5, 20.1, 14.2, 14.1, 13.7.

Dihydropyridines.

1-benzyl-2,3-diethyl-4,5,6-trimethyl-1,2-dihydropyridine, 1-cyclohexyl-2,3-diethyl-4,5,6-trimethyl-1,2-dihydropyridine, 2,3-diethyl-4,5,6-trimethyl-1-phenyl-1,2-dihydropyridine, 1-benzyl-3,4-diethyl-1-methyl-3,5,6,7-tetrahydro-2H-cyclopenta[c]pyridine, 1-benzyl-2-isopropyl-4,5,6-trimethyl-3-methyl carboxylate 1-phenyl-1,2-dihydropyridine, 1-benzyl-3-ethyl-2-isopropyl-4,5,6-trimethyl-1,2-dihydropyridine, 1-benzyl-2,3-diethyl-5,6-dimethyl-4-phenyl-1,2-dihydropyridine, 1-benzyl-2,3-diethyl-5-methyl-1,2-dihydropyridine and 1-benzyl-2,3-diethyl-4-methyl-1,2-dihydropyridine were prepared according to literature procedures.[3b]



1-Benzyl-6-butyl-2,3-diethyl-4,5-dimethyl-1,2-dihydropyridine. To a 4 dram vial were added 230 mg of *N*-benzyl-3-methyloct-2-en-4-imine (1.00 mmol, 1 equiv), 18 mg of $[RhCl(coe)_2]_2$ (0.025 mmol, 2.5 mol %) dissolved in 2.0 mL of toluene, 10.5 mg of [4-(dimethylamino)phenyl]diethylphosphine (0.050.0 mmol, 5.0 mol %) dissolved in 2.0 mL of toluene, 0.35 mL of 3-hexyne (3.0 mmol, 3.0 equiv) and toluene (6.0 mL) in an inert atmosphere box. The vial was then sealed, removed from the inert atmosphere box, and heated to 75 °C for 2 h. The vial was then opened, and the solvent removed in vacuo. The resulting residue was purified by filtration over basic activity III alumina, in a nitrogen atmosphere, eluting with sparged hexanes. 1-Benzyl-6-butyl-2,3-diethyl-4,5-dimethyl-1,2-dihydropyridine was obtained in 77% yield (240 mg, 0.77 mmol) as a colorless oil. ^{1}H NMR (C_6D_6) δ 7.29 (d, *J* = 7.6 Hz, 2H), 7.19 (t, *J* = 7.6 Hz, 2H), 7.08 (m, 1H), 4.15 (d, *J* = 15.7 Hz, 1H), 3.84 (d, *J* = 15.7 Hz, 1H), 3.07 (m, 1H), 2.29 (m, 1H), 2.23 – 2.06 (m, 2H), 1.79 (s, 3H), 1.76 – 1.69 (m, 4H), 1.69 – 1.58 (m, 2H), 1.54 (m, 1H), 1.44 – 1.21 (m, 3H), 0.97 – 0.84 (m, 9H). ^{13}C NMR (C_6D_6) δ 141.4, 137.5, 128.5, 128.4, 127.1, 126.5, 125.2, 113.0, 61.8, 54.5, 31.8, 29.1, 24.8, 24.7, 14.4, 14.2, 13.8, 13.3, 11.1. IR (cm^{-1}): 2955, 2927, 2869, 1649. HRMS (ES+) calcd for $C_{22}H_{33}N$ $(M + H)^+$: 312.2686. Found: 312.2684.



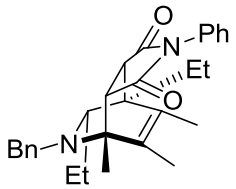
1-Benzyl-2,3,5-triethyl-4,6-dimethyl-1,2-dihydropyridine. To a 4 dram vial were added 201 mg of *N*-benzyl-3-ethylpent-3-en-2-imine (1.00 mmol, 1 equiv), 18 mg of $[RhCl(coe)_2]_2$ (0.025

mmol, 2.5 mol %) dissolved in 2.0 mL of toluene, 10.5 mg of [4-(dimethylamino)phenyl]diethylphosphine (0.050 mmol, 5.0 mol %) dissolved in 2.0 mL of toluene, 0.35 mL of 3-hexyne (3.0 mmol, 3.0 equiv) and toluene (6.0 mL) in an inert atmosphere box. The vial was then sealed, removed from the inert atmosphere box, and heated to 75 °C for 2 h. The vial was then opened, and the solvent was removed in vacuo. The resulting residue was purified by filtration over basic activity III alumina, in a nitrogen atmosphere, eluting with sparged hexanes. 1-Benzyl-2,3,5-triethyl-4,6-dimethyl-1,2-dihydropyridine was obtained in 62% yield (180 mg, 0.62 mmol) as a pale yellow oil. ^{1}H NMR (C_6D_6) δ 7.32 – 7.28 (m, 2H), 7.24 (m, 2H), 7.14 (m, 1H), 4.25 (d, *J* = 15.8 Hz, 1H), 3.89 (d, *J* = 15.8 Hz, 1H), 3.17 (m, 1H), 2.35 – 2.20 (m, 3H), 1.87 (s, 3H), 1.85 – 1.76 (m, 4H), 1.70 (m, 1H), 1.35 (m, 1H), 1.05 (t, *J* = 7.4 Hz, 3H), 0.95 (m, 6H). ^{13}C NMR (C_6D_6) δ 141.2, 132.6, 128.5, 128.4, 127.0, 126.6, 124.4, 118.8, 62.1, 54.7, 25.00, 24.99, 21.6, 15.8, 15.3, 13.37, 13.36, 10.8. IR (cm^{-1}): 2957, 2927, 2867, 1643. HRMS (ES+) calcd for $C_{20}H_{29}N$ $(M + H)^+$: 284.2373. Found: 284.2369.

III. General Procedures for Diels-Alder Reactions. Method A: The indicated dihydropyridine (0.15 mmol) was placed in a sealable glass vessel, equipped with a stir bar, in an inert atmosphere box. To the reaction vessel was added *N*-phenylmaleimide (27.3 mg, 0.16.0 mmol, 1.05 equiv) dissolved in 1.5 mL of dichloromethane. The reaction vessel was then sealed, removed from the inert atmosphere box, and the mixture was stirred at ambient temperature. After reaction completion the reaction vessel was opened, and the solvent was removed in vacuo. The resulting residue was purified by column chromatography on silica gel (5:1 hexanes:ethyl acetate).

Method B: The indicated dihydropyridine (0.15 mmol) was placed in a sealable glass vessel, equipped with a stir bar, in an inert atmosphere box. To the reaction vessel was added the desired alkene (1.5 mmol, 10.0 equiv). The reaction vessel was then sealed, removed from the inert atmosphere box, and the mixture was stirred at ambient temperature. After reaction completion the reaction vessel was opened, and the solvent was removed in vacuo. The resulting residue was purified by column chromatography on silica gel.

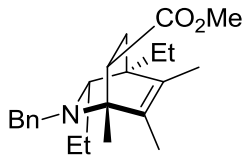
IV. Preparation and Characterization of Diels-Alder Products.



3.3a

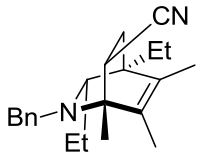
3.3a was prepared by method A for 16 h, using 1-benzyl-2,3-diethyl-4,5,6-trimethyl-1,2-dihydropyridine (40.4 mg). **3.3a** was obtained in a 84% isolated yield (55.8 mg, 0.13 mmol) as a

foamy solid. ^{1}H NMR ($CDCl_3$) δ 7.49 – 7.20 (m, 8H), 7.09 (m, 2H), 4.28 (d, *J* = 15.1 Hz, 1H), 3.49 (d, *J* = 15.1 Hz, 1H), 3.38 (d, *J* = 7.8 Hz, 1H), 3.10 (d, *J* = 7.8 Hz, 1H), 2.55 (m, 1H), 2.43 (m, 1H), 1.82 – 1.66 (m, 7H), 1.56 (s, 3H), 1.27 – 1.18 (m, 2H), 1.10 (t, *J* = 7.3 Hz, 3H), 0.65 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 177.1, 176.4, 142.7, 135.3, 133.0, 132.5, 129.4, 128.7, 128.4, 128.3, 126.9, 126.8, 67.2, 59.9, 57.0, 46.0, 45.8, 43.3, 25.7, 21.9, 21.4, 14.4, 14.3, 10.4, 8.2. IR (cm^{-1}): 2962, 2923, 1700, 1599. HRMS (ES+) calcd for $C_{29}H_{34}N_2O_2$ $(M + H)^+$: 443.2693. Found: 443.2689.



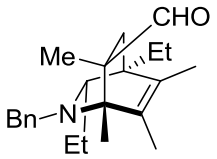
3.3b

3.3b was prepared by method B for 16 h, using 1-benzyl-2,3-diethyl-4,5,6-trimethyl-1,2-dihydropyridine (40.4 mg) and methyl acrylate (0.14 mL). **3.3b** was purified by column chromatography on silica gel (20:1 hexanes:ethyl acetate) and obtained in a 89% isolated yield (47.5 mg, 0.13 mmol) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.37 (d, *J* = 7.4 Hz, 2H), 7.27 (m, 2H), 7.18 (m, 1H), 4.19 (d, *J* = 15.4 Hz, 1H), 3.59 (s, 3H), 3.41 (d, *J* = 15.4 Hz, 1H), 3.08 (dd, *J* = 9.8, 5.1 Hz, 1H), 2.28 (m, 1H), 1.81 (dd, *J* = 12.5, 9.8 Hz, 1H), 1.76 (s, 3H), 1.63 (m, 5H), 1.37 (dd, *J* = 12.5, 5.1 Hz, 1H), 1.19 – 1.12 (m, 4H), 1.11 – 1.04 (m, 1H), 0.91 (t, *J* = 7.6 Hz, 3H), 0.59 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 176.0, 143.9, 134.1, 133.7, 128.24, 128.15, 126.5, 69.7, 59.5, 56.5, 51.6, 44.2, 41.7, 34.0, 26.5, 26.3, 21.9, 14.4, 13.9, 10.7, 8.8. IR (cm^{-1}): 2926, 2860, 1724. HRMS (ES+) calcd for $C_{23}H_{33}NO_2$ $(M + H)^+$: 356.2584. Found: 356.2578.



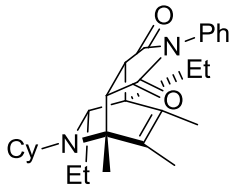
3.3c

3.3c was prepared by method B for 16 h, using 1-benzyl-2,3-diethyl-4,5,6-trimethyl-1,2-dihydropyridine (40.4 mg) and acrylonitrile (0.10 mL). **3.3c** was purified by column chromatography on silica gel (20:1:0.1 hexanes:tertbutylmethylether:triethylamine) and obtained in a 90% isolated yield (48.0 mg, 0.14 mmol) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.33 (d, *J* = 7.5 Hz, 2H), 7.28 (m, 2H), 7.20 (m, 1H), 4.10 (d, *J* = 15.1 Hz, 1H), 3.41 (d, *J* = 15.1 Hz, 1H), 3.10 (dd, *J* = 10.0, 3.9 Hz, 1H), 2.35 – 2.30 (m, 1H), 2.00 (dd, *J* = 13.0, 10.0 Hz, 1H), 1.82 (s, 3H), 1.77 (s, 3H), 1.64 (m, 2H), 1.43 – 1.34 (m, 4H), 1.16 (m, 1H), 1.06 – 0.97 (m, 1H), 0.90 (t, *J* = 7.5 Hz, 3H), 0.55 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 142.6, 135.5, 134.7, 128.4, 128.2, 126.9, 123.2, 69.6, 59.2, 56.9, 41.7, 34.3, 31.1, 26.7, 26.1, 21.9, 14.8, 14.2, 10.8, 8.6. IR (cm^{-1}): 2966, 2931, 2871, 2230, 1604. HRMS (ES+) calcd for $C_{22}H_{30}N_2$ $(M + H)^+$: 323.2482. Found: 323.2484.



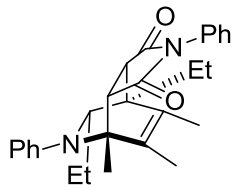
3.3d

Preparation of **3.3d**. 1-Benzyl-2,3-diethyl-4,5,6-trimethyl-1,2-dihydropyridine (40.4 mg, 0.15 mmol) and crotonaldehyde (0.12 mL, 1.5 mmol, 10 equiv) were dissolved in dichloromethane (0.3 mL) in a sealable glass vessel in an inert atmosphere box. $ZnCl_2$ (21.5 mg, 0.16 mmol, 1.05 equiv) was placed in a sealable glass vessel, equipped with a stir bar, in an inert atmosphere box. The reaction vessels were sealed and removed from the inert atmosphere box. The vessel with $ZnCl_2$ was cooled to 0 °C. The solution of 1-benzyl-2,3-diethyl-4,5,6-trimethyl-1,2-dihydropyridine and crotonaldehyde was added dropwise by syringe to the $ZnCl_2$, in a nitrogen atmosphere. The resulting reaction mixture was stirred at 0 °C for 6 h. The reaction was then quenched with 1.0 mL saturated ammonium chloride solution followed by extraction with dichloromethane (5 mL X 3). The combined organic layers were dried over Na_2SO_4, and the solvents removed in vacuo. The resulting residue was purified by column chromatography on silica gel (20:1 hexanes:ethyl acetate). **3.3d** was obtained in a 65% isolated yield (33.1 mg, 0.10 mmol) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 9.16 (d, *J* = 4.7 Hz, 1H), 7.39 – 7.33 (m, 2H), 7.29 – 7.23 (m, 2H), 7.17 (t, *J* = 7.3 Hz, 1H), 4.23 (d, *J* = 15.7 Hz, 1H), 3.58 (d, *J* = 15.7 Hz, 1H), 2.54 (m, 2H), 1.92 – 1.85 (m, 2H), 1.83 (m, 2H), 1.65 (s, 3H), 1.34 – 1.19 (m, 2H), 1.11 – 1.04 (m, 6H), 0.99 (t, *J* = 7.4 Hz, 3H), 0.64 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 204.1, 143.8, 136.0, 134.8, 128.3, 128.0, 126.6, 66.9, 62.1, 58.5, 55.4, 45.0, 31.8, 26.6, 24.1, 22.2, 15.3, 15.1, 14.1, 11.2, 9.7. IR (cm^{-1}): 2960, 1714, 1604. HRMS (ES+) calcd for $C_{23}H_{33}NO_2$ $(M + H)^+$: 340.2635. Found: 340.2632.



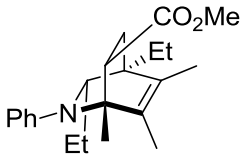
3.3e

3.3e was prepared by method A for 16 h, using 1-cyclohexyl-2,3-diethyl-4,5,6-trimethyl-1,2-dihydropyridine (39.2 mg). **3.3e** was obtained in a 79% isolated yield (51.5 mg, 0.12 mmol) as a foamy solid. ^{1}H NMR ($CDCl_3$) δ 7.44 – 7.38 (m, 2H), 7.36 – 7.31 (m, 1H), 7.07 – 7.03 (m, 2H), 3.19 (d, *J* = 7.7 Hz, 1H), 2.97 – 2.89 (m, 2H), 2.86 (m, 1H), 2.27 (m, 1H), 1.86 – 1.74 (m, 4H), 1.74 – 1.70 (m, 3H), 1.69 (s, 3H), 1.65 (m, 5H), 1.52 (m, 1H), 1.43 – 1.23 (m, 4H), 1.21 – 1.10 (m, 4H), 0.82 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 176.8, 176.4, 136.6, 132.53, 132.51, 129.3, 128.6, 126.8, 59.2, 58.2, 57.0, 50.7, 46.4, 43.4, 36.5, 31.3, 28.9, 27.6, 27.3, 26.4, 22.1, 21.2), 14.6, 14.3, 11.6, 8.3. IR (cm^{-1}): 2925, 2852, 1700, 1600. HRMS (ES+) calcd for $C_{28}H_{38}N_2O_2$ $(M + H)^+$: 435.3006. Found: 435.2988.



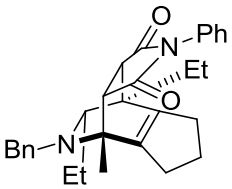
3.3f

3.3f was prepared by method A for 16 h, using 1-phenyl-2,3-diethyl-4,5,6-trimethyl-1,2-dihydropyridine (38.3 mg). **3.3f** was obtained in a 70% isolated yield (46.1 mg, 0.11 mmol) as a foamy solid. ^{1}H NMR ($CDCl_3$) δ 7.45 – 7.40 (m, 2H), 7.38 – 7.30 (m, 3H), 7.20 – 7.14 (m, 3H), 7.10 – 7.05 (m, 2H), 3.35 (m, 3H), 2.51 (m, 1H), 1.89 – 1.79 (m, 1H), 1.79 (s, 3H), 1.75 (s, 3H), 1.48 – 1.38 (m, 1H), 1.35 (s, 3H), 1.14 (t, *J* = 7.3 Hz, 3H), 1.12 – 1.03 (m, 1H), 0.66 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 176.6, 176.5, 149.1, 135.1, 133.2, 132.5, 130.8, 129.4, 129.1, 128.8, 126.9, 125.8, 65.1, 59.5, 47.8, 46.2, 43.7, 26.0, 22.0, 21.8, 14.4, 14.2, 11.1, 8.0. IR (cm^{-1}): 2925, 2872, 1701, 1594. HRMS (ES+) calcd for $C_{28}H_{32}N_2O_2$ $(M + H)^+$: 429.2537. Found: 429.2525.



3.3g

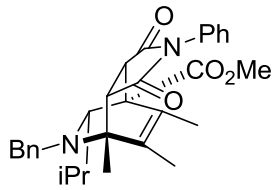
3.3g was prepared by method B for 72 h, using 1-phenyl-2,3-diethyl-4,5,6-trimethyl-1,2-dihydropyridine (38.3 mg). **3.3g** was obtained in a 84% isolated yield (43.1 mg, 0.13 mmol) as a white crystalline solid. mp = 76.0-78.0 ºC. IR (cm^{-1}): . ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 2H), 7.19 – 7.15 (m, 2H), 7.14 – 7.09 (m, 1H), 3.52 (s, 3H), 3.20 (m, 1H), 3.01 (m, 1H), 2.09 (m, 1H), 1.80 (s, 3H), 1.75 (s, 3H), 1.80 – 1.64 (m, 3H), 1.49 (m, 1H), 1.03 – 0.93 (m, 7H), 0.56 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 175.7, 149.6, 134.4, 133.5, 131.0, 128.7, 125.1, 66.7, 59.0, 51.5, 46.0, 41.9, 34.1, 27.1, 26.5, 22.5, 14.3, 14.2, 11.4, 8.7. IR (cm^{-1}): 2952, 2923, 2856, 1720, 1593. HRMS (ES+) calcd for $C_{22}H_{31}NO_2$ $(M + H)^+$: 342.2428. Found: 342.2426.



3.3h

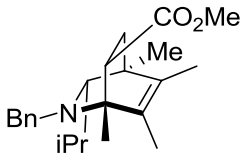
3.3h was prepared by method A for 24 h, using 2-benzyl-3,4-diethyl-1-methyl-3,5,6,7-tetrahydro-2H-cyclopenta[c]pyridine (42.2 mg). **3.3h** was obtained in a 73% isolated yield (48.0 mg, 0.11 mmol) as a foamy solid. ^{1}H NMR ($CDCl_3$) δ 7.44 (m, 2H), 7.37 (m, 3H), 7.31 (m, 2H), 7.27 – 7.21 (m, 1H), 7.09 (m, 2H), 4.27 (d, *J* = 14.8 Hz, 1H), 3.46 (m, 2H), 3.13 (m, 1H), 2.53 (m, 2H), 2.49 – 2.41 (m, 1H), 2.41 – 2.26 (m, 3H), 1.99 – 1.75 (m, 3H), 1.59 (s, 3H), 1.17 (m, 2H), 1.09 (t, *J* = 7.4 Hz, 3H), 0.60 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 176.9, 176.1, 144.0,

142.5, 142.4, 132.5, 129.4, 128.7, 128.44, 128.40, 127.0, 126.7, 67.9, 59.0, 56.5, 46.8, 45.7, 44.6, 32.5, 32.2, 25.6, 23.5, 21.6, 20.6, 10.2, 7.8. IR (cm^{-1}): 2927, 2847, 1702, 1599. HRMS (ES+) calcd for $C_{30}H_{34}N_2O_2$ $(M + H)^+$: 455.2693. Found: 455.2696.



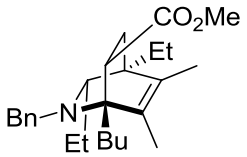
3.3i

Preparation of **3.3i**. 1-Benzyl-2-isopropyl-3-methylcarboxylate-4,5,6-trimethyl-1,2-dihydropyridine (47.0 mg, 0.15 mmol) was placed in a sealable glass vessel, equipped with a stir bar, in an inert atmosphere box. To the reaction vessel was added *N*-phenylmaleimide (27.3 mg, 0.160 mmol, 1.05 equiv) dissolved in 0.15 mL of dichloromethane. The reaction vessel was then sealed, removed from the inert atmosphere box, and the mixture was stirred at ambient temperature. After reaction completion the reaction vessel was opened, and the solvent was removed in vacuo. The resulting residue was purified by column chromatography on silica gel (5:1 hexanes:ethyl acetate). **3.3i** was obtained in a 73% yield (53.3 mg, 0.11 mmol) as a white, crystalline solid. mp = decomposition starting at 173 ºC. ^{1}H NMR ($CDCl_3$) δ 7.44 – 7.34 (m, 5H), 7.34 – 7.29 (m, 2H), 7.23 (m, 1H), 7.08 – 7.04 (m, 2H), 4.29 (d, *J* = 15.9 Hz, 1H), 3.86 – 3.80 (m, 4H), 3.59 (d, *J* = 15.9 Hz, 1H), 3.47 (d, *J* = 8.0 Hz, 1H), 2.91 (d, *J* = 2.2 Hz, 1H), 2.08 (d, *J* = 0.9 Hz, 3H), 1.72 (d, *J* = 0.9 Hz, 3H), 1.59 – 1.52 (m, 1H), 1.49 (s, 3H), 0.72 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 176.6, 172.1, 142.3, 136.6, 132.1, 129.8, 129.5, 128.9, 128.5, 128.0, 127.0, 126.7, 73.1, 61.5, 57.7, 53.4, 52.2, 47.3, 44.5, 32.8, 21.3, 20.7, 18.6, 17.4, 14.2. IR (cm^{-1}): 2950, 2888, 1700, 1598. HRMS (ES+) calcd for $C_{30}H_{34}N_2O_2$ $(M + H)^+$: 487.2591. Found: 487.2571.



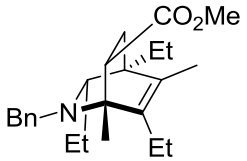
3.3j

3.3j was prepared by method B for 16 h, using 1-benzyl-2-isopropyl-3,4,5,6-tetramethyl-1,2-dihydropyridine (40.4 mg) and methyl acrylate (0.14 mL). **3.3j** was purified by column chromatography on silica gel (20:1 hexanes:ethyl acetate) and obtained in a 96% isolated yield (51.2 mg, 0.14 mmol) as a colorless oil ^{1}H NMR ($CDCl_3$) δ 7.39 (2H), 7.29 – 7.25 (m, 2H), 7.17 (t, *J* = 7.3 Hz, 1H), 4.19 (d, *J* = 16.6 Hz, 1H), 3.58 (s, 3H), 3.51 (d, *J* = 16.6 Hz, 1H), 3.12 (dd, *J* = 9.5, 5.2 Hz, 1H), 2.16 (d, *J* = 1.8 Hz, 1H), 1.75 (s, 3H), 1.68 – 1.58 (m, 5H), 1.46 (dd, *J* = 12.5, 5.2 Hz, 1H), 1.12 (s, 3H), 1.06 (s, 3H), 0.74 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 175.8, 144.4, 133.4, 133.3, 128.2, 127.8, 126.4, 60.4, 57.1, 51.6, 44.1, 40.4, 40.0, 31.7, 22.1, 21.7, 21.1, 19.3, 14.3, 14.2. IR (cm^{-1}): 2951, 2927, 1725, 1602. HRMS (ES+) calcd for $C_{23}H_{33}NO_2$ $(M + H)^+$: 356.2584. Found: 356.2577.



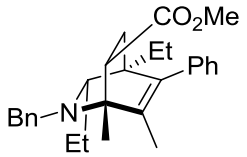
3.3k

3.3k was prepared by method B for 48 h, using 1-benzyl-6-butyl-2,3-diethyl-4,5-dimethyl-1,2-dihydropyridine (46.7 mg) and methyl acrylate (0.14 mL). **3.3k** was purified by column chromatography on silica gel (20:1 hexanes:ethyl acetate) and obtained in a 66% isolated yield (39.4 mg, 0.10 mmol) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.38 (d, *J* = 7.2 Hz, 2H), 7.32 – 7.25 (m, 2H), 7.22 (t, *J* = 7.2 Hz, 1H), 4.19 (d, *J* = 12.4 Hz, 1H), 3.62 (s, 3H), 3.13 – 3.03 (m, 2H), 2.22 (m, 1H), 1.91 – 1.80 (m, 3H), 1.79 – 1.69 (m, 7H), 1.59 (q, *J* = 7.5 Hz, 2H), 1.50 (m, 1H), 1.45 – 1.30 (m, 3H), 0.97 (t, *J* = 7.3 Hz, 3H), 0.87 t, *J* = 7.5 Hz, 3H), 0.80 – 0.70 (m, 1H), 0.21 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 175.9, 141.4, 136.8, 132.2, 130.0, 128.3, 127.1, 67.0, 62.6, 57.2, 51.6, 45.8, 42.1, 33.8, 32.6, 28.2, 27.2, 26.1, 23.9, 15.0, 14.6, 14.3, 11.1, 8.8. IR (cm^{-1}): 2954, 2871, 1730, 1602. HRMS (ES+) calcd for $C_{26}H_{39}NO_2$ $(M + H)^+$: 398.3054. Found: 398.3037.



3.3l

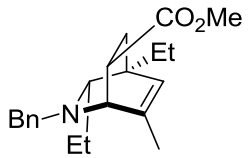
3.3l was prepared by method B for 16 h, using 1-benzyl-2,3,5-triethyl-4,6-dimethyl-1,2-dihydropyridine (42.5 mg) and methyl acrylate (0.14 mL). **3.3l** was purified by column chromatography on silica gel (20:1 hexanes:ethyl acetate) and obtained in a 90% isolated yield (49.9 mg, 0.14 mmol) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.37 (m, 2H), 7.29 – 7.24 (m, 2H), 7.18 (m Hz, 1H), 4.20 (d, *J* = 15.6 Hz, 1H), 3.58 (s, 3H), 3.44 (d, *J* = 15.6 Hz, 1H), 3.07 (dd, *J* = 9.7, 5.2 Hz, 1H), 2.27 (m, 1H), 2.26 – 2.18 (m, 1H), 2.00 (dq, *J* = 14.8, 7.5 Hz, 1H), 1.82 – 1.75 (m, 4H), 1.63 (q, *J* = 7.5 Hz, 2H), 1.41 (dd, *J* = 12.5, 5.2 Hz, 1H), 1.24 – 1.17 (m, 4H), 1.16 – 1.08 (m, 1H), 0.92 (m, 6H), 0.62 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 175.8, 144.1, 139.1, 134.5, 128.2, 128.0, 126.5, 69.9, 59.8, 56.6, 51.6, 44.5, 41.6, 34.0, 26.3, 26.2, 21.5, 21.2, 14.2, 13.6, 10.8, 8.8. IR (cm^{-1}): 2964, 2928, 2871, 1727, 1602. HRMS (ES+) calcd for $C_{24}H_{35}NO_2$ $(M + H)^+$: 370.2741. Found: 370.2731.



3.3m

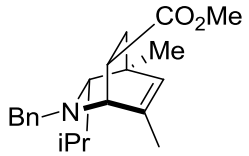
3.3m was prepared by method B for 16 h, using 1-benzyl-2,3-diethyl-5,6-dimethyl-4-phenyl-1,2-dihydropyridine (49.7 mg) and methyl acrylate (0.14 mL). **3.3m** was purified by column chromatography on silica gel (20:1 hexanes:ethyl acetate) and obtained in a 73% isolated yield (45.6 mg, 0.11 mmol) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.44 (d, *J* = 7.5 Hz, 2H), 7.31 (m,

4H), 7.24 (d, *J* = 7.0 Hz, 1H), 7.20 (m, 2H), 7.15 (d, *J* = 8.1 Hz, 1H), 4.31 (d, *J* = 15.5 Hz, 1H), 3.64 (s, 3H), 3.53 (d, *J* = 15.5 Hz, 1H), 3.25 (m, 1H), 2.31 (m, 1H), 1.94 (m, 1H), 1.63 (m Hz, 1H), 1.58 – 1.48 (m, 1H), 1.46 (s, 3H), 1.44 – 1.33 (m, 1H), 1.28 – 1.16 (m, 5H), 0.68 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 175.9, 143.5, 141.4, 140.0, 136.4, 130.7, 129.0, 128.30, 128.25, 128.2, 127.9, 126.6, 126.5, 70.5, 60.0, 57.4, 51.7, 44.9, 42.9, 34.1, 29.2, 27.6, 21.9, 16.1, 12.4, 8.3. IR (cm^{-1}): 2949, 2871, 1726, 1599. HRMS (ES+) calcd for $C_{28}H_{35}NO_2$ $(M + H)^+$: 418.2741. Found: 418.2739.



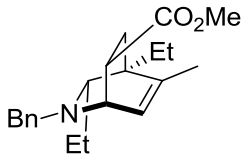
3.3n

3.3n was prepared by method B for 16 h, using 1-benzyl-2,3-diethyl-5-methyl-1,2-dihydropyridine (36.2 mg) and methyl acrylate (0.14 mL). **3.3n** was purified by column chromatography on silica gel (20:1 hexanes:ethyl acetate) and obtained in a 79% isolated yield (38.8, 0.12 mmol) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.41 (m, 2H), 7.34 (m, 2H), 7.26 (m, 1H), 5.52 (s, 1H), 3.84 (d, *J* = 14.4 Hz, 1H), 3.64 (d, *J* = 14.4 Hz, 1H), 3.56 (s, 3H), 3.31 – 3.25 (m, 2H), 2.10 (m, 1H), 1.78 – 1.70 (m, 1H), 1.69 – 1.60 (m, 4H), 1.58 – 1.38 (m, 3H), 1.17 (m, 1H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.86 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 175.7, 140.8, 140.3, 129.6, 129.62, 128.56, 127.1, 67.5, 57.9, 56.7, 51.8, 41.5, 37.0, 32.6, 27.9, 26.1, 20.1, 11.3, 8.6. IR (cm^{-1}): 3027, 2962, 2926, 2871, 2799, 1727, 1603. HRMS (ES+) calcd for $C_{21}H_{29}NO_2$ $(M + H)^+$: 328.2271. Found: 328.2265.



3.3o

3.3o was prepared by method B for 16 h, using 1-benzyl-2-isopropyl-3,5-dimethyl-1,2-dihydropyridine (36.2 mg) and methyl acrylate (0.14 mL). **3.3o** was purified by column chromatography on silica gel (20:1 hexanes:ethyl acetate) and obtained in a 89% isolated yield (43.7, 0.13 mmol) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.42 (m, 2H), 7.36 – 7.31 (m, 2H), 7.25 (m, 1H), 5.49 (s, 1H), 3.92 (d, *J* = 15.0 Hz, 1H), 3.64 (d, 15.0 Hz, 1H), 3.54 (s, 3H), 3.32 – 3.23 (m, 2H), 2.09 (m, 1H), 1.80 (m, 1H), 1.70 – 1.61 (m, 4H), 1.54 (m, 1H), 1.16 (s, 3H), 0.95 – 0.90 (d, *J* = 7.1 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 175.6, 141.0, 139.2, 131.0, 128.6, 128.2, 127.0, 72.9, 58.1, 57.1, 51.8, 38.5, 38.1, 37.2, 31.5, 23.1, 22.3, 19.9, 19.3. IR (cm^{-1}): 2956, 2924, 2871, 1705, 1594. HRMS (ES+) calcd for $C_{21}H_{29}NO_2$ $(M + H)^+$: 328.2271. Found: 328.2265.



3.3p

3.3p was prepared by method B for 16 h, using 1-benzyl-2,3-diethyl-4-methyl-1,2-dihydropyridine (36.2 mg) and methyl acrylate (0.14 mL). **3.3p** was purified by column chromatography on silica gel (20:1 hexanes:ethyl acetate) and obtained in a 81% isolated yield (39.8, 0.12 mmol) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.42 (m, 2H), 7.34 (m, 2H), 7.27 (m, 1H), 5.88 (d, *J* = 5.9 Hz, 1H), 3.87 (d, *J* = 13.8 Hz, 1H), 3.63 – 3.53 (m, 4H), 3.46 (m, 1H), 3.32 – 3.26 (m, 1H), 2.17 (m, 1H), 1.79 – 1.58 (m, 8H), 1.48 (m, 1H), 1.10 – 1.00 (m, 1H), 0.98 – 0.92 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 175.9, 144.7, 140.1, 129.0, 128.6, 127.3, 125.7, 66.3, 58.8, 52.0, 51.5, 43.0, 36.9, 30.8, 26.6, 25.4, 18.7, 11.3, 8.5. IR (cm^{-1}): 3028, 2926, 2870, 1727, 1601. HRMS (ES+) calcd for $C_{21}H_{29}NO_2$ $(M + H)^+$: 328.2271. Found: 328.2270.

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Appendix: X-ray Crystal Data

Single crystals of **3.3g** were obtained from a pentane solution at room temperature. This solution was evaporated to dryness.

The space group is chiral but the flack parameter refined to 0.41(16).

Figure 3.1. ORTEP representation of **3.3g**. Hydrogen atoms omitted for clarity, 35% displacement ellipsoids.

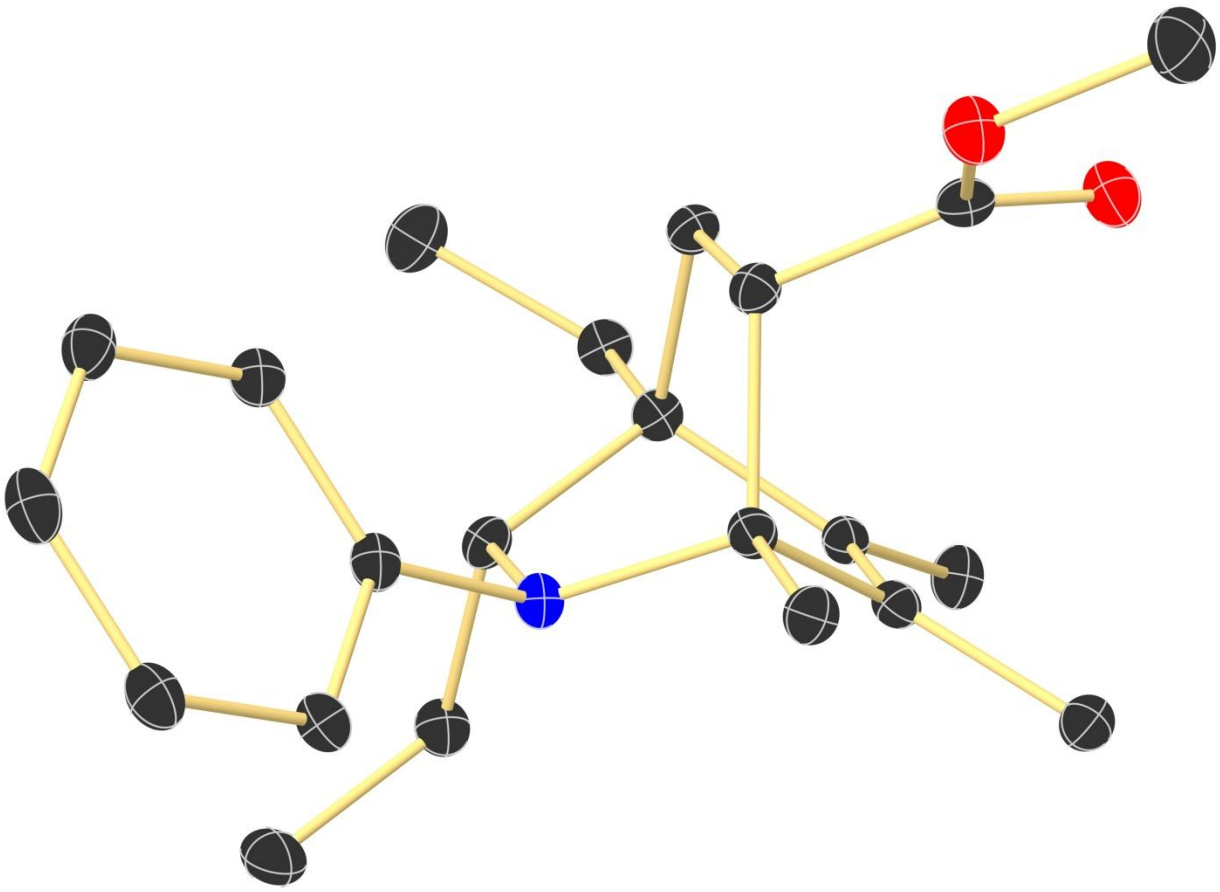

Table 3.1. Summary of X-ray crystallographic analysis for **3.3g**.

Empirical formula	$C_{22}H_{31}NO_2$	
Formula weight	341.48	
Temperature	93(2) K	
Wavelength	1.54187 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 7.6187(2) Å	a= 90°.
	b = 15.2421(3) Å	b= 99.420(7)°.
	c = 8.3982(6) Å	g = 90°.
Volume	962.09(8) $Å^3$	
Z	2	
Density (calculated)	1.179 Mg/m^3	
Absorption coefficient	0.578 mm^{-1}	
F(000)	372	
Crystal size	0.30 x 0.15 x 0.05 mm^3	
Theta range for data collection	5.89 to 68.32°.	
Index ranges	-8<=h<=8, -18<=k<=18, -10<=l<=10	
Reflections collected	11258	
Independent reflections	3185 [R(int) = 0.0407]	
Completeness to theta = 68.32°	95.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9717 and 0.8458	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3185 / 1 / 233	
Goodness-of-fit on F^2	0.981	
Final R indices [I>2sigma(I)]	R1 = 0.0261, wR2 = 0.0636	
R indices (all data)	R1 = 0.0265, wR2 = 0.0642	
Absolute structure parameter	0.42(16)	
Largest diff. peak and hole	0.138 and -0.123 $e.Å^{-3}$	

Table 3.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **3.3g**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	2406(2)	7658(1)	8762(1)	17(1)
C(11)	783(2)	7413(1)	7725(2)	18(1)
C(12)	-914(2)	7588(1)	8073(2)	19(1)
C(13)	-2435(2)	7358(1)	7002(2)	23(1)
C(14)	-2294(2)	6942(1)	5562(2)	24(1)
C(15)	-616(2)	6760(1)	5206(2)	24(1)
C(16)	906(2)	6999(1)	6265(2)	21(1)
C(1)	3152(2)	6995(1)	10010(2)	17(1)
C(17)	3260(2)	6101(1)	9227(2)	19(1)
C(2)	1875(2)	6963(1)	11311(2)	17(1)
C(18)	2480(2)	6288(1)	12593(2)	18(1)
O(1)	3652(1)	6384(1)	13734(1)	24(1)
O(2)	1552(1)	5533(1)	12321(1)	23(1)
C(19)	2094(2)	4849(1)	13488(2)	30(1)
C(3)	1810(2)	7896(1)	12012(2)	18(1)
C(4)	3030(2)	8537(1)	11272(2)	18(1)
C(20)	2950(2)	9454(1)	12042(2)	21(1)
C(21)	1160(2)	9917(1)	11701(2)	28(1)
C(5)	2399(2)	8563(1)	9419(2)	17(1)
C(22)	3522(2)	9170(1)	8538(2)	21(1)
C(23)	2914(2)	9203(1)	6720(2)	31(1)
C(6)	4943(2)	7337(1)	10873(2)	17(1)
C(24)	6557(2)	6755(1)	11031(2)	21(1)
C(7)	4880(2)	8131(1)	11544(2)	17(1)
C(25)	6417(2)	8603(1)	12524(2)	23(1)

Table 3.3. Bond lengths [Å] and angles [°] for **3.3g**.

N(1)-C(11)	1.4401(18)
N(1)-C(5)	1.4862(16)
N(1)-C(1)	1.4989(16)
C(11)-C(16)	1.3953(19)
C(11)-C(12)	1.3972(19)
C(12)-C(13)	1.390(2)
C(12)-H(12)	0.9500
C(13)-C(14)	1.385(2)
C(13)-H(13)	0.9500
C(14)-C(15)	1.387(2)
C(14)-H(14)	0.9500
C(15)-C(16)	1.390(2)
C(15)-H(15)	0.9500
C(16)-H(16)	0.9500
C(1)-C(17)	1.5212(17)
C(1)-C(6)	1.5281(19)
C(1)-C(2)	1.5791(17)
C(17)-H(17A)	0.9800
C(17)-H(17B)	0.9800
C(17)-H(17C)	0.9800
C(2)-C(18)	1.5063(18)
C(2)-C(3)	1.5426(18)
C(2)-H(2)	1.0000
C(18)-O(1)	1.2065(17)
C(18)-O(2)	1.3502(16)
O(2)-C(19)	1.4443(16)
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800
C(3)-C(4)	1.5477(18)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-C(7)	1.5224(19)
C(4)-C(20)	1.5453(18)

C(4)-C(5)	1.5525(18)
C(20)-C(21)	1.520(2)
C(20)-H(20A)	0.9900
C(20)-H(20B)	0.9900
C(21)-H(21A)	0.9800
C(21)-H(21B)	0.9800
C(21)-H(21C)	0.9800
C(5)-C(22)	1.5311(18)
C(5)-H(5)	1.0000
C(22)-C(23)	1.522(2)
C(22)-H(22A)	0.9900
C(22)-H(22B)	0.9900
C(23)-H(23A)	0.9800
C(23)-H(23B)	0.9800
C(23)-H(23C)	0.9800
C(6)-C(7)	1.3394(18)
C(6)-C(24)	1.5037(19)
C(24)-H(24A)	0.9800
C(24)-H(24B)	0.9800
C(24)-H(24C)	0.9800
C(7)-C(25)	1.501(2)
C(25)-H(25A)	0.9800
C(25)-H(25B)	0.9800
C(25)-H(25C)	0.9800

C(11)-N(1)-C(5)	114.19(10)
C(11)-N(1)-C(1)	116.00(10)
C(5)-N(1)-C(1)	112.94(10)
C(16)-C(11)-C(12)	117.89(13)
C(16)-C(11)-N(1)	118.27(12)
C(12)-C(11)-N(1)	123.81(12)
C(13)-C(12)-C(11)	121.21(13)
C(13)-C(12)-H(12)	119.4
C(11)-C(12)-H(12)	119.4
C(14)-C(13)-C(12)	120.30(14)
C(14)-C(13)-H(13)	119.8

C(12)-C(13)-H(13)	119.8
C(13)-C(14)-C(15)	119.09(14)
C(13)-C(14)-H(14)	120.5
C(15)-C(14)-H(14)	120.5
C(14)-C(15)-C(16)	120.71(13)
C(14)-C(15)-H(15)	119.6
C(16)-C(15)-H(15)	119.6
C(15)-C(16)-C(11)	120.79(13)
C(15)-C(16)-H(16)	119.6
C(11)-C(16)-H(16)	119.6
N(1)-C(1)-C(17)	110.06(10)
N(1)-C(1)-C(6)	108.03(10)
C(17)-C(1)-C(6)	113.79(11)
N(1)-C(1)-C(2)	107.38(10)
C(17)-C(1)-C(2)	110.73(10)
C(6)-C(1)-C(2)	106.59(10)
C(1)-C(17)-H(17A)	109.5
C(1)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5
C(1)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5
C(18)-C(2)-C(3)	112.49(10)
C(18)-C(2)-C(1)	111.40(10)
C(3)-C(2)-C(1)	107.30(10)
C(18)-C(2)-H(2)	108.5
C(3)-C(2)-H(2)	108.5
C(1)-C(2)-H(2)	108.5
O(1)-C(18)-O(2)	122.44(12)
O(1)-C(18)-C(2)	125.79(12)
O(2)-C(18)-C(2)	111.76(12)
C(18)-O(2)-C(19)	114.63(11)
O(2)-C(19)-H(19A)	109.5
O(2)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
O(2)-C(19)-H(19C)	109.5

H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5
C(2)-C(3)-C(4)	111.75(10)
C(2)-C(3)-H(3A)	109.3
C(4)-C(3)-H(3A)	109.3
C(2)-C(3)-H(3B)	109.3
C(4)-C(3)-H(3B)	109.3
H(3A)-C(3)-H(3B)	107.9
C(7)-C(4)-C(20)	113.88(11)
C(7)-C(4)-C(3)	106.55(10)
C(20)-C(4)-C(3)	109.64(10)
C(7)-C(4)-C(5)	106.72(10)
C(20)-C(4)-C(5)	111.70(10)
C(3)-C(4)-C(5)	108.05(10)
C(21)-C(20)-C(4)	115.87(11)
C(21)-C(20)-H(20A)	108.3
C(4)-C(20)-H(20A)	108.3
C(21)-C(20)-H(20B)	108.3
C(4)-C(20)-H(20B)	108.3
H(20A)-C(20)-H(20B)	107.4
C(20)-C(21)-H(21A)	109.5
C(20)-C(21)-H(21B)	109.5
H(21A)-C(21)-H(21B)	109.5
C(20)-C(21)-H(21C)	109.5
H(21A)-C(21)-H(21C)	109.5
H(21B)-C(21)-H(21C)	109.5
N(1)-C(5)-C(22)	110.20(10)
N(1)-C(5)-C(4)	109.27(10)
C(22)-C(5)-C(4)	113.18(11)
N(1)-C(5)-H(5)	108.0
C(22)-C(5)-H(5)	108.0
C(4)-C(5)-H(5)	108.0
C(23)-C(22)-C(5)	113.74(12)
C(23)-C(22)-H(22A)	108.8
C(5)-C(22)-H(22A)	108.8
C(23)-C(22)-H(22B)	108.8

C(5)-C(22)-H(22B)	108.8
H(22A)-C(22)-H(22B)	107.7
C(22)-C(23)-H(23A)	109.5
C(22)-C(23)-H(23B)	109.5
H(23A)-C(23)-H(23B)	109.5
C(22)-C(23)-H(23C)	109.5
H(23A)-C(23)-H(23C)	109.5
H(23B)-C(23)-H(23C)	109.5
C(7)-C(6)-C(24)	125.51(13)
C(7)-C(6)-C(1)	114.63(12)
C(24)-C(6)-C(1)	119.66(11)
C(6)-C(24)-H(24A)	109.5
C(6)-C(24)-H(24B)	109.5
H(24A)-C(24)-H(24B)	109.5
C(6)-C(24)-H(24C)	109.5
H(24A)-C(24)-H(24C)	109.5
H(24B)-C(24)-H(24C)	109.5
C(6)-C(7)-C(25)	125.86(13)
C(6)-C(7)-C(4)	113.65(12)
C(25)-C(7)-C(4)	120.47(11)
C(7)-C(25)-H(25A)	109.5
C(7)-C(25)-H(25B)	109.5
H(25A)-C(25)-H(25B)	109.5
C(7)-C(25)-H(25C)	109.5
H(25A)-C(25)-H(25C)	109.5
H(25B)-C(25)-H(25C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 3.4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **3.3g**. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	17(1)	14(1)	18(1)	0(1)	1(1)	-1(1)
C(11)	18(1)	14(1)	20(1)	4(1)	0(1)	-1(1)
C(12)	20(1)	16(1)	21(1)	2(1)	2(1)	-2(1)
C(13)	19(1)	21(1)	28(1)	6(1)	1(1)	-1(1)
C(14)	23(1)	24(1)	23(1)	4(1)	-5(1)	-5(1)
C(15)	27(1)	25(1)	19(1)	1(1)	0(1)	-2(1)
C(16)	22(1)	21(1)	19(1)	2(1)	3(1)	-1(1)
C(1)	18(1)	17(1)	16(1)	1(1)	2(1)	0(1)
C(17)	20(1)	16(1)	21(1)	-1(1)	3(1)	1(1)
C(2)	15(1)	16(1)	19(1)	0(1)	3(1)	-1(1)
C(18)	16(1)	19(1)	20(1)	-1(1)	6(1)	-1(1)
O(1)	23(1)	25(1)	23(1)	4(1)	-1(1)	-4(1)
O(2)	26(1)	16(1)	27(1)	3(1)	2(1)	-3(1)
C(19)	32(1)	20(1)	38(1)	10(1)	6(1)	0(1)
C(3)	17(1)	18(1)	20(1)	-1(1)	4(1)	1(1)
C(4)	19(1)	16(1)	19(1)	-1(1)	3(1)	0(1)
C(20)	22(1)	18(1)	21(1)	-2(1)	2(1)	-1(1)
C(21)	29(1)	19(1)	36(1)	-6(1)	4(1)	3(1)
C(5)	16(1)	15(1)	20(1)	-2(1)	2(1)	0(1)
C(22)	22(1)	18(1)	23(1)	2(1)	3(1)	-2(1)
C(23)	30(1)	37(1)	25(1)	7(1)	5(1)	-9(1)
C(6)	18(1)	18(1)	16(1)	3(1)	4(1)	0(1)
C(24)	19(1)	20(1)	23(1)	0(1)	4(1)	0(1)
C(7)	17(1)	19(1)	16(1)	3(1)	2(1)	-2(1)
C(25)	22(1)	20(1)	27(1)	0(1)	0(1)	0(1)

Table 3.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **3.3g**.

	x	y	z	U(eq)
H(12)	-1031	7869	9060	23
H(13)	-3576	7487	7258	28
H(14)	-3331	6784	4829	29
H(15)	-508	6469	4226	29
H(16)	2044	6879	5992	25
H(17A)	2062	5908	8750	29
H(17B)	3783	5676	10046	29
H(17C)	4004	6142	8383	29
H(2)	654	6802	10758	20
H(19A)	3367	4731	13542	45
H(19B)	1415	4314	13164	45
H(19C)	1866	5037	14551	45
H(3A)	2186	7874	13196	21
H(3B)	570	8115	11794	21
H(20A)	3294	9394	13226	25
H(20B)	3847	9834	11655	25
H(21A)	840	10023	10539	42
H(21B)	1236	10478	12278	42
H(21C)	251	9548	12067	42
H(5)	1145	8782	9217	21
H(22A)	3479	9770	8980	26
H(22B)	4775	8971	8757	26
H(23A)	3147	8636	6245	46
H(23B)	3567	9665	6253	46
H(23C)	1636	9329	6490	46
H(24A)	7618	7096	11469	31
H(24B)	6685	6524	9967	31
H(24C)	6420	6267	11759	31
H(25A)	7489	8239	12606	35
H(25B)	6150	8718	13607	35

H(25C)	6617	9160	11999	35