Michael addition with an olefinic pyridine: organometallic nucleophiles and carbon electrophiles.

Michael R. Stentzel and Douglas A. Klumpp*

Department of Chemistry and Biochemistry

Northern Illinois University

DeKalb, Illinois 60115

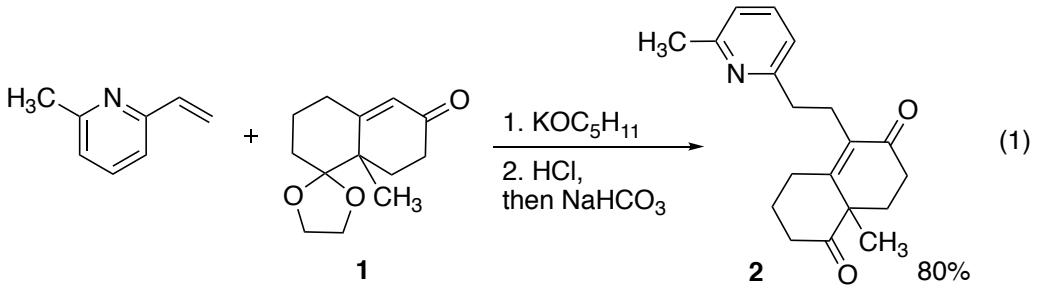
Email: dklumpp@niu.edu ORCHID ID: https://orcid.org/0000-0001-5271-699X

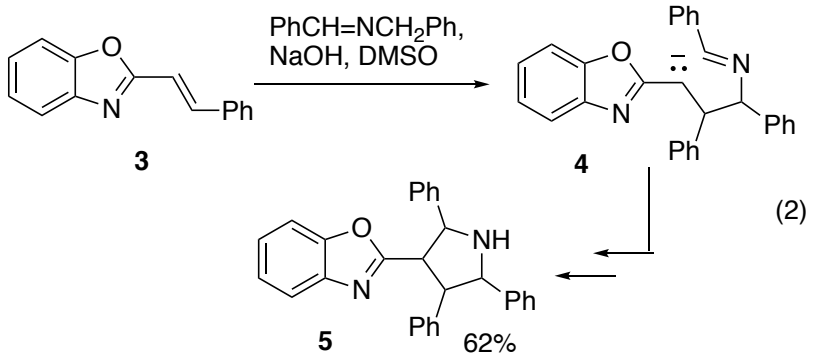
Abstract:

The conjugate addition reactions of *trans*-1,2-di-(2-pyridyl)ethylene have been studied. This substrate reacts with organolithium nucleophiles and the resulting anionic intermediates may be trapped by proton or various carbonyl-based electrophiles. It is suggested that the dipyridyl structure stabilizes the intermediate carbanion, allowing the Michael adduct to be captured by an added electrophile.

Michael (or conjugate) addition was first reported in the late 1800s.[1] These initial reports described the addition of stabilized nucleophiles to α,β-unsaturated carbonyl compounds. Subsequent developments extended this chemistry to a wide variety of nucleophiles and Michael acceptors.[2] In 1947, Doering and Weil reported the base-promoted conjugate addition of malonate esters with 2- and 4-vinylpyridine - demonstrating that olefinic *N*-heterocycles are effective Michael acceptors.[3] Despite decades of work, the vast majority of conjugate additions

involve nucleophilic attack at the olefinic *N*-heterocycle followed a protonation to complete the addition.[4] For example, Danishefsky and coworkers used 6-vinylpicoline in the addition reaction - generating a nucleophile from enone **1** and completing the addition with protonation (eq 1).[5] Only a few examples of conjugate addition are known in which nucleophilic attack at the olefinic *N*-heterocycle is followed the reaction of an electrophile other than a proton. One such



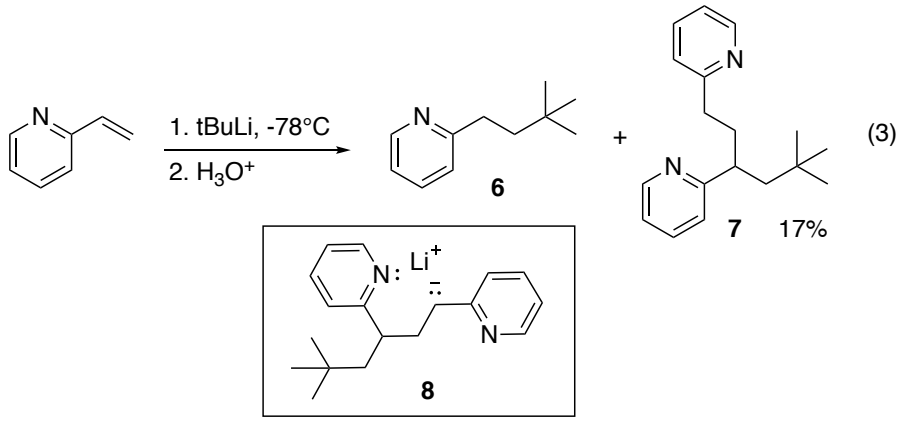


example is the cycloaddition involving the benzoxazole derivative **3** (eq 2).[6] Deprotonation of N-benzylidenebenzyl amine leads to nucleophilic attack and formation of the anionic intermediate **4**, followed by reaction at the electrophilic imine group and product (**5**) formation. In contrast to the chemistry with *N*-heterocycles, it is common to use varied electrophiles in the conjugate addition reactions of α,β-unsaturated carbonyl compounds. In the reactions of α,β-unsaturated carbonyl compounds with anionic nucleophiles, the resulting enolate intermediates have been

captured by electrophiles such as aldehydes, acid halides, and others.[2b] In the following Note, we describe Michael additions to an olefinic pyridine with organolithium nucleophiles and carbon-centered electrophiles. A key aspect of this chemistry involves the formation of a stabilized anionic intermediate following reaction with the organolithium reagent.

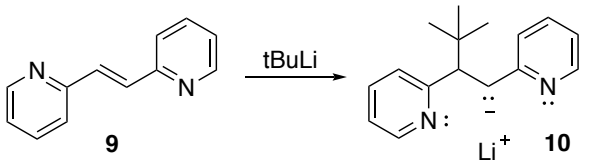
Results and Discussion

It has been previously reported that olefinic *N*-heterocycles react poorly with reagents such as organolithium and Grignard reagents.[7] Our initial efforts to react olefinic *N*-heterocycles with organolithium olefinic *N*-heterocycles reagents were also unsuccessful. In an attempt to react 2-vinylpyridine with tBuLi and capture the anionic intermediate with a proton source, only a trace amount of the adduct **6** was obtained and the only major product isolated was the dimeric species **7** (eq 3). Clearly, product **7** is formed by nucleophilic attack by tBuLi at



2-vinylpyridine. However, the resulting anionic intermediate evidently reacts with a second equivalent of 2-vinylpyridine to eventually provide compound **7** from protonation. This suggested to us that the second carbanionic intermediate, species **8**, must possess at least some kinetic stability – perhaps from internal stabilization of the carbon-lithium ionic bond.

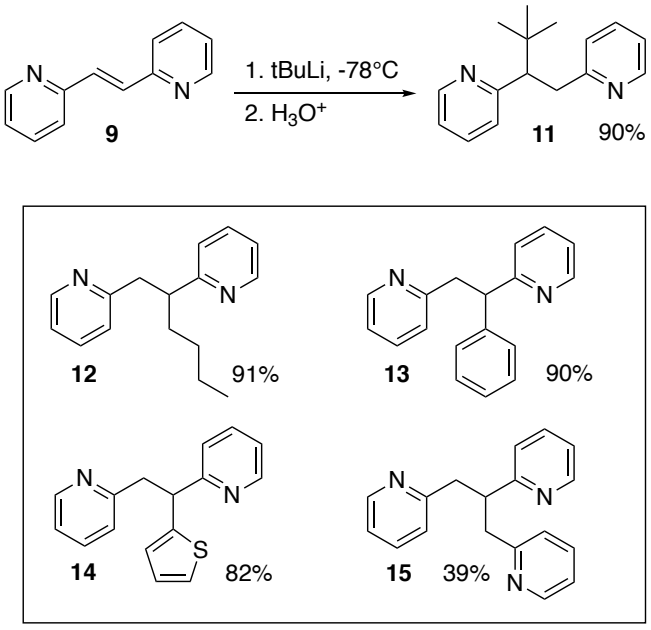
With this consideration, we hypothesized that 1,2-di-(2-pyridyl)ethylene (**9**) could exhibit a similar kinetic stability and enable the resulting carbanionic intermediate (**10**) to be trapped efficiently with electrophiles (eq 4). To test this hypothesis, we reacted substrate **9** with a



(4)

variety of organolithium reagents and quenched the resulting solutions with aqueous acid (Table 1). The results indicate that 1,2-di-(2-pyridyl)ethylene (**9**) reacts efficiently with organometallic reagents – leading to addition products **11-15**. This includes aliphatic and

Table 1. Products and yields from the reactions of **9** with organolithium reagents.



aromatic organolithium reagents. Product **15** is prepared from 2-picolyllithium and compound **9**. The low yield of product **15** is due in part to difficulties in purifying **15** by silica gel

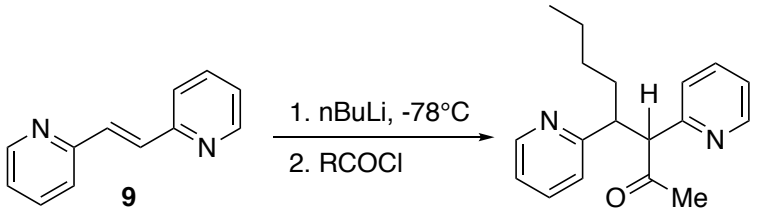
chromatography. The generally good yields of the addition products suggest reasonably stable anionic intermediates and the potential for reactions with other electrophiles.

When compound **9** is reacted with butyllithium followed by acid chlorides, the addition products are formed in fair to good yields Table 2. Thus, compound **9** reacts with BuLi and acetyl chloride to provide the addition product **16** in good yield. In order to obtain a clean conversion to product, it is necessary to add the solution of the carbanionic, butyllithium adduct to a solution of acetyl chloride. If acetyl chloride is added to a solution of the butyllithium adduct, product **16** is formed along with significant quantities of compound **12**. Presumably, compound **12** is formed by the reaction of the carbanionic intermediate and product **16** – at the acidic α-hydrogen. Product **16** is isolated as a single diastereomer. Likewise, products **17-18** and **21-23** are obtained as single diastereomers, but compounds **19** and **20** are obtained as the mixture of diastereomers.

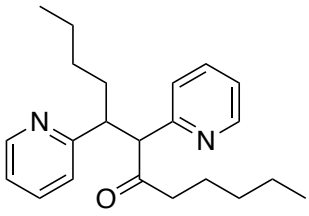
In addition to acid chloride electrophiles, chloroformate electrophiles provide compounds **24-26** and **30** in fair yields. NMR analysis of crude products indicates that single diastereomers are formed in with **24-26** while a mixture of diastereomers are obtained with **30**. Similarly, the addition may be accomplished with cyclohexanone, providing adduct **27** as a single diastereomer in 69% yield. A sulfonyl chloride has been shown to give the adduct **28** in fair yield. NMR indicates that product **28** is formed as the mixture of diastereomers (3:2 ratio). A similar conversion utilizing diethylcarbamoyl chloride was not successful.

The conversions above are consistent with the formation of a relatively stable carbanionic intermediate from nucleophilic attack by butyllithium and related organometallics. Although it has been previously reported that both organolithium and Grignard reagents fail to

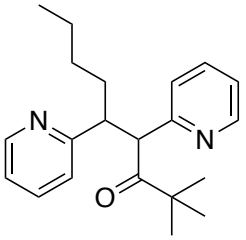
Table 2. Addition products and yields from compound **9** and butyllithium with acid chlorides.



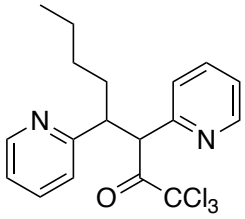
9 **16** 80%[a]



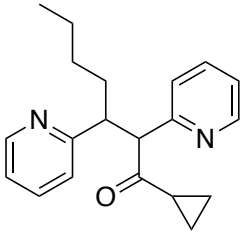
17 64%[a]



18 80%[a]



19 47%[b]



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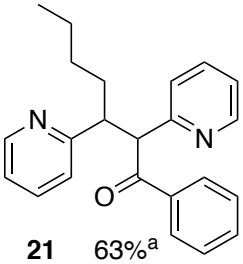

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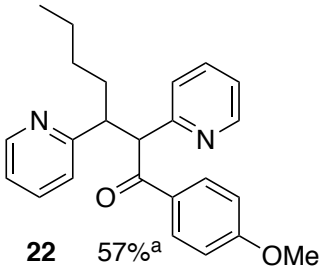

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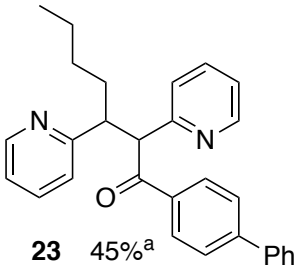
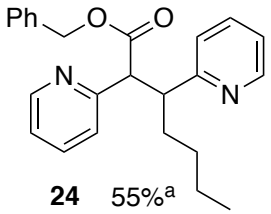


23 45%[a]

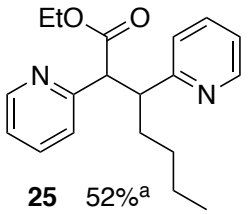
[a]Isolated as the single diastereomer (DL mixture).
[b]Isolated as the diastereomeric mixture.

Table 3. Products from the addition reactions of organometallics and various electrophiles.

9



24 55%[a]



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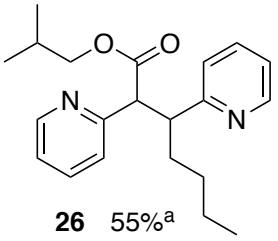
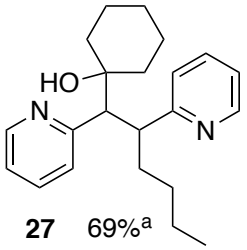
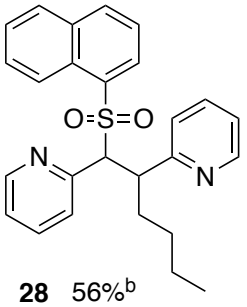


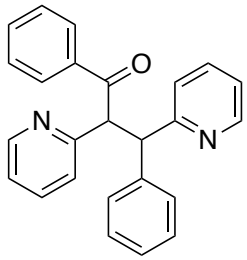
26 55%[a]



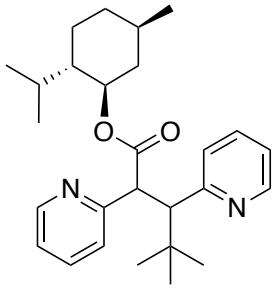
27 69%[a]



28 56%[b]



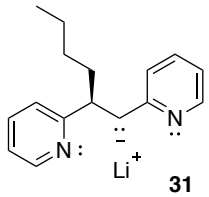
29 67%[a]



30 31%[b]

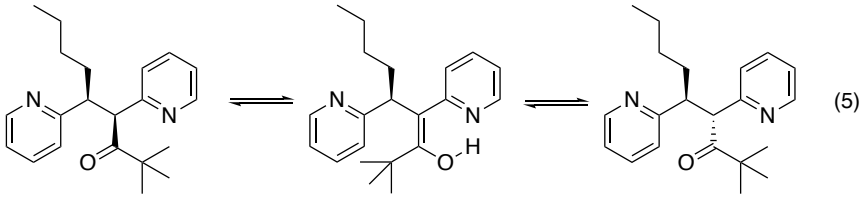
[a]Isolated as the single diastereomer (DL mixture).
[b]Isolated as the diastereomeric mixture.

react with olefinic pyridines,[7] substrate **9** evidently will react with organolithium reagents. Thus, butyllithium couples with **9** to provide the carbanionic intermediate **31**. Like the dimeric



31

intermediate from 2-vinylpyridine (i.e., **8**), it is plausible that species **31** is stabilized by favorable interactions between the pyridyl nitrogen and lithium cation. As such, intermediate **31** is sufficiently long-lived that it may be successfully captured by electophiles. Regarding product stereochemistry, some addition products were isolated as racemic mixtures of a single compound while others were obtained as mixtures of diastereomers. It is suggested that these product distributions are the result of thermodynamic control for the carbonyl-substituted products. For example in the case of product **18**, isomerization between epimers **18 (*S,R*)** and **18 (*S,S*)** is expected to occur readily, as the enol **32** benefits from a stabilizing hydrogen bond to the pyridyl group (eq 5). DFT calculations estimate the energy difference between the two



(5)

18 (S,R) 1.7 kcal/mol | **32** 13.2 kcal.mol | **18 (S,S)** 0.0 kcal/mol

epimers to be 1.7 kcal/mol.[8] While the enol tautomer (**32**) is just 13.2 kcal/mol above structure **18 (S,S)**. This should allow for rapid interconversion between **18 (*S,R*)** and **18 (*S,S*)** at ambient temperatures and the formation of thermodynamically controlled product mixtures.

Conclusions

We have found that 1,2-di-(2-pyridyl)ethylene (**9**) reacts effectively with organolithium reagents. It is suggested that the intermediate Michael adducts exhibit kinetic stability by stabilization of the carbanion salts. With the long-lived intermediates, it becomes possible to complete the addition chemistry with electrophiles other than proton. Thus, we demonstrate that it is possible to expand the scope of Michael addition reactions with olefinic *N*-heterocycles, if the intermediate carbanions are stabilized by structural effects.

Experimental

Reagents and solvents were purchased from commercial suppliers and used as received. Synthetic reactions were done using oven dried glassware under an inert atmosphere. NMR spectra were obtained from Bruker Avance III NMR spectrometers (300 or 500 MHz). Low-resolution mass spectra were obtained from an Agilent 6890 gas chromatograph equipped with a 5973 mass-selective detector. High-resolution mass spectra were obtained from a Bruker Maxis Plus Quadrupole Time-of-Flight mass spectrometer.

2,2'-(5,5-Dimethylhexane-1,3-diyl)dipyridine (7). A solution of *tert*-butyllithium 0.9 mL (1.5 M, 1.4 mmol) is cooled to 0 °C and to this solution is slowly added 2-vinylpyridine (0.075 mL, 0.696 mmol in 5 mL THF). After stirring for 1 hr, the mixture is quenched with deoxygenated water and diluted with dichloromethane. The organic phase is separated and washed twice with saturated brine, and then dried with Na_2SO_4. Silica gel chromatography yields compound **7**

(0.032 g, 0.119 mmol, 17%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25^{o}C): δ 8.54 (d, J=3.99 Hz, 1H), 8.47 (d, J=4.34 Hz, 1H), 7.58-7.49 (m, 2H), 7.14 (d, J=7.85 Hz, 1H), 7.09-7.01 (m, 3H), 2.95-2.87 (m, 1H), 2.73-2.62 (m, 1H), 2.54-2.44 (m, 1H), 2.11-2.02 (m, 2H), 1.97 (t, J=4.94 Hz, 1H), 1.58 (dd, J=14.04 Hz, J=2.93 Hz, 1H), 0.74 (s, 9H). ; ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ 166.2, 162.0, 149.2, 149.1, 136.2, 136.1, 123.1, 122.7, 121.0, 120.8, 49.3, 44.4, 38.5, 36.4, 31.2, 29.9. Low-Resolution MS (EI): 268 (M+), 253, 211, 197, 183, 176, 163, 154, 144. High-Resolution MS (ESI) (M+H), calcd for $C_{18}H_{25}N_2$, 269.2018, found, 269.2020.

General Procedure A. A solution is prepared from anhydrous THF (3 mL) and 1,2-bis(2-pyridyl)ethylene (0.075 g, 0.41 mmol). The mixture is cooled to -78 °C and the organolithium reagent (0.5 mmol) is then slowly added. The solution is stirred for 1 hr, after which deoxygenated water is added, and the resulting mixture is allowed to warm to room temperature. To this solution is added 0.5 mL of saturated NH_4Cl and the product is partition between the aqueous phase and dichloromethane. The organic phase is separated and washed twice with saturated brine, and then dried with Na_2SO_4. Silica gel chromatography yields pure addition product.

2,2'-(3,3-Dimethylbutane-1,2-diyl)dipyridine (11). Using General Procedure A, 1,2-bis(2-pyridyl)ethylene (0.08 g, 0.44 mmol) provides compound **11**(95.2 mg, 0.396 mmol, 90%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25^{o}C): δ 8.49 (dd, J= 4.91 Hz, J=0.96 Hz, 1H), 8.39 (d, J=3.95 Hz, 1H), 7.34 (td, J=8.39 Hz, J=1.82 Hz, 1H), 6.97-6.92 (m, 1H), 6.90-6.84 (m, 2H), 6.76 (d, J=7.92 Hz, 1H), 3.47-3.39 (m, 1H), 3.25-3.11 (m, 2H), 0.99 (s, 9H).; ^{13}C NMR (75 MHz, $CDCl_3$, 25

°C): δ 162.2, 161.6, 148.9, 148.4, 135.6, 135.0, 125.4, 123.6, 120.9, 120.5, 57.8, 38.0, 34.2, 28.3. Low-Resolution MS (EI): 240 (M+), 225, 218, 209, 195, 184, 169, 156, 148. High-Resolution MS (ESI) (M+H), calcd for $C_{16}H_{21}N_2$, 241.1705, found, 241.1701.

2,2'-(Hexane-1,2-diyl)dipyridine (12). Using General Procedure A, 1,2-bis(2-pyridyl)ethylene (73.2 mg, 0.402 mmol) provides compound **12** (87.6 mg, 0.366 mmol, 91%) as a light-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ 8.53 (d, J=4.59 Hz, 1H), 8.46 (d, J=4.33 Hz, 1H), 7.39 (heptd, J=7.76 Hz, J=1.82 Hz, 2H), 7.02-6.90 (m, 3H), 6.82 (d, J=7.85 Hz, 1H), 3.31-3.20 (m, 1H), 3.18-3.06 (m, 2H), 1.88-1.75 (m, 1H), 1.71-1.59 (m, 1H), 1.28-0.99 (m, 4H), 0.75 (t, J=7.35 Hz, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 164.1, 160.6, 149.3, 149.1, 135.8, 123.6, 123.5, 121.1, 120.8, 48.1, 44.3, 34.8, 29.7, 22.6, 13.9. Low-Resolution MS (EI): 240 (M+), 225, 211, 197, 183, 169, 154, 148. High-Resolution MS (ESI) (M+H), calcd for $C_{16}H_{21}N_2$, 241.1705, found, 241.1703.

2,2'-(1-Phenylethane-1,2-diyl)dipyridine (13). Using General Procedure A, 1,2-bis(2-pyridyl)ethylene (79.2 mg, 0.435 mmol) provides compound **13** (101.83 mg, 0.391 mmol, 90%) as a light yellow solid in 90% yield. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ 8.56 (d, J= 4.21 Hz, 1H), 8.49, (d, J= 4.32 Hz, 1H), 7.45 (td, J=8.39 Hz, J= 1.72, 1H), 7.36-7.34 (m, 3H), 7.25-7.19 (m, 2H), 7.16-7.11 (m, 2H), 7.04-6.91 (m, 3H), 4.77 (t, J=7.80 Hz, 1H), 3.82 (q, J=7.05 Hz, 1H), 3.53 (q, J=6.83 Hz, 1H).; ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 162.8, 160.1, 149.1, 143.3, 136.2, 135.9, 128.7, 128.4, 128.1, 127.1, 126.4, 123.5, 121.3, 121.0, 53.2, 43.5. Low-Resolution MS (EI): 260 (M+), 245, 230, 217, 204, 193, 182, 167, 152. High-Resolution MS (ESI) (M+H), calcd for $C_{18}H_{17}N_2$, 261.1329, found, 261.1399.

2,2'-(1-(Thiophen-2-yl)ethane-1,2-diyl)dipyridine (14). Using General Procedure A with modification (2-thienyllithium is reacted with substrate **9** at 25 °C for 12 hrs), 1,2-bis(2-pyridyl)ethylene (74.8 mg, 0.411 mmol) provides compound **14** (89.76 mg, 0.337 mmol, 82%) as a light tan solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25^{o}C): δ 8.60 (d, J=3.89 Hz, 1H), 8.52 (d, J=4.20 Hz, 1H), 7.53 (td, J=8.59 Hz, J=1.76 Hz, 1H), 7.42 (td, J=8.32 Hz, J=1.66 Hz, 1H), 7.18-7.02 (m, 4H), 6.94 (d, J=7.72 Hz, 1H), 6.86 (d, J=3.41 Hz, 2H), 5.03 (t, J=7.76 Hz, 1H), 3.66 (ddd, J=31.98 Hz, J=8.05 Hz, J=5.50 Hz, 2H).; ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ 162.1, 159.4, 149.3, 149.2, 146.6, 136.5, 136.0, 126.4, 124.6, 124.2, 123.9, 123.0, 121.7, 121.2, 48.8, 45.1. Low-Resolution MS (EI): 266 (M+), 251, 233, 219, 207, 188, 174, 154. High-Resolution MS (ESI) (M+H), calcd for $C_{16}H_{15}N_2S$, 267.0956, found, 267.0947.

2,2',2''-(Propane-1,2,3-triyl)tripyridine (15). A solution containing 2-picoline (37.4 mg, 0.411 mmol) and 3 mL THF is cooled to -78 ^{o}C and *n*-BuLi solution (0.493 mmol) is added dropwise. The resulting mixture is stirred 1 hr and then transferred slowly to a cold (-78 ^{o}C) solution of 1,2-bis(2-pyridyl)ethylene (74.9 mg, 0.411 mmol) in 3 mL THF. The solution is stirred for 1 hr, after which deoxygenated water is added, and the resulting mixture is allowed to warm to room temperature. To this solution is added 0.5 mL of saturated NH_4Cl and the product is partition between the aqueous phase and dichloromethane. The organic phase is separated and washed twice with saturated brine, and then dried with Na_2SO_4. Following column chromatography, compound **15** (44.14 mg, 0.16 mmol, 39%) is isolated as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25^{o}C): δ 8.55 (d, J=4.83 Hz, 1H), 8.46 (d, J= 4.81 Hz, 1H), 7.43-7.31 (m, 3H),

7.01-6.97 (m, 3H), 6.92 (d, J=7.78 Hz, 2H), 6.81 (d, J=7.88 Hz, 1H), 3.96-3.86 (m, 1H), 3.26 (ddd, J=17.69 Hz, J=7.31 Hz, J=5.77 Hz, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ 162.9, 160.2, 149.3, 149.2, 135.9, 135.8, 123.7, 123.7, 121.3, 120.9, 48.0, 43.5. Low-Resolution MS (EI): 275 (M+), 219, 207, 195, 183, 169, 154.High-Resolution MS (ESI) (M+H), calcd for $C_{18}H_{18}N_3$, 276.1501, found, 276.1509.

General Procedure B. A solution of 1,2-bis(2-pyridyl)ethylene (75 mg, 0.41 mmol) on 7 mL THF is cooled to -78 °C and n-BuLi solution (0.49 mmol) is slowly added. After stirring for 1 hr, the mixture is slowly transferred to a cold solution (-78 °C) of the electrophilic reagent (1 mmol) in THF (3 mL). The solution is stirred for 1 hr, after which deoxygenated water is added, and the resulting mixture is allowed to warm to room temperature. The product mixture is then partitioned between dilute sodium bicarbonate and dichloromethane. The aqueous phase is extracted three times with portions of dichloromethane, the organic extracts are combined, and washed with brine, dried over anhydrous sodium sulfate. After filtration and removal of solvent, the crude product is isolated by column chromatography.

3,4-Di(pyridin-2-yl)octan-2-one (16). Using General Procedure B, 1,2-bis(2-pyridyl)ethylene (75 mg, 0.41 mmol) provides compound **16** (92.6mg, 0.328 mmol, 80%) as an orange oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25^{o}C): δ 8.42 (d, J=4.79 Hz, 1H), 8.38 (d, J=4.67 Hz, 1H), 7.36-7.25 (m, 2H), 6.98 (d, J=7.82 Hz, 1H), 6.93-6.86 (m, 2H), 6.83 (d, J=7.71 Hz, 1H), 4.46 (d, J=11.04 Hz, 1H), 3.75 (td, J=11.07 Hz, J=3.29 Hz, 1H), 2.19 (s, 3H), 1.89-1.80 (m, 1H), 1.78-1.68 (m, 1H), 1.34-1.06 (m, 4H), 1.01-0.84 (m, 2H), 0.77 (t, J=7.81 Hz, 2H).; ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ 206.8, 161.8,

157.1, 149.3, 149.1, 136.1, 135.5, 124.6, 124.2, 121.6, 120.9, 66.7, 48.9, 33.4, 30.3, 29.6, 22.5, 13.9. Low-Resolution MS (EI): 282 (M+), 267, 239, 225, 210, 195, 183, 169, 148. High-Resolution MS (ESI) (M+H), calcd for $C_{18}H_{23}N_2O$, 283.1810, found, 283.1809.

7,8-Di(pyridin-2-yl)dodecan-6-one (17). Using General Procedure B, 1,2-bis(2-pyridyl)ethylene (98.3 mg, 0.54 mmol) provides compound **17** (116.9 mg, 0.346 mmol, 64%) as the mixture diastereomers and yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25^{o}C): δ 8..43-8.41 (m, 1H), 8.34-8.32 (m, 1H), 7.37-7.26 (m, 2H), 7.07 (d, J=7.84 Hz, 1H), 6.92-6.85 (m, 3H), 4.51 (d, J=11.08 Hz, 1H), 3.75 (td, J=10.95 Hz, J=3.38 Hz, 1H), 2.48-2.42 (m, 2H), 2.34 (t, J=7.57 Hz, 2H), 1.86-1.71 (m, 1H), 1.69-1.62 (m, 2H), 1.56-1.44 (m, 2H), 1.65-1.29 (m, 4H), 1.24-1.08 (m, 7H), 0.89-0.84 (m, 4H), 0.79-0.71 (m, 6H). ; ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ 208.8, 161.5, 156.8, 148.9, 148.5, 136.5, 136.1, 124.6, 124.2, 121.7, 121.2, 65.4, 48.9, 43.4, 34.4, 33.4, 31.4, 31.1, 29.6, 24.7, 22.3, 13.8, 13.8. High-Resolution MS (ESI) (M+H), calcd for $C_{22}H_{31}N_2O$, 339.2436, found 339.2427.

2,2-Dimethyl-4,5-di(pyridin-2-yl)nonan-3-one (18). Using General Procedure B, 1,2-bis(2-pyridyl)ethylene (76.3 mg, 0.419 mmol) to provide compound **18** (95.07 mg, 0.233 mmol, 70%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25^{o}C): δ 8.47 (d, J=3.97 Hz, 1H), 8.28 (d, J=3.97 Hz, 1H), 7.34-7.22 (m, 2H), 7.05 (d, J=7.91 Hz, 1H), 6.92-6.83 (m, 2H), 6.69 (d, J=7.75 Hz, 1H), 4.83 (d, J=11.05 Hz, 1H), 3.66 (td, J=12.08 Hz, J=2.94 Hz, 1H), 1.97-1.84 (m, 1H), 1.62-1.52 (m, 1H), 1.29-1.12 (m, 3H), 1.08 (s, 9H), 0.93-0.84 (m, 1H), 0.77 (t, J=7.28 Hz, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ 213.5, 161.7, 157.9, 148.9, 135.9, 135.6, 124.6, 123.7, 121.2, 121.0, 60.9, 51.4, 45.6, 33.4,

29.8, 26.5, 22.5, 13.9. Low-Resolution MS (EI): 324 (M+), 309, 267, 239, 224, 210, 195, 183, 169, 148. High-Resolution MS (ESI) (M+H), calcd for $C_{21}H_{29}N_2O$, 325.2280, found, 325.2279.

1,1,1-Trichloro-3,4-di(pyridin-2-yl)octan-2-one (19). Using General Procedure B, 1,2-bis(2-pyridyl)ethylene (75.5 mg, 0.415 mmol) provides compound **19** (75.09 mg, 0.195 mmol, 47%) as the mixture of diastereomers and yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25^{o}C): δ 8.46 (dd, J=4.78 Hz, J=0.90 Hz, 1H), 8.42 (dd, J=4.63 Hz, J=0.75 Hz, 1H), 7.43-7.30 (m, 2H), 7.04 (d, J=7.81 Hz, 1H), 7.00-6.96 (m, 1H), 6.94-6.89 (m, 1H), 6.87 (d, J=7.81 Hz, 1H), 5.30 (d, J=9.64 Hz, 1H), 3.63 (td, J=10.08 Hz, J=3.29 Hz, 1H), 2.32-2.21 (m, 1H), 2.05-1.92 (m, 1H), 1.36-1.19 (m, 2H), 1.17-0.95 (m, 2H), 0.79 (t, J=7.32 Hz, 3H). ; ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ 161.1, 160.8, 149.9, 149.5, 149.3, 149.2, 136.8, 136.2, 135.9, 135.7, 125.2, 124.6, 123.1, 123.1, 122.7, 122.5, 121.8, 121.4, 67.2, 66.4, 53.7, 32.3, 31.7, 29.4, 29.2, 22.5, 22.3, 13.9, 13.7 Low-Resolution MS (EI): 239, 233, 209, 195, 183, 169, 148. High-Resolution MS (ESI) (M+H), calcd for $C_{18}H_{20}Cl_3N_2O$, 385.0641, found 385.0678.

1-Cyclopropyl-2,3-di(pyridin-2-yl)heptan-1-one (20). Using General Procedure B, 1,2-bis(2-pyridyl)ethylene (98.6 mg, 0.542 mmol) provide compound **20 (**103.6 mg, 0.336 mmol, 62%) as a mixture of diastereomers and pale-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25^{o}C): δ 8.38-8.36 (m, 1H), 8.33-8.30 (m, 1H), 7.32-7.19 (m, 2H), 6.98 (d, J=8.08 Hz, 1H), 6.87-6.84 (m, 1H), 6.83-6.79 (m, 2H), 4.53 (d, J=11.05 Hz, 1H), 3.74 (td, J=10.88 Hz, J=3.33 Hz, 1H), 3.13-3.08 (m, 1H), 2.14-2.05 (m, 1H), 1.89-1.58 (m, 3H), 1.23-1.13 (m, 3H), 1.02-0.92 (m, 3H), 0.72 (t, J=7.25 Hz, 3H). ; ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ 208.8, 164.0, 161.9, 160.6, 149.3, 149.2, 149.0, 136.0, 135.8,

135.4, 124.6, 124.1, 123.6, 123.4, 121.4, 121.1, 120.8, 66.7, 48.8, 48.1, 44.2, 34.7, 33.5, 29.6, 29.6, 22.6, 22.5, 21.1, 13.9, 11.2, 11.0. Low-Resolution MS (EI): 240, 225, 211, 197, 183, 169, 154, 148. High-Resolution MS (ESI) (M+H), calcd for $C_{20}H_{25}N_2O$, 309.1967, found 309.1963.

1-Phenyl-2,3-di(pyridin-2-yl)heptan-1-one (21). Using General Procedure B, 1,2-bis(2-pyridyl)ethylene (76.1 mg, 0.418 mmol) provides compound **21** (90.71 mg, 0.263 mmol, 63%) as light-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25^{o}C): δ 8.48 (d, J=4.78 Hz, 1H), 8.29 (d, J=4.95 Hz, 1H), 8.13 (d, J=7.26 Hz, 2H), 7.47 (t, d=8.17 Hz, 1H), 7.38 (t, J=8.15 Hz, 2H), 7.33-7.26 (m, 2H), 7.15 (d, J=7.85 Hz, 1H), 6.92-6.79 (m, 3H), 5.39 (d, J=10.93 Hz, 1H), 3.92 (td, J=11.74 Hz, J=3.16Hz, 1H), 1.99-1.86 (m, 1H), 1.81-1.72 (m, 1H), 1.29-1.09 (m, 3H), 1.01-0.88 (m, 1H), 0.74 (t, J=7.19 Hz, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ 198.5, 161.9, 157.6, 149.2, 149.2, 137.4, 136.1, 135.5, 133.0, 128.9, 128.5, 124.7, 123.7, 121.3, 121.0, 61.1, 50.3, 33.7, 29.8, 22.5, 13.9. Low-Resolution MS (EI): 344 (M+), 287, 259, 239, 224, 209, 196, 183, 169. High-Resolution MS (ESI) (M+H), calcd for $C_{23}H_{25}N_2O$, 345.1967, found, 345.1964.

1-(4-Methoxyphenyl)-2,3-di(pyridin-2-yl)heptan-1-one (22). Using General Procedure B, 1,2-bis(2-pyridyl)ethylene (94.2 mg, 0.518 mmol) provides compound **22** (110.47 mg, 0.295 mmol, 57%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25^{o}C): δ 8.47-8.45 (m, 1H), 8.27-8.25 (m, 1H), 8.13 (d, J=8.93 Hz, 2H), 7.33-7.25 (m, 2H), 7.17 (d, J=7.97 Hz, 1H), 6.91-6.78 (m, 5H), 5.35 (d, J=10.87 Hz, 1H), 3.89 (td, J=10.87 Hz, J=3.38 Hz, 1H), 3.78 (s, 3H), 1.98 (s, 1H), 1.93-1.82 (m, 1H), 1.78-1.68 (m, 1H), 1.23.1.13 (m, 2H), 0.99-0.84 (m, 1H), 0.73 (t, J=7.49 Hz, 3H). ; ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ 197.1, 163.5, 162.0, 157.9, 149.1, 149.1, 136.1, 135.5, 131.3, 130.3, 124.7, 123.5,

121.3, 121.0, 113.7, 60.6, 55.4, 50.3, 33.7, 29.8, 22.5, 13.9. Low-Resolution MS (EI): 240, 225, 211, 197, 183, 169, 154, 148. High-Resolution MS (ESI) (M+H), calcd for $C_{24}H_{27}N_2O_2$, 375.2073, found 375.2066.

1-([1,1'-Biphenyl]-4-yl)-2,3-di(pyridin-2-yl)heptan-1-one (23). Using General Procedure B, 1,2-bis(2-pyridyl)ethylene (98.3 mg, 0.54 mmol) provides compound **23** (102.2 mg, 0.243 mmol, 45%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25^{o}C): δ 8.52 (dd, J=5.00 Hz, J=0.96 Hz, 1H), 8.33 (dd, J=5.00 Hz, J=0.77 Hz, 1H), 8.25 (d, J=8.46 Hz, 2H), 7.64 (d, J=8.46 Hz, 2H), 7.59-7.57 (m, 2H), 7.46-7.30 (m, 5H), 7.22 (d, J=7.69 hz, 1H), 6.96-6.84 (m, 3H), 5.47 (d, J=10.95 H, 1H), 3.97 (td, J=10.76 Hz, J=3.27 Hz, 1H), 1.99-1.91 (m, 1H), 1.86-1.76 (m, 1H), 1.31-1.14 (m, 3H), 1.02-0.94 (m, 1H), 0.78 (t, J=7.25 Hz, 3H). ; ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ 198.1, 161.9, 157.6, 149.3, 149.2, 145.7, 139.8, 136.2, 136.0, 135.6, 129.6, 128.9, 128.2, 127.2, 127.2, 124.7, 123.7, 121.4, 121.1, 61.1, 50.4, 33.8, 29.8, 22.5, 13.9. Low-Resolution MS (EI): 240, 197, 183, 154, 148. High-Resolution MS (ESI) (M+H), calcd for $C_{29}H_{29}N_2O$, 421.2280, found 421.2272.

Benzyl 2,3-di(pyridin-2-yl)heptanoate (24). Using General Procedure B, 1,2-bis(2-pyridyl)ethylene (78.4 mg, 0.431 mmol) provides compound **24** (88.75 mg, 0.237 mmol, 55%) as a mixture of diastereomers and bronze oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25^{o}C): δ 8.64-863 (m, 1H), 8.52-8.51 (m, 1H), 8.43-8.39 (m, 2H), 7.65 (td, J=7.66 Hz, J=1.78 Hz, 1H), 7.52 (td, J=7.76 Hz, J=1.78 Hz, 1H), 7.43 (d, J=7.79 Hz, 1H), 7.36-7.33 (m, 1H), 7.27 (s, 6H), 7.19-7.16 (m, 4H), 7.08-7.02 (m, 3H), 6.95-6.86 (m, 6H), 5.18 (d, J=10.12 Hz, 2H), 4.86 (d, J=7.66 Hz, 2H), 4.52 (d, J=11.35 Hz, 1H), 4.39 (11.21 Hz, 1H), 3.76 (td, J=10.94 Hz, J=3.14 Hz, 2H), 1.99-1.87 (m, 1H), 1.82-1.73

(m, 1H), 1.64-1.52 (m, 1H), 1.26-1.14 (m, 4H), 1.15-1.05 (m, 3H), 0.98-0.88 (m, 4H), 0.76 (t, J=7.11 Hz, 3H), 0.65 (t, J=7.25 Hz, 3H). ; ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 172.0, 171.6, 162.5, 161.4, 157.4, 157.1, 149.8, 149.1, 136.6, 136.0, 136.0, 135.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6, 126.9, 124.9, 124.7, 124.5, 124.1, 122.3, 121.7, 121.4, 121.1, 66.5, 66.0, 59.0, 58.5, 49.6, 48.6, 33.4, 32.2, 29.5, 29.9, 22.5, 22.4, 13.9, 13.8. High-Resolution MS (ESI) (M+H), calcd for $C_{24}H_{27}N_2O_2$, 375.2073, found, 375.2067.

Ethyl 2,3-di(pyridin-2-yl)heptanoate (25). Using General Procedure B, 1,2-bis(2-pyridyl)ethylene (76.0 mg, 0.417 mmol) to provide compound **25** (67.79 mg, 0.217 mmol, 52%) as an orange oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ 8.41 (d, J=3.98 Hz, 1H), 8.38 (d, J=3.90 Hz, 1H), 7.35-7.26 (m, 2H), 7.03 (d, J=7.98 Hz, 1H), 6.93-6.84 (m, 3H), 4.28 (d, J=11.29 Hz, 1H), 4.22-4.09 (m, 2H), 3.72 (td, J=11.10 Hz, J=3.31 Hz, 1H), 1.99-1.87 (m, 1H), 1.85-1.74 (m, 1H), 1.34-1.25 (m, 2H, 1.19 (t, J=6.79 Hz, 3H), 1.17-1.05 (m, 1H), 1.01-0.92 (m, 1H), 0.77 (t, J=7.28 Hz, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 172.2, 161.4, 157.3, 149.1, 149.0, 135.9, 135.5, 124.7, 123.9, 121.6, 121.0, 60.8, 59.1, 49.6, 33.3, 29.5, 22.5, 14.1, 13.9. Low-Resolution MS (EI): 312 (M+), 283, 267, 256, 239, 223, 210, 195, 183, 165, 148. High-Resolution MS (ESI) (M+H), calcd for $C_{19}H_{25}N_2O_2$, 313.1916, found, 313.1911.

Isobutyl 2,3-di(pyridin-2-yl)heptanoate (26). Using General Procedure B, 1,2-bis(2-pyridyl)ethylene (75.9 mg, 0.419 mmol) provides compound **26** (78.31 mg,0.23 mmol, 55%) as an orange oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ 8.42 (d, J=4.21 Hz, 1H), 8.37 (d, J=4.00 Hz, 1H), 7.36-7.26 (m, 2H), 7.04 (d, J=7.81 Hz, 1H), 6.92-6.85 (m, 3H), 4.31 (d, J=11.05 Hz, 1H), 3.88 (sept,

J= 6.27 Hz, 2H), 3.73 (td, J=10.99 Hz, J=3.37 Hz, 1H), 1.96-1.78 (m, 3H), 1.29-1.12 (m, 3H), 1.01-0.91 (m, 1H), 0.81 (d, J=6.81 Hz, 6H), 0.77 (t, J=7.26 Hz, 3H). ; ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ 172.3, 161.5, 157.4, 149.1, 135.9, 135.5, 124.7, 123.9, 121.6, 121.0, 70.8, 59.1, 49.5, 33.4, 29.5, 27.7, 22.5, 18.9, 18.9, 13.9. Low-Resolution MS (EI): 340 (M+), 297, 283, 267, 239, 220, 210, 195, 183, 169, 148. High-Resolution MS (ESI) (M+H), calcd for $C_{21}H_{29}N_2O_2$, 341.2229, found, 341.2226.

1-(1,2-Di(pyridin-2-yl)hexyl)cyclohexanol (27). Using General Procedure B, 1,2-bis(2-pyridyl)ethylene (75.2 mg, 0.413 mmol) provides compound **27** (96.47 mg, 0.285 mmol, 69%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25^{o}C): δ 8.19 (d, J= 3.93 Hz, 1H), 8.12 (d, J=3.70 Hz, 1H), 7.35-7.26 (m, 2H), 6.89-6.81 (m, 4H), 5.72 (s, 1H), 3.70 (hept, J=4.60 Hz, 1H), 3.08 (d, J=3.73 Hz, 1H), 2.15-2.08 (m, 1H), 2.05-1.93 (m, 1H), 1.90-1.82 (m, 1H), 1.81-1.70 (m, 1H), 1.66-1.59 (m, 2H), 1.56-1.46 (m, 2H), 1.32-1.17 (m, 6H), 1.10-1.06 (m, 2H), 1.03-0.95 (m, 2H), 0.79 (t, J=7.28 Hz, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ 163.4, 161.8, 147.9, 147.4, 135.3, 135.0, 125.9, 125.4, 120.7, 120.3, 74.0, 59.3, 46.7, 38.2, 36.9, 35.3, 30.2, 25.9, 22.7, 22.3, 22.2, 14.0. Low-Resolution MS (EI): 338 (M+), 295, 281, 239, 225, 210, 197, 183, 162, 148. High-Resolution MS (ESI) (M+H), calcd for $C_{22}H_{31}N_2O$, 339.2436, found, 339.2433.

2,2'-(1-(Naphthalen-1-ylsulfonyl)hexane-1,2-diyl)dipyridine (28). Using General Procedure B, 1,2-bis(2-pyridyl)ethylene (90.8 mg, 0.499 mmol) provides compound **28** (120.13 mg, 0.279 mmol, 56%) as a mixture of diastereomers and a bronze oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25^{o}C): δ 8.67 (dq, J= 4.85 Hz, J= 0.85 Hz, 1H), 8.62 (dq, J= 4.87 Hz, J= 0.92 Hz, 1H), 8.46 (dq, J= 4.84 Hz, J=

0.90 Hz, 1H), 8.43 (dq, J= 4.86 Hz, J= 0.90 Hz, 1H), 7.71-7.59 (m, 2H), 7.44-7.31 (m, 4H), 7.27-7.21 (m, 2H), 7.19-7.14 (m, 1H), 7.06 (d, J= 7.76 Hz, 1H), 7.02-6.97 (m, 1H), 6.95-6.91 (m, 1H), 6.88 (d, J= 7.82 Hz, 1H), 5.33 (d, J= 10.19 Hz, 1H), 5.31 (d, J= 9.72 Hz, 1H), 3.64 (td, J= 11.31 Hz, J= 3.35 Hz, 2H), 2.32-2.21 (m, 1H), 2.06-1.93 (m, 1H), 1.76-1.63 (m, 1H), 1.38-1.16 (m, 5H), 1.15-0.93 (m, 6H), 0.80 (t, J= 7.38 Hz, 5H), 0.66 (t, J= 7.38 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ 161.1, 160.8, 159.0, 149.9, 149.5, 149.3, 149.2, 136.8, 136.2, 135.9, 135.7, 125.2, 124.6, 123.2, 123.1, 122.8, 122.5, 121.8, 121.4, 67.2, 66.4, 53.8, 32.3, 31.7, 29.4, 29.2, 22.5, 22.3, 13.9, 13.7. Low-Resolution MS (EI): 430 (M+), 239, 225, 210, 197, 183, 148. High-Resolution MS (ESI) (M+H), calcd for $C_{26}H_{27}N_2O_2S$, 431.1793, found, 3431.1787.

1,3-Diphenyl-2,3-di(pyridin-2-yl)propan-1-one (29). Using General Procedure B, 1,2-bis(2-pyridyl)ethylene (225 mg, 1.23 mmol) provides compound **29** (159 mg, 0. mmol, 67%) as a mixture of diastereomers and bronze oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25^{o}C): δ 8.47 (d, J= 3.97 Hz, 1H), 8.41 (d, J= 4.63 Hz, 1H), 8.18 (td, J= 9.29 Hz, J= 1.43 Hz, 1H), 8.07 (d, J= 7.25 Hz, 2H), 7.84 (d, J= 7.05 Hz, 1H), 7.61 (d, J= 7.26 Hz, 2H), 7.51-7.48 (m, 2H), 7.45-7.40 (m, 5H), 7.34 (t, J= 7.94 Hz, 3H), 7.19 (t, J= 7.60 Hz, 3H), 7.07 (t, J= 7.43 Hz, 1H), 6.95-6.91 (m, 2H), 6.35 (d, J= 11.66 Hz, 1H), 5.38 (d, J= 11.76 Hz, 1h). ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ 197.5, 169.8, 160.9, 157.0, 149.2, 148.6, 141.4, 137.0, 136.6, 133.0, 132.0, 130.0, 128.9, 128.6, 128.5, 128.4, 128.4, 127.41, 126.7, 124.2, 121.8, 121.4, 59.5, 55.4. Low-Resolution MS (EI): 364 (M+), 239, 225, 210, 197, 183, 148. High-Resolution MS (ESI) (M+H), calcd for $C_{25}H_{21}N_2O$, 365.1654, found, 365.1648.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 4,4-dimethyl-2,3-di(pyridin-2-yl)pentanoate (30). Using General Procedure B, 1,2-bis(2-pyridyl)ethylene (225 mg, 1.23 mmol) provides compound **29** (159 mg, 0.377 mmol, 31%) as a mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$ with 1% TMS, 25^{o}C): 8.58-8.60 (m, 1H), 8.47-8.49 (m, 1H), 7.48-7.63 (m, 3H), 0.04 (s, 2H), 7.26-7.30 (m, 1H), 7.11-7.16 (m, 1H), 7.02-7.07 (m, 1H), 4.71-4.80 (m, 1H), 4.16-4.28 (m, 1H), 3.77-3.83 (m, 1H), 1.35-1.55 (m, 2H), 1.0-1.35 (m, 3H), 0.52-0.90 (m, 17H), 0.50 (d, J= 6.9 Hz, 1H), 0.26 (d, J= 6.9 Hz, 1H), 0.20 (d, J= 6.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$ with 1% TMS, 25 ^{o}C): 171.8, 171.5, 163.0, 162.9, 159.1, 158.9, 149.3, 149.2, 148.2, 148.0, 136.4, 136.3, 126.1, 135.0, 135.0, 125.9, 124.5, 124.2, 122.1, 122.1, 121.0, 120.9, 73.9, 73.9, 73.7, 57.1, 57.0, 56.9, 56.7, 46.8, 46.5, 40.2, 39.6, 34.4, 34.1, 34.1, 31.1, 31.0, 29.2, 29.2, 25.3, 25.2, 23.0, 22.2, 21.8, 20.8, 20.5, 15.6, 15.5, 0.97. High-Resolution MS (ESI) (M+H), calcd for $C_{27}H_{39}N_2O_2$, 423.3012, found, 423.3019.

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(8) For details regarding the calculations, see Supporting Information.

Graphical Abstract