Note

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

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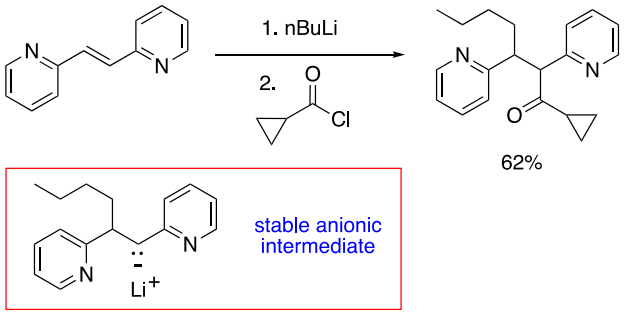
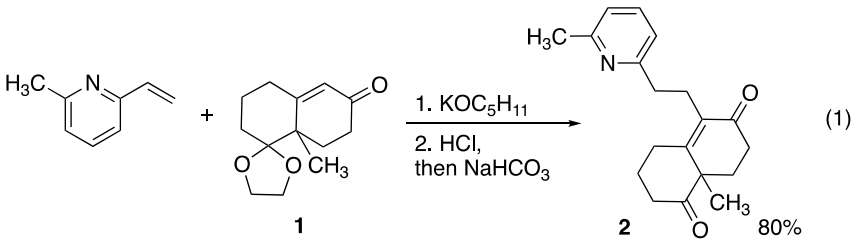


Abstract:

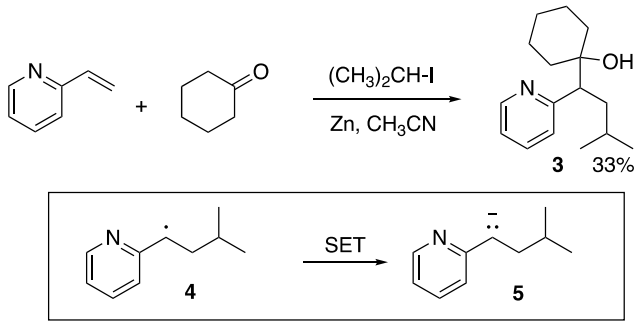
The conjugate addition reactions of *trans*-1,2-di-(2-pyridyl)ethylene have been studied. This substrate reacts with organolithium nucleophiles and the resulting anionic intermediates may be trapped by proton or various carbonyl-based electrophiles. It is suggested that the dipyridyl structure stabilizes 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 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 addition reactions 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 conjugate addition reactions to prepare steroid analogs. Generating a nucleophile from enone **1**, the addition reaction was completed with a protonation (eq 1).[5] Although more than 15



(1)

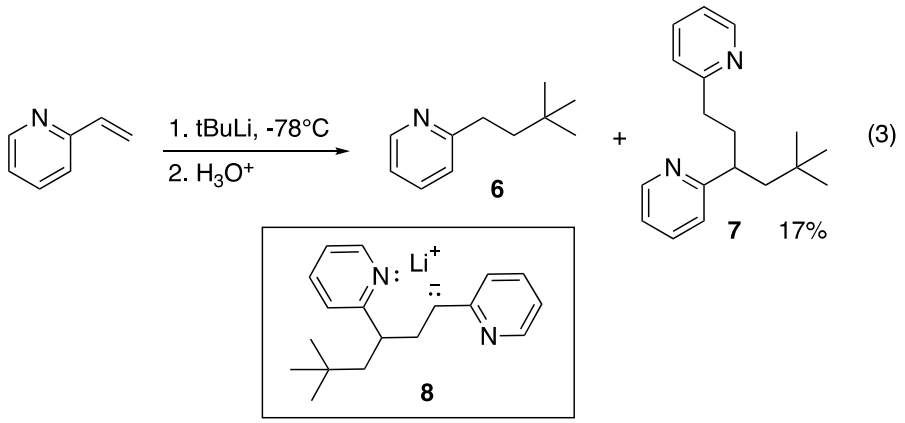
different types of *N*-heterocyclic systems have been shown to undergo conjugate additions at olefinic groups, there are very few examples of intermediate carbanionic species being captured in reactions with electrophiles other than proton.[4] In contrast, it is common to use varied electrophiles in the conjugate addition reactions of α,β-unsaturated carbonyl compounds, as the enolate intermediates may be captured by electrophiles such as aldehydes, acid halides, and others.[2b] Given the value of functionalized *N*-heterocycles in pharmaceutical and other applications, the development of this synthetic chemistry could be very useful. Nishiguchi and coworkers described an example of this chemistry by the zinc-promoted



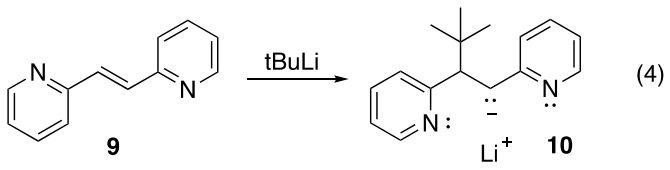
(2)

coupling of vinylpyridines, alkyl iodides, and carbonyl electrophiles (eq 2).[6] In these conversions, 2-vinylpyridine provides addition products such as the cyclohexanone adduct (**3**). A mechanism is proposed involving alkyl radical addition to the olefin (**4**), subsequent reduction to the anionic intermediate **5**, and the reaction of **5** with the carbonyl electrophile. In the following Note, we describe conjugate addition reactions 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.

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

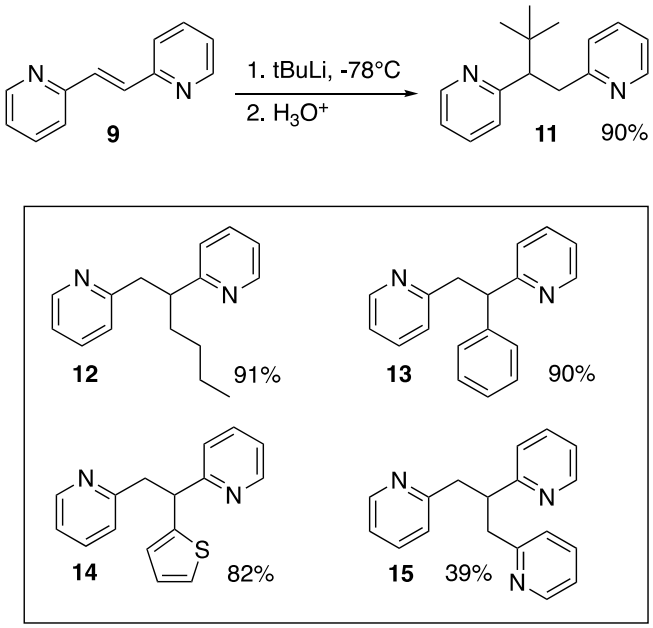


2-vinylpyridine. However, the resulting anionic intermediate evidently reacts with a second equivalent of 2-vinylpyridine to eventually provide compound **7** from protonation. This suggested to us that the second carbanionic intermediate, species **8**, must possess at least some kinetic stability –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

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

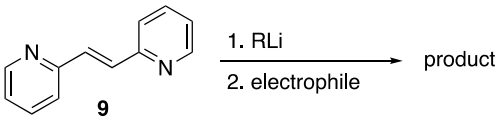


and the potential for reactions with other electrophiles.

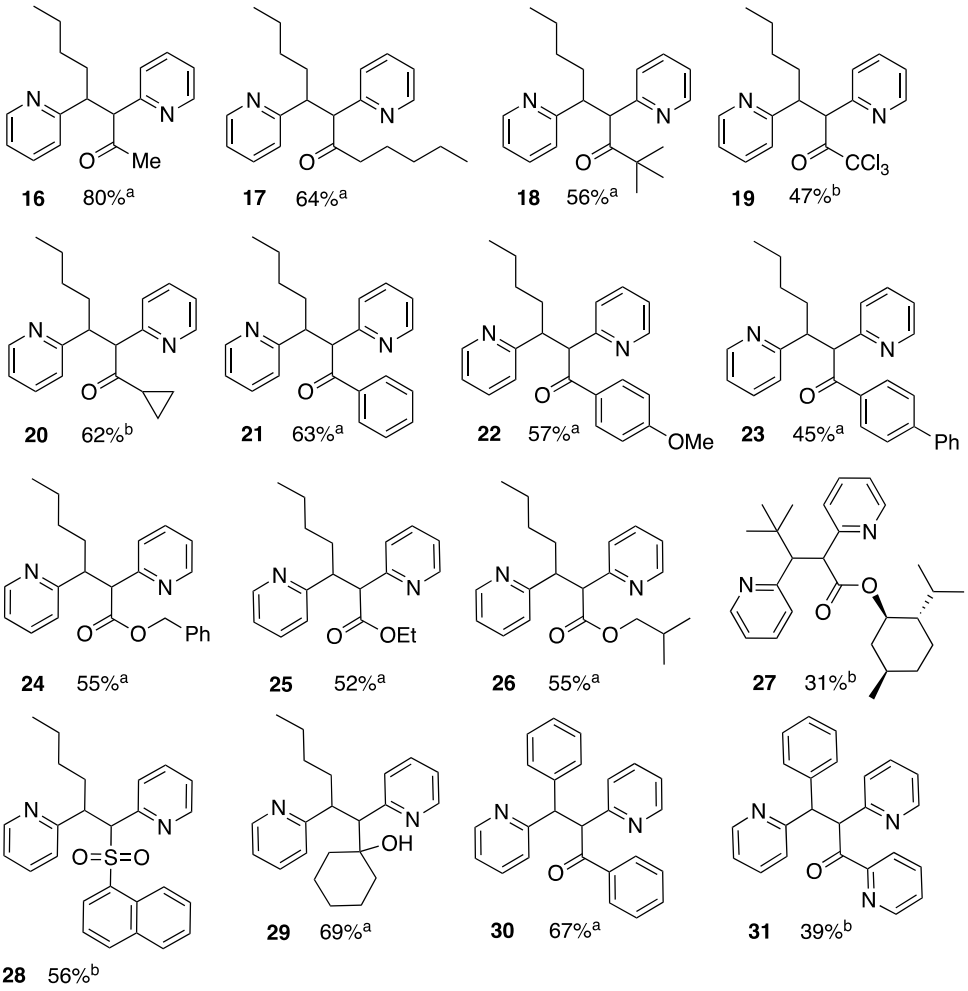
When compound **9** is reacted with butyllithium followed by acid chlorides, the addition products (**16-23** and **30**) are formed in fair to good yields (Table 2). Thus, compound **9** reacts with BuLi and acetyl chloride to provide the addition product **16** in good yield. Optimization studies showed that it is necessary to add the solution of the 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**. Products **17-18**, **21-23**, and **30** are obtained as single diastereomers, but compounds **19** and **20** are obtained as the mixture of diastereomers. Each of these products are obtained from the respective acid chlorides.

In addition to acid chloride electrophiles, chloroformate electrophiles provide compounds **24-27** in fair yields. NMR analysis of crude products indicates that single

Table 2. Addition products and yields from compound **9** and organolithium reagents and with carbon electrophiles.



9



16 80%[a] **17** 64%[a] **18** 56%[a] **19** 47%[b]

20 62%[b] **21** 63%[a] **22** 57%[a] **23** 45%[a]

24 55%[a] **25** 52%[a] **26** 55%[a] **27** 31%[b]

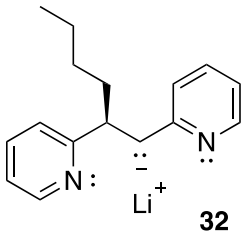
28 56%[b] **29** 69%[a] **30** 67%[a] **31** 39%[b]

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

diastereomers are formed in with **24-26** while a mixture of diastereomers are obtained with **27**. A similar conversion utilizing diethylcarbamoyl chloride was not successful. A sulfonyl chloride has been shown to give the adduct **28** in fair yield as the mixture of diastereomers (3:2 ratio). The addition may also be accomplished with cyclohexanone, providing adduct **27** as a single

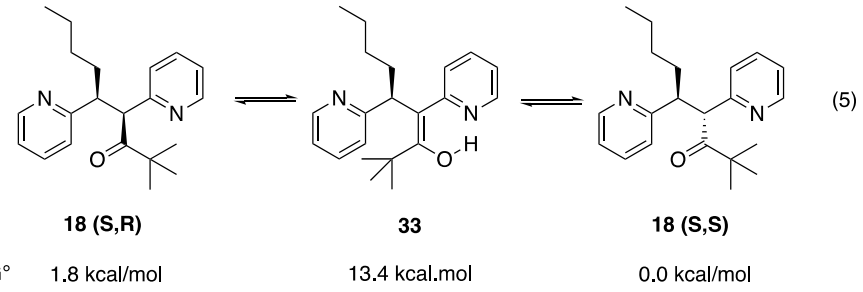
diastereomer in 69% yield. In the synthesis of product **31**, an ester was successfully used as the carbon electrophiles (ethyl picolinate).

The conversions above are consistent with the formation of a relatively stable anionic intermediate from nucleophilic attack by butyllithium and related organometallics. Although it has been previously reported that both organolithium and Grignard reagents fail to react with olefinic pyridines,[7] substrate **9** evidently will react with organolithium reagents. Thus, butyllithium couples with **9** to provide the adduct, intermediate **32**. Like the dimeric



32

intermediate from 2-vinylpyridine (i.e., **8**), it is plausible that species **32** is stabilized by favorable interactions between the pyridyl nitrogen and lithium cation. As such, intermediate **32** is sufficiently long-lived that it may be successfully captured by electrophiles. 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 **33** benefits from a stabilizing hydrogen bond to the pyridyl group (eq 5). DFT calculations estimate the energy difference between the two



(5)

epimers to be 1.8 kcal/mol.[8] While the enol tautomer (**33**) is just 13.4 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 carbanionic 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 anionic species are stabilized by structural effects.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at:

•^{1}H and ^{13}C NMR spectra for new compounds.

•Computational methods and results.

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 (hexanes:ethyl acetate) 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{^{1}H} 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. HRMS (ESI) m/z: [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 (hexanes:ethyl acetate) 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 after silica gel chromatography (hexanes:ethyl acetate). ^{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{^{1}H} (75 MHz, $CDCl_3$, 25 ^{o}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. HRMS (ESI) m/z: [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 after silica gel chromatography (hexanes:ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$, 25^{o}C): δ 8.49

(d, J=4.59 Hz, 1H), 8.46 (d, J=4.33 Hz, 1H), 7.34-7.45 (m, 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{^{1}H} (75 MHz, $CDCl_3$, 25 ^{o}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. HRMS (ESI) m/z: [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 after silica gel chromatography (hexanes:ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$, 25^{o}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{^{1}H} (75 MHz, $CDCl_3$, 25 ^{o}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. HRMS (ESI) m/z: [M + H]+ Calcd for $C_{18}H_{17}N_2$ 261.1392; Found, 261.1385.

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 after silica gel chromatography (hexanes:ethyl acetate). ^{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{^{1}H} (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. HRMS (ESI) m/z: [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 (hexanes:ethyl acetate), 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{^{1}H} (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. HRMS (ESI) m/z: [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 (hexanes:ethyl acetate).

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 after silica gel chromatography (hexanes:ethyl acetate). ^{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{^{1}H} (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. HRMS (ESI) m/z: [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 after silica gel chromatography (hexanes:ethyl acetate). ^{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{^{1}H} (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. HRMS (ESI) m/z: [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, 56%) as a yellow oil after silica gel chromatography (hexanes:ethyl acetate). ^{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{^{1}H} (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. HRMS (ESI) m/z: [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 after silica gel chromatography (hexanes:ethyl acetate). ^{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{^{1}H} (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. HRMS (ESI) m/z: [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 after silica gel chromatography (hexanes:ethyl acetate). ^{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{^{1}H} (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. HRMS (ESI) m/z: [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 after silica gel chromatography (hexanes:ethyl acetate). ^{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{^{1}H} 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. HRMS (ESI) m/z: [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 after silica gel chromatography (hexanes:ethyl acetate). ^{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{^{1}H} 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. HRMS (ESI) m/z: [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 after silica gel chromatography (hexanes:ethyl acetate). ^{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 Hz, 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{^{1}H} 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. HRMS (ESI) m/z: [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 after silica gel chromatography (hexanes:ethyl acetate). ^{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). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$, 25 ^{o}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. HRMS (ESI) m/z: [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 after silica gel chromatography (hexanes:ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$, 25^{o}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). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$, 25 ^{o}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. HRMS (ESI) m/z: [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 after silica gel chromatography (hexanes:ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$, 25^{o}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{^{1}H} 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. HRMS (ESI) m/z: [M + H]+ Calcd for $C_{21}H_{29}N_2O_2$ 341.2229; Found 341.2226.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 4,4-dimethyl-2,3-di(pyridin-2-yl)pentanoate (27). 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 and oil after silica gel chromatography (hexanes:ethyl acetate). ^{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{^{1}H} 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. HRMS (ESI) m/z: [M + H]+ Calcd for $C_{27}H_{39}N_2O_2$ 423.3012; Found, 423.3019.

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 after silica gel chromatography (hexanes:ethyl acetate). ^{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{^{1}H} 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. HRMS (ESI) m/z: [M + H]+ Calcd for $C_{26}H_{27}N_2O_2S$ 431.1793; Found, 3431.1787.

1-(1,2-Di(pyridin-2-yl)hexyl)cyclohexanol (29). 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 after silica gel chromatography (hexanes:ethyl acetate). ^{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{^{1}H} NMR (75 MHz,

$CDCl_3$, 25 °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. HRMS (ESI) m/z: [M + H]+ Calcd for $C_{22}H_{31}N_2O$ 339.2436; Found, 339.2433.

1,3-Diphenyl-2,3-di(pyridin-2-yl)propan-1-one (30). 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 after silica gel chromatography (hexanes:ethyl acetate). ^1H NMR (300 MHz, $CDCl_3$, 25°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). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 25 °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. HRMS (ESI) m/z: [M + H]+ Calcd for $C_{25}H_{21}N_2O$ 365.1654; Found, 365.1648.

3-Phenyl-1,2,3-tri(pyridin-2-yl)propan-1-one (31). A solution of 1,2-bis(2-pyridyl)ethylene (1.0 g, 5.49 mmol) on 20 mL THF is cooled to -78 °C and PhLi solution (5.5 mmol) is slowly added. After stirring for 2 hr, ethyl picolinate (6 mmol) is added. The solution is stirred for 3 hr and allowed to warm to room temperature. The mixture is the quenched with 20 mL of deoxygenated water and further diluted with 20 mL of ethyl ether. Following extracting of the

organic products, the aqueous phase is extracted a second time with ethyl ether. The organic extracts are washed twice with brine solution, dried over anhydrous sodium sulfate, and filtered. All but ca. 15 mL of solvent is removed using a rotary evaporator and the resulting reddish solution is place in a sealed flask and cooled to -20°C. After one week, a crop of red crystals are filtered off and compound **31** is isolated (0.79 g, 2.16 mmol, 39%) as the mixture of diastereomers in a 1.4:1.0 ratio. MP 148-151 °C (THF : ether). ^{1}H NMR (500 MHz, $CDCl_3$, 25^{o}C): δ 8.69-8.71 (m), 8.44-8.50 (m), 8.33-8.34 (m), 7.95 (d, *J* = 7.8 Hz), 7.87 (d, *J* = 7.9 Hz), 7.64-7.73 (m), 7.49-7.52 (m), 7.27-7.39 (m), 7.15-7.24 (m), 6.98-7.10 (m), 6.88-6.93 (m), 6.70 (d, *J* = 10 Hz), 5.39-5.43 (m).). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$ with 1% TMS, 25 ^{o}C): major isomer, δ 198.4, 162.3, 157.5, 153.3, 149.2, 149.1, 148.8, 141.9, 136.6, 136.2, 135.9, 128.9, 128.0, 126.5, 126.4, 126.3, 124.3, 122.5, 121.3, 121.1, 58.0, 55.1. HRMS (ESI) m/z: [M + H]+ Calcd for $C_{27}H_{39}N_2O_2$ 366.1601; Found 366.1610.

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References

(1) a. Michael, A. Ueber die Addition von Natriumacetessig- und Natriummalonsäureäthern zu den Aethern ungesättigter Säuren. b. Michael, A. Ueber die Addition von Natriumacetessig- und Natriummalonsäureäther zu den Aethern ungesättigter Säuren. *J. Prakt. Chim.* **1894**, *49*, 20-25.

(2) a. Cordova, A. “Catalytic Asymmetric Conjugate Reactions” Wiley:VHC, 2010. b. Perlmutter, P. “Conjugate Addition in Organic Synthesis.” Pergamon: Oxford, 1992. c. Reznikov, Alexander N.; Klimochkin, Yuri N. Recent Developments in Highly Stereoselective Michael Addition Reactions Catalyzed by Metal Complexes. *Synthesis*, **2020**, *52*, 781-795. d. Malkar, Radhika S.; Jadhav, Amarsinh L.; Yadav, Ganapati D. Innovative catalysis in Michael addition reactions for C-X bond formation. *Mol. Catal.* **2020**, *485*, 110814. e. Vargova, D.; Nemethova, I.; Plevova, K.; Sebesta, R. Asymmetric Transition-Metal Catalysis in the Formation and Functionalization of Metal Enolates. *ACS Catal.* **2019**, *9(4)*, 3104-3143. f. Zheng, K.; Liu, X.; Feng, X. Recent Advances in Metal-Catalyzed Asymmetric 1,4-Conjugate Addition (ACA) of Nonorganometallic Nucleophiles. *Chem. Rev.* **2018**, *118(16*), 7586-7656. f. Alonso, D. A.; Baeza, A.; Chinchilla, R.; Gomez, C.; Guillena, G.; Pastor, I. M.; Ramon, D. J. Recent Advances in Asymmetric Organocatalyzed Conjugate Additions to Nitroalkenes. *Molecules* **2017**, *22(6)*, 895/1-895/51. g. Hayashi, M.; Matsubara, R. Recent topics on catalytic asymmetric 1,4-addition. *Tetrahedron Lett.* **2017**, *58(19)*, 1793-1805. h. Phelan, J. P.; Ellman, J. A. Conjugate addition–enantioselective protonation reactions. *Beil. J. Org. Chem.* **2016**, *12*, 1203-1228.

(3) Doering, W. M.; Weil, R. A. N. Electrophilic Reactions of 2- and 4-Vinylpyridines. *J. Am. Chem. Soc.* **1947**, *69*, 2461-2466.

(4) Klumpp, D. A. Conjugate Additions to Vinyl-Substituted Aromatic *N*-Heterocycles. *SynLett* **2012**, *23*, 1590-1604.

(5) Danishefsky, S.; Cain, P.; Nagel, A. Bis annelations via 6-methyl-2-vinylpyridine. Efficient synthesis of dl-D-homoestrone. *J. Am. Chem. Soc.* **1975**, *97*, 380-388.

(6) Mineyama, K.; Maekawa, H.; Kohsaka, A.; Yamamoto, Y.; Nishiguchi, I. Zn-promoted regio- and sequence-selective one-pot joining reactions of three components: vinylpyridines, alkyl iodides, and carbonyl compounds (or nitriles). *Tetrahedron* **2009** 7706-7711.

(7) a. Houpis, I. N.; Lee, Jaemoon; Dorziotis, I.; Molina, A.; Reamer, B.; Volante, R. P.; Reider, P. J. Ni-catalyzed nucleophilic conjugate additions of Grignard and organozincate reagents to substituted 4-vinylpyridines. General synthesis of phosphodiesterase IV inhibitors. *Tetrahedron* **1998**, *54(7)*, 1185-1195. b. For an example of copper catalyzed reactions, see: Jumde, R. P; Lanza, F.; Pellegrini, T.; Harutyunyan, S. R. Highly enantioselective catalytic synthesis of chiral pyridines. *Nature Commun.* **2017**, *8*, 2058.

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

Graphical Abstract