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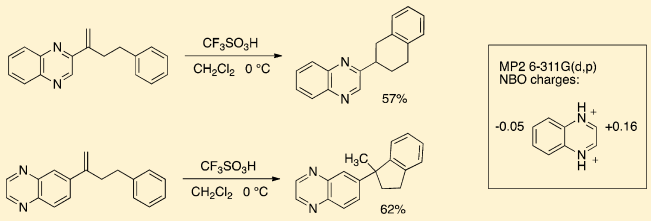
Intramolecular Conjugate Additions with Heterocyclic Olefins

Kenneth N. Boblak, Makafui Gasonoo, Yiliang Zhang, and Douglas A. Klumpp*

Department of Chemistry and Biochemistry, Northern Illinois University, DeKalb, Illinois 60115, United States

Supporting Information

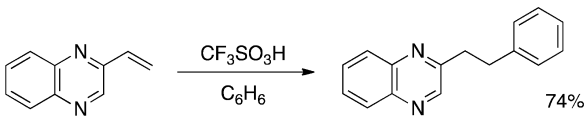
ABSTRACT: The intramolecular reactions of olefinic *N*-heterocycles have been studied. In triflic acid-promoted reactions, conjugate addition is observed with pyrazine-, 2-pyrimidine-, and 2-quinoxaline-based olefins and a phenyl group nucleophile. Markovnikov addition is observed with pyridine and 5-quinoxaline-based olefins. These results are in accordance with previous observations relating the type of addition—conjugate or Markovnikov—to the positions of olefinic substituents of the *N*-heterocycle.



INTRODUCTION

Conjugate addition chemistry with vinyl-substituted *N*-heterocycles has been known since 1947.[1] Doering and Weil described the base-promoted conjugate additions of diethylmalonate to 2- and 4-vinylpyridine,[2] and thereafter, it was recognized that vinyl-substituted *N*-heteroaromatic compounds were potential Michael acceptors. Since these pioneering studies, vinyl-substituted *N*-heterocycles have been shown to react with a variety of strong and moderately strong nucleophiles. This includes chemistry with amines,[3] alcohols,[4] thiols,[5] enamines,[6] enolates[7] and other carbanionic species.[a] Very few examples are known that involve weak nucleophiles, such aromatic compounds or alkanes.

We recently described the superacid-promoted conjugate addition reactions of vinyl-substituted *N*-heterocycles.[9,10] In these conversions, a series of vinyl-substituted diazines were shown to undergo conjugate addition reactions with the weak nucleophile benzene, such as quinoxaline (eq 1).[9] It was also



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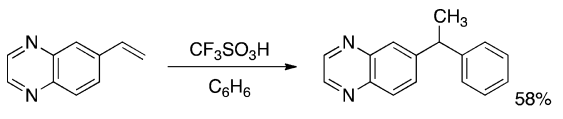
observed that Markovnikov-type addition reactions occur with some isomeric substrates (eq 2)[9] and with azines, such as



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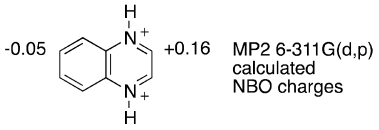
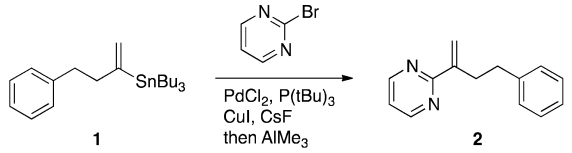


pyridine.[10,11] We proposed that the addition reactions were controlled by the charge distributions in the doubly protonated diazines. Conjugate addition tends to be favored when the vinyl-group is at a carbon bearing a large positive charge, whereas Markovnikov addition is favored at more negatively charged carbons, as shown with the calculated NBO charges on doubly protonated quinoxaline. It was proposed that the relatively high electron density at the C-6,7 position allowed for carbocation formation and the resulting Markovnikov addition. Conversely, the more positive ring carbons strongly destabilize carbocation intermediates while also promoting conjugate addition with the nucleophile benzene.

Although intramolecular reactions of strong nucleophiles with vinyl-substituted *N*-heterocycles are known,[3e,f,12] there are no examples of similar chemistry with aryl nucleophiles. Given the value of functionalized heterocycles, we have sought to determine if intramolecular conjugate addition is possible with weak aryl nucleophiles and vinyl-substituted *N*-heterocycles. Moreover, we were interested in determining if the type of addition—Markovnikov versus conjugate addition—may be correlated to regioisomeric effects and the type of heterocyclic ring. The results of these studies are presented here.

RESULTS AND DISCUSSION

The studies began with the synthesis of several types of heterocyclic substrates. Two methods were found to be useful: direct Stille coupling of a vinyl stannane (eq 3) and via an aldol



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condensation (eq 4). The requisite vinyl stannane (**1**) was prepared from 4-phenyl-1-butyne using a published procedure.[13] Using $PdCl_2$, the Stille coupling provided derivatives of

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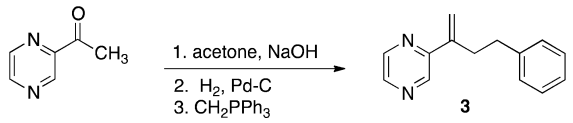
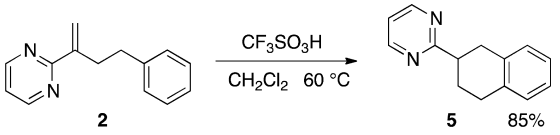


(4)

pyridine, pyrimidine (i.e., **2**), and quinoxaline.[14] An alternative synthetic route was developed using an aldol condensation, reduction, and Wittig reaction. However, this synthetic strategy was somewhat limited by low yields of the Wittig olefination.

In accordance with our previous studies, superacid-promoted reactions of vinyl-substituted diazines provides the conjugate addition products from pyrimidine, pyrazine, and quinoxaline substrates (eqs 5−7). We had previously shown that 2-



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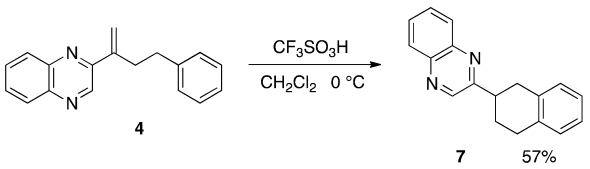
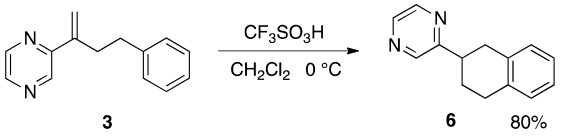


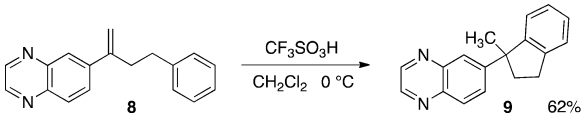
(7)

vinylpyrimidine undergoes conjugate addition with benzene in the CF_3SO_3H-promoted reaction. Thus, the intramolecular reaction provides tetralin derivative **5** in good yield from substrate **2**. Vinyl-substituted pyrazines and quinoxalines have also been shown to undergo conjugateadditions with benzene and, likewise, both systems give the expected tetralin products (**6** and **7**) from the corresponding olefins.



(6)

In our previous studies related to intermolecular chemistry, it was shown that 2-vinylquinoxaline gives a product from conjugate addition, whereas 6-vinylquinoxaline gives the product from Markovnikov addition (eqs 1 and 2). Intramolecular chemistry follows the same regioisomeric pattern. As described above, compound **4** provides the conjugate addition product (**7**) by cyclization (eq 7). With substitution at the 6-position, the Markovnikov addition product (**9**) is formed as the only major product (eq 8).



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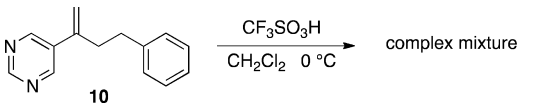
A similar transformation was attempted with the 5-substituted pyrimidine (**10**), but this gave a complex product mixture, including resinous oligomeric material, from which no major products could be isolated (eq 9). A variety of reaction

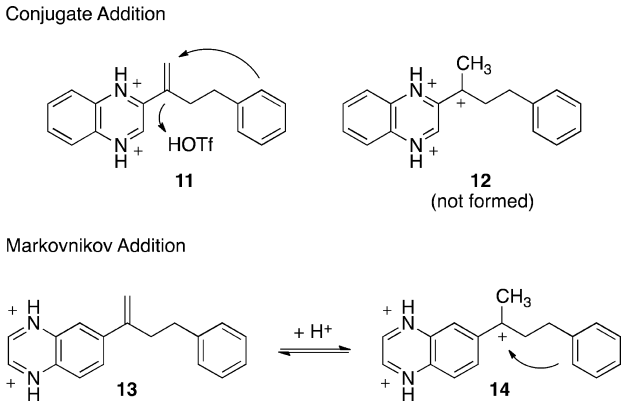


(9)

conditions were attempted for this transformation and all gave similar results. It is not entirely clear why intramolecular Markovnikov addition does not occur with compound **10**, especially because the quinoxaline system **8** undergoes Markovnikov addition. In previous theoretical calculations,[9] the 5-position of the diprotonated pyrimidine ring is shown to have a relatively large amount of electron density with an NBO charge of −0.29 at C5. A similar calculation of diprotonated quinoxaline estimated an NBO charge of −0.05 at C6. This subtle difference in electron densities may explain the varied chemistry with compounds **10** and **8** (and the respective carbocation intermediates). Our previous study of intermolecular reactions did show that Markovnikov additions were problematic for some vinyl-substituted diazines. This may reflect the inherent difficulty of generating tricationic intermediates even in superacidic media.

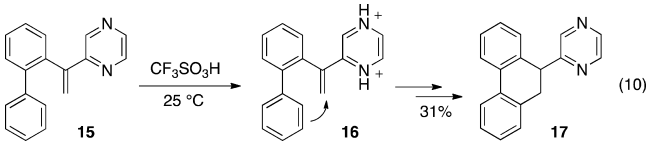
It is proposed that the intramolecular reactions occur by two basic pathways: conjugate and Markovnikov additions (Scheme 1). The pK_a values (from H_2O) of quinoxaline have been

Scheme 1



estimated to be 0.56 and −5.52,[15] so it may be assumed that the ring nitrogen atoms of quinoxaline derivatives **4** and **8** are fully protonated in excess superacid (CF_3SO_3H, H_o −14.1). Thus, quinoxaline **4** should provide dicationic species **11** from protonation at the ring nitrogen atoms (Scheme 1). As described above, carbocation formation is inhibited in this case because protonation at the terminal carbon would generate a highly destabilized carbocation (**12**). Similar acid−base chemistry occurs with the pyrimidine and pyrazine systems, favoring conjugate addition in these cases. With Markovnikov addition, the carbocation site may be formed because there is relatively high electron density at the heterocyclic ring carbon (6-position). Thus, diprotonated quinoxaline **13** may be protonated at the olefin to form carbocationic intermediate **14**, leading to Markovnikov-type addition. Despite the formation of a tricationic ion (**14**), the carbocation site is adjacent to a ring carbon with high electron density. Moreover, the three positive charges are fairly well separated.

In accordance with this proposal, the two types of addition reactions were observed with biphenyl nucleophiles (eqs 10



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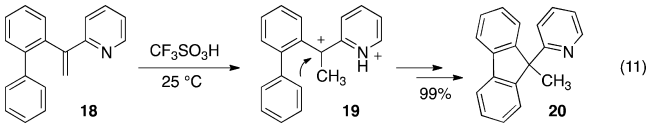
and 11). Olefinic pyrazine **15** leads to conjugate addition product **17** as the only major product (eq 10). There is no



(11)

evidence for the isomeric Markovnikov addition product. This product is consistent with the formation of the deprotonated species (**16**) followed by conjugate addition. In contrast, pyridine derivative **18** undergoes a reaction in superacid to give Markovnikov addition product **20** in quantitative yield (eq 11). With the monoprotonated pyridinium ring adjacent to the olefin group, a second protonation may occur to give requisite carbocation **19**. The substrates **15** and **18** were prepared from the respective heterocyclic nitriles and [1,1′-biphenyl]-2-ylmagnesium bromide followed by conversion of the intermediate ketones to the olefins (**15** and **18**) by Peterson olefination.

CONCLUSIONS

In summary, we have found that cyclizations of diazine-based olefins follow the same regioisomeric patterns observed in intermolecular reactions. As described in our previous report,[9] these reactions are controlled by charge distributions in the protonated *N*-heterocycles. The contrasting chemistry of azines and diazines is also noted, as the diazines give highly charged ring systems capable of undergoing conjugate addition, whereas azines (such as pyridyl systems) give Markovnikov addition with phenyl group nucleophiles.

EXPERIMENTAL SECTION

General. All reactions were performed using oven-dried glassware under an argon atmosphere. Trifluoromethane sulfonic (triflic) acid was freshly distilled prior to use and, following reactions, may be recovered and recycled quantitatively.[16] All commercially available compounds and solvents were used as received. ^{1}H and ^{13}C NMR were performed using either a 500 or 300 MHz spectrometer; chemical shifts were made in reference to NMR solvent signals. Low-resolution mass spectra were obtained from a gas chromatography instrument equipped with a mass-selective detector. High-resolution mass spectra were obtained from a commercial analytical laboratory; a time-of-flight (TOF) mass analyzer was used for the samples.

Preparation of Heterocyclic Olefins, General Method A. Heterocyclic bromide (0.5 mmol) is combined with palladium(II) chloride (2.0 mg, 0.01 mmol), copper iodide (3.8 mg, 0.02 mmol), and cesium fluoride (151.9 mg, 1.0 mmol) in a dry 10 mL round-bottom flask. Tri-*n*-butyl(4-phenylbut-1-en-2-yl)stannane (0.274 g, 0.65 mmol)[13] is then added as a solution in DMF, followed by tri-*t*-butylphosphine (0.020 mL, 1 M in toluene). The resulting mixture is heated to 100 °C and stirred for 12 h. Following this period, the mixture is cooled to 0 °C in an ice bath; trimethylaluminum (2.5 mL, 2.0 M in toluene) is added dropwise over 5 min, and the solution is stirred for 3 h. The mixture is then poured into a NaOH (10 mL, 1 M aqueous) solution and stirred until gas evolution ceases. The product mixture is partitioned between dichloromethane and water. The aqueous phase is extracted with dichloromethane, and the combined organic extracts are washed with water (2×) and NaCl brine (2×). After drying the solution with anhydrous Na_2SO_4, the solvent is evaporated. The product is then purified by column chromatography (silica gel, ethyl acetate/hexane).

Cyclization of Olefins, General Method B. Heterocyclic olefin (0.2 mmol) is dissolved in 1.0 mL of dichloromethane and cooled to 0 °C. Triflic acid (0.5 mL, 2.8 mmol) is added dropwise, and the mixture is stirred for 4 h at 0, 25, or 60 °C. The resulting mixture is poured over ice to which is added 50 mL of $CHCl_3$. The aqueous solution is then made basic by the addition of 10 M NaOH (pH ∼8), and the mixture is partitioned in a separatory funnel. The aqueous layer is extracted twice with $CHCl_3$; the combined organic extracts are washed with water and then brine, and the solution is dried over anhydrous sodium sulfate. The product is isolated by silica gel chromatography (hexanes/ethyl acetate).

Preparation of Olefins, General Method C. Ketone (1 mmol) is dissolved in 15 mL of anhydrous diethyl ether; $(CH_3)_3SiCH_2MgCl$ (4 mmol, 4 mL of 1 M solution in THF) is added, and the solution is heated to reflux. After stirring for 4 h, the solution is cooled in an ice bath, and concentrated HCl (5 mL) is added dropwise. The resulting mixture is heated to 70 °C, stirred for an additional 12 h, and then cooled prior to neutralizing with 10 M NaOH (pH ∼8). The product mixture is partitioned between ethyl acetate and water, and the aqueous layer is extracted twice with ethyl acetate. The combined organic extracts are washed with water and then brine and dried over anhydrous sodium sulfate. The product is isolated by silica gel chromatography (hexanes/ethyl acetate).

*2-(4-Phenylbut-1-en-2-yl)pyrimidine (**2**).* Using general method A, 2-bromopyrimidine (0.0795 g, 0.5 mmol) gives compound **2** (0.0475 g, 0.23 mmol, 45%), which is isolated as a clear, yellow liquid. R_f = 0.32 (hexane/ethyl acetate, 5:1). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.92−3.05 (m, 4H) 5.53 (s, 1H), 6.51 (s, 1H), 7.16−7.23 (m, 2H), 7.27−7.33 (m, 4H), 8.78 (s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 34.8, 35.0, 119.1, 120.2, 125.8, 128.3, 128.6, 142.2, 146.4, 156.7, 165.7. Low-resolution mass spectrum (EI) *m*/*z*: 210 (M+), 195, 106, 91. High-resolution mass spectrum (CI; M + 1) for $C_{14}H_{15}N_2$: calcd, 211.1235; found, 211.1231.

*2-(1-Methylene-3-phenyl-propyl)pyrazine (**3**).* Adapting a published procedure,[17] acetylpyrazine (1.89 g, 15.5 mmol), benzaldehyde (2.4 mL, 23 mmol), and diisopropylethylamine (1 mL) are dissolved in 40 mL of anhydrous pyridine, and the mixture is heated to reflux. After stirring for 18 h, the mixture is concentrated and subjected to column chromatography (hexanes/EtOAc, 1:1) to provide 3-phenyl-1-pyrazin-2-yl-propenone (**21**) as a yellow solid (1.16 g, 5.5 mmol, 36%). Compound **21** (1.14 g, 5.4 mmol) is dissolved in 150 mL of absolute ethanol, and 5% Pd−C is added (100 mg). Hydrogen gas is bubbled through the solution for 5 min, and then the flask is sealed. A hydrogen filled balloon is attached to the flask. After 1 h, the reaction mixture is filtered through a plug of Celite and concentrated under reduced pressure. Column chromatography (hexanes/ether, 1:1) is used and 3-phenyl-1-(pyrazin-2-yl)propan-1-one (**22**) (467 mg, 2.2 mmol, 41%) is isolated as a yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.10 (t, 2H, J = 7.6 Hz), 3.57 (t, 2H, J = 7.6 Hz), 7.20−7.33 (m, 5H), 8.64 (dd, 1H, J = 1.5 Hz, 2.4 Hz), 8.76 (d, 1H, J = 2.4 Hz), 9.25 (d, 1H, J = 1.4 Hz). ^{13}C NMR ($CDCl_3$, 500 MHz): δ 29.6, 39.5, 126.1, 128.5, 129.0, 140.9, 143.5, 143.6, 147.4, 147.8, 200.4. Low resolution mass spectra (EI) *m*/*z*: 212 (M+), 184, 80. High-resolution mass spectrum (CI; M + 1) for $C_{13}H_{13}N_2O$: calcd, 213.1028; found, 213.1031.

Methyltriphenylphosphonium bromide (1.57 g, 4.4 mmol) is suspended in 30 mL of anhydrous ether and then cooled to 0 °C. *t*-Butyl lithium (5.3 mmol) is added slowly to the suspension. After 2 h, 3-phenyl-1-pyrazin-2-yl-propan-1-one **22** (0.467 g, 2.2 mmol) is dissolved in 20 mL anhydrous ether and is slowly introduced to the flask via a transfer loop. The reaction mixture is warmed to 25 °C and stirred for another 2 h. After filtration, product **3** is isolated by column chromatography (hexanes/Et_2O, 4:1) as a brown oil (162 mg, 35%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.85−2.89 (m, 2H), 2.96−3.01 (m, 2H), 5.41 (s, 1H), 5.85 (s, 1H), 7.21−7.32 (m, 5H), 8.46 (d, 1H, J = 2.4 Hz), 8.56−8.57 (m, 1H), 8.80 (d, 1H, J = 1.2 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 34.7, 35.1, 117.3, 126.0, 128.4, 128.5, 141.6, 142.2, 142.8, 143.5, 145.1, 153.8. Low-resolution mass spectrum (EI) *m*/*z*: 210 (M+), 209, 195, 106, 105, 91. High-resolution mass spectrum for $C_{14}H_{14}N_2$: calcd, 210.11570; found, 210.11592.

*2-(4-Phenylbut-1-en-2-yl)quinoxaline (**4**).* Using general method A, 2-bromoquinoxaline (0.1045 g, 0.5 mmol) gives compound **4** (0.0685 g, 0.2 mmol, 52%), which is isolated as a clear, colorless oil. R_f = 0.37 (hexanes/ethyl acetate, 5:1). ^{1}H NMR ($CDCl_3$, 500 MHz): δ

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2.94−3.16 (m, 4H), 5.61 (s, 1H), 6.02 (s, 1H), 7.21−7.34 (m, 5H), 7.74−7.80 (m, 2H), 8.11 (d, J = 1.4, 1H), 8.13 (d, *J* = 1.6, 1H), 9.14 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 34.9, 35.3, 118.6, 125.9, 128.4, 128.5, 129.0, 129.5, 129.7, 130.1, 141.3, 141.8, 141.9, 143.3, 146.1, 152.7. Low-resolution mass spectrum (EI) *m*/*z*: 260 (M+), 245, 156, 91. High-resolution mass spectrum (CI; M + 1) for $C_{18}H_{16}N_2$: calcd, 261.1392; found, 261.1393.

*2-(1,2,3,4-Tetrahydronaphthalen-2-yl)pyrimidine (**5**).* Using general method B, 2-(4-phenylbut-1-en-2-yl)pyrimidine **2** (0.0483 g 0.23 mmol) gives compound **5** (0.0411 g, 0.20 mmol, 85%), which is isolated as a clear liquid. R_f = 0.22 (hexanes/diethyl ether, 2:1). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.03−2.11 (m, 1H), 2.36−2.39 (m, 1H), 2.96−3.13 (m, 2H), 3.18−3.47 (m, 3H), 7.14−7.21 (m, 5H), 8.75 (d, *J* = 4.9, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 28.8, 29.5, 34.4, 43.8, 118.8, 125.7, 125.7, 128.4, 128.9, 129.2, 136.2, 136.2, 157.1, 173.7. Low-resolution mass spectrum (EI) *m*/*z*: 210 (M+), 195, 181, 94. High-resolution mass spectrum (CI; M + 1) for $C_{14}H_{15}N_2$: calcd, 211.1235; found, 211.1233.

*2-(1,2,3,4-Tetrahydro-naphthalen-2-yl)pyrazine (**6**).* Using general method B (80 °C), compound **3** (10 mg, 0.048 mmol) provides product **6** (8 mg, 0.038 mmol, 80%), which is isolated as a brown oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.06−2.13 (m, 1H), 2.22−2.27 (m, 1H), 2.97−3.26 (m, 5H), 7.14−7.18 (m, 4H), 8.48 (s, 1H), 8.57−8.59 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 29.0, 29.3, 35.2, 40.4, 125.8, 125.9, 128.9, 129.1, 135.8, 135.9, 142.6, 143.7, 144.1, 160.6. Low-resolution mass spectra (EI) *m*/*z*: 210 (M+), 195, 117, 94. High-resolution mass spectrum (EI) for $C_{14}H_{14}N_2$: calcd, 210.1157; found, 210.1160.

*2-(1,2,3,4-Tetrahydronaphthalen-2-yl)quinoxaline (**7**).* Using general method B, 2-(4-phenylbut-1-en-2-yl)quinoxaline **4** (0.0379 g, 0.15 mmol) gives compound **7** (0.0217 g, 0.84 mmol, 57%), which is isolated as a dark yellow resin. R_f = 0.25 (hexanes/ethyl acetate, 7:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.12−2.26 (m, 2H), 2.98−3.51 (m, 5H), 7.18 (s, 4H), 7.72−7.81 (m 2H), 8.09−8.14 (m, 2H), 8.87 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.1, 29.4, 34.9, 125.8, 126.0, 129.0, 129.1, 129.2, 130.0, 135.8, 135.9, 141.6, 145.0, 160.0. Low-resolution mass spectra (EI) *m*/*z*: 260 (M+), 245, 231, 144, 117. High-resolution mass spectrum (CI; M + 1) for $C_{18}H_{17}N_2$: calcd, 261.1392; found, 261.1389.

*6-(4-Phenylbut-1-en-2-yl)quinoxaline (**8**).* Using general method A, 6-bromoquinoxaline (0.2828 g, 1.4 mmol) gives compound **8** (0.1162 g, 0.44 mmol, 33%), which is isolated as a yellow resin. R_f = 0.27 (hexanes/ethyl acetate, 9:1). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.85−3.01 (m, 4H), 5.30 (d, *J* = 0.9, 1H), 5.58 (s, 1H), 7.93 (dd, *J* = 1.9, 8.8, 1H), 7.21−7.33 (m, 5H), 8.11 (d, *J* = 8.8, 1H), 8.17 (d, *J* = 1.5, 1H), 8.87 (d, *J* = 12.4, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 34.7, 37.1, 115.5, 126.0, 128.4, 128.43, 129.0, 129.3, 141.5, 142.7, 143.2, 144.3, 145.2, 146.5. Low-resolution mass spectra (EI) *m*/*z*: 260 (M+), 130, 104, 91. High-resolution mass spectrum (CI; M + 1) for $C_{18}H_{17}N_2$: calcd, 261.1392; found, 261.1392.

*6-(1-Methyl-2,3-dihydro-1H-inden-1-yl)quinoxaline (**9**).* Using general method B, 6-(4-phenylbut-1-en-2-yl)quinoxaline **8** (0.0495 g, 0.19 mmol) gives compound **9** (0.0309 g, 0.12 mmol, 62%), which is isolated as a cloudy, colorless resin. R_f = 0.20 (hexanes/ethyl acetate, 7:1). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.84 (s, 3H), 2.31−2.57 (m, 2H), 2.88−3.07 (m, 2H), 7.08−7.24 (m, 4H), 7.69 (dd, *J* = 2.0, 8.9, 1H), 7.94 (d, *J* = 1.8, 1H), 8.03 (d, *J* = 8.9, 1H), 8.83 (s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 27.3, 30.5, 43.7, 52.5, 124.2, 124.8, 126.0, 126.9, 127.1, 129.0, 130.4, 141.7, 142.8, 143.5, 144.4, 150.0, 151.7. Low-resolution mass spectra (EI) *m*/*z*: 260 (M+), 245, 230, 115, 91. High-resolution mass spectrum (CI; M + 1) for $C_{18}H_{17}N_2$: calcd, 261.1392; found, 261.1385.

*5-(4-Phenylbut-1-en-2-yl)pyrimidine (**10**).* Using general method A, 5-bromopyrimidine (0.0795 g, 0.5 mmol) gives compound **10** (0.0360 g, 0.17 mmol, 34%), which is isolated as a clear, colorless resin. R_f = 0.34 (hexanes/ethyl acetate, 5:1). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.79−2.86 (m, 4H), 5.28 (s, 1H), 5.42 (s, 1H), 7.16−7.32 (m, 5H), 8.86 (s, 2H), 9.20 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 34.4, 36.4, 116.3, 126.2, 1283, 128.5, 134.6, 140.8, 141.9, 154.1, 157.4. Low-resolution mass spectra (EI) *m*/*z*: 210 (M+), 104, 92, 91, 65. High-resolution mass spectrum for $C_{14}H_{14}N_2$: calcd, 210.11570; found, 210.11612.

*2-(1-([1,1′-Biphenyl]-2-yl)vinyl)pyrazine (**15**).* Magnesium turnings (3.0 mmol, 0.73 g) are heated in an oven for 1 h. After cooling, 10 mL of anhydrous diethyl ether, 2-bromobiphenyl (2.0 mmol, 0.209 g), and a crystal of iodine are added. The flask is fitted with a reflux condenser and heated briefly to initiate formation of the Grignard reagent. The mixture is stirred for 1 h at 25 °C and then cooled to 0 °C. The 2-cyanopyrazine (0.2102 g, 2.0 mmol in 10 mL of diethyl ether) is then added; the solution is allowed to warm to 25 °C, and it is stirred 12 h. The mixture is then quenched with 6.0 M HCl and stirred for 1 h. The aqueous layer is made basic (pH ∼8) by the addition of 10 M NaOH, and the mixture is partitioned in a separatory funnel. The aqueous phase is extracted twice with ethyl acetate, and the combined organic extracts are washed with water and then brine. The resulting solution is then dried over anhydrous sodium sulfate and [1,1′-biphenyl]-2-yl(pyrazin-2-yl)methanone **23** (0.3152 g, 1.2 mmol, 61%) is isolated as a light yellow solid. Mp 97.5−98.1 °C. R_f = 0.26 (hexane/ethyl acetate, 5:1). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.10−7.24 (m, 5H), 7.52 (dd, *J* = 1.0, 7.7 Hz, 1H), 7.56 (dt, *J* = 1.2, 7.6 Hz, 1H), 7.65−7.69 (m, 1H), 7.75 (dd, *J* = 1.3, 7.7 Hz,1H), 8.30 (dd, *J* = 1.6, 2.4 Hz, 1H), 8.43 (d, *J* = 2.5 Hz, 1H), 8.94 (d, 1.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 127.5, 127.6, 128.3, 129.2, 129.6, 129.8, 131.7, 137.4, 140.3, 142.1, 143.1, 145.1, 146.3, 149.6, 197.5. Low-resolution mass spectrum (EI) *m*/*z*: 260 (M+), 231, 181, 153, 152. High-resolution mass spectrum (CI, M + 1) for $C_{17}H_{13}N_2O$: calcd, 261.1028; found, 261.1028.

Using general method C, [1,1′-biphenyl]-2-yl(pyrazin-2-yl)-methanone **23** (0.1190 g, 0.46 mmol) gives compound **15** (0.0174 g, 0.12 mmol, 15%), which is isolated as a dark yellow oil. R_f = 0.14 (hexanes/ethyl acetate, 9:1). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.17 (d, *J* = 1.3 Hz, 1H), 6.17 (d, *J* = 1.3 Hz, 1H), 7.46−7.53 (m, 9H), 8.17 (s, 1H), 8.18−8.20 (m, 1H), 8.31 (t, *J* = 2.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 121.4, 126.8, 127.8, 127.8, 128.7, 129.2, 130.2, 130.8, 138.3, 141.0, 142.3, 143.32, 147.1, 150.1. Low-resolution mass spectra (EI) *m*/*z*: 258 (M+), 257, 202, 178, 165, 128. High-resolution mass spectrum (CI; M + 1) for $C_{18}H_{15}N_2$: calcd, 259.1235; found, 259.1240.

*2-(9,10-Dihydrophenanthren-9-yl)pyrazine (**17**).* Using general method B (25 °C), 2-(1-([1,1′-biphenyl]-2-yl)vinyl)pyrazine **15** (0.0164 g, 0.064 mmol) gives compound **17** (0.0051 g, 0.02 mmol, 31%), which is isolated as a dark yellow resin. R_f = 0.07 (hexanes/ethyl acetate, 9:1). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.34−3.50 (m, 2H), 4.47 (t, *J* = 5.8 Hz, 1H), 7.10 (d, *J* = 7.4 Hz, 1H), 7.17−7.34 (m, 4H), 7.43 (t, *J* = 7.2 Hz, 1H), 7.62−8.11 (m, 4H), 8.81 (dd, *J* = 8.2, 29.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 29.7, 34.9, 44.6, 122.7, 123.7, 124.3, 127.4, 127.9, 128.1, 128.7, 128.71, 134.4, 136.6, 142.5, 144.1, 144.4, 158.2. Low-resolution mass spectra (EI) *m*/*z*: 258 (M+), 257, 178, 165, 80. High-resolution mass spectrum (CI; M + 1) for $C_{18}H_{15}N_2$: calcd, 259.1235; found, 259.1236.

*2-(1-([1,1′-Biphenyl]-2-yl)vinyl)pyridine (**18**).* As described above, 2-bromobiphenyl (2.0 mmol, 0.209 g) is used to prepare the corresponding Grignard reagent from Mg turnings (3.0 mmol, 0.73 g), which is combined with 2-cyanopyridine (0.2088 g, 2.0 mmol) to give [1,1′-biphenyl]-2-yl(pyridin-2-yl)methanone **24** (0.3498 g, 1.3 mmol, 68%), which is isolated as a white solid.

Using general method C, [1,1′-biphenyl]-2-yl(pyridin-2-yl)-methanone (0.1653 g, 0.6 mmol) gives 2-(1-([1,1′-biphenyl]-2-yl)vinyl)pyridine **18** (0.0291 g, 0.11 mmol, 18%), which is isolated as a clear resin. R_f = 0.26 (hexanes/ethyl acetate, 9:1). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.53 (d, *J* = 18.2 Hz, 1H), 6.18 (d, *J* = 18.2 Hz, 1H), 6.88−7.50 (m, 12H), 8.43 (d, *J* = 4.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 120.0, 121.7, 122.1, 126.5, 127.5, 127.7, 128.2, 129.1, 130.1, 130.9, 135.9, 139.4, 141.1, 141.4, 148.7, 149.2, 157.8. Low-resolution mass spectra (EI) *m*/*z*: 257 (M+), 256, 180, 178, 127, 79. High-resolution mass spectrum (CI; M + 1) for $C_{19}H_{16}N$: calcd, 258.1283; found, 258.1285.

*2-(9-Methyl-9H-fluoren-9-yl)pyridine (**20**).* Using general method B (25 °C), 2-(1-([1,1′-biphenyl]-2-yl)vinyl)pyridine **18** (0.0307 g, 0.12 mmol) gives compound **20** (0.0307 g, 0.12 mmol, >99%), which is isolated as a yellow resin. R_f = 0.31 (hexanes/ethyl acetate, 9:1). ^{1}H

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NMR ($CDCl_3$, 500 MHz): δ 7.11 (s, 3H), 6.66 (d, J = 8.0 Hz, 1H), 7.11 (dd, J = 5.0, 6.6 Hz, 1H), 7.29−7.33 (m, 2H), 7.37 (dt, J = 1.7, 7.7 Hz, 1H), 7.41 (dt, J = 1.0, 7.7 Hz, 1H), 7.41 (dt, J = 1.0, 7.5 Hz, 2H), 7.44 (s, 1H), 7.46 (s, 1H), 7.82 (d, J = 7.6 Hz, 2H), 8.68 (d, J = 4.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 24.8, 57.2, 120.2, 121.1, 121.6, 124.4, 127.5, 127.7, 136.2, 140.0, 148.8, 152.4, 163.6. Low-resolution mass spectra (EI) m/z: 257 (M+), 256, 242, 241, 179, 178, 165, 128, 79. High-resolution mass spectrum (CI; M + 1) for $C_{19}H_{16}N$: calcd, 258.1283; found, 258.1285.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01701.

NMR spectra of new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dklumpp@niu.edu.

Notes

The authors declare no competing financial interest.

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